PHARMACOLOGY

AND

THERAPEUTICS

By

ARTHUR R. CUSHNY, M.A., M.D., LL.D., F.R.S.

Late Professor of Materia Medica and Pharmacology in the University of Edinburgh

TWELFTH EDITION, THOROUGHLY REVISED

By

C. W. EDMUNDS, A.B., M.D.

Professor of Materia Medica and Therapeutics in the University of Michigan, Ann Arbor, Mich.

AND

J. A. GUNN, M.A., M.D., D.Sc., F.R.C.P.

Professor of Pharmacology and Director of the Nuffield Institute for Medical Research, University of Oxford, Oxford, England

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PREFACE TO THE TWELFTH EDITION.

WHEN the first edition of this book appeared, in 1899, it was recognized as being "the first severely critical, rigorously scientific, general text-book to be written in English by an experimental pharmacologist." For a quarter of a century successive editions from Cushny's master hand played an important part in sifting and promulgating the advances in knowledge of the subject with which it deals. In the preface to the Eighth Edition (1924) he quoted prophetically from "the Schoole of Salerne" (1607) the farewell verse;

> And here I cease to write, but will not cease
> To wish you live in health, and die in peace;
> And ye our Physicke rules that friendly read,
> God grant that Physicke you may never need.

When Cushny himself "ceased to write" and we were entrusted with the task of preparing the ninth, tenth and eleventh editions, we professed our desire to maintain, not merely the critical spirit of the book, but the text as far as possible. We were well aware that no one could adequately replace the original author himself, but from the way in which the book has maintained its popularity with teachers and students, we venture to hope that the spirit which inspired the earlier editions has not been wholly lost.

In the tenth edition very considerable changes were required to bring the book in accord with the British Pharmacopœia of 1932, and the last edition brought it into line with the eleventh decennial revision of the Pharmacopœia of the United States (1936). The opportunity was then taken not only to revise the text but also to make a very considerable rearrangement of the order of the book. The present edition incorporates changes introduced by the publication of the Appendix to the British Pharmacopœia of 1936 and the Supplements to the U. S. Pharmacopœia of 1937 and 1939.

No strictly scientific or completely logical arrangement of the heterogeneous group of substances used as drugs is yet possible. Drugs grouped together by reason of possessing a common pharmacological action may differ from one another in respect of other pharmacological actions; drugs used for a specific therapeutic purpose may have little otherwise in common either chemically or pharmacologically. In spite of this, the subject can be made more intelligible and repetition can be avoided by such arrangement as is possible. In this book drugs are grouped together sometimes because they act at a common point, *e. g.*, hypnotics, sometimes because they have a common therapeutic use, *e. g.*, anthelmintics: and sometimes because of a chemical similarity, *e. g.*, heavy

metals. When in doubt, we have decided the arrangement with a view to convenience in teaching the subject and ease of learning it.

The increasing volume of pharmacological research throughout the world, as well as the growing interest in scientific therapeutics, yearly adds so much to our knowledge that, in a book of this kind, many chapters require a considerable amount of revision every two or three years. The main function of this book has always been to serve as a textbook for medical students and practitioners. Consequently stress is laid especially upon those drugs which are either of therapeutic importance or are of theoretical significance in regard to the site or nature of pharmacological action. The field of pharmacology, however, includes the physiological and toxic actions of all chemical substances. Every year witnesses the investigation of many new pharmacological agents, especially new synthetic compounds, some of which offer no prospect of therapeutic use and others which exhibit little novelty of action. An attempt to include all of these would make the book unwieldy and would defeat its primary purpose. On the other hand, we have included brief references to some substances, *e. g.*, rarer metals, which do not seem at the moment to possess much importance for medicine but the actions of which may be of interest to workers in cognate sciences.

Anything approaching a complete bibliography would add too much to the size and cost of the book, and so place it beyond the range of many students and practitioners. Generally speaking, we have contented ourselves, as was Cushny's practice, with giving such references as either indicate pioneer researches on a particular subject or as contain in themselves a good bibliography. We hope that in this way the bibliography given may afford a first aid toward the more complete study of the literature.

J. A. G.
C. W. E.

ARTHUR ROBERTSON CUSHNY.

(1866-1926)

DR. ARTHUR R. CUSHNY was born at Fochabers, Scotland, on March 6, 1866. He was educated at the local school and subsequently at the University of Aberdeen, where he graduated M. A. in 1886 and M.B.C.M. (with highest honors) in 1889. Under tenure of a fellowship awarded by his University, he worked for a year at Berne under the celebrated physiologist, Hugo Kronecker, and later at Strassburg under Oswald Schmiedeberg, then the most distinguished pharmacologist in Europe. After acting for two years as assistant to Schmiedeberg, he was invited to succeed J. J. Abel in the chair of Pharmacology at Ann Arbor. Here he remained until 1905, when he returned to England to become the first occupant of the chair of Pharmacology at University College, London, and in 1918 succeeded Sir Thomas Fraser at Edinburgh, where he remained until his sudden death in 1926.

One of his most important contributions to medical science was his research upon the pathological physiology of the mammalian heart, and especially his study of the cardiac arrhythmias. These studies led him to conclude that auricular fibrillation was probably a cause of certain forms of cardiac irregularities which were seen in the human subject. As is well known, this theory was later shown to be correct by studies carried out upon patients by workers in various parts of the world.

Other outstanding contributions were his study of the action of the digitalis glucosides, culminating in his monograph, "The Action and Uses in Medicine of Digitalis and Its Allies," 1925; his investigations of the function of the kidney and the action of diuretics, leading up to the critical summary, "The Secretion of Urine," published in 1917. His quantitative study of the action of the optical isomers was made the subject of the Dohme Lectures, delivered at Johns Hopkins University in 1925, under the general title, "Biological Relations of Optically Isomeric Substance." Apart from these major interests, he made a large number of important researches covering a wide field of pharmacological inquiry, as shown by the bibliography which appeared in the *Journal of Pharmacology and Experimental Therapeutics* (**27**, 265, 1926).

Dr. Cushny possessed to an unusual degree a constructive and original mind with balanced and critical judgment. These qualities added to his unswerving love and pursuit of truth, the breadth and accuracy of his knowledge, and his power of gaining the affections of his fellow workers all over the world, made him one of the most influential figures in the great advances of pharmacology in the first quarter of the twentieth century.

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A TEXT-BOOK OF PHARMACOLOGY.

INTRODUCTION.

PHARMACOLOGY is the study of the changes induced in living organisms by the administration in a state of minute division of such unorganized substances as do not act merely as foods. Many of the best known of these substances are used to counteract the effects of disease, or to reinforce the tissues in their struggle to maintain their functions, when these are rendered abnormal. These substances are known as *drugs*, and the art of applying drugs in disease is termed *Therapeutics*. Other substances may be of no value in disease, but are of importance because they act as *poisons*, that is, cause dangerous or fatal symptoms in man or animals when they are ingested in quantity. The practical study of the effects of these poisons in man—the diagnosis and the treatment of poisoning, and the methods of detecting the poison—is termed *Toxicology*. But the description and explanation of the symptoms induced by chemical substances belong to the field of pharmacology, whether these substances be drugs or poisons. It is indeed impossible to distinguish between drugs and poisons. Most remedies given in excess cause toxic symptoms, while many poisons are valuable remedies in small doses. Further the actions of many substances are investigated which may never come to be used medicinally as "drugs" but such investigation forms an essential part of pharmacology.

Active agents are formed within the body but the study of them belongs in the first place to the domain of physiology, so long at least as they are not introduced from without. Here no distinct borderline exists between physiology and pharmacology but the scope of their territories may be illustrated by the position of a substance like epinephrine. Epinephrine is a hormone manufactured by the suprarenal gland and the effects produced by this internal formation of epinephrine constitute a part of physiology, a science which deals with the life of the normal organism. Epinephrine may, however, be artificially prepared or synthesized and administered medicinally in doses which may produce concentrations in the blood different from those which occur normally in the body. So used, it becomes a "drug." Conversely, acetyl-choline was first studied as a pharmacological agent but has later become of physiological importance from its occurrence and activities in the body. It is especially true of the hormones and of various salts that occur in the body that they come under the domains both of physiology and of pharmacology and the relative importance of a substance to one or other of these sciences may alter with advance in knowledge.

Pharmacology is related equally closely to biochemistry. Thus the part played by vitamins in the normal economy of the organism can be regarded as the immediate concern of biochemistry as that science is now

usually defined. On the other hand, cod-liver oil had appeared in our pharmacopœias as a "drug," before its value as a source of vitamins was discovered, and now other preparations containing vitamins appear in pharmacopœias or "official lists of medicines." Some brief account of vitamins is therefore, usually included in books on pharmacology.

Similarly the borderline between pathology and pharmacology is sometimes indistinct. Pharmacology may be regarded as the study of the organism rendered abnormal by drugs, while pathology is the study of the organism rendered abnormal by disease. Many of the features of disease are now recognized to be due to the presence of unorganized poisons formed in or by the tissues, poisons which may be allied to, or even identical with, substances used as drugs. Indeed, a substance like histamine may be regarded, under different conditions, as a physiological, pharmacological, or pathological agent. The study of bacteria and of the toxins produced by them belongs primarily to bacteriology. Bacterial toxins are however, related to vegetable toxins, such as ricin, which is obtained from the seeds of Ricinus communis, which have long appeared in pharmacopœias. Now that vaccines and antitoxins have found a place in pharmacopœias as remedial agents, some brief reference to them is of convenience in a book on Pharmacology so that the student may have all official remedies simultaneously under review.

Pharmacology is in fact really a department of biology very closely related to other sciences which may be included by that term. It is neither possible nor advisable that the boundaries of these allied sciences should be too strictly limited. Consequently, though in the great majority of cases there need be little hesitation in deciding whether or not a substance is a "drug" and should therefore come under the scope of pharmacology, there is unavoidably some overlapping, and some account must here be given of remedial agents which would not be regarded as "drugs" in the ordinary sense.

The great interest of pharmacology does not lie in its purely biological aspects, however, but in its relation to the treatment of disease. As long as we are ignorant of how a remedy acts in any disease, the treatment is purely empirical; when the mode of action is understood, much greater accuracy can be attained in the treatment. The object of pharmacology is to provide a scientific foundation for therapeutics and to increase the resources of the art of healing. The exact way in which a drug changes the diseased condition can often be followed only imperfectly in man, and recourse must be had to experiments on healthy or diseased animals to elucidate the principles on which it should be employed. In addition, the experimental investigation of new chemical bodies has very frequently demonstrated properties which are of therapeutic value; almost all the new drugs introduced in the last half-century have found their way to the wards through the experimental laboratories.

Pharmacology is one of the most recent developments of medical and biological science. It is true that from the earliest times attempts have been made to explain the effects of drugs on the then prevailing theories of pathology, but the objective study of the action of drugs on

the organism has been almost entirely developed since the middle of the nineteenth century. The study of drugs was termed *Materia Medica* up to this time, and comprised an examination of their botanical and chemical properties along with some account of the diseases in which they had proved of value. This descriptive rather than experimental study has been continued under the name of *Pharmacognosy*, but is now pursued chiefly by pharmacists. Undoubtedly the student of medicine ought to know those characters of drugs which are of importance in modifying their action and application, but it is undesirable that his valuable time should be occupied in the detailed description of crude substances, which he may probably never have an opportunity of seeing in his future practice.

Another subject which now occupies a much less prominent position in medical study than formerly is *Pharmacy*, or the art of preparing drugs for therapeutic use. Some general knowledge of the methods used is no doubt indispensable to the educated physician, if mainly as an aid to prescribing; but the details may be left to the pharmacist. With the decay of the complex prescription the study of pharmacy by medical students has become less imperative. The relations of medicine to pharmacy have greatly changed in recent years. The physician is dependent upon the manufacturer for his supply of drugs. Many manufacturers now not only make drugs of established reputation but seek to discover new remedies, for which purpose they may have both chemical and pharmacological laboratories at their disposal. A commercial firm not unnaturally endeavors to recoup itself for the expenses of preliminary unproductive research by the profits on the sale of a new drug, which is frequently registered under a proprietary name. The physician is nowadays liable to be overwhelmed by such new remedies, some of which are new only in name and others only slight variants of known drugs. On the other hand, many valuable drugs have been introduced in this way. The physician must endeavor to assess the value of therapeutic claims and should make it a rule not to prescribe substances or preparations of the composition of which he is ignorant. Modern progress in therapeutics has brought other changes in its train. Many alkaloids and synthetic compounds are now distributed in forms which require no manipulation by the retail pharmacist. The practice of giving remedies by injection is becoming increasingly common, often necessitating that the preparations be put up by the manufacturer in ampoules which require no further "dispensing." This has led to a decline of individual prescribing and dispensing. This change is perhaps inevitable but will have less serious consequences so long as the preparation which the practitioner prescribes is to him not merely a name but something with whose composition and properties he is adequately conversant.

METHOD OF ACTION OF DRUGS.

Stimulation, Depression, Irritation.—When a cell is affected by a poison, the extent of its activity is changed but not the kind. In other words, the effects of drugs are quantitative, not qualitative; the activity of living

matter may be changed, but the form which the activity assumes is unchangeable.

Drugs which increase the activity of any organ or function are said to *stimulate* it, while those which lessen the activity are said to *depress* it. Another condition induced by drugs is *irritation,* for although this term is often applied loosely as a synonym for stimulation, the two conditions are not identical. Stimulation is properly used to indicate an increase in the specialized function of a cell, producing, for instance, in the spinal cord an increase in the reflex excitability. Irritation, on the other hand, is used rather in reference to the changes in the conditions common to all forms of living matter, that is, it indicates a change in the nutrition and growth of the cell, rather than in the specialized functions. Irritation may thus be induced in all kinds of tissues and is the commonest change caused by drugs in the less differentiated forms, such as the connective tissues and ordinary epithelia; while stimulation is met with in the more highly specialized cells, such as those of the heart, nervous system, or secretory glands In many instances the irritant action of drugs may be explained by their known reactions with the proteins of the cell; for example, substances which dissolve proteins, or precipitate them, or withdraw fluid from them, all tend to cause irritation when they are applied to living tissues. In other cases irritation appears to be induced through some action the nature of which is quite unknown.

When stimulation is prolonged or excessive, the protoplasm generally becomes depressed and finally loses its activity entirely (paralysis). Some authorities have asserted that depression is invariably preceded by stimulation, and that stimulation sufficiently prolonged invariably leads to depression and paralysis. Both statements are too absolute, although they are true in the great majority of cases. For example, the action of atropine on the terminations of the cardiac inhibitory nerves is purely depressant. Even the most minute quantities of this alkaloid never increase the activity of these terminations, for a quantity too small to weaken them has apparently no effects whatever, and as the dose is increased, the first effect is depression.

Depression, whether induced directly, or following on stimulation, has been shown in several instances to resemble the fatigue induced by the prolonged exercise of the normal organ, and it is probably true that depression and fatigue are, in all instances, identical in appearance, although not necessarily identical in cause. For example, the phenomena of fatigue of the terminations of the motor nerves in muscle resemble those induced by curare, but the fatigued terminations rapidly recover while the curarized recover only when the poison is eliminated.

In most cases an excessive dose of a stimulating poison leads to depression and paralysis. The cell becomes functionally dead, but if the failure of its function does not involve the death of the organism, it may recover and reassume its ordinary function as if no stage of inactivity had intervened. Excessive irritation, on the other hand, leads to actual death and disintegration, from which there is no recovery. For example, the cells of the spinal cord are first stimulated and later

paralyzed by a large dose of strychnine, but this is not fatal to cold-blooded animals, and after a few days the spinal cord regains its normal function, as the poison is eliminated. On the other hand, the injection of an irritant into the subcutaneous tissues causes structural changes. If only a small quantity be injected, this condition is recovered from, although it generally leaves evidence of its presence in the form of an increase in the fibrous tissue. But if the irritation be intense, the cells undergo degeneration and die, and an abscess is formed. The cells thus destroyed can never recover as the paralyzed ones do. They are either absorbed, or removed by the opening of the abscess, and their room is filled by the overgrowth of the neighboring tissues.

When the effects of a drug are only temporary and the tissue returns to its normal activity when the drug is eliminated, the action is said to be *rerersible;* this is the case for most forms of stimulation and depression and for mild irritation. When the cells do not recover but have to be replaced by new growth, the action is *irreversible.*

Distribution and Concentration.—The distribution of a drug in the different tissues and organs of the body must influence its action; and it might be expected that those organs which contain it in largest proportions would show greater changes than others in which it is present in smaller amounts. But this is found not to be true in many instances; for example, the liver often contains larger quantities of alkaloids than any other tissue, yet no symptoms may arise from this organ. The relative concentration in which a drug is present in the different tissues thus does not determine the extent to which these are involved in the action. But if an organ reacts to a drug, the degree of its reaction depends on the concentration in which the drug is presented to it, and the problem in therapeutics is very generally to bring up the concentration in one organ to the efficient threshold without involving other organs; for example, in chloroform anæsthesia the object is to cause sufficient concentration in the brain and spinal cord without involving the heart and respiration.

The concentration of a drug in a cell depends in the first instance on the concentration in which it is present in the surrounding fluids and in many cases there seems to be no greater concentration than is in accord with diffusion, the drug being present in the cell in the same concentration as in the fluid. In other instances the drug is deposited in the cell in some form of combination, chemical or physical, and the diffusion continues until the cell may contain the whole of the drug and the surrounding fluid is free from it. As the drug is accumulated in the cell it may finally reach a strength that provokes reaction, but in some instances the drug accumulates in large amount without interfering with the functions of the cell.

The concentration of a drug in the tissues depends primarily on the dose given, but this is modified by the rate of absorption and the rate at which the body frees itself from the drug by excreting it, or changing it into harmless forms. Small divided doses of a remedy may thus never cause the same symptoms as the administration of the same amount undivided. The most striking instance of this is offered in

anæsthesia, for during an operation of an hour's duration much larger amounts of chloroform or ether are taken into the tissues than would be fatal if inhaled more rapidly; the fatal concentration is not reached because excretion is going on at the same time as absorption.

Elective Affinity of Drugs. Protoplasm Poisons.—Most drugs have an elective affinity for certain definite tissues. Thus, some attack the heart only, others the central nervous system and others the terminations of the motor nerves in muscle. Among the cardiac poisons again, some act on the ventricle, others on the auricle, and among the poisons of the central nervous system, some act primarily on the cortex, others on the medulla oblongata and others on the spinal cord. This elective affinity is not merely a question of degree, as is sometimes stated, for a drug which has a powerful action on the brain may have no effect on the heart except when administered in such quantities as alter the physical characters of the blood. A drug may even alter different structures in diametrically opposite directions. Thus, atropine depresses certain nerve terminations, but stimulates the brain; curare, which paralyzes the peripheral terminations of the motor nerves, stimulates the spinal cord. In some instances the immunity of a cell to the action of a drug may perhaps be explained by the latter failing to penetrate into its interior, but this is not true in all cases.

The fields of activity of different drugs vary greatly in extent. One may comprise only the terminations of the secretory fibres in the sweat glands (agaricin), while another, which affects these in the same way, may involve many other terminations in its action (atropine). Most poisons, however, while acting on a certain narrow area in small doses, extend the limits of their activity when larger quantities are ingested. Thus, a poison which acts in small doses on the medulla oblongata only, may, when exhibited in larger quantities, involve the spinal cord and the brain, and in still greater concentration may affect the heart and other organs. No poison is known that acts equally on all organs and tissues, but those which have a wide field of operation are often known as *protoplasmic poisons*. These paralyze any form of living matter when they are brought in contact with it in sufficient quantity, but if they are injected into the blood and thus distributed equally throughout the body, they invariably select some special organs as the chief seat of their activity. This is exactly parallel to the behavior of chemical agents in the laboratory. For example, acetate of lead added to a solution of a chloride, or of a sulphate, precipitates it, but, added to a mixture of the two, throws down more of the sulphate than of the chloride. Nitrate of silver, on the other hand, precipitates the chloride only. Acetate of lead may be compared to the protoplasm poisons, nitrate of silver to those with a less extensive field of action. As protoplasmic poisons affect a large number of different forms of living matter, it follows that they alter the nutrition rather than specialized functions.

Local, General and Remote Actions.—The *local* action of a drug is that induced at the point of application before it enters the circulation, the *general* or systemic action is that due to its elective affinity for certain

organs to which it is carried by the blood. The local effects are very often entirely different in nature from the general action, for a drug may act as an irritant at the point of application and as a depressant to the brain when it is carried to it in the blood. Local effects may be induced wherever the drug can be applied—to the skin, the alimentary tract, the respiratory passages, and the other mucous membranes. They also occur in the subcutaneous tissues when the poison is injected hypodermically, and in any of the deeper organs and tissues which can be reached by the needle of the syringe. Local remedies may cause irritation, or may protect the surface from irritation, may depress the sensory end-organs and cause local anæsthesia, or lessen secretion, or alter the functions at the point of application in many other ways. They may also have remote effects, as will be mentioned. Many drugs have only a local action, because they are not absorbed, are absorbed in inactive forms, or are excreted or deposited as rapidly as they pass into the circulation, so that enough is not present in the blood at any one time to induce general effects. On the other hand, many powerful poisons have little or no effect at the point of application, but possess an elective affinity only for some organ to which they are carried by the circulation.

Drugs change directly only those organs and tissues with which they come into immediate contact. But the alteration of one part of the organism very often entails that of another to which the drug may not have access, or for which it has no special affinity, because impulses are transmitted through the nerves, or changes are induced in the circulation and nutrition. Thus irritation of the skin may alter the rate of the pulse by impressions being transmitted by the cutaneous nerves and reflected along the inhibitory nerves of the heart. Similarly a poison that weakens the heart may induce disorder of the respiration, from the circulation being deficient in the medulla oblongata; and depression of the brain may lessen the oxidation in the muscles, because it leads to lessened movements. These secondary changes, which are not due to the direct action of the drugs on the organs concerned, are known as *remote* or *indirect* effects.

General Theories of Pharmacological Action.—A number of drugs affect the organism only through their obvious *physical* properties, as when an inert oily body is applied to an abraded surface and promotes its healing by protecting it from irritation and from the evaporation of fluid, or when common salt absorbed into the blood changes its osmotic tension, and thus alters the distribution of fluids in the tissues. On the other hand, many effects are due to simple *chemical* reactions; for instance, bicarbonate of sodium may be used to neutralize the hydrochloric acid of the gastric juice, just as it combines with acid in a test-tube, and many of the effects of oxalates arise from their forming insoluble salts with the calcium of the tissues. In the great majority of drug effects, however, no such simple relations as these obtain and the mode of action remains unknown. This ignorance is not surprising when one considers the extreme complexity of even the simplest living cell and also the complex structure of many drugs. One view which has been widely held pos-

tulates that when a drug affects a cell it enters into a definite chemical combination with the constituent protoplasm, similar to the ordinary compounds of the chemical laboratory. There are difficulties in many cases in the way of acceptance of this theory, one of which is that the same action may be induced by a series of drugs which have no chemical reactions in common and which therefore cannot be supposed to enter into the same chemical combination with the cell protoplasm. For these reasons there has been a tendency to attribute the action of drugs rather to their physical properties, and there can be no question that these play a large part in determining the effects; for example, unless a drug is soluble in the fluids of the body it cannot be absorbed and circulate in the blood, and, similarly, unless it is soluble in the cell contents it may have difficulty in entering the cells. Many drug effects have been ascribed to this selective absorption alone, a drug acting on all cells into which it can enter, by changing the relations of the cell constituents in which it is dissolved; but objections have been raised to this view which cannot be neglected. (See Meyer-Overton theory of narcosis.) Similarly, attention has been drawn to the possibility that some effects may arise from the drugs altering the surface tension of a cell in relation to the surrounding fluids. It has been shown that in some cases in which true chemical combinations were believed to be formed between cell constituents and drugs, the connection is really of the loose nature known as "adsorption compounds," which are best illustrated in the combination of dyes with fibres (see Heavy Metals); the formation of these adsorption compounds is associated with a change of electrical charge, and some authorities are disposed to attribute some other pharmacological actions to a similar change in electrical state. Much evidence has been accumulated to show that a drug may act on the surface of a cell or may enter the cell and act (or fail to act) on its interior, and that the effects produced differ in the two cases. Straub has brought forward some evidence that certain very powerful drugs act by altering the cell surface without penetrating into the interior, while others effect changes only as they penetrate the surface, and lose their efficiency as they accumulate in the interior. Changes in the intracellular membranes have been suggested by others as an explanation of most drug effects; it is held that a drug may reduce the permeability of the cellular membranes by altering their electric charges and thus retard the free passage of ions which is necessary for full activity; other poisons may accelerate their movement, and thus increase the activity. From the present state of knowledge the only legitimate conclusion seems to be that the activity of drugs depends on a large variety of factors and that pharmacological action cannot be brought under any one law, either chemical or physical. The importance of the following points has, however, been clearly established. The surface membrane of cells shows selective permeability to drugs, as it does to salts, allowing some to pass rapidly, others slowly, others not at all. The distribution of drugs is affected by differential solubility, by absorption, and by chemical reaction, and the relative importance of these factors varies with different drugs. In the case of many powerful drugs it has been

shown that the amount of a drug required to produce a strong action on a cell is too small to form a monomolecular layer over the whole surface. The cell surface cannot, therefore, be pictured as a uniform structure but rather as a mosaic, and a drug may react with a few molecules on the cell surface and so alter its activities by changing its surface pattern. Summarizing the evidence Clark[1] concludes that the simplest possible conception of the action of most potent drugs is that they unite with certain specific receptors (in or on the cells) which may form only an insignificant part of the surface. The action of a drug on any cell involves at least two separate processes, namely a chemical reaction and the biological response to this reaction. The time relations of these two processes vary in the case of different drug actions. It must also be remembered that a drug may produce a powerful action without exerting any direct effect on the cell in the ordinary sense. For example, many if not all of the actions of physostigmine can be explained by its inhibiting the esterase which destroys acetyl-choline in the tissues.

Chemical Constitution and Pharmacological Action.—In 1868 Crum Brown and Fraser published their classical paper on the relation between chemical constitution and pharmacological action and since then continuous attempts have been made to develop and extend their original conceptions. It was supposed that, if the action of a drug is due to a chemical combination between it and the tissues, substances of a similar chemical structure would have similar physiological actions, and in this event the action of a drug might to some extent be foretold from a consideration of its structural formula, provided that the action of similar compounds was already known. For example, methyl, ethyl and propyl alcohols resemble one another closely in their physiological actions, and it might be predicted that butyl and amyl alcohols would act similarly. In point of fact they do, and the pharmacological action of this series of alcohols is, so far, apparently related to their chemical composition. Moreover when the toxicity of this series of alcohols was carefully investigated, it was found that there is a progressive increase in acute toxicity as one proceeds from the lowest to the highest member of the series. It might be predicted, therefore, that alcohols higher than amyl alcohol might be progressively more toxic, but as a matter of experience these proved to be harmless because they became insoluble in the fluids of the body. This result is typical of one way in which the attempt to correlate physiological action and chemical constitution breaks down in detail, because an alteration in the physical properties of a substance may entirely alter its physiological action, though its type of chemical structure remains the same. Resemblances in action may in fact, depend upon some physical property which is common to a group and which has a more immediate bearing on their action than the actual structure; and wherever an attempt is made to follow the relationship between chemical composition and pharmacological action in detail, the analogy may break down because factors which it is impossible to deduce from the chemical structure or formulæ, intrude themselves. Also, side

[1] *Clark, A. J.* Mode of Action of Drugs on Cells, Edward Arnold & Co., 1933, and "General Pharmacology," Handbuch der exp. Pharmakologie, Springer, Berlin, 1937.

actions which do not admit at present of chemical explanation, may appear in one member of a chemical group and be absent in another. For example, methyl alcohol, though less poisonous from the point of view of minimum lethal dose than ethyl alcohol, has a highly toxic action on the optic nerve which is not displayed by ethyl alcohol.

Though it is impossible in the present state of knowledge to determine with any certainty the pharmacological action of a drug from a mere consideration of its chemical structure, yet in many cases it is found that substances of closely related structure do exert similar pharmacological actions, and this fact is of great importance in the discovery of new drugs. For example, the discovery of the exact chemical structure of epinephrine led to the synthesis and pharmacological investigation of a large number of related compounds, many of which resemble epinephrine in action, and general conclusions could be drawn as to the type of compound which is likely to exert an action similar to epinephrine.[1]

An interesting branch of this problem has been the investigation of optically isomeric substances.[2] It was found, for example, that l-hyoscyamine is twice as powerful as dl-hyoscyamine (atropine) and that the lævo compound is twelve to twenty times as active as the dextro compound. Optical rotation in this case, and in most cases, markedly affects physiological action. Usually but not always, the lævo compound is the more active of the two. In such directions important advances have been made in correlating structure and action, and possibly such advances may lead farther with the growth of biochemical knowledge.

Pharmacological Syndromes.—Claude Bernard showed that the motor paralysis produced by curare is due to an action on the nerve ends in voluntary muscle and that this action is exerted on all voluntary muscles in a manner qualitatively alike. This discovery suggested—what was not a self evident truth—that a drug which acted on the nerve ends in one voluntary muscle would act similarly on the nerve ends in all other voluntary muscles. On the assumption that curare acts upon some specific chemical receptor, it follows that there is a chemical uniformity in all such nerve ends and that they all possess the specific chemical receptor upon which curare acts. Subsequent research has extended the value of this conception. Thus a great variety of effects may be produced by epinephrine, all of which are due to its stimulating sympathetic nerve ends, and the fact that epinephrine acts upon all sympathetic nerves is hardly explicable upon any other hypothesis than upon the existence of some common chemical factor in sympathetic terminations in different organs. Such a group of pharmacological actions which are subserved by a common type of physiological mechanism and may be presumed to be due to a common chemical reaction between the drug and the tissues may be regarded as a "homogenous syndrome," however varied the resulting biological responses may be.

There is, further, evidence that pharmacological actions may run in groups when no such single chemical explanation can at present be given. Thus acetylcholine acts in a particular way on nerve ends in voluntary muscle, on parasympathetic nerve ends and on autonomic ganglia. What is more remarkable is that certain other drugs not necessarily related chemically to acetyl-choline act in the same way on the same three sites. This group of actions which tend to run together may be called a heterogenous syndrome, and, again on the assumption that pharmacological action depends upon interactions of the drug

[1] *Barger and Dale.* Jour. Physiol., **41**, 19, 1910.

[2] *Cushny.* Biological Relations of Optically Isomeric Substances, Baltimore, 1926.

with a specific chemical receptor; such a "heterogenous syndrome" suggests that at least one such receptor may be common, not only to all nerve ends in voluntary muscle but also to parasympathetic nerve-ends and to autonomic ganglia.

There is some evidence that a similar conception may afford an explanation not only of specific actions but even of the action of drugs which have hitherto been regarded as "general protoplasmic poisons." Thus quinine produces a great variety of pharmacological actions, on the circulation, on voluntary and involuntary muscle, on the central nervous system as well as on less specialized protozoa. This has no immediate significance for the study of syndromes because, with an alkaloid of such complex structure as quinine, the action on the nervous system might be due to one grouping in the molecule and the action on muscle to another.

The problem is significantly advanced, however, when it is found that another alkaloid, harmine, which has no known chemical resemblance to quinine, produces the same complex series of effects. In fact, the production of a similar group of actions by two chemically unrelated substances is difficult to explain upon the present theories of pharmacological action unless upon the assumption of a common receptor occurring in all the varied tissues upon which the two alkaloids act. This conception of heterogenous syndromes has a two-fold provocative value. From the point of biochemistry it suggests that, in spite of the differences—structural, functional and chemical—between different tissues, a particular receptor may nevertheless occur in different tissues and that, substances whether chemically related or not, which happen to combine with this receptor will produce the same group of pharmacological effects. From the point of pharmacology it is of value in facilitating investigation, for the discovery of a particular action on one organ may prompt the search for a whole group of actions. This is already a commonplace in pharmacological investigation of homogenous syndromes. The possibility of the occurrence of heterogenous syndromes has hardly yet been exploited.[1]

Chemotherapy.—This term has become associated with the specific treatment of infections by artificial remedies.[2] Specific remedies, for example quinine in malaria, have been known for centuries. When the parasitic origin of this disease was discovered, the remedial action of quinine was ascribed to its toxic action on the malarial parasite, whereby the actual cause of the disease was destroyed.

The parasite in question is a protozoal organism, which at one stage of its history inhabits the blood of man and gives rise to the symptoms of malaria. It is distantly related to the white blood corpuscle. When quinine is given in malaria, the alkaloid circulates in the blood and tissues, all of which, including the parasite, are equally exposed to the action of quinine. For quinine to be a practical remedy it was necessary for it to exert a more powerful action on the parasite than, for example, on the white blood corpuscles; otherwise they would be killed by the same concentration of quinine. It was also necessary that a toxic action on the parasite should be exerted by a concentration of quinine insufficient to damage seriously any tissue of the patient. Quinine fulfils this condition sufficiently well for it to be of practical use, though it is not an ideal remedy because it may produce undesirable symptoms in man when given in a dose sufficient to be effective in killing off the malarial organism. Cinchona bark contains a large number of alkaloids, more or less closely related in chemical constitution to quinine. These

[1] *Gunn.* Arch. Internat. d. Pharm. et de Thér., **50**, 386, 1935.
[2] *Dale.* Brit. Med. Jour., ii, 219, 1924.

other alkaloids have also been tried in malaria to see whether they were superior to quinine for this purpose.

This is one type of chemotherapeutic investigation, the deliberate search for a remedy for an infection from a group of nearly related chemical compounds one of which is known to have a specific action in the disease in question. It would seem that the word "specific" as applied to therapeutic agents had come to acquire vaguely a double meaning. The remedy is specific in the sense that it has a more powerful action on the parasite than on the tissues of the host; it is frequently also specific in the sense that usually a remedy has a much more powerful action on one particular pathogenic organism than on other, often nearly related, parasites.

Not only a great impetus but a new orientation was given to investigation of this kind by the genius of Ehrlich, of whose brilliant work in this connection only a brief account of one example can be given here. It was known that many diseases in man and lower animals were due to infection by organisms of the type of trypanosomes. It had also been discovered that an organic compound of arsenic, atoxyl, had some curative action in diseases of this type. But atoxyl, in the doses required to exert a curative action, was very poisonous, often producing serious effects, such as blindness.

Ehrlich prepared and investigated a whole series of organic arsenical compounds with a view to discovering one which would be more curative and less poisonous than atoxyl—one which would be, in his nomenclature, more parasitotropic and less organotropic. Eventually he discovered one, 606, also known as salvarsan and arsphenamine, which proved to be superior, as a remedy for syphilis, to any remedy previously available. It was also curative in some allied diseases but it was of little value in sleeping-sickness. The quest has gone on since Ehrlich's early work, for arsenical compounds which should be less toxic even than arsphenamine and which should be more efficacious than arsphenamine in some forms of trypanosomiasis. Thus new compounds have been introduced, and there is every reason to suppose that further improvements in therapeutics will continue to result from this alliance between synthetic chemistry and experimental pharmacology.

Two factors, especially, are necessary for chemotherapeutic investigation. The first is directed chemical research, whereby new compounds modified in certain directions can be made available for pharmacological investigation. The second is the production of a disease in the lower animals. If, as is the case with trypanosomes, a disease can be reproduced in small animals like rats and mice, a large number of controlled experiments can rapidly be carried out. Thus a preliminary knowledge can be acquired as to whether the drug is likely to have a curative action in a particular infection, as to what are its toxic or undesirable actions and what would be an approximate dosage. The final test of its value in a corresponding disease in man must be done on man himself.

The original conception of the value of a specific remedy being based upon a ratio between its toxicity for a pathogenic organism and its toxicity for the tissues of the host, has required considerable modifica-

tion in the light of later investigations. It has been found for example, that a drug which is curative in a disease due to a particular parasite may have no obvious action on this parasite *in vitro*. Moreover while it may cure one species of animal infected with a particular parasite, it may fail to cure another species infected with the same parasite. For these and other reasons, some of which will be mentioned in the section on organic arsenic compounds, it has become abundantly manifest that coöperation of the tissues of the host plays an important part in the curative action of most, if not all, specific remedies.

CONDITIONS MODIFYING THE EFFECTS OF DRUGS.

The effects of drugs on the living organism are subject to some modifications in certain individuals and under some conditions, which it is of importance that the physician should recognize, as the dose has to be altered when they are present. One of these is the **Size and Weight.** If the same amount of a poison be distributed through the tissues of a large individual as of a small one, the concentration is lower in the organs of the former and less effect is therefore observed. This has been ascertained chiefly in animal experiment, in which the effects of drugs can be estimated much more exactly than in man, but it undoubtedly holds good for human beings also. Very large individuals, then, require a somewhat larger dose than ordinary persons, while in treating individuals of small stature, the dose has to be reduced.

The **Age** of the patient has also to be taken into account in prescribing. Children ought to receive much smaller doses than adults. The more powerful action of drugs in children is due mainly to their smaller size, in part to the more active growth of certain tissues and to the less complete development of others, such as the central nervous system. The dose for a child is generally calculated according to Young's formula, in which a fraction obtained by dividing the age by the (age + 12), is taken as the proportion of the adult dose required; thus, for a child of four years, the dose would be $\left(\frac{4}{4+12}=\right)\ \frac{1}{4}$ of the adult dose; or more simply according to Dilling's formula, in which the fraction of the adult dose is $\frac{\text{age}}{20}$.

Neither Young's formula nor any of the others which have been devised in its stead is to be regarded as more than a very general approximation, to which there are many exceptions. For example, the narcotics, particularly opium and its preparations, must be given during the first year of life in much smaller quantities than are indicated by Young's rule, while alcohol may be administered in comparatively large doses.

The usual dose advised may be taken as that suitable for an adult of twenty to sixty years. After this age is passed, it is again reduced somewhat. There are exceptions to this rule also, large doses of the purgatives, for example, being often necessary in old people. Where great accuracy of dosage is necessary, the dose may have to be given per pound or kilogram weight of the body.

Sex.—Women generally require somewhat smaller doses than men, because of their smaller size. It is often stated that their tissues also react more strongly to drugs, but this is certainly not a general rule.

Temporary conditions also influence the activity of drugs. Thus, *after a meal,* a drug is absorbed more slowly than when it is taken fasting, and any local irritant action is also less marked, because the drug is diluted by the contents of the stomach. *Affections of the stomach and intestine* may also modify the effects of drugs; little absorption occurs in the stomach except of drugs that are soluble in oils and lipids, and if the movement of the stomach is lessened or any spasm of the pylorus is present, they may reach the absorbing mucous membrane of the bowel more slowly and thus their effects are retarded or slight; irritant drugs naturally cause more disturbance of the stomach in these cases. Vomiting and diarrhœa, of course, tend to lessen the action of drugs by removing them rapidly from the alimentary canal.

During *pregnancy,* purgatives have to be used with great care, because they may induce congestion of the pelvis, and lead to miscarriage. Drugs acting on the uterus, or inducing a marked fall of blood pressure, are to be avoided because the former may cause the evacuation of the uterine contents, while the latter may lead to asphyxia of the fœtus. Many drugs pass from the mother to the child, and this is to be borne in mind, as quantities which are insufficient to poison the former may have more serious effects on the latter. During *lactation,* it is important to remember that active bodies may be excreted in the milk, and may either act on the child or render the milk distasteful to it. In *menstruation,* purgatives are to be avoided, as they tend to increase the flow, and all very active drugs are to be used with care or abandoned temporarily.

The **Time of Administration** has also some influence on the effects of drugs. The body is generally more resistant in the morning than in the evening, especially in the case of narcotic drugs; thus a dose of a soporific which may have little or no effect in the early hours, induces sound sleep when given in the evening, partly because the brain is already fatigued and depressed, but also because the action of the drug coincides with the normal time for sleep.

Idiosyncrasy is used to denote an unusual or peculiar reaction to a drug. Some persons react more readily than usual to the ordinary dose, while in other instances a much larger quantity can be taken without any effect. Others, again, show symptoms which are entirely different from, and which may, in fact, be diametrically opposed to those ordinarily observed. These idiosyncrasies are naturally more frequently seen and are better known, when they arise from widely used drugs. Thus the modern antipyretics have so often induced abnormal symptoms that these are well known, but it is not improbable that if other drugs had been used, or rather abused, to the same extent, they would be found to induce unusual reactions in an equally large number of individuals. An idiosyncrasy usually cannot be explained in the present state of knowledge, but some conditions which have been termed idiosyncrasies are probably due to abnormally rapid, or to retarded, absorp-

tion or excretion. Idiosyncrasies are not confined to human beings, for not infrequently one animal reacts quite differently from others of the same species.

As has been mentioned, one form of idiosyncrasy consists in the failure of the individual to react to the ordinary dose of a drug. This is known as **Tolerance,**[1] and this particular form of idiosyncrasy may be termed *congenital* tolerance. Certain species of animals tolerate quantities of drugs which would be fatal to others of the same size. In fact, so frequently is this the case that it is impossible to determine the fatal dose of any drug on an animal from experiments performed upon others of a different species, even though it be nearly related. One of the most remarkable examples of this form of tolerance is met with in the hedgehog, which resists large doses of many very active poisons. Another well-known example is the tolerance of the rabbit to large quantities of atropine.

A form of tolerance which is a matter of everyday observation is that induced by the prolonged use of a drug, which has been called *acquired* tolerance, or mithridatism, from the tradition that Mithridates protected himself in this way from the danger of poisoning. The most familiar example of this form of tolerance is that acquired for tobacco (nicotine); the first cigar often induces violent poisoning, but if a habit be formed, considerable amounts of nicotine may be absorbed without apparent harm, because the tissues become accustomed to the presence of small quantities of nicotine, and thus fail to react to it. Nicotine, in fact, becomes a normal constituent of the tissues. This tolerance is entirely different from the immunity induced by toxins (see Toxins), and it is desirable that the two terms should be kept distinct.

An important form of tolerance is the resistance developed by trypanosomes and other parasites for certain drugs (see Organic Arsenic Compounds).

Very often while some tissues acquire tolerance for a poison, others fail to do so, and either react in the same way as before or may suffer from the prolonged use of excessive quantities; for example, although after prolonged use morphine loses its action on the brain, so that large doses have to be given to relieve pain, tolerance is less developed in the bowel, so that constipation continues to be induced by smaller amounts; similarly in a dog tolerant to morphine, the cardiac inhibitory centre retains its sensitiveness to it. Some animals fail to develop tolerance for certain drugs; for example the rabbit remains sensitive to morphine after prolonged treatment. It is to be noted that tolerance is soon lost if the drug be discontinued for some time. This is of great importance in cases of opium-eating, for a person who has taken opium for a long time acquires a tolerance for the drug, so that sometimes enormous quantities are required in order to induce the ordinary effects; but if the habit be discontinued for some time, the tolerance is lost, and a dose which would formerly have had little effect may now induce dangerous poisoning. The prolonged use of one drug may establish tolerance for others of the same class. Thus chronic drunkards become less sensitive

[1] *Gunn.* Physiol. Rev., **3**, 42, 1923.

to large quantities of alcohol, and are also more resistant to the action of ether than ordinary persons, this being due to the fact that ether and alcohol act on the same nerve cells in the same direction, and probably induce the same changes in the protoplasm.

In some instances when tolerance is established for a drug, it is found that the tissues destroy more of it than previously (morphine and alcohol), or excrete it more rapidly, as is said to occur under atropine in some animals, or perhaps absorb it less readily (arsenic). The drug thus never reaches the same concentration in the tissues and the absence of action is thus partly explained. In addition to this, however, the organs normally affected become less susceptible to the drug; for though in morphine tolerance much more is destroyed than in normal persons, enough remains in the blood to cause deep narcosis in ordinary people, yet no symptoms are induced in the patient.

The **Cumulative Effect** of drugs is another phenomenon caused by their continued ingestion. Small doses of certain drugs taken repeatedly for some time eventually cause symptoms which are much more marked than those that follow the first dose. This seems due to the accumulation of considerable quantities in the tissues. The absorption may be more rapid than the excretion, and each new dose thus adds to the total quantity in the blood and organs more than is lost in the same time by excretion. The classical example of cumulative action is that of digitalis, but it is much more frequently induced by such drugs as mercury, arsenic, or the iodides, for the so-called chronic poisoning induced by these is really an example of cumulative action. Another form of cumulation is said by Straub to occur in chronic lead poisoning; here the symptoms appear to arise not from the poison collecting in the tissues until it reaches an efficient concentration, but from the cumulative effect of continually repeated injuries from the presence of lead, though these injuries are individually too slight to be noted. Cumulative action may occur along with tolerance, as has been stated. Thus the tolerance of certain tissues for nicotine does not protect others from the effects of the abuse of tobacco.

Synergists.—The presence of another drug having the same effects in the body often increases the action of a remedy to an unexpected extent. This is the ground for the prescription of several remedies acting in the same way. For example, several purgatives prescribed together often act more efficiently than any one given in quantity equal to all of them. This is easily explicable upon the assumption that, although all are alike in their chief features, they differ in the details of their reactions, so that parts of the alimentary canal which might escape one are affected by another, and the mixture thus acts more universally than any one of the components. Other examples of synergism are offered by the narcotics, for it has been shown that a mixture of morphine and chloral, for example, is more efficient than either administered alone in larger dose. Another recent example is offered by the use of mercury and arsenical compounds in syphilis, which act better together than when either is used alone. The importance of synergism is often exaggerated, but in some examples

the increased activity of one drug in the presence of another is remarkable.[1]

On the other hand, a drug may fail to elicit any symptoms if an **antagonistic** substance is present in the body. Thus in cases where a powerful nervous depressant, such as chloroform, has been inhaled, strychnine may have little or no effect on the spinal cord in doses which would normally increase the reflexes to a marked extent. In the same way, if the terminations of the inhibitory fibres of the heart are paralyzed by atropine, a poison which normally slows the heart by stimulating these terminations will have no effect in the usual doses.

Similar modifications of the effects of drugs may be induced by poisons formed by pathological changes in the tissues, or by an unusual state of irritation or of depression of the tissues themselves. For example, the excitable uterus of pregnancy may react by contraction to certain drugs which excite both the motor and the inhibitory nerves and which in the more inert non-gravid organ cause relaxation. Similarly, in hot weather and in tropical climates, purgatives are found more efficient than in colder climates, because the mucous membrane is more irritable than usual, as shown by the frequent occurrence of diarrhœa without drugs. In the same way when an antagonistic poison is formed in the tissues in the course of a disease, a drug may have little or no effect.

Pathological conditions often modify the effects of drugs to a very considerable extent, and in a way which cannot be explained at present. For example, the antipyretics reduce the temperature in fever, but have no effect on it in health; the bromides lessen the convulsions in epilepsy, but have much less effect in depressing the brain in normal persons. The question may therefore be raised whether the examination of the effects of drugs in normal animals is of much value in indicating their therapeutic action. But in reply it may be said that in a large number of instances drugs are given, not in order to act upon the diseased tissues, but upon healthy ones. The object of the therapeutist is very generally not to restore the diseased tissue but to relieve it from work, and to allow it rest so as to promote its restoration by nature. For instance, in diseases of the cardiac valves, drugs are given, not with the object of restoring their integrity, but to act upon the healthy heart muscle, and to obviate the disturbance of the circulation which is caused by the destruction of the valves. So that usually drugs are given to act on normal tissues, or on tissues which are so little affected by disease that they react to remedies in the same way as the normal. Actually the response of a tissue in a pathological condition may not differ much from that of a normal tissue; for example, the exsected human appendix may show almost normal spontaneous movements and respond normally to drugs when it is in a condition of severe inflammation.[2] In other cases the action of drugs on diseased tissues or on

[1] *Fühner.* Arch. f. exp. Path. u. Pharm., **82**, 51, 1917.
[2] *Gunn* and *Whitelocke.* Brit. Jour. Surg., **2**, 92, 1914.

the causes of disease may be investigated by inducing the disease in animals, as has been done very largely in recent years in various infectious diseases. (See Chemotherapy.)

METHODS OF ADMINISTRATION.

Drugs are applied for their **Local Action** to the skin, to the mucous membranes of the alimentary, respiratory, and genito-urinary tracts, and to the conjunctiva and cornea. Even deeper tissues and organs can be treated locally by the injection of remedies into them. The objects of local medication are very diverse, and can be treated of only in connection with the individual drugs. The methods of application are also so numerous that only a few of the chief can be mentioned. Drugs intended for application to the skin are often formed into salves or ointments (unguenta) by mixing them with oily or fatty substances, which adhere to the skin and do not dry up, and which, in addition to serving as a means of applying an active substance, protect the surface from the air and from irritation. Other preparations for application to the skin, such as the plasters (emplastra), resemble the ointments in their general characters, but also give mechanical support and bind surfaces together from their being spread on paper or cloth, which thus serves as a flexible splint. The collodions and cerates resemble the plasters, the oleates the ointments. In addition to these special preparations, drugs may be applied to the skin in solutions, or as powders, or solid masses may be used to cauterize it.

The methods of applying drugs to the alimentary tract and to the lungs for their local action are for the most part similar to those used for drugs which are intended to be absorbed. The mouth and throat may be washed out with solutions, which are gargled (gargarismata), or may be treated with powders, or lozenges (trochisci), which are slowly dissolved and thus permit of a more prolonged and constant action in the mouth than is possible if the drug be swallowed immediately. The nose may be washed out with solutions of active drugs, or powders may be drawn into the nostrils as snuffs; the latter often cause sneezing, and are sometimes known as sternutatories, or errhines. The larynx may be treated locally by the application of powders or of very small quantities of fluids by the aid of the laryngoscopic mirror and probe. Solutions are generally used for application to the conjunctiva, but a more permanent effect can often be obtained from ointments, lamellæ, or powders which are less liable to be washed away by the tears. The urethra, vagina and uterus are treated by the injection of solutions, or by ointments and powders. Bougies, which are occasionally advised, are formed by incorporating an active drug in some substance which is solid at ordinary temperatures, but melts when introduced into the organ and allows the drug to come into contact with the surface. The rectum may similarly be treated by the injection of drugs in solution or suspension (enemata), or by the use of suppositories. Drugs are not infrequently applied by the rectum in order to elicit their action after absorption, but much oftener for

their local action on the bowel. Enemata may be either large (a pint or more) or small (2-5 cc., ½-1 fl. dr.). The large enemata are used either to wash out the intestines, and may then contain an antiseptic or astringent, or to induce peristalsis and evacuation of the bowel, when they are made up of water with or without soap or other slightly irritant substances. The small enemata are used chiefly to induce evacuation, and contain more irritant substances, such as glycerin alone or along with some more active body. Suppositories are usually formed of cacao-butter, which is solid at room temperature, but melts at the temperature of the body.

Drugs whose **General Action** is to be elicited after their absorption are given by the mouth, except when some special character in them or in the disease renders some other method preferable. They may be given by the mouth in solution in water, alcohol, oils, or other more or less indifferent bodies. The disagreeable taste of many remedies, however, often precludes this method, and these may be ordered in the form of pills, or in capsules, which are formed of gelatin or similar substances and are dissolved in the stomach and intestines. Very often the disagreeable taste may be concealed by the addition of sugar, or of some strongly tasting but agreeable body, such as a volatile oil. Insoluble drugs may be given as powders, as they have little or no taste. Powders are also used as a means of administering soluble drugs, if they have not a disagreeable taste and have no marked local action, but very deliquescent drugs should not be given in this form. Insoluble drugs are sometimes ordered in suspension in mucilaginous fluids; and oils, which are distasteful to many people, may be given mixed with water and gums (emulsions).

The rate of absorption from the *alimentary canal* varies greatly with different drugs and also with the form in which they are administered. The first point will be treated of in connection with the individual drugs. As regards the second, it may be stated that drugs are more rapidly absorbed when they are swallowed in solution, and that, when much inert and insoluble matter is associated with them, their absorption is much retarded. This fact is taken advantage of in practice by giving drugs in solution when rapid absorption is desirable, and by giving less pure forms when the local action on the stomach and bowel is to be elicited. The more concentrated the solution, the greater is the irritant action on the stomach, and thus where irritation of the stomach is desired, either the solid drug or a strong solution is given; but as a general rule the local action on the stomach is to be avoided, and drugs are therefore ordered in as dilute solution as is possible without increasing the bulk to too great an extent. It is to be noted that drugs which are insoluble in the test-tube may be rendered soluble by the action of the gastric and intestinal juices, while many which are given in solution are precipitated by the proteins in the stomach.

Drugs absorbed from the stomach and intestine are carried to the liver before reaching the general circulation, and this is of great importance in determining their effects in the body, as some of them are

retained in that organ, and are either entirely destroyed or escape so slowly that they have no perceptible effect.

Drugs are occasionally introduced into the *rectum* so as to obtain their general action. The local effects on the stomach are thus avoided and some of the drug reaches the circulation without passing through the liver; morphine and opium are sometimes so administered. Drugs are absorbed more slowly from the rectum than from the small intestine but absorption may begin sooner than when a drug is given by mouth, as in the latter case the drug may be delayed in the stomach.

Another important method of administering drugs for their general action and also for their local effects is by inhalation into *the lungs*. Only volatile drugs can be used thus for their general action. They are absorbed very rapidly, owing to the extensive surface to which they are applied, and also because volatile substances penetrate the tissues more readily than others. The best examples of inhalation are offered by the general anæsthetics, chloroform and ether. Most substances absorbed by the lungs are also excreted by them, and this leads to an important practical point in regard to the anæsthetics. For the passage of gases or vapors through the lining epithelium of the alveoli depends in most instances upon their partial pressure, that is, upon their concentration in the air and blood respectively. Accordingly, when the air contains more chloroform vapor than the blood, the anæsthetic passes into the blood, but as soon as the condition is reversed, and the blood contains more chloroform than the air of the alveoli, it commences to pass backward. The more concentrated the vapor inhaled, the more chloroform is contained in the cubic centimeter of blood, and the greater is the action on the nervous centres and the heart.

Less volatile substances are sometimes inhaled into the lungs for their local action, and even non-volatile bodies suspended in a spray or vapor may be thrown into the respiratory passages, but it may be questioned whether these last really reach the alveoli except in traces.

Drugs are rarely administered by other mucous membranes for their general effects. An exception must be made of the nasal mucous membrane, which is highly vascular and affords a rapidly absorbing surface. Especially drugs which are destroyed by digestive juices and so are ineffective when given by mouth, *e. g.*, pituitary extract, may be administered by introduction into the nasal cavity. It must be remembered that symptoms may arise from the unwanted absorption of a drug which is being used for its local action; even death has occasionally occurred, for example, from the absorption of cocaine from the nose or urethra when it has been applied to these mucous membranes as a local anæsthetic. Similarly, drugs applied as dressings to wounds or abrasions have often given rise to severe or fatal poisoning from being absorbed into the blood.

Drugs are also applied to *the skin* in order to elicit their general action. Volatile bodies are certainly absorbed by it, although much more slowly than by the lungs or by the stomach and intestine. Solutions in water of non-volatile drugs are not absorbed from the skin, but solutions of certain remedies in alcohol, oils, fats, ether, and some

other substances which are capable of dissolving or mixing with the fatty covering of the skin, are absorbed fairly rapidly if they are rubbed in thoroughly. This method of application (inunction) has been used chiefly for the absorption of mercury, as the local action on the stomach and bowel is thus avoided. (See Mercury.) Alkaloids do not appear to be absorbed by the skin even when dissolved in oils or alcohol.

The *hypodermic method* is being more widely used every year. By this method drugs are injected through a fine hollow needle into the subcutaneous, or, in the case of more irritant substances, into the muscular tissue, where they meet with fewer sensory nerves. Absorption occurs more rapidly than when drugs are given by the mouth, the local action on the alimentary canal is avoided, and the physician is more certain that the whole of the remedy is effective, provided it is soluble and is not precipitated at the point of injection. At the same time, the method has certain drawbacks, the chief of which are the pain of the injection and the danger of injecting a powerful remedy into one of the subcutaneous veins. Hypodermic injections should be made only by the physician or trained attendant. The needle and syringe ought to be sterilized, and the substance injected should be aseptic. As a general rule, solutions in water or in dilute alcohol are used for injection, but the insoluble salts of mercury have also been injected, suspended in oil (see Mercury). Irritant drugs are to be avoided as far as possible, as they cause great pain, swelling and sometimes suppuration or sloughing, even when the injection has been carried out aseptically. If there is any doubt as to the irritant action of a drug, the injection should be made into muscle (gluteus) as disastrous results have followed from ignorance of the local action of such remedies as quinine or calcium salts. Ringer's solution should be used instead of plain water when possible. Hypodermic injection is used very largely to elicit the general action of a remedy, but also for the local effects, as when cocaine is injected in order to produce local anæsthesia. As the absorption from the subcutaneous tissues is usually more rapid than that from the stomach and intestine, when the drug is in perfect solution, the dose has to be reduced. As a general rule, about one-half of the ordinary amount is sufficient.

Deeper injections are sometimes made for their local action on the organs. Thus, antiseptics have been injected into lung cavities, caustics into tumors, local anæsthetics into the spinal canal, and direct applications have been made to the nerves in sciatica and other similar disorders.

Intravenous injection is the most certain and rapid method of bringing drugs into the circulation and tissues, and has long been used in experiments on animals and more recently in man in diseases in which it is desired to induce a definite concentration of a remedy in the blood rapidly (syphilis, malaria, urgent heart failure, etc.). A long hypodermic needle is passed directly into one of the superficial veins of the arm and after all air has been expelled from the needle and syringe, the dissolved drug is slowly injected in quantities of the solution which may vary from 1 cc. to 200 cc. The drug must be in complete solution and must not react with the protein of the blood; thus strongly acid drugs and dissociable salts of the heavy metals should be avoided; on the other hand,

drugs, *e. g.*, tartar emetic, which are too irritant for hypodermic injection may sometimes be given intravenously. The most perfect asepsis should be aimed at. The dose is usually much smaller than that given by the mouth, but no general rule can be given. The toxicity of a drug by intravenous injection is often greatly reduced by injecting it slowly and well diluted.

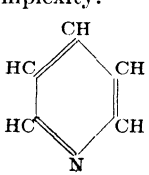
Quite recently the galvanic current has been employed to aid in securing the penetration of certain drugs into the deeper tissues where they may be taken up by the blood stream and act particularly upon the tissues in the neighborhood of the point of application. In this method, which is known as "*electrophoresis*" or "*common ion transfer,*" it is possible under proper conditions to secure the action of the drug employed upon the deeper tissues without at the same time bringing about systemic effects, although occasionally symptoms are produced indicating a general action.

This method of "common ion transfer" is especially applicable to treatment of the extremities and is employed to secure an action upon the blood-vessels in certain vasospastic conditions such as are found in Raynaud's disease, etc. As acetyl-beta-methyl choline is being employed in this manner, further details of the use of the electric current for this purpose will be discussed under that heading.

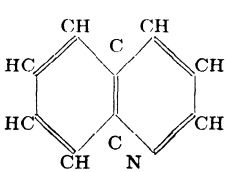
THE CHEMICAL CHARACTERS OF DRUGS.

Many substances which induce changes in the living organism are comparatively simple chemical compounds. In the inorganic materia medica are found many salts, bases and acids, and a few uncombined elements, such as mercury and sulphur, while organic chemistry offers alcohols, ethers, phenols, ketones and an ever increasing number of more complex synthetic compounds. But some groups of substances which occur widely in plants require some discussion before the individual members are taken up severally.

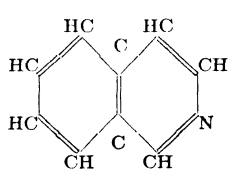
The first group of these is formed by the **Alkaloids**, which are substituted ammonias, and have a more or less strongly alkaline reaction, so that they are often known as the vegetable bases. They contain carbon, hydrogen, nitrogen, and, as a general rule, oxygen, although some of them, such as coniine, are devoid of it. Like ammonia, they combine readily with acids without eliminating hydrogen, and the salts thus formed resemble those of ammonia in many respects, among others in being thrown out of combination by the fixed alkalies. Many vegetable alkaloids are derived from pyridine, quinoline and isoquinoline by the addition of hydrogen, and generally by the substitution of one or more of the hydrogen atoms by side chains of greater or less complexity.



Pyridine



Quinoline



Isoquinoline

Many alkaloids have, however, a very complex constitution. The structural formulæ of the most important alkaloids will be given, when they are known, but apart from this any detailed consideration of the chemical structure of alkaloids is beyond the scope of this book.

Some of the vegetable alkaloids have been formed synthetically in the laboratory, and the constitution of some of the others is perfectly well known, but many of them have not yet been isolated, and there are probably others whose existence is not even suspected. These vegetable alkaloids occur in almost all parts of plants, although they are found in greatest abundance in the seeds and roots. The same alkaloid is often found in most of the plants of a genus, or it may occur in one or two species of a genus and in other plants which are in no way related. Very often several alkaloids are found in a plant, and these may differ entirely in their action on animals, although not infrequently all the alkaloids of a plant resemble each other in their effects. The alkaloids are found most abundantly in dicotyledonous plants, but some are obtained from the monocotyledons. Muscarine, ergotoxine and other bases are found in the fungi, and alkaloids have been isolated from the suprarenal capsule of animals and from the skin of the salamander.

The alkaloids are very often only slightly soluble in water, but form salts which are generally more soluble. Many of the bases are dissolved by ether, chloroform and amyl alcohol, while the salts are insoluble in these. Both bases and salts are generally fairly soluble in alcohol. The hydroxides and carbonates of the alkalies and the alkaline earths precipitate the alkaloids from solutions of the salts in water, a point of some importance in prescribing these bodies.

Another important class of vegetable poisons is formed by the **Glucosides** (glycosides), or saccharides, which are esters (compound ethers) composed of sugars and hydroxyl substances, and which liberate sugar when they are heated with acids, or sometimes with alkalies, or when certain unorganized ferments act on them. The sugar formed in this way is often glucose, but not invariably so; the other decomposition products have been identified only in a few instances. Many of the glucosides contain only carbon, hydrogen and oxygen, a few have nitrogen in addition, and one or two, sulphur. In some instances the remainder, after the sugar is split off, is an alkaloid, *e. g.*, solanidine. Glucosides differ greatly in their solubility in water and alcohol; comparatively few of them are soluble in ether. Some of the glucosides are powerful poisons, others have little or no action.

Resins, an ill-defined group, are found in many plants, and are characterized by their smooth, shining fracture, and by their insolubility in water and solubility in ether, chloroform, volatile oils, benzol and, in many cases, in alcohol. They seem to be formed in plants by the oxidation of volatile oils, and are often acid or anhydride in character, while others are apparently alcohols or esters. The resins are almost invariably composed of several different substances mixed together.

Oleoresins are solutions of resins in ethereal oils, which lend them a characteristic odor and taste. The term "*Balsam*" is often used as synonymous with oleoresin, but most writers restrict it to those oleo-

resins which contain benzoic or cinnamic acid along with other constituents. *Gum-resins* are mixtures of resins and gums, generally containing some volatile oils. They are insoluble in water, but the resin is suspended in it by the gum. On the other hand, the resin is dissolved by alcohol, while the gum remains insoluble.

Gums are amorphous, transparent substances, composed of carbohydrates of the formula $(C_6H_{10}O_5)_n$ and are thus nearly related to cellulose and starch. Some of them are soluble in water, while others merely swell to a jelly in it; they are insoluble in alcohol. They generally occur in plants in combination with calcium, magnesium or potassium; they have no poisonous action, but form a protective covering for irritated surfaces, and are largely used to suspend in water substances which are insoluble in it, such as resins and oils.

Volatile oils (v. p. 234) occur in plants in large numbers.

Fats, oils, sugars, acids, starch, proteins, coloring matter, ferments and other bodies which occur in plants, and are contained in many of the preparations used in therapeutics, are not generally possessed of any action of importance.

THE PHARMACOPŒIAS AND PHARMACOPŒIAL PREPARATIONS

Almost all governments have found it necessary to regulate the preparation of drugs used in therapeutics, and for this purpose issue at intervals codes of instructions defining the characters of the drugs and giving the exact formulæ according to which they are to be prepared for use. These codes are known as **Pharmacopœias**, and some differences exist between those of different countries, although the most important drugs are found in all of them. All the drugs used in therapeutics are not found in the pharmacopœias, for these are issued only at intervals of several years, and in the meantime valuable remedies may be introduced. The pharmacopœia of the United States is revised every ten years and the eleventh revision was published in 1936. Two supplements have appeared, one in 1937 and one in 1939. The British Pharmacopœia will in future also be revised every ten years. The last edition appeared in 1932 but an appendix to it was published in 1936. The next full revision is due for 1941 and the intention is that in future the U. S. P. and B. P. should be revised alternately so that a new edition of one or the other will be published every five years. The official definition of therapeutic substances is of advantage to both physician and pharmacist, as it assures the former that the drug he prescribes will have a uniform quality, wherever in the country it is dispensed, while the pharmacist is saved from the continual preparation of remedies in different forms, by their being prescribed in one recognized strength.

Apart from the official pharmacopœias, other lists of drugs and formulæ are published for the guidance of medical practitioners and pharmacists. Thus the American Pharmaceutical Association issues the "National Formulary" (N. F.), a collection of formulæ which is also a legal standard, and the American Medical Association publishes annually "New and Non-official Remedies" (N. N. R.), which contains descriptions of proprietary drugs which are marketed in an

acceptable manner. The Council of the Pharmaceutical Society of Great Britain publishes the "British Pharmaceutical Codex" (B. P. C.), with the object of providing recognized formulæ for medicines which are not officially recognized in the British Pharmacopœia. The last edition appeared in 1934.

The pharmacopœias contain a large number of pure substances such as salts, acids, bases, alkaloids, and these require no further description. On the other hand, many of the drugs are given in an impure form, either because the active principle is unknown, or because its isolation is attended with difficulty and expense. Thus many of the vegetable remedies are presented in the pharmacopœias as solutions or solids which contain not only the active principle but gums, sugars, coloring matter, and many other impurities. These are provided in different forms to allow of variation in their administration. In addition, the pharmacopœias contain a number of official prescriptions, that is, mixtures of active substances in such proportions as are ordinarily prescribed. These are generally designated by the addition of "compound" (compositus) to the name of the chief ingredient. Most pharmacopœias continue to use Latin in the titles of the drugs, and this is not due to mere pedantry or conservatism, as is often stated. For the popular name of a drug is often used for several different substances, while the Latin name in a prescription indicates that drug which is known by the term in the pharmacopœia.

Many crude or unprepared drugs are found in the pharmacopœias, such as leaves, roots, flowers, or even whole plants. These are used chiefly for the preparation of other more readily applicable remedies, but are sometimes prescribed as powders or in pills.

The following preparations[1] are official:

a. *Aqueous Preparations.*

Aquæ, medicated waters, generally contain only traces of some volatile substance, such as an ethereal oil or chloroform, in solution in water, and these are used in prescriptions as more agreeable to the taste and smell than pure water but have little further effect. In the U. S. P. the solutions of ammonia and hydrogen peroxide are also included under aquæ, but these are used only to elicit the specific effects of these drugs. In the B. P. these strong solutions are included in the liquores.

Liquores (U. S. P.) are solutions in water of soluble substances. Many of these are 1 per cent in strength.

Liquores (B. P.) are solutions in the widest sense, in water, alcohol, or other fluids.

Decocta (U. S. P.) or decoctions, are solutions of vegetable principles, which are obtained by boiling parts of plants in water.

Infusa, or infusions, are solutions obtained by soaking parts of plants in water, which may be hot or cold, but is not kept boiling. Infusions and decoctions are weak preparations and tend to decompose rapidly. Many drugs in the B. P. have both a fresh infusion (Infusum Recens) and a concentrated infusion (Infusum Concentratum). The latter diluted with seven times its volume of distilled water yields a product resembling the fresh infusion.

[1] The student is advised to omit the following list for the present, and to refer to it only as he takes up the preparations of the individual drugs Most of these preparations are found in both pharmacopœias. Those which occur only in the British are indicated by B. P., while those which are confined to the United States are marked U. S. P.

Misturæ, or mixtures, are preparations in which substances insoluble in water are suspended in it by means of gums or similar viscid substances, or are mixtures of solutions.

Emulsa (U. S. P.), emulsions, are formed by suspending oils in water by means of gums or other viscid bodies. The B. P. contains no official emulsions.

Mucilagines, mucilages, are solutions in water of gums, starch, and similar colloid bodies.

Magmas (U. S. P.), or milks, are suspensions of bulky, white insoluble preparations in water.

Syrupi, syrups, are strong solutions of sugar in water, which may be used alone, or may be impregnated with more active bodies. Similar preparations formed with honey instead of syrup (sometimes known as *mellita*) are official, as Mel Boracis (B. P.).

Lotions (B. P.), lotions, or washes. This term is used to designate a preparation of mercury, the black wash.

b. *Alcoholic Preparations.*

Spiritus, spirits, are solutions of volatile bodies in alcohol, and often owe their chief action to the solvent and not to the drug contained in it.

Elixiria, elixirs, are sweetened aromatic preparations containing diluted alcohol or glycerin.

Tincturæ, tinctures, are solutions in alcohol of medicinal substances, which are generally formed from parts of plants by maceration or percolation. They contain both volatile and non-volatile ingredients, but the latter are generally the more important.

Fluidextracta (U. S. P.), *Extracta Liquida* (B. P.), fluidextracts, are prepared from plants by forming solutions in water or more frequently in alcohol, and evaporating them until the solutions contain as many cubic centimeters as the original crude drugs weighed in grammes; that is, the volume of the fluid extract corresponds to the weight of the crude drug. When the active principle is assayed, however, the liquid extract is diluted to contain a definite amount of it, and without reference to the quantity of the crude drug used.

The tinctures and fluid extracts are the most commonly used liquid preparations, and most of the important drugs are prepared in one or both of these forms.

c. *Other Fluid Preparations.*

Glycerita (U. S. P.) or *Glycerina* (B. P.) are solutions of medicinal substances in glycerin.

Collodia, collodions, are solutions of medicinal substances in collodion, which is itself a solution of pyroxylin in alcohol and ether.

Aceta, or medicated vinegars, are solutions of medicinal substances in vinegar or diluted acetic acid.

Linimenta, liniments, embrocations, are preparations in which active remedies are dissolved or suspended in dilute alcohol, oils, or water. They generally contain an oil or soap and are intended to be applied to the skin.

d. *Solid and Semi-solid Preparations.*

Extracta, extracts, are formed from solutions such as tinctures, decoctions, or infusions by evaporation, which is continued until there remains a solid mass. The extracts thus contain all the substances which are taken up by the solvent, except those which are driven off or decomposed at the temperature at which evaporation is carried on.

Pilulæ, pills, are globular masses of small size, such as admits of their being easily swallowed. They are formed from extracts, or from powders, by the addition of some substance to give them the necessary cohesion and consistency. Pills generally weigh 0.1-0.3 G. (2–5 grs.). The U. S. P. determines the composition and size of the official pills, so that the doses can be modified only

by ordering several pills to be taken at one time. The B. P. leaves the pills unformed, so that they may be prescribed of any size. The Pilulæ of the B. P. really correspond not to the Pilulæ, but to the Massæ of the U. S. P.

Massæ (U. S. P.), masses, are preparations made up of the proper consistency for pills. They are invariably prescribed in the form of pills.

Confectiones, confections or electuaries, are soft, solid preparations consisting of sugar or honey impregnated with some more active body.

Suppositoria, or suppositories, are intended for insertion into the rectum, urethra, or vagina, and are, except in one or two cases, formed by mixing the active ingredient with cacao-butter. Suppositories for the rectum are conical in shape and weigh about a gramme (15 grs.). Those for the urethra (*bougies*) are of the same weight, but are pencil-shaped, while the vaginal suppositories are globular, and weigh about 3 grammes (45 grs.).

Pulveres, powders, are simply dry substances in a state of fine division. Most of the official powders are mixtures of several active bodies.

Triturationes (U. S. P.), triturations, are formed from powders by diluting them with nine parts of sugar of milk.

Tabellæ, tablets (B. P.) are formed of chocolate in which an active drug is incorporated, and weigh 5 grs. or less.

Trochisci, troches, or lozenges, are solid masses, generally of a flattened shape, and consist of powders or other bodies, incorporated in sugar and gum.

Lamellæ (B. P.), or discs, are small discs formed of gelatin with some glycerin, each weighing $\frac{1}{10}$–$\frac{1}{10}$ gr. They are impregnated with an active drug, and are applied to the conjunctiva in order to elicit the local effects.

Unguenta, ointments, salves, are soft, oily substances which are applied to the skin by rubbing. (See page 217.)

Oculenta (B. P.) are ointments for the eye.

Cerata (U. S. P.), cerates, resemble ointments, but are rendered harder by the addition of wax. (See page 219.)

Emplastra, plasters, are adhesive bodies of a still harder consistency than cerates, and soften only when heated.

Cataplasmata (B. P.), poultices, are soft, pasty preparations for application to the surface of the body. Only one, Cataplasma Kaolini, is official, but many unofficial poultices are in common use.

Unofficial Preparations.

Cachets are thin discs of dough of the shape of a soup-plate and varying from $\frac{1}{2}$ in. to $1\frac{1}{2}$ in. in diameter. When two of them are placed together with their concave sides toward each other, they form a receptacle in which powders are dispensed. The edges stick together when they are moistened. A somewhat similar method of dispensing is in gelatin *capsules*, which may be hard or soft, and which are made in different sizes. The hard capsule is used for solids, the soft for liquids. Sometimes the latter contain as much as 15 cc. ($\frac{1}{2}$ fl. oz.), but these are difficult to swallow.

Tablettæ, tablet triturates, or compressed tablets, are formed from fine powders which are moistened and rendered coherent by some liquid and then compressed in moulds. They are generally about 5 grs. in weight, and disintegrate in the stomach more rapidly than other preparations.

Enemata, clysmata, or clysters, are liquid substances injected into the rectum for their local or general effects. (See page 28.)

BIOLOGICAL ASSAY.

The accurate use of drugs in therapeutics involves that the amount of active principle given in each dose must be as uniform as possible and not subject to irregular variations. In most cases the strength of a preparation can be determined by ordinary chemical methods, and this is required for most of the more powerful substances used

in therapeutics. This cannot be done for certain important drugs, however, because the active constituents are insufficiently known, or when known cannot be isolated quantitatively. This has led to the method of biological assay, in which the strength of a preparation is estimated by its effects on living animals or tissues. Biological assay was first used industrially to determine the strength of the antitoxic sera, and soon afterward Houghton introduced it to regulate the strength of the preparations of the digitalis series, from which it has been extended to several other substances, and it has now received recognition in pharmacopœias.

The principle underlying biological assay is that a definite quantity of a drug will always produce a certain degree of deflection from the normal in the same animal or in animals of the same species. The reaction, it is true, is not always identical, for many conditions may alter the extent to which an animal reacts to a drug, and every precaution must be taken to keep the conditions uniform in making these tests. For example, the reaction varies inversely with the weight of the animals, and these must be taken as nearly as possible of the same weight and age or, if this is not possible, the dose must be calculated in terms of the weight of the animal. And when great accuracy is required, the test must be done upon a series of animals sufficiently large to eliminate the variations and idiosyncrasies that cannot be controlled. These tests require special training and laboratory experience and are very time-consuming. The method is not likely to be substituted for chemical assay when the latter is available and adequate. In the case of some drugs, *e. g.*, the organic arsenicals, living tissues can detect differences that are not discovered by available physico-chemical methods and the latter have to be supplemented by biological tests for therapeutic activity and for toxicity. Most preparations requiring biological assay are either preparations from plants, animal organ extracts, or antitoxic sera. Such preparations cannot be tested chemically but yet require to be given in physiologically accurate dosage.

The accuracy and value of biological assay depend upon scrupulous attention to details of procedure and no abbreviated description of a method would enable one to carry out a biological assay. The methods fully described in the pharmacopœias and elsewhere must be consulted. It is only possible here to mention the official preparations which require such standardization and to give some indication of the principles involved.

In biological assay the object is to compare quantitatively the effects of a preparation with those of a standard. For the U. S. P., standard preparations are supplied under the authority of the Board of Trustees of the U. S. Pharmacopœia; and for the B.P., by the National Institute for Medical Research, London.

PREPARATIONS IN THE U. S. P. REQUIRING BIOLOGICAL ASSAY.

Aconite.—Tincture of aconite is assayed by determining the quantity necessary to kill guinea-pigs of 250-350 G. weight within six hours when injected hypodermically; the standard of comparison being aconitine; one cubic centimeter of the tincture having a potency equivalent to 0.15 mg. of aconitine.

Digitalis and Strophanthin are tested by finding the minimal quantity required to arrest the frog's heart in systole within one hour. The standard of comparison for digitalis is a powder of digitalis leaves, the potency of which has been carefully ascertained in relation to the International Standard Powder adopted by the Health Organization of the League of Nations. For Strophanthin the standard adopted is Ouabain.

Epinephrine preparations are assayed by comparing the rise in blood-pressure in anæsthetized dogs caused by intravenous injections of the preparation and of a standard solution of epinephrine respectively.

Ergot.—Ergot, in the form of the fluid extract, is administered by intramuscular injection to single-comb leghorn cocks. Its potency per gram must be equivalent to not less than 0.5 mg. ergotoxine-ethane sulfonate when measured by the darkening produced in the comb of the cock. For the fluid extract of ergot the same standard of potency has been adopted.

Pituitary Solution.—Pituitary solution is assayed by observing the contraction caused by it in the uterus of the virgin guinea-pig. The uterus is excised and suspended in oxygenated Ringer's solution and its movements are registered by attaching it to a lever writing on a rotating drum. The addition of pituitary preparations causes a marked contraction and this is compared with one caused by a definite amount of a standard powdered pituitary; 1 cc. of the solution of pituitary being equivalent in activity to 0.005 G. of the standard pituitary powder.

Cod-liver oil is tested for its vitamin A and D content through observations carried out upon rats kept under standard conditions and on a standard diet.

Liver and stomach preparations used for the treatment of pernicious anemia are tested for their potency by their ability to bring about certain changes in the blood of patients which are suffering from this disease and are in relapse, and subsequently to maintain a normal blood count in such persons. Authority over these products is vested in the U. S. P. "Anti-anemic Preparations Advisory Board."

Pepsin must digest 3000 times its weight of egg albumen when tested under the official conditions.

Arsphenamine and **Neoarsphenamine** have to comply with certain tests for toxicity as outlined by the National Institute of Health of the U. S. Public Health Service.

The various antitoxic sera are also standardized according to methods prescribed by the Public Health Service and their potency is designated in units, 1 cc. of *Diphtheria antitoxin* containing 500 units; *Scarlet Fever antitoxin* containing 400 units in a cubic centimeter; and *Tetanus antitoxin*, not less than 300 units per cubic centimeter. The "unit" in the case of the Tetanus antitoxin is approximately twice as strong as the "International Unit" as described by the Health Organization of the League of Nations.

PREPARATIONS IN THE B. P. REQUIRING BIOLOGICAL ASSAY.

Digitalis.—The preparation is compared with a standard preparation by some method which measures the action on cardiac muscle. Two methods are recommended; the first determines the lethal dose in frogs by injection into the dorsal lymph sac; the end-point for the second is the amount required to produce arrest of the heart when injected intravenously at a slow rate in cats or guinea-pigs anæsthetized and under artificial respiration.

Strophanthus.—Strophanthus is assayed in a similar way.

Neoarsphenamine.—Neoarsphenamine must comply with a test for absence of undue toxicity and with a test for therapeutic potency.

For toxicity, it is tested in comparison with the standard preparation on mice or rats, by the injection of doses given intravenously. For therapeutic potency, it is tested on a series of mice, or rats, infected with a suitable strain of pathogenic trypanosomes, such as Trypanosoma Equiperdum.

Sulpharsphenamine.—Sulpharsphenamine is tested in a similar way.

Pituitary (Posterior Lobe) Extract.—The activity of a sample of pituitary (posterior lobe) extract is determined by comparing its activity with that of the standard Preparation of Pituitary (Posterior Lobe) Extract by a biological method based on an action on the muscle of the uterus, or by a method which has been shown to give results similar to those obtained by such a method.

Insulin.—The potency of a sample of insulin is determined by comparing the dose of it necessary to produce hypoglycemia in rabbits or convulsions in mice with the dose of the Standard Preparation of Insulin necessary to give the same effects.

Vitamin A. Young rats are fed on a diet deficient in vitamin A until they have ceased to grow. The effect on growth of the preparation to be tested is compared with that of a standard preparation. (A spectrophotometric method may also be used.)

Vitamin B. The test is similar in character to that for vitamin A.

Vitamin C. When guinea-pigs are given a diet free from vitamin C, symptoms of scurvy appear, *e. g.*, changes in the structure of the teeth or the occurrence of tender gums or hemorrhages The degree of protection produced by the preparation to be tested is compared with that afforded by a standard preparation of l-ascorbic acid.

Antirachitic Vitamin (Vitamin D).—(*a*) *Curative.*—Young rats are fed on a rachitogenic diet for about three weeks, and the degree of rickets produced may be determined by roentgen-ray photographs of the bones. The degree of healing produced in ten to fourteen days by the preparation to be tested is compared with that produced by a standard preparation.

(*b*) *Prophylactic.*—Two similar groups of young rats are fed on a rachitogenic diet, one group receiving daily doses of the preparation to be tested, the other of the standard preparation. The degree of prophylaxis is estimated by the average percentage of ash in the bones of the two groups at the end of about five weeks.

Antitoxins and Sera.—Biological standardization is required for antidysentery serum, antipneumococcus serum (Types I and II), diphtheria antitoxin, gas gangrene antitoxins (œdematiens, perfringens and vibrion septique), staphylococcus antitoxin and tetanus antitoxin The principle of the methods employed in each case is similar, the potency of the sample to be tested being compared with that of a standard preparation in their efficacy to protect animals against the toxic or lethal effects of a fixed dose of the particular toxin.

Old Tuberculin.—The potency of a sample of old tuberculin is tested by comparing the dose of it necessary to produce its specific toxicity in guinea-pigs or other animals infected with the Bacillus tuberculosis with the dose of the standard preparation of Old Tuberculin necessary to give the same effects.

PART I.

THE ACTION OF INORGANIC SUBSTANCES.

I. WATER AND SALTS.

As a basis for consideration of the action of water and salts, the living cell may be regarded as a solution of colloids and crystalloids surrounded by a limiting membrane. This membrane is composed of a complex colloidal mixture of lipoids and proteins and serves to preserve the integrity of the cell and to prevent the indiscriminate diffusion of substances from the protoplasm into the surrounding medium. Most animal cells are permeable to water and to some salts, and are therefore capable of changing their dimensions by absorbing or giving up water. The extracellular fluids of the blood, lymph and tissues are composed of a solution of salts and other substances in water; and unless the osmotic pressure of these fluids was maintained approximately equal to that of the cell contents, the cells, having walls permeable to water, would be subject to rapid changes in size and composition. In spite, however, of the great variations in the amount of water ingested and absorbed, in the amount of water eliminated by skin and kidneys, and the wide variations in the amount of salts in the diet, it is found that the body fluids maintain a remarkable constancy in the total percentage of salt that they contain and an even more remarkable constancy in the relative proportions of essential individual ions. In regard to the latter property of the body fluids it has been held to be significant that the ratio of the essential ions in these fluids is the same as that which occurs in sea water, and that perhaps even the higher vertebrates have, though an æonian inheritance, conserved the same environment of the cells as that which was possessed by the primitive organisms from which they are so remotely sprung.

Soluble salts exist in the body mainly as ions, and each ion exerts the same osmotic pressure as an undissociated molecule. Seeing that different molecules and ions have quantitatively identical effects on osmotic pressure, it is possible to consider the osmotic changes produced by water and salts merely from the point of view of the total number of molecules and ions in solution, and regardless of any specific and chemical effects that these ions individually produce.

Molecules and ions in solution by their migration distribute themselves equally throughout a solvent. Thus when a solution of salt is brought into immediate contact with one containing sugar, the salt molecules and ions rapidly diffuse into the sugar solution and the sugar molecules into the salt solution until the whole becomes homogeneous,

each fraction of the solution finally containing uniformly the same amount of sugar and salt. If a membrane were interposed between the two solutions of such a character that it was freely and equally permeable to water, sugar and salt, the result would be the same. Cell membranes, however, are not equally permeable to water and solutes. Pure water diffuses readily into nearly all cells, but most dissolved substances meet with some resistance in entering cells, and different tissues vary in this respect. When a more dilute solution is separated from a more concentrated one by a membrane, which allows more ready passage of the solvent than the solute, uniformity of the system can only be obtained by passage of the solvent from the less to the more concentrated solution; and the latter will increase in volume. If this increase in volume be prevented by containing the solution within unyielding walls, a pressure will be developed which is called the osmotic pressure. The amount of this osmotic pressure depends upon the difference in concentration, but is independent of the type, of ions and molecules upon each side of the membrane.

For determining the reactions of animal cells to variations in the osmotic pressure of extracellular fluids, the red blood corpuscles are particularly suited. They are easily obtainable, already separate, and the changes they undergo in size and shape can be readily observed. Within the envelope of the red cell are salts and colloids in solution, which solution therefore possesses a definite osmotic pressure. Water penetrates readily into these cells and when they are placed in distilled water, water passes into them until they swell up and rupture. Sodium chloride hardly penetrates the red blood corpuscles. The mere fact that, though they are continuously laved by the plasma, they contain a higher concentration of potassium and a lower concentration of sodium than the surrounding plasma, proves that the wall of the red cells must be very impermeable to these ions, which otherwise would soon attain the same concentration inside and outside the cell. When the red cells are placed in a solution of sodium chloride of the same osmotic pressure as (*i. e.*, isotonic with) that in the interior of the cell, there is no movement of water into the interior, since the water of the surrounding solution is held back by the sodium chloride. The corpuscles will, therefore, remain unaltered in shape and composition. If a solution of lower osmotic pressure (hypotonic) is employed, a certain amount of water is taken up from it by the cell, the weaker solution of sodium chloride being unable to compete with the attraction of the stronger solution in the interior of the cell. On the other hand, if a solution of higher osmotic pressure (hypertonic) be used, it withdraws water from the cell, because the salts in the interior are unable to retain the water against the stronger concentration outside.

Somewhat similar changes will occur in all animal cells as the result of changes in their osmotic environment. Thus a muscle immersed in distilled water will swell up from imbibition of water and soon lose its excitability. A heart is rapidly arrested if perfused with distilled water. Such tissues will, however, retain their configuration, and for a time their excitability, if kept in a solution of sodium chloride of the same

osmotic pressure as the interior of the cells. For mammals such a solution contains 0.9 per cent of sodium chloride in distilled water. It is often called physiological or normal saline solution, but it must be remembered that it is "normal" only in respect of its osmotic pressure.

The cells in the body undergo continual readjustments in accordance with changes in the osmotic pressure of the body fluids, consequent upon variations in the absorption and elimination of water. So far as the interior of the body is concerned the changes in osmotic pressure and the currents they produce are only of moderate degree, as the functioning and even the life of the tissues is only possible within a certain range of osmotic pressure above and below the normal. The changes that occur are also not of so simple a character as has been described for the behavior of red cells in a solution of sodium chloride, mainly because different cells show differences in selective permeability to different salts. Ammonium chloride, for example, in contradistinction to sodium chloride penetrates red cells readily, and in solutions of this salt the red cells behave almost as if they were placed in distilled water. They are readily permeable to urea but not to sugar. Cells may even differ in their permeability to water itself. For example, water is readily absorbed from the intestine but scarcely at all from the stomach, but this can scarcely be due to difference in the osmotic pressure of the interior of the cells lining these viscera. With these considerations it is possible to consider more generally the effects of water and salts.

1. **Water.**—Water penetrates into the superficial cells of the skin, which therefore become swollen and softened by prolonged immersion in it. Water is not absorbed into the circulation through the skin in mammals, but is absorbed more easily by less protected surfaces, and pure water applied to surfaces like the conjunctiva or nasal mucous membrane or the surface of a wound may cause irritation and pain from the disturbance of the normal relation of salt and fluid in the surface cells. Isotonic solutions, on the other hand, cause no pain.

The amount of water ingested in food and drink varies enormously. Very little absorption of water occurs in the stomach but it is rapidly absorbed in the small intestine, so that only about 350 cc. of fluid chyme passes through the ileo-cæcal valve daily. Much of the remaining water is absorbed in the large intestine, especially in the cæcum and ascending colon, the contents of which are still quite soft, leaving a final weight of the fæces of about 135 G. daily. Apart from ingested water there is an important internal circulation of water, as the amount in the salivary, gastric and intestinal secretions may amount to 4 litres, which is almost completely reabsorbed before reaching the cæcum.

When water is absorbed from the bowel, the proportion of solids and liquid in the blood is of course changed, and fewer corpuscles and less solid matter are found in a cubic millimetre. The blood contains a lower percentage of colloids than before and this reduces the osmotic resistance to filtration through the glomerular capsules in the kidney, so that the secretion of urine is increased. One of the functions of the kidney is to maintain constant the osmotic pressure of the plasma.

When water is injected intravenously it does not lead to immediate diuresis as it is taken up rapidly by the tissue cells. The muscles and subcutaneous tissues especially take up considerable stores of water, which can be given up as required. When there is excessive loss of water, *e. g.*, from profuse sweating or diarrhœa, the plasma becomes more concentrated and water can pass from the tissues into the plasma to restore the normal conditions. The concentration of salt in sweat is lower than that in the body fluids, so that sweating tends to concentrate the salts in the blood. This provokes thirst, and the ingestion of water again dilutes the plasma. All the factors concerned in water metabolism cannot be explained by simple diffusion and osmosis, and there is some evidence of a central control of the water exchanges between the tissues and the blood. Pituitary extract has a remarkable effect in inhibiting water diuresis and the diuresis of diabetes insipidus, and may produce this effect by a central action.

A detailed consideration of all the factors involved in water exchange in the body belongs rather to the domain of physiology. Mention may be made here, however, of the deliberate use of water to effect a therapeutic purpose. Consideration of the value of spa waters may be deferred until the action of salt is considered as, though the effect of these waters is mainly due to the water, they usually contain more or less salt.

Water is used especially in febrile conditions to relieve thirst and to promote perspiration and diuresis. It tends to keep the mouth clean and wash out the stomach, as the latter absorbs little or none. It might be expected that a liberal supply of water would tend to keep the fæces moist and so relieve constipation. It is ineffective for this purpose because most of the water ingested is absorbed in the small intestine, and in constipation the more prolonged residence of the contents in the large intestine gives longer time for absorption of the relatively small proportion of water that passes the ileo-cæcal valve. If, however, a non-absorbable salt like magnesium sulphate be added to water, the absorption of water is checked and the fæces become more fluid.

The administration of large quantities of water might be expected to have some effect on general tissue change, owing to increased diuresis as well as the passage of water in and out of cells, leading to a more complete removal of the waste products. Actually, only a slight increase in the nitrogen and sulphur eliminated in the urine results from the ingestion of large quantities of water. The amount of proteins and fats absorbed from the alimentary canal does not appear to be altered by the administration of large amounts of water.

Heavy Water or **deuterium oxide** differs from ordinary water in that hydrogen is replaced by an isotope of atomic weight 2, and its specific gravity is approximately 1.107. It differs from ordinary water in its physical properties, especially in being much more viscous. Ordinary water contains a small proportion of heavy water. The physiological effects of replacing ordinary water by deuterium oxide have been studied in recent years especially by Barbour and his co-workers.

Administration of almost pure deuterium oxide, resulting in the body becoming 40 to 50 per cent saturated with it, causes death of mice in about seven days,

the chief symptoms being loss of weight, fall of temperature, ataxia and dyspnea. The flow of urine is diminished, possibly due to the higher viscosity of the fluid impeding glomerular filtration.

Smaller amounts of D_2O (20 per cent saturation) cause an increase, larger amounts a decrease, of metabolic rate. Several effects suggest a sympathomimetic action, *e. g.*, a pilomotor response and the contraction of melanophores of Fundulus heteroclitus, which is prevented by ergotoxine and potentiated by epinephrine.

Concentrations of over 90 per cent are fatal to tadpoles and to some worms and fish. Evidence from different sources goes to show that deuterium interferes with enzyme activity; *e. g.*, the fermentation of sugars is much retarded. Barbour suggests that many of the pharmacological effects of heavy water can be explained by its protective action on hormones like epinephrine and acetylcholine, possibly due to the inhibition of activity of such enzymes as acetylcholinase.

The substitution of hydrogen by deuterium has been studied also in other compounds. If the carbon-bound hydrogen of a physiologically active compound is replaced by deuterium, the metabolism of such compounds after administration to the animal can be studied by tracing the route taken by the deuterium.

The pharmacological activity of a compound may be at least quantitatively altered by deuterium substitution, for example, in ethyl alcohol, $C_2D_5O.D$ having considerable stronger action than C_2H_5OH. Deuterium is of interest, both direct and indirect, for pharmacological investigations, but at present there is no sufficient evidence that heavy water has any therapeutic utility.

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2. **Sodium Chloride.**—The most typical example of salt action is presented by chloride of sodium, for this salt is always present in large quantities in the body, and has practically no specific action; the sodium and chloride ions are ordinary and necessary constituents of the fluids of the body. The action of this salt is therefore limited to the alteration in the physical properties of the fluids, which its presence in excess or in limited amount induces.

Most of the tissues hitherto examined in regard to this point have proved permeable by both the Na and Cl ions, but in every case there is a certain amount of resistance offered so that the presence of salt in the fluid round a cell always prevents water from diffusing freely into the interior; *i. e.*, sodium chloride solution exerts osmotic pressure on the cell. The molecular weight of common salt being small, the osmotic changes induced by it are greater than those induced by an equal weight of most other salts, because a larger number of molecules exist in each gram. It also dissociates into its two ions more readily than many others, and this lends it still greater osmotic power.

Weak (hypotonic) salt solutions generally produce effects similar to those, already described, due to water only. Isotonic salt solution is non-irritant and has no positive action. Strong salt solutions irritate, from withdrawal of water from the cells.

In the mouth salt has a characteristic taste. Salt in the diet has little effect on digestion apart from the fact that a small quantity of salt in

the food renders it more palatable to most people and this increases the reflex flow of gastric juice. Large amounts of hypertonic salt solution causes withdrawal of fluid and shrinkage of the cells of the mucous membrane of the stomach, which may set up sufficient irritation to cause reflex vomiting. Part of this irritation may be due to penetration of the salt itself, because the more penetrating salts have a greater tendency to produce vomiting. Thus ammonium chloride produces vomiting more readily than sodium chloride; sodium sulphate less readily.

Little if any salt is absorbed from the stomach but it is freely absorbed from the intestine. The cells of the intestinal mucous membrane are so easily permeable by sodium chloride that hypotonic or isotonic solutions are absorbed almost as rapidly as pure water. The absorption of stronger solutions may be preceded by a period in which the fluid of the bowel actually increases, water diffusing into it from the blood. At the same time the salt is being absorbed and the solution eventually becomes isotonic and is absorbed.

The blood and lymph are affected by the osmotic changes consequent upon absorption of salt. When hypotonic solutions enter the blood. they increase the volume of the blood but lessen its concentration This causes an increase of capillary pressure (the arterial tension remaining unchanged) which induces a flow of lymph from the blood-vessels into the lymph spaces. When the blood is rendered hypertonic by the injection of strong salt solution, water from the lymph spaces passes into the blood-vessels by osmotic attraction. The absorption of either water or salt may therefore lead to a reduction in the concentration of the colloids of the blood, in the former case the hydræmia being produced by the water ingested, while in the case of salt absorption the hydræmia is produced by the water absorbed into the blood from the lymph. The absorption of water and of salts sets up osmotic currents which promote the interchange of fluid between the blood and the lymph spaces.

The changes in the blood and lymph are followed by an increased activity of the **Excretory Organs.** Thus the urine[1] is much augmented by the injection of salt solution into the blood, less so by the absorption of water or salt solution from the stomach and bowel. The presence of salt or water in the blood in excess leads to increased interchange of water between the tissues and blood and the latter becomes diluted, that is, contains a lower percentage of colloids than normally. This reduces the osmotic resistance to filtration, so that a more abundant flow occurs through the glomerular capsule into the tubules. Here water and salt are absorbed in certain definite proportions; if the salt is present in the filtrate in higher proportions than normally, it is rejected by the epithelium of the tubules and finds its way into the ureters, while if the proportion of salt is low, some of the water fails

[1] The following explanation of the diuresis is based upon the theory that all the constituents of the urine are filtered off by the glomerulus, and that some of them, notably much of the fluid and the alkali chlorides, are reabsorbed in passing through the tubules. See "Secretion of the Urine," Cushny 1926.

to be taken up and similarly passes out as urine. The increased glomerular filtrate contains more urea, phosphates, and other constituents which are not absorbed in the tubules, and the amount of these in the urine is thus increased, though their percentage may fall.

When very large amounts of isotonic salt solution are thrown into the blood, the organism may have difficulty in excreting it rapidly enough, and the tissues are therefore found to be swollen and œdematous in some parts of the body.

When salt solution is injected into the serous cavities or into the lymph spaces, absorption occurs in the same way as from the alimentary canal, except that in the case of the serous cavities diffusion seems to play a greater, and the other forces a smaller rôle, than in the stomach and intestine.

Strong salt solutions injected into animals either hypodermically or intravenously sometimes prove fatal, apparently from the withdrawal of fluid from the central nervous system. The symptoms in mammals are increasing lassitude and weakness, with augmented reflex excitability, tremors, and finally convulsions. The circulation is only slightly affected until just before death, when the blood-pressure falls suddenly. The red-blood cells are found to be much shrunken, and hæmorrhages are found in different organs; the lungs are œdematous, and the intestinal mucous membrane is swollen and congested.

The **Salts of the Urine** are increased by diuresis from any cause, as has been stated; both sodium and potassium are augmented, but especially the sodium, which is present in larger proportions in the plasma and therefore forms a larger constituent of the glomerular secretion. This increase in the sodium salts is, of course, particularly marked when diuresis is induced by common salt, but when potassium salts increase the urine, the sodium also generally predominates in it and this would eventually lead to the loss of all the sodium in the blood of herbivora, whose food contains large quantities of potassium; but after a certain amount of sodium has been lost, potassium causes no further excretion, so that the tissues are protected from the total loss of sodium chloride, which would be fatal to them.

In fevers, especially in pneumonia, the excretion of chlorides is often diminished. This is believed to be due to the tissues in fever taking up more water and chloride, reducing the volume and the chloride content of the blood.

Bunge states that in both man and animals a diet rich in potassium causes an appetite for common salt, while a diet which does not contain an excess of potassium does not develop this desire. Thus herbivorous animals and agricultural peoples seek for salt, because vegetable foods contain large quantities of potassium, while the carnivora and the hunting peoples require no salt and often have a distaste for it, owing to their food containing a larger relative proportion of sodium salts. This instinctive appetite he regards as a means by which nature protects the tissues from excessive loss of sodium.

Therapeutic Uses. Water and salt are rarely or never prescribed as such, but are used to a very large extent in medicine, and great virtues have been ascribed to them in a number of pathological conditions.

They are used for their local action, and for the supposed alterations in the tissue-change and in the excretions produced by them after

their absorption into the blood. In general, patients are sent to watering places and baths, where, as Sir Walter Scott says, "the invalid often finds relief from his complaints, less from the healing virtues of the spa itself, than because his system of ordinary life undergoes an entire change, in his being removed from his ledger and account books—from his legal folios and progresses of title deeds—from his counters and shelves—from whatever else forms the main source of his constant anxiety at home, destroys his appetite, mars the custom of his exercise, deranges the digestive powers, and clogs up the springs of life." At the same time the drinking of large quantities of weak salt solutions, and the constant bathing in somewhat irritating fluids, may exercise a therapeutic action in many cases, and may at any rate aid the hygienic conditions. Whether the water contains salt or not, it must be remembered that in bathing the action is a purely local one, for neither the salt nor the water is absorbed. The slightly irritant effect on the skin may, however, improve its circulation and nutrition, and thereby be efficacious in some skin diseases. By continued use the sensitiveness of the skin vessels to heat and cold may also possibly be deadened. The changes in the metabolism induced by bathing in strong salt solution are merely trifling. Special baths are very frequently recommended for some diseases, probably without justification; the greater the concentration, the greater is the effect on the skin, and it is of no importance which of the neutral salts is in the solution, or whether small traces of iron or other metals are present; alkaline baths act more on the skin than others.

In diseases of the stomach the drinking of large quantities of water or of weak salt solutions may also be beneficial. The action is similar to that on the skin—a mild irritation, owing to the swelling of the more superficial cells of the epithelium and the increased movement of the fluid in them and in the deeper layers. In some cases of insomnia hot water sometimes causes sleep, probably by causing dilatation of the gastric vessels, and thereby withdrawing the blood from the brain.

In many diseases in which the symptoms point to a disorder of the metabolism, water and salt solutions are advised. Thus gout and rheumatism are frequently treated by sending the patient to watering places, on the theory that the tissues are washed out thoroughly and the waste products thus removed. As a matter of fact, the more recent work in this direction shows that large quantities of water and dilute salt solutions have little or no effect on the uric acid excretion, which was formerly believed to be much diminished. This fact does not necessarily involve the inference that the treatment is erroneous, for it is now generally recognized that gout is not really due to the failure of the uric acid excretion. Many cases are unquestionably benefited by the springs, although it may be questioned how much of the improvement is due to the water taken, and how much of it ought to be ascribed to the changed conditions of life.

The bath treatment has been recommended for numerous diseases in which the salt and water could not possibly have any beneficial action, and in which the remedial agent is the climate, and perhaps the faith of the patient in the water. Belief in the healing power of cer-

tain natural water is one of the most ancient of all therapeutic theories, is found among altogether uncivilized peoples, and has been incorporated in many religions. It is not to be wondered at that in some nervous disorders the faith of the patient and auto-suggestion perform some marvelous "cures."

In obesity the drinking of some waters, such as those of Kissingen and Homburg, has been advised. These waters contain from 0.2-1.4 per cent sodium chloride, and it seems very doubtful if they have any effects in themselves; many hold that the benefits accruing from the treatment are really due to the hygienic measures followed, and that the waters play only an insignificant rôle.

Salt in solid form or in strong solution is used occasionally as an emetic in cases of emergency, as in poisoning, and generally produces vomiting rapidly, owing to the irritant action on the stomach. In nitrate of silver poisoning it arrests the corrosive action by the formation of the insoluble silver chloride.

Salt solution is often used instead of water in enemata and when concentrated possesses an irritant action on the bowel, producing peristalsis. Strong solutions are sometimes thrown into the rectum to destroy thread worms.

Isotonic salt solutions (0.6-0.9 per cent), are often administered when the body has lost much fluid, as they are rapidly absorbed and are devoid of irritant action; thus in hemorrhage these solutions are injected subcutaneously, intravenously, or per rectum. A rapid improvement in the circulation follows, and this has given rise to the erroneous opinion that such saline infusions stimulate the heart directly as well as by the mechanical effect of the increase in the fluids of the body; this theory has led to infusions being made in weakness of the heart from other causes than hæmorrhage. Some of the symptoms of cholera are believed to be due to the loss of water and chlorides, and these are said to be relieved by the injection of salt solutions, though the mortality does not seem materially altered. The intravenous and subcutaneous injection of salt solution has been recommended in uremia and similar intoxications, with the idea of washing out the poisons through the kidneys; the same results can often be obtained by drinking large quantities of water.

In the U. S. P. physiological salt solution (*Liquor Sodii Chloridi Physiologicus*) contains 0.85 per cent of salt in freshly distilled water, and the solution must be sterilized. The B. P. calls for 0.9 per cent sodium chloride.

The isotonic salt solution ordinarily employed for hæmorrhage and other purposes is inferior to the Ringer's solution,[1] which contains the other salts of the alkalies in approximately the proportions in which they are found in the plasma; for excised organs live for many hours in this balanced solution, while they lose their vitality rapidly in an isotonic solution of sodium chloride. The presence of lime salts is particularly important.

[1] Ringer's solution suitable for mammals contains 8.5 G. NaCl, 0.3 G. KCl, 0.2 G. $NaHCO_3$, and 0.2 G. $CaCl_2$ in a litre of distilled water.

The water which is used to dissolve the salts must be recently distilled and kept aseptic; otherwise the fluid, if injected intravenously or hypodermically, is liable to cause fever symptoms from the presence of toxic substances derived from dead bacteria.

Ringer's solution or sodium chloride solution injected intravenously dilutes the blood plasma and lessens its osmotic resistance to filtration, and the whole of the injected fluid quickly passes out of the vessels into the tissues and the urine. If the object aimed at is to wash out the tissues, Ringer's solution is suitable, but if it is desired to retain the fluid in the vessels (for example, after profuse hæmorrhage), some substance which offers great resistance to filtration must be added. Bayliss has advocated the addition to the injection fluid of 6 per cent gum acacia, which has the effect of retaining the fluid in the vessels longer and also of giving it the same viscosity as the plasma. Clinical observations show that this new fluid possesses advantages over Ringer's solution in hæmorrhage and shock. Ringer's solution is used in surgery to wash out the peritoneal cavity, which would be injured by distilled water.

According to a recent view, the retention of sodium chloride in the tissues may lead to the retention of fluid and may thus tend to cause œdema and dropsy. These conditions have therefore been treated by a diet containing a low proportion of salt, and in a certain number of cases with some success.

PREPARATIONS.

U. S. P. and B. P.

LIQUOR SODII CHLORIDI PHYSIOLOGICUS, physiological saline solutions. U. S. P. 0.85 per cent; B. P., 0.9 per cent sodium chloride in distilled water.

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3. **Saline Diuretics.**—The amount of urine is increased by all solids which are eliminated by the kidney, as well as by an excess of fluid in the blood. For the kidney is unable to excrete solids except in solution, and every molecule which is passed through it carries with it a certain

amount of water to augment the secretion. Only substances which can circulate in the body in considerable quantities can be used to increase the urine in this way, and in practice the chief diuretics of this class are comprised of the indifferent salts and similar harmless bodies. In order to act as diuretics these must be readily absorbed from the alimentary tract and this excludes a large class of salts which increase the urine greatly when they are injected intravenously, but which are absorbed with difficulty and are therefore used mainly for their effects on the intestine (see Saline Cathartics, p. 275).

Among the saline diuretics are the chlorides of sodium, potassium and ammonium, though these are seldom prescribed for this purpose; their diuretic action is seen, however, in the treatment at spas and water-places. The cerebral action of the bromides precludes their use as diuretics, though an increased secretion of urine accompanies their use in therapeutics. The iodide of potassium is often added to other diuretics to reinforce their action, but is liable to induce other symptoms when given in large quantities. The typical saline diuretics are the nitrates of the alkalies and the urea group.

The **Nitrates** have a cool, saline taste, and ordinary doses taken in water have no effect except to produce an augmented flow of urine. They have long been used as diuretics, more especially the nitrate of potassium. The diuresis is generally attributed to the salt-action, which increases the exchange of fluid between the blood and lymph and thus promotes the filtration in the kidney. The presence of nitrate and potassium ions in the filtrate retards the reabsorption of fluid in the tubules and thus leads to a larger proportion reaching the ureters.

Large quantities in concentrated solution may cause gastro-intestinal irritation, giving rise to pain in the stomach region, nausea, vomiting, and sometimes diarrhœa, and blood may be present in the vomited matter and in the stools. The urine is often abundant, but may be scanty or entirely suppressed. In rare cases these symptoms were followed by muscular weakness, apathy, collapse, and eventually coma and death. At the autopsy the stomach and intestines were found red and congested, and contained blood extravasations. The kidney is said to have presented the symptoms of acute nephritis and hæmorrhages in some cases of poisoning.

The effects of nitrates are for the most part those of an indifferent and diffusible salt, but it is possible that this may be reinforced by some further irritant action, for smaller quantities of the nitrates than of the chlorides are sufficient to induce irritation, and solutions of the nitrates isotonic with the blood cause irritation and congestion in the intestine and are slowly absorbed. This irritant effect of the nitrates has been explained by Binz and Barth as the result of the reduction of the nitrates to nitrites in the alimentary canal and tissues, but no symptoms of nitrite action seem to have been observed in cases of poisoning with nitrates. Haldane has shown that nitrite is formed from the nitrate used in the preservation of meat by salting, and that some nitrous-oxide hæmoglobin is formed and gives a bright red color to the meat. The presence of this pigment may perhaps explain the red color of the

intestine in some cases of poisoning in which extravasations of blood are not marked.

The fate of the nitrates in the body is still obscure owing to difficulties in their quantitative estimation. Some of that ingested undergoes reduction in the alimentary tract and tissues, for the nitrite reactions are given by some organs and by the urine. And it seems likely that a portion may undergo still further reduction to ammonia or some of its compounds. Most of it appears in the urine as nitrate when large doses are given, but some investigators state that after moderate quantities in man (1–3 G.) they could observe no nitrate in the urine, the whole having undergone some change in the passage through the body. Some of the nitrate seems to be excreted in the saliva and perspiration, possibly unchanged, although it is rapidly reduced to nitrite in these secretions, and may in fact be changed to this form in the secretory cells.

Urea in the course of its excretion through the kidney carries with it a considerable amount of water, and when injected intravenously is a powerful diuretic. It is rapidly absorbed from the intestine and is practically devoid of action in the tissues even in large doses. Its diuretic action arises partly from its restraining water from being absorbed in the tubules, which are unable to take up much urea from the glomerular filtrate. In chronic interstitial nephritis the excretion of urea is impaired, but not in chronic parenchymatous nephritis. Urea is recommended as a diuretic in the latter condition, in which the saline diuretics are less useful as the chloride excretion is impaired. Twenty grams of urea given by mouth produce a rapid diuresis and normally the whole of the urea is excreted within twenty-four hours.

Ammonium Acetate and **Citrate** are indifferent salts but undergo oxidation in the tissues and finally form urea which acts as a diuretic in passing through the kidney. They were formerly supposed to increase the secretion of sweat but this action is insignificant.

Therapeutic Uses.- The saline diuretics are seldom used except as ingredients of diuretic mixtures; *e. g.*, along with digitalis, or to render the urine more dilute and thus to reduce its acidity in irritation of the genito-urinary tract. They were formerly employed largely in fevers and in various disorders of the metabolism, such as rheumatism or gout, but in none of these have they proved useful. The nitrates are to be given with care when there is any irritation of the stomach and intestine. Authorities differ as to whether these diuretics may be prescribed in irritation of the kidney, but in every case they ought to be well diluted.

Paper impregnated with saltpetre is used in asthma by burning it in the sick room, when the pyridine and nitrites relieve the spasms by relaxing the bronchial muscles. Saltpetre may be used in cigars or cigarettes for the same purpose, and these may contain also the leaves of belladonna or some of its allies, as they have a special action on the bronchial muscle.

PREPARATIONS.

POTASSII NITRAS (U. S. P., B. P.), nitre, saltpetre (KNO_3), 0.3 G. (5 grs.); B. P., 5–15 grs.; colorless crystals with a cool, saline taste, very soluble in water, prescribed in dilute solution.

UREA (B. P.) ($CO(NH_2)_2$), colorless crystals with a cool saline taste, soluble in equal parts of water. Dose, 1–16 G. (15–240 grs.), in solution.

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II. SALTS OF THE ALKALIES.

1. **Potassium Salts.**—The effects of potassium in the organism can best be studied by administering the chloride, as the Cl ion is practically devoid of action and the symptoms induced by potassium chloride must therefore be due either to the "salt-action" or to the potassium. The salt-action can be discounted by comparing the symptoms with those of an isotonic solution of sodium chloride, and when this is done it is found that potassium has a distinctly poisonous action, which is chiefly manifested on the central nervous system and the heart. Some of the effects of potassium have been said to be due to its being feebly radioactive (Zwaardemaker), and attempts have been made to substitute for it small quantities of other radioactive metals; but the connection between its action in the tissues and its radioactivity has not been established.

In the frog the central action is shown by the spontaneous movements becoming weak and slowly performed, and by their completely disappearing much earlier than in sodium chloride experiments. In mammals the chief nervous symptoms are great muscular weakness and apathy. The respiration becomes rapid and labored, probably from the anæmia of the centre. Potassium first increases the activity of the spinal centres and then paralyzes them in mammals, but this is concealed by the depression of the heart when the drug is injected intravenously.

The depression of the heart is shown in the frog by weakness, slowness and irregularity when chloride of potassium is injected subcutaneously, but is more clearly demonstrated by the rapid failure of an excised heart when a chloride of potassium solution is perfused through it. An isotonic solution of common salt also brings the heart to standstill after a time, but potassium chloride acts much more quickly, and, in fact, the former may restore the heart beat after it has been stopped by potassium, which proves conclusively that the latter has a specific poisonous action in addition to any salt-action. Ringer, however, found that the beat of the frog's heart perfused with a solution of common

salt was not so satisfactory as that of one perfused with the same solution to which some potassium salt had been added, probably because when the fluid perfused contains no potassium, some of the salts of that metal diffuse out of the muscle cells and this disturbs the ratio between the potassium and sodium which is necessary to life.

The mammalian heart is also injured by the action of potassium when the salt is injected intravenously, as is shown by weakness and dilatation, slowness of the pulse, heart block, and finally by ventricular fibrillation not infrequently; the fibrillation is due to a combination of increased automaticity and intraventricular block (Nahum and Hoff). The blood-pressure falls abruptly partly from this action on the heart, which appears to be a direct one on the muscle, but a reflex vasodilation from an action on the carotid sinus may also play a part (Hauss and Chen). The poisonous action of potassium on the heart has given rise to exaggerated apprehensions of the danger of using its salts in therapeutics, and it may therefore be noted that potassium has no effect on the heart when given by the stomach, and that very much larger quantities of potassium are taken daily in the food by thousands of persons than are ever prescribed in medicine. Bunge estimates the amount of potassium in the food of some classes at 50-100 G. ($1\frac{1}{2}$-3 oz.) per day. The absence of effects from the potassium ion when the salts are taken by the mouth is due to their rapid excretion in the urine.

The failure of the heart is the cause of death in mammals when potassium salts are injected into a vein, the respiration and the reflexes often persisting for a few seconds afterward. When potassium salts are injected into an artery, so that they can reach the peripheral vessels before the heart, they cause marked vasoconstriction with an abrupt rise in the blood-pressure; this action appears to be a direct one on the walls of the arterioles for the most part, though it is possible that this is reinforced by stimulation of the medullary and spinal vasomotor centres (Mathison).

Potassium has some action on muscle in the frog, the contraction seeming to be somewhat greater in height, though shorter in length, and there being less tendency to contracture. Muscle exposed in a solution of potassium chloride dies much sooner than in an isotonic solution of sodium chloride. Unstriated muscle suspended in a solution of potassium chloride undergoes contraction, which may be removed by replacing the potassium with sodium.

Chloride of potassium has also some depressant action on the peripheral nerves, for they lose their irritability rapidly when they are exposed to its solutions. A concentrated solution applied to an exposed nerve causes contractions of the muscles which are supplied by it, but these are weaker and last a shorter time than those elicited by a similar solution of common salt. This is explained by the depressant action of the potassium opposing the irritation which it induces through its salt-action.

Feldberg and Vartianeri have shown that potassium chloride stimulates the ganglion cells when perfused through the superior cervical ganglion in the cat and increases the excitability of the cells to preganglionic stimuli and to acetylcholine. There is some evidence too that potassium may play a part in the transmission of nerve impulses. Wilson and Wright found that potassium has an anti-curare action.

The absorption of potassium salts is followed by the same changes in the movements of the fluids of the body as have been described in the case of sodium

chloride (page 45). This generally results in diuresis with an increase in the potassium and the sodium and chloride in the urine. The potassium salts are generally credited with greater diuretic properties than those of sodium. Strong solutions of potassium chloride are said to be more irritating to the stomach and also in the subcutaneous tissues, than those of sodium chloride; this would indicate that potassium has a specific irritant action apart from its salt-action, which is not unlikely, although it cannot be said to have been demonstrated satisfactorily as yet.

Miller has shown that young male rats require 15 mg. of potassium daily for growth and that females need only half that amount. If the supply is less than 1 mg. daily death follows in a few weeks. For maintenance of adult rats only 2 mg. of potassium daily are required.

Therapeutic Uses of Potassium.—Apart from the superior diuretic action of the potassium over the sodium ion, there is little to choose for most purposes between potassium and sodium salts. In some cases the potassium salt may be more suitable because of some physical property, *e. g.*, potassium bromide is less deliquescent than sodium bromide, in other cases the preference for potassium salts is merely traditional. The salt most commonly employed as a diuretic is potassium acetate, the nitrate being now rarely used. Recently caution has been urged against the indiscriminate use of potassium salts in Bright's disease as the retention of potassium may cause cardiac failure.

Recent clinical experience has shown that potassium has a definite effect on the contraction of voluntary muscles, either on the peripheral neuro-muscular transmission or on the contractile response of the muscles. In the condition known as "familial periodic paralysis" the serum potassium is abnormally low during the paralytic attacks, paralysis developing when the serum potassium falls below 12 mg. per 100 cc. Administration of potassium chloride by mouth raises the serum potassium and abolishes the paralysis. Large doses of potassium chloride also cause some improvement in muscular contraction in myasthenia gravis.

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2. **Lithium, Caesium, Rubidium.**—In regard to the action of the rarer alkalies, Lithium, Cæsium and Rubidium, comparatively little is known. They seem to have some effect in depressing the spinal cord in the frog, but it is uncertain whether this is, like the action of sodium chloride, merely due to the presence of large quantities of salts in the body, or whether they have a specific action on the nerve cells. Lithium seems to have some further depressant action on the motor nerves, and to weaken the muscular contraction. It acts much less powerfully on the mammalian heart than potassium, but has some effect in weakening it. Its chief effects are exercised in the alimentary tract, for gastro-enteritis and extravasations of blood into the stomach and bowel are induced by its subcutaneous or intravenous injection and these are the cause of death in fatal poisoning in animals. Such violent effects are less easily elicited by the administration of lithium by the mouth, though vomiting and purging have been caused in animals by this method also, and disturbance of the alimentary tract has sometimes followed from lithium treatment in man. Some of the lithium is excreted in the bowel, and in this respect this metal appears to form a con-

trast to potassium and sodium and to resemble rather the group of alkaline earths. Most of it appears in the urine, however, and here the excretion is slow, for traces may be found in it for many days or even weeks after a single administration.

Rubidium seems to act on the frog's heart and on muscle cells in much the same way as potassium. It is slowly excreted by the kidneys; traces are found also in the fæces, especially if diarrhœa occurs, as is not infrequently the case.

Cæsium resembles lithium in causing inflammatory reactions in the alimentary tract, leading to vomiting and diarrhœa, when it is injected hypodermically or when large doses are given by the mouth. It is partly excreted along the alimentary tract in mammals. In the frog it induces weakness of the muscles and paralysis. According to Kisch, cæsium salts have an action on the excitability of the frog's heart similar to that of calcium but on its contractility similar to that of potassium.

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3. **Ammonium.**—Although ammonium is not a metal, its behavior in the body resembles in many points that of the fixed alkalies, and it may therefore best be studied along with them. The solutions of ammonia and the gas itself are strongly alkaline and therefore powerful irritants, and the general action of the ammonium ion can be determined only by the examination of those of its salts in which, as in ammonium chloride, the effects of the anion can be neglected. The action of chloride of ammonium is due to the specific action of the base and to the salt-action.

Action.—Its most striking effect is the stimulation of the **Central Nervous System,** which is induced when it is injected subcutaneously or intravenously. The reflex irritability is much increased, and this may be followed by tetanic convulsions, both in frogs and mammals. These convulsions persist after division of the cervical spinal cord and destruction of the medulla oblongata and brain, and are evidently caused by changes in the spinal cord, similar to those met with in strychnine poisoning. The medullary centres are also involved, for the respiration very often ceases for a moment, and then becomes much accelerated, and in some instances deeper, from stimulation of the centre.

The blood-pressure rises from contraction of the peripheral arterioles, induced by stimulation of the vasomotor centre, while the heart is sometimes slowed from increased activity of the inhibitory centre, but is said to be accelerated in other cases; whether this arises from action on the cardiac muscle or on the accelerator centre is still unknown.

During the convulsions the respiration is arrested and the blood-pressure becomes extremely high. If large enough quantities be in-

jected, the stimulation is followed by paralysis of the central nervous system and the animal dies of asphyxia, but if artificial respiration be carried on, it recovers rapidly, from the salt being eliminated.

In the frog ammonium chloride tends to paralyze the terminations of the **Motor Nerves**, but little or no such action is met with in mammals. This marked curare-like action differentiates the ammonium tetanus of the frog from that seen under strychnine, as the spasms last a shorter time, and soon become weaker, from the impulses failing to reach the muscles through the depressed terminations. The **Muscles** themselves are also acted on by ammonium in much the same way as by potassium. Ammonium chloride is credited with rendering the mucus secretion of the stomach and bronchi more abundant and less tenacious, but there seems little foundation for this belief.

Ammonium salts penetrate most cells of the body more freely than the salts of the fixed alkalies, and solutions of ammonium chloride are therefore **absorbed** more rapidly from the stomach and intestine than those of sodium or potassium chloride. They permeate into the blood cells with still greater freedom, and, in fact, solutions of the chloride of ammonium meet with little more resistance in entering the red-blood corpuscles than does distilled water. If ammonium be combined with a non-permeating ion it penetrates the blood cells or the intestinal epithelium with difficulty, however, so that the sulphate of ammonium is slightly cathartic, although less so than the sulphates of the fixed alkalies. (See Saline Cathartics.) The epithelium of the lungs has been stated to be impermeable by the ammonium ion, but this appears to be incorrect (McGuigan).

When ammonium salts are taken by the mouth, they have little or no tendency to cause symptoms from either the central nervous system or the heart. No case is known in which convulsive attacks could be shown to be due to the direct action on the central nervous system in man, and it is very doubtful whether the circulation is affected at all. In some cases of poisoning with ammonium hydroxide, convulsions have occurred, but these seem to be due to the violent irritation caused by the strong alkali.

Excretion.—Some ammonium is excreted unchanged in the urine, while some is changed to urea. This transformation, which probably takes place in the liver chiefly, proceeds very rapidly, so that considerable quantities may be injected slowly into a vein without inducing any symptoms whatever. This formation of urea occurs more readily in the herbivora than in man and the carnivora, and is especially seen when the ammonium is given in the form of the carbonate or of salts which are oxidized to the carbonate in the body, such as the acetate and citrate; in the herbivora the abundant fixed alkali of the blood and tissues displaces the ammonium of such salts as the chloride, and the carbonate of ammonium thus formed is changed to urea, while in the carnivora and man, the supply of fixed alkali is less abundant and the ammonium chloride is not changed to the same extent.

When ammonium chloride is ingested, the NH_3 portion reacts with carbon dioxide to form urea, liberating hydrochloric acid. This causes

a reduction of the alkaline reserve of the blood. J. B. S. Haldane has shown that large doses of ammonium chloride may produce acidæmia with resulting hyperpnœa and a fall of CO_2 tension. This is accompanied by diuresis, apparently because the acidosis lessens the amount of salts adsorbed by the tissue proteins, and diuresis is produced by the salts thus liberated in the blood.

Ammonium salts of the inorganic acids and of benzoic acid all produce an acidosis as described while this is apparently not true of ammonium acetate, perhaps due to its rapid destruction and removal as carbon dioxide by the lungs.

The urine is often increased by the exhibition of ammonium salts; ammonium nitrate apparently being the most active. It is to be noted that, while the alkaline salts of the fixed alkalies render the urine less acid or even alkaline, ammonium salts have no such effect, because they are excreted as urea or as neutral salts.

In birds and reptiles ammonia is apparently excreted as uric acid.

The **Substituted Ammonias** of the methane series, such as methylamine, and some of those of the aromatic series resemble ammonium in their general effects, but the stimulation of the central nervous system is not often so marked. In general terms, those compounds in which one hydrogen atom is substituted, tend to cause greater nervous stimulation than those in which two or three such substitutions are made, while this action is again more prominent in those in which four alkyl groups are combined with the nitrogen. In addition, most of these compounds seem to have a more depressant action on the central nervous system afterward than ammonium, and they all tend to weaken and eventually to paralyze the terminations of the motor nerves. Some of them slow the heart by an action resembling that of muscarine, while others act on the peripheral ganglia like nicotine.

The ammonium bases formed from the natural alkaloids appear to have less action on the central nervous system, but act like curare on the terminations of the motor nerves.

Therapeutic Uses.—Ammonium chloride is prescribed chiefly for its effects on the respiratory mucous membranes, and is a very common constituent of expectorant mixtures for bronchitis and catarrh. It acts as an expectorant mainly by reflex irritation of the stomach, and increases the bronchial secretion. A lozenge is often used for sore throat, and chloride of ammonium solutions are occasionally inhaled or sprayed into the throat. It has also been prescribed in gastric catarrh with benefit in some cases, but whether this is due to its acting on the mucous secretion is unknown.

In larger doses it may be used to increase the acidity of the urine and as a diuretic. It may cause nausea and should be given well diluted.

Preparations.

Ammonii Chloridum (NH_4Cl), a white, crystalline, powder, odorless, with cool saline taste. Soluble 1 in 3 of water. Dose, U. S. P. 1 G. (15 grs.); B. P. 0.3–4 G. (5–60 grs.).

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III. SALTS OF THE ALKALINE EARTHS.

1. **Calcium.**—The salts of calcium are present in very large amount in the tissues of animals, and considerable interest attaches to their absorption, excretion, and general action. They form the great mass of the inorganic constituents of the bones and teeth of the vertebrates and of the shells of the invertebrates. In addition they are present to a considerable amount in the soft tissues and body fluids and are, in fact, essential to most forms of living matter, and to the activity of certain ferments.

Calcium and the other alkaline earths differ from the alkalies in possessing comparatively few very soluble salts, and they seldom effect such changes in the physical properties of the fluids of the body as have been described under salt-action and chloride of sodium. Even the soluble salts penetrate with greater difficulty into the various tissues of the body, which seem to have less affinity for them than for the salts of the alkalies. They precipitate colloids, such as the proteins, in more dilute solutions than the salts of the alkalies, and the precipitate is not redissolved by dilution with water. This precipitation of proteins appears to account for the pain and irritation which follow the subcutaneous injection of the more readily dissociable salts such as the chloride.

Action.—The soluble lime salts are **Absorbed** with difficulty from the stomach and intestine and retard the absorption of fluid. They would presumably have a cathartic action were they not thrown out of solution very readily by the alkaline fluids. In addition calcium forms insoluble salts with all of the cathartic anions. The greater proportion of the lime, taken either in the food or as a remedy, unquestionably leaves the body in the stools unabsorbed, while a smaller quantity of it is taken up from the alimentary canal whether the lime be administered in a soluble or in an insoluble form. This circulates in the blood, partly as diffusible salts but partly in combination with proteins, and is slowly excreted, unless there is a deficiency in the supply of lime, when it may be utilized by the tissues. When larger quantities are thrown into the blood by intravenous or hypodermic injection, the calcium of the blood remains abnormally high for a short time, but all the calcium thus injected is not in the circulation throughout its stay in the body. Some of it is temporarily deposited in some unknown organ, and is gradually withdrawn and excreted after the first excess is eliminated.

The *serum* in health contains about 10 mg. Ca per 100 cc. Of this only about 2 mg. exist as calcium ions, and only about 6 mg. are able to

pass through a collodion membrane. The remaining 4 mg. are in some indiffusible combination with protein, or possibly with lipids. The Ca in the serum is remarkably constant, so that some mechanism must exist to maintain a balance between absorption, deposition and elimination. Factors which have been found to assist in controlling the concentration in the serum are the amount and availability of the calcium in the food, the body stores, the reaction of the tissue, the presence or absence of vitamin D, and the parathyroid hormone.

The normal calcium requirements for a healthy adult have been estimated at 0.5 G. of calcium per day. This is a minimum amount and more is required during growth, pregnancy or lactation. An ill-balanced diet may easily contain too little calcium. Cow's milk contains about 0.12 per cent of calcium, about five times as much as human milk. A pint of cow's milk provides a full day's ration of calcium in an easily assimilable form.

The lime is **Excreted** in part in the urine, but for the most part through the epithelium of the large intestine. The relative amounts excreted by the kidney and bowel seem to be determined by the quantity of available phosphates among other factors; if these are present in large quantities in the blood, the calcium is excreted mainly in the bowel in the form of calcium phosphate. Excess of chlorides in the body fluids has the opposite effect, more calcium appearing in the urine. The elimination of calcium thus appears to vary with the character of the combinations which it can form; if these are soluble they appear in the urine, while the insoluble ones tend to pass into the stools. The administration of calcium increases the elimination of magnesium in the urine, and similarly magnesium absorbed leads to a larger excretion of calcium in the urine, while that in the fæces may be diminished.

The calcium absorbed has no obvious effects; constipation is often induced by lime, but it is uncertain whether this arises from action on the intestinal neuromuscular apparatus, or is the result of the calcium precipitating the superficial protein in the bowel and thus forming a protective covering over the epithelium and lessening the reflex peristalsis (compare tannin group). Except under special circumstances, the calcium of the food is always sufficient to supply the needs of the organism, so that lime salts given as remedies have after absorption no specific action due to the calcium, but owe their activity to the anion exclusively. Even with an increase in the calcium of the serum of 20 per cent, such as occurs in osteitis fibrosa, no symptoms (apart from the local bone conditions) appear from excess of calcium. A large excess of calcium in the blood is accompanied by definite symptoms as discussed in connection with the effects of the parathyroid hormone (see p. 585).

The action of calcium on isolated organs is complicated by the fact that it must always be applied along with sodium in order to maintain the osmotic equilibrium, and sodium appears to modify the lime action considerably, as will be discussed later. But calcium appears to depress the neuromuscular connections in striated muscle like curare, and later to weaken the muscle itself. The removal of lime is said to increase the irritability of the terminations of the autonomic nerves in mammals; on the other hand the vagus is stated to lose its inhibitory action on the heart perfused with calcium-free salt solution.

Soluble calcium salts injected directly into the blood-vessels have an action re-

sembling that of digitalis in some respects. They first accelerate and strengthen the heart, and in large quantities bring it to a standstill, and also have a marked effect in contracting the vessels when perfused through them. In this way they may sometimes diminish the diuresis and glycosuria in animal experiments. Large quantities injected intravenously contract the pupil to pin-point size, apparently from action on the fibres of the sphincter muscle, for atropine has little effect on the myosis. Asphyxia causes dilatation after calcium, however, in the same way as in morphine poisoning. These effects are absent when the salts are taken up from the bowel, no doubt owing to their slow absorption.

There is some not altogether convincing evidence that lime salts lessen the permeability of the cells of the tissues; for example, it is stated that, when an animal has been treated with lime salts, the intravenous injection of iodides does not induce pleural effusion and œdema, while it has this effect in untreated animals; the statement that strong irritants may be applied to the conjunctiva without swelling and effusion in these treated animals is certainly erroneous as was shown repeatedly in experiments on the poison gases during the World War. Minot has shown that the circulatory failure occurring in guanidine poisoning is caused by loss of plasma fluid and that this loss can be reduced by adequate calcium medication.

Balanced Salt Solutions.—A curious relationship has been shown to exist between the calcium and potassium salts. Thus when a frog's heart is perfused with sodium chloride solution containing a trace of calcium, the movements are not entirely normal, the contraction being somewhat prolonged and the relaxation much retarded. If a trace of potassium chloride is added, however, the contraction becomes normal in character. On the other hand the effect of potassium on the frog's heart is antagonized by the addition of lime. The same holds true for voluntary muscle, the salts of calcium tending to neutralize the effects of potassium, and *vice versa*, and in several other relations an antagonism has been observed between these two metals Another marked antagonism was shown by Meltzer, that toxic quantities of magnesium can be completely neutralized by calcium. And, as the symptoms of magnesium poisoning in mammals are characteristic, the recovery of animals when calcium is injected is very striking; magnesium induces narcosis and anæsthesia, which is immediately counteracted by calcium, and the animal assumes its normal posture.

Another question of interest is the relation between sodium and calcium. It has already been noted that the frog's heart perfused with sodium chloride solution soon ceases to beat, but can be restored by the addition of calcium and potassium to the circulating medium. The ordinary explanation (Ringer, Howell) is that the calcium and potassium are necessary to the activity of the heart and that when pure salt solution is perfused these elements diffuse into it and are lost from the heart muscle; this diffusion is prevented if calcium and potassium be contained in the solution, and the heart, retaining the salts essential to its activity, continues to beat. Another explanation has been offered by Loeb, who supposes that the lime and potassium are not directly essential, but that they neutralize the poisonous effects of sodium. This poisonous action of sodium has not been generally recognized, but is well shown by the behavior of a small fish (fundulus) living in salt water, which can be transferred to distilled water without injury, thus showing that neither sodium nor calcium is necessary in its environment. But if it be put in sodium chloride solution of the same strength as sea water, it dies, so that sodium is poisonous to it unless when antagonized by the other constituents of sea water; the essential elements are calcium and potassium, for when these are added to the injurious sodium solution, the fish lives as well as in sea water. This series of experiments certainly forms a strong support for Loeb's theory that calcium is not directly essential to rhythmic movement, but only neutralizes the effects of sodium. On the other hand, the calcium salts themselves are poisonous when they are not counterbalanced by sodium and potassium; in this, as in many other instances, there must be maintained between the inorganic constituents of the surrounding fluid an equilibrium, such as exists in sea water in the case of the fundulus, and in the blood plasma in the case of the heart and other organs.

Lime Starvation.—Excess of calcium in the organism is therefore little to be apprehended from the ordinary methods of administration, and lime salts are seldom used in therapeutics to induce changes through their presence in excess in the blood, like other remedies, such as morphine or strychnine. Another question arises, however, namely, whether the organism may not be rendered abnormal by a deficiency in the supply of lime, and whether this deficiency may be remedied by the administration of calcium salts.

The effects of a deficiency of lime in the food have been the subject of several very careful investigations, and while the adult animal does not seem to suffer greatly from a very considerable reduction of the calcium of the food, young growing animals develop marked abnormalities, resembling closely those observed in rickets and osteomalacia in the human subject. In lime starvation, as in rickets, there is a lessened deposit of lime in the bones, which retain their cartilaginous consistency and show other deviations from the normal condition; in rickets the bones alone are involved, while in animals deprived of calcium the soft tissues also show a lessened content of lime salts. Deficiency of the lime in the food naturally affects young animals more than adults, because the former require calcium to build up the growing skeleton. But if the lime of the food is greatly reduced while a special demand is made on the lime reserve of the body, the bones in the adult may also suffer; thus in pregnant animals, in which lime has to be supplied for the fœtal skeleton, weakness of the bones of the mother simulating the osteomalacia of human pregnancy has been observed when the lime of the food was reduced. Only when the serum calcium has been reduced to 60 or 70 per cent of the normal value do immediate symptoms which can be attributed to such a diminution make their appearance. The most constant change accompanying such a reduction is increased excitability of the peripheral nerves.

The effects of the withdrawal of lime have been studied in some **Isolated Organs.** Thus Ringer compared the behavior of the frog's heart when perfused with solutions of the salts of the alkalies with that of one perfused with the same solutions to which minute traces of lime were added, and found that the efficiency of the heart was much increased and that it survived longer under the latter conditions; Locke has shown that a similar relation exists between the mammalian heart and the inorganic elements of serum. Lime salts exercise a similar effect in voluntary muscle, which survives much longer when perfused with salt solution containing calcium than when sodium chloride solutions alone are used. Both the heart and skeletal muscle eventually cease to contract on electrical stimulation when perfused with sodium chloride solution alone, but recover when traces of lime salts are added to it. In the same way, the irritability of the frog's nerve persists much longer in salt solution containing a lime salt than in unmixed salt solution, and may be restored by the addition of lime, when it has disappeared under the prolonged action of the 0.6 per cent chloride of sodium solution. Ciliated epithelium continues to wave rhythmically longer in lime solution than in distilled water, in which it swells up and rapidly loses its activity. This probably explains the observation that some fish die very soon in distilled water but survive in water in which traces of lime are present. Lime is also necessary for the development of various ova; for instance, frog spawn kept in water devoid of lime salts fails to develop, or develops abnormally.

Lime salts are also indispensable in some processes which are not dependent on the presence of living cells. Thus rennet does not coagulate milk except when a lime salt is present, and the **Coagulation of the Blood** may be prevented by precipitating its calcium salts in the form of oxalates. Hammarsten has shown that the lime salts are not necessary to the formation of fibrin, for this occurs in oxalate solutions if fibrin-ferment is added to fibrinogen. But the fibrin-ferment is not formed except in the presence of calcium salts, and when oxalates are added to the blood before this ferment is developed, they prevent its formation and hinder clotting. When lime salts are added, the ferment is liberated and coagulation occurs at once. In other words, lime is not necessary for the activity of the fibrin-ferment, but for its development from the prothrombin or zymogen, in which it exists in the circulating blood.

Other ferments act in the absence of available lime salts. Thus pepsin digests when instead of hydrochloric, oxalic acid is added to it, but it is unknown whether pepsin is formed from pepsinogen in the absence of lime. The trypsinogen of the pancreas may be changed to trypsin by lime salts.

The higher organisms, both animals and plants, have thus been shown to require lime for some of their functions, and it is probably necessary for many others in which its importance has not yet been recognized. The lowest forms of life, however, including the bacteria and some of the moulds, seem to be able to live without it. To induce the effects of lime starvation it is not always necessary to withdraw lime from the food, for they may be caused by the presence of any substance which prevents the dissociation of the calcium ion, such as sodium oxalate, citrate or fluoride. Food containing large quantities of oxalate salts has in some cases induced symptoms in animals resembling those of lime starvation, and it seems probable that most of the symptoms of fluoride action are also explicable from their precipitating the lime salts of the food and of the blood. (See Oxalates and Fluorides.)

Therapeutic Uses.—As has already been stated no condition is known to which any advantage is gained by raising the calcium content of the tissues above the normal. Calcium is used therapeutically therefore only in conditions of abnormalities of calcium metabolism, especially, of course, of deficiency.

In *rickets* there is unquestionably too little lime in the bones, and administration of lime was thought to be rational, because symptoms similar to those of rickets have been induced in young animals whose food contained too small a proportion of lime. But the administration of calcium salts was found to have little or no influence on the disease, which indeed occurred when there was ample lime in the food. The disease has now been shown to be due to shortage of vitamin D, and to be curable by substances rich in vitamin D such as cod-liver oil, irradiated ergosterol, or by exposure to sunlight and ultra-violet radiation. Shortage of vitamin D may either cause deficient calcium absorption from the bowel or interference with the process of ossification and

in the circumstances there is no advantage in giving calcium above the normal amount in food, in the routine treatment of rickets.

During *pregnancy* the constant demand on the part of the growing fœtus for calcium puts a heavy tax on the calcium metabolism of the maternal tissues and the serum calcium is frequently somewhat diminished especially toward the end of pregnancy. A low serum calcium has also been found in eclampsia. It is important that the maternal diet should contain a liberal daily ration of calcium both during pregnancy and during lactation, when the calcium requirements may be nearly doubled. The condition of osteomalacia occurring in pregnancy is not, however, arrested merely by giving calcium salts in food, but is prevented if vitamin D be given in addition.

In *tetany*, following the removal of, or injury to, the parathyroid glands during the operation of thyroidectomy, the serum calcium is definitely reduced. The administration of parathyroid extract, which mobilizes the calcium of the bones and tissues, increases the serum calcium and relieves the condition. Oral administration of calcium in excess, but especially intravenous injection, can also give prompt but transient relief.

In tetany and *spasmophilia* following rickets, the serum calcium is also low, but the use of parathyroid extract is contra-indicated, except as an emergency, since the increased serum calcium is obtained by removal of calcium from the bones which are already deficient in it. Tetany disappears when the rickets is treated in the usual way, but for temporary purposes the tetany may be controlled by the administration of large doses of calcium by mouth or smaller doses intravenously.

Calcium chloride has been used to a limited extent as a diuretic in some forms of *nephritis*. In severe nephritis the total calcium of the serum is reduced but the beneficial action of calcium chloride does not seem to be due entirely to calcium replacement. Its action here has been explained by the fact that the calcium so given is retained or excreted in the intestine as carbonate. The freed chloride ions can thus cause an increased acidity, and, to correct this, sodium is excreted as sodium chloride, accompanied by large amounts of water. Ammonium chloride, which causes a similar type of acidosis, also acts as a diuretic in these conditions.

It has also been proposed to treat with calcium cases in which the blood is less capable of clotting than normally—particularly *hæmophilia;* and it has been tried in conditions like *purpura and tuberculosis* in which there is no prolongation of the coagulation time of the blood. In most of these cases there is no evidence of calcium deficiency and there is little convincing evidence of the value of calcium therapy. Injections of calcium chloride have been recommended in the preoperative preparation of patients with *jaundice* to reduce the risk of bleeding.

Calcium salts have also been employed in a variety of diseases in which there appears to be a lack of tone, or an undue permeability of the vessels, *e. g.*, in Raynaud's disease, urticaria and angioneurotic œdema, and also in conditions of increased permeability of serous membranes, *e. g.*, in pleural or peritoneal effusions. In serum sickness the

administration of large doses of calcium is stated to reduce the duration of the rash and the severity of the itching, nausea and headache. While there is some evidence that calcium diminishes the permeability of animal membranes, the evidence of the value of calcium in these conditions is at present conflicting.

The preparations of the **oxide** and **hydrate** owe their activity chiefly to their alkalinity and not to the calcium, but differ from the hydrates of the alkalies in their insolubility and in their slow absorption. Lime water tends to neutralize the gastric juice and has an astringent effect in the intestine which is probably due to its forming an insoluble compound with the surface proteins, in the same way as tannic acid. Lime water is used in some dyspeptic conditions, especially in vomiting. It is often added to milk in intestinal irritation in children and in typhoid fever, as it is said that milk thus treated coagulates in finer particles than when given alone, and is better digested and less liable to disturb the intestine. Lime water or syrup of lime is also used as an intestinal astringent in diarrhœa, especially in children. As an antacid in the stomach, lime is inferior to magnesia and other alkalies, because it tends to delay the evacuation of the contents. It has also been sprayed against the false membrane of diphtheria, which it is said to dissolve. Lime water is not applicable in cases of acid poisoning, as it contains much too little of the base to be serviceable, but the syrup may be used, or lime shaken up with water (milk of lime). The treatment with lime is specially indicated in cases of oxalate poisoning.

Lime water has been used externally as a protective, mildly astringent application to ulcers, and the lime liniment, no longer official, was formerly much used in the treatment of burns. It derived its name of Carron oil from having been used for this purpose in the iron works at Carron.

The preparations of the **carbonate** of lime are used as antacids in hyperacidity of the stomach, especially when this is combined with a tendency to diarrhœa. The mixture, or the aromatic powder B. P., is the form generally used, and may be prescribed with opium or with other astringents. Chalk has also been used in rickets.

Externally, prepared chalk is used as a powder to protect irritated parts of the skin and occasionally in ulceration; it is the chief ingredient in most tooth powders. In older treatises on therapeutics great virtues are ascribed to various natural objects which are composed for the main part of chalk or other salts of lime, and among which burned bones, coral, coralline and cuttlefish bone may be mentioned.

Preparations.

Calcii Chloridum (U. S. P., B. P.) ($CaCl_2$), a white salt with a sharp, saline taste, very deliquescent and soluble in water. Dose, U. S. P., 1 G. (15 grs.); B. P., 0.6–2 G. (10–30 grs.). By intramuscular injection, 0.03–0.1 G. ($\frac{1}{2}$–1$\frac{1}{2}$ grs.); by intravenous injection, 0.3–1 G. (5–15 grs.).

Calcii Lactas (U. S. P., B. P.) ($Ca(C_3H_5O_3)_2,5H_2O$), a white, almost tasteless powder soluble in 18.5 parts of water. Dose, U. S. P., 1 G. (15 grs.); B. P., 1–4 G. (15–60 grs.).

Calcium chloride is the salt which gives the least complicated calcium action. It has a strong attraction for water and is readily dissociable and is therefore

more irritant than the chlorides of the alkalies and other alkaline earths; it ought to be prescribed only in dilute solution, and should not be injected into the subcutaneous tissues or muscle, as it causes great pain and sometimes even sloughing. Instead of the chloride, the lactate has been employed in the same doses and has the advantage of dissociating more slowly and thus causing less pain and irritation when it is injected.

CALCII GLUCONAS (U.S.P.) Oral 5 G. (75 grs.), Intravenous 1 G. (15 grs.); *Calcium Gluconate* has been extensively used in recent years as a substitute for the chloride or lactate. It is a white granular powder, slowly soluble in water.

CALCII HYDROXIDUM (B. P.), slaked lime ($Ca(OH)_2$), may also be used as a disinfectant. 0.3-1 G. (5-15 grs.).

LIQUOR CALCII HYDROXIDI (U. S. P., B. P.), lime water, is a saturated solution of calcium hydrate or slaked lime and contains about 0.15 per cent. It is a clear fluid with a saline and feebly caustic taste. 15 cc. (4 fl. drs.); B. P., 30-120 mils. (1-4 fl. oz.).

CRETA PRÆPARATA (U. S. P.), CRETA (B. P.), prepared chalk, chalk purified by washing and suspension in water ($CaCO_3$). 1 G. (15 grs.); B. P., 1-4 G. (15-60 grs.).

PULVIS CRETÆ COMPOSITUS (U. S. P.), a mixture of prepared chalk, sugar and acacia. 2 G. (30 grs.).

PULVIS CRETÆ AROMATICUS (B. P.), aromatic chalk powder, contains chalk along with sugar and a number of carminatives belonging to the group of volatile oils. 0.6-4 G. (10-60 grs.).

PULVIS CRETÆ AROMATICUS CUM OPIO (B. P.) is a mixture of 39 parts of the aromatic powder with 1 of opium, and therefore contains $2\frac{1}{2}$ per cent of opium. 0.6-4 G. (10-60 grs.).

MISTURA CRETÆ (U. S. P.), chalk mixture, is compound chalk powder suspended in cinnamon water. 15 cc. (4 fl. drs.).

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2. **Barium.**—Barium is the most poisonous of the alkaline earths, but resembles the others in penetrating with difficulty into the epithelium of the alimentary canal, and is therefore absorbed very slowly. It has a characteristic action on many forms of muscular tissue, resembling closely that of veratrine, and the contraction of the frog's muscle under barium is thus stronger than normally, and is greatly prolonged; this action is not opposed by curare and is therefore believed to be exerted on the contractile substance directly. Barium has a somewhat similar action on all forms of muscle. Thus the smooth muscle of nearly every organ is stimulated by barium, *e. g.*, of the gut, bronchi, etc. The frog's heart beats more strongly, but more slowly from a similar action on the muscle fibres,

and eventually assumes an irregular peristaltic form of contraction, followed by arrest in systole, as in digitalis poisoning. Barium has been suggested as a substitute for digitalis but it is questionable whether it really acts in the same way. There are some noticeable differences; for example, the toad's heart shows a high tolerance for glucosides of the digitalis group but not for barium. Furthermore digitalis acts on the heart in concentration much lower than those which affect smooth muscle, but this is not true of barium.

In the mammal barium salts injected intravenously cause violent tonic and clonic spasms, from stimulation of the spinal cord and medulla; in sufficient quantities, they finally paralyze the spinal cord. Intravenous injection also provokes the contraction of involuntary muscle in all organs, with vomiting, purging, evacuation of the bladder, etc. The blood-pressure is enormously increased at first, due especially to constriction of the arterioles. In fatal poisoning in animals hæmorrhages have been found in the stomach, intestine, kidney and other organs. Intravenous injection of isotonic sodium sulphate has been recommended as an antidote in acute $BaCl_2$ poisoning (Rise).

Barium is quite incapable of replacing calcium in its relations to living matter, and accordingly chloride of sodium solutions to which barium chloride has been added do not tend to keep the frog's heart active as do those containing lime. Some authors hold that barium can replace calcium to an imperfect degree in the coagulation of the blood, but this is denied by others. Potassium salts tend to neutralize the effect of barium on the heart and muscles, the relation resembling that which they bear to lime.

Barium is absorbed slowly from the intestine and is found to be stored in the bones to some extent, and to be excreted by the intestinal epithelium, only traces appearing in the urine.

It has seldom been used in practical therapeutics. In veterinary practice it is often employed as a purgative.

BARII SULPHAS (U. S. P., B. P.), BARIUM SULPHATE.—A fine, white, insoluble powder. Due to the fact that barium sulphate passes through the body unchanged, it is used in taking roentgenograms of the gastro-intestinal tract. It may be given by mouth mixed with the food, or in an enema when the colon is to be examined. When used for this purpose, barium sulphate must be very pure, as contamination with more soluble salts such as the chloride or sulphide may make it dangerously toxic.

3. **Strontium.**—Strontium is a comparatively inert substance even when injected directly into the blood, resembling calcium in its action in the body as far as is known, but being even less poisonous. Small doses given intravenously raise the blood-pressure mainly by increased cardiac action, large doses cause apnœa and death from arrest of the heart (Boriani). It prolongs the contraction of muscle though only to a slight extent. It has not the antagonistic effects to magnesium in the nervous system which are possessed by calcium, but it antagonizes the broncho-dilator action of magnesium. It is absorbed very slowly from the intestine like the other alkaline earths, and is deposited in small quantities in the bones of growing animals, especially when there is a deficiency of lime in the food; but it cannot be used to replace the calcium of the food, animals treated thus showing the symptoms of lime starvation. It is excreted in small quantities by the urine, but mainly by the bowel. Strontium salts have been used to a limited extent in therapeutics, not for the effect of the strontium ion, but for the bromide, iodide or salicylate anions. They possess no advantage over the corresponding salts of potassium and sodium.

4. **Magnesium Salts.**—The magnesium salts have been shown by Meltzer to have a very powerful action when injected hypodermically or intravenously. The most characteristic effect is complete anæsthesia, resembling that induced by the chloroform group, and ending in fatal cases in paralysis of the respiratory centre. This arises mainly from direct affection of the central nervous system, and immediate recovery follows the injection of a calcium salt. Higher concentrations of magnesium in the blood have a curare-like action, also antagonized by calcium (see Calcium). The magnesium anæsthesia does not appear to arise from its penetrating into the brain cells, for no significant amount can

be obtained by analysis, while large quantities are found in the plasma. Applied to a nerve trunk, magnesium salts in 25 per cent solution act in the same way as cocaine, paralyzing first the afferent and later the efferent fibres, and injected into the intradural space they cause complete anæsthesia of the lower part of the body like cocaine; magnesium sulphate has, in fact, been employed occasionally for surgical operations and in the treatment of tetanus. The anæsthesia lasts much longer and this renders it unsuitable for surgical work, but several cases of tetanus treated by subdural injection of magnesium sulphate have recovered. (Dose, about 0.02 G. per kg. in man.) The same anæsthetizing action is seen in the lower invertebrates when a magnesium salt is added to the water in which they live. Magnesium has comparatively little effect on the heart, tending to lessen the excitability of the vagus, and this effect may also be abolished by lime salts. It reduces the irritability of the intestine when injected intravenously and arrests the peristalsis aroused by physostigmine or barium. It also appears to have some effect on the myoneural receptors in muscle, for it arrests the twitchings induced by physostigmine and in large doses interrupts the path from nerve to muscle in the same way as curare. It produces curarisation of the muscles of crabs, which are unaffected by curare itself. When injected intravenously magnesium produces a fall of blood-pressure mainly due to vasodilatation. The bronchi are dilated in some animals. In small doses magnesium salts cause a reduction, in large doses an increase, in blood sugar. None of these effects is normally elicited when magnesium salts are given by the mouth, as that absorbed is excreted rapidly and there is never enough accumulated in the blood to have any action. Rarely some depression of the nervous system has been observed when very large doses of magnesium sulphate have been given by mouth without producing purgation. Magnesium is excreted by the kidney and traces may appear in the secretions from other organs. It is eliminated rapidly, almost the whole appearing in the urine within forty-eight hours, and this excretion of magnesium is attended by an increase in the calcium of the urine, while that of the fæces may diminish.

Human blood plasma contains about 3 mgs. of Mg. per 100 G. and the red blood corpuscles about double that amount. The latter seem to be impermeable to the Mg. ion.

A form of tetany has been described in young dogs as the result of deprivation of magnesium, the animals ultimately dying of convulsions.

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IV. MISCELLANEOUS ANIONS.

1. **Oxalates and Fluorides.** — The *oxalates* (NaOOC—COONa) and the *fluorides* owe the greater part of their action to their power of precipitating the calcium of the tissues, though they may also cause other effects; this precipitation

renders them poisonous to most forms of living matter, of which lime is generally an essential constituent. The oxalate action may be removed in many instances by adding lime salts in excess.

In the frog they cause depression and final paralysis of the central nervous system, and later of the terminations of the peripheral nerves and the muscles and heart; twitching and fibrillary contractions of the voluntary muscles are often observed first.

In mammals there is apparently at first a stimulation of the medullary centres, for rapid, deep breathing occurs in the rabbit, and vomiting and nausea in the dog, and according to some observers, the arterial tension is first increased through stimulation of the vasomotor centre. Later the movements are wanting in coordination, the respiration becomes slow and dyspnœic, the heart is weak, and the animal becomes comatose and dies, sometimes in convulsions.

In cases of oxalate poisoning in man, the early symptoms are great muscular weakness, twitching of the muscles, especially of those of the face, more rarely convulsions, later there follows collapse with a weak, fluttering pulse, pallor or cyanosis, coma and death.

Oxalates are very poisonous to all forms of animal life and to plants containing chlorophyll, but are harmless to the moulds, bacteria and some algæ. The fluorides are equally poisonous to the higher organisms, and in addition have considerable antiseptic power, 1 part in 200 of water being sufficient to arrest the growth of bacteria. Both are absorbed with great difficulty from the stomach and intestine, and cause irritation and effusion of liquid except in very dilute solutions. Added to the blood outside or inside the body, they prevent its coagulation, and the rennet ferment also fails to coagulate milk in the presence of small quantities of oxalate. The frog's heart is much weakened by the addition of oxalate of sodium to the blood perfused through it, while the mammalian heart is not affected by very small quantities, but if the injection of oxalate be continued, becomes suddenly weaker. According to some observers, the terminations of the autonomic nerves are rendered more excitable under oxalates, and this manifests itself in salivation, ready dilation of the pupil, variations in the rate of the heart, and in an abnormal sensitiveness to epinephrine and pilocarpine (Chiari and Frohlich).

Practically the whole of the oxalate ingested is excreted in the urine in the form of oxalate of calcium, and the insoluble crystals are often deposited along the urinary tubules and may stop them up entirely and thus cause anuria, congestion, and inflammation of the kidney; albuminuria is often the most marked symptom in slight poisoning in man. The deposits of oxalates often form white lines running from the base to the apex of the renal pyramids, which are quite evident macroscopically at the autopsy. Small oxalate calculi have also been produced in the pelvis of the kidney, bladder, or ureter through the prolonged administration of oxalate to animals. Not infrequently these renal changes are the only lesions found post mortem in cases of poisoning with oxalates.

The prolonged administration of oxalates to animals has been found to induce changes in the skeleton identical with those arising from lime starvation; for example, sheep fed on plants containing much oxalate are found to have less lime in the bones than usual.

The oxalates are not used in therapeutics. In cases of oxalate poisoning the natural antidote is lime, which forms an insoluble precipitate in the stomach and may also relieve the symptoms induced by the withdrawal of lime from its normal combination in the tissues. At the same time large quantities of water and diuretics may be given in order to wash out the crystals of oxalate from the urinary tubules. Oxalate poisoning has sometimes occurred in man from the use of vegetables containing much oxalic acid, *e. g.*, rhubarb leaves.

Accidental and even suicidal poisoning with oxalates is not uncommon.

The other members of the oxalate series, *malonates* ($CH_2(COONa)_2$) and *succinates* ($(CH_2)_2(COONa)_2$), differ from the oxalates in being much less poisonous, the fatal dose of malonate of sodium being about twenty times that of the oxalate, and the succinate being almost indifferent. The malonate is almost completely oxidized in the tissues, and succinate disappears completely.

It is significant that malonic and succinic acids form much more soluble salts with lime than does oxalic acid. Both malonate and succinate of sodium are absorbed only slowly from the intestine, and act as saline cathartics.

The fluorides are powerful local irritants, small quantities applied to the conjunctiva causing congestion and inflammation. Both fluorides and oxalates irritate the stomach and induce nausea and vomiting. This irritation of the alimentary tract may perhaps explain the retarded growth and loss of appetite in rats treated with fluorides (Sollmann). In experimental chronic poisoning with fluorides the chief effects produced were changes in the bones and teeth, anæmia, hepatic lesions and a cachexia often fatal after two or three months.

In recent years cases of poisoning by sodium fluoride have been described, arising usually from the use of this substance as an insecticide and from its being mistaken for laxative or baking powders. The chief symptoms are nausea, vomiting and diarrhœa, accompanied by cramp-like abdominal pains. Clonic convulsions have occurred occasionally and a peculiar gray-blue cyanosis has been observed in some cases. Chronic fluoride poisoning, arising from the use of fluorides in industry, has also been described, giving rise especially to changes in the bones and mottling of the teeth.

The fluorides absorbed from the alimentary canal are excreted by the urine, but this takes place very slowly, and much of the fluoride is stored up in the body, some in the liver and skin, but most in the bones in the form of calcium fluoride. Crystals of this very insoluble salt are found in masses in the Haversian canals, and increase the hardness and brittleness of the bones.

Hydrofluoric acid is an exceedingly powerful caustic, destroying the mucous membranes wherever it comes in contact with them. It has been observed that workers in certain departments of glass factories, in which the atmosphere contains a small amount of this acid, are very seldom attacked by tuberculosis, and an attempt has been made to treat pulmonary phthisis by the inhalation of very dilute vapors. The results have not been successful, although there is no question that hydrofluoric acid is a powerful germicide.

Sodium fluorosilicate (Na_2SiF_6) has also been used as an antiseptic in solution. It has been found to cause nausea, eructation, and slowness of the pulse when swallowed.

Fluorides have been recommended in Graves' disease, though their method of action is not satisfactorily explained. For this purpose sodium fluoride has been given both by mouth and by intravenous injection.

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2. **Sulphides.**—The ordinary sulphides of the alkalies are of little importance in themselves, as they are seldom used in therapeutics. The effect of hydrosulphuric acid, however, apart from its local irritant action, is due to the sulphide which it forms in the blood, and the study of this powerful poison therefore involves a preliminary examination of the effects of the sulphides. Again, sulphur is in itself inert, but is changed to sulphides and hydrosulphuric acid in the alimentary canal, and the effects induced by its administration are due to these bodies, and not to the original element (p. 266).

Action.—The sulphides act as irritants in the stomach and bowel, and in the latter induce increased peristalsis and purgation. When injected subcutaneously in the frog, sodium sulphide causes a narcotic condition from depression of the central nervous system, and in sufficient quantities weakens the skeletal muscle and the heart, which continues to beat after complete paralysis has been obtained, but eventually ceases in diastole. After the narcosis has lasted for some time, there follows a marked increase in the reflex irritability, with convulsions resembling those of strychnine poisoning in their general character, but differing from them in lasting continuously for weeks or even months at a time. The animal lies in an extended and tense condition throughout, and passes into complete opisthotonos on being touched.

Sulphides injected intravenously in mammals induce violent convulsions, which seem to be of cerebral origin, for they do not occur in the hind limbs when the spinal cord is cut. The respiration is at first accelerated and later dyspnœic and finally ceases, this, along with the paralysis of the vasomotor centre, being the cause of death. The heart does not seem to be seriously affected except indirectly through the failure of the respiration and the fall of the blood-pressure.

Sulphide solutions added to drawn blood reduce the oxyhæmoglobin at once, and give the blood a dark venous color. At the same time a compound of sulphide and hæmoglobin is formed, known as sulpho-hæmoglobin or as sulpho-methæmoglobin, and gives the blood a greenish color when a thin layer is examined, while a thicker layer is dark red-brown. This sulpho-hæmoglobin possesses a characteristic spectrum, marked by a dark line in the red to the left of the D line. Larger quantities give an olive-green color to the blood, and the spectrum of sulpho-hæmoglobin disappears. When sulphides are injected into frogs, and more especially when sulphuretted hydrogen is inhaled, the blood gives the characteristic spectrum during life, but this does not seem to be the case in mammals, although sulpho-hæmoglobin is formed soon after death. The blood changes are not the cause of death in poisoning, as was formerly supposed, but the direct action of the sulphides on the central nervous system.

Sulphides absorbed into the blood are rapidly oxidized, and are excreted in the urine in the form of sulphates and of organic sulphur compounds of unknown constitution. Small quantities escape by the lungs, and give the breath the disagreeable odor of sulphuretted hydrogen, and some is excreted in this form in the perspiration.

The sulphides dissolve the horny epidermis and hair very readily when they are applied to the skin. If the application is continued, some irritation and redness is produced.

Hydrosulphuric Acid (sulphuretted hydrogen, hydrogen sulphide (H_2S)) is a gas with strong irritant properties, which it shares with other acids (see page 95) and has not infrequently given rise to poisoning, as it is formed in large quantities in the course of the putrefaction of sulphur compounds such as proteins. Sewer gas often contains it in quantity, and workmen employed in cleansing sewers or cesspools have often suffered from its effects. When inhaled in concentrated form it is almost immediately fatal, the patient losing consciousness at once, and the respiration ceasing after a few seconds. In smaller quantities it causes immediate unconsciousness, lasting for several hours and then passing into fatal coma, which is often interrupted by violent convulsions. In both of these forms the symptoms are due to the direct action of the sulphides on the brain and medulla oblongata. Persons exposed to a very dilute vapor of

sulphuretted hydrogen suffer from local irritation of the eyes, nose and throat, indicated by pain and congestion of the conjunctiva, sneezing, dryness and soreness of the mouth and throat, and a reflex increase in the secretion of tears, saliva, and mucus. Headache, dulness, giddiness, and loss of energy are complained of; the symptoms frequently appear only some time after the exposure to the poison. Death in animals exposed to these dilute fumes is due in part to œdema of the lungs caused by the local irritant action. One part of hydrosulphuric acid in 5,000 of air is sufficient to induce symptoms in man, and an atmosphere containing one part in 2,000 can be respired for only a short time, and gives rise to alarming symptoms; about one part of hydrosulphuric acid in 1,000 parts of air is sufficient to poison a man fatally in ten minutes.

The poisonous effect of sulphuretted hydrogen is due in part to its local irritant action, in part to its directly affecting the central nervous system. The changes in the blood occur during life only after very concentrated gas is inhaled, although they may indicate the poison after death from more dilute vapor, for the tissues in general tend to assume a green color sooner after hydrosulphuric acid poisoning than in the course of ordinary putrefaction.

Hydrogen sulphide is destructive to most forms of life, even when present in comparatively small amount. The microbes of putrefaction, which produce it themselves, are eventually killed by this gas, unless it escapes freely.

Preparations.

Potassa Sulfurata (U S P.), Potassa Sulphurata (B. P.), liver of sulphur (Hepar Sulphuris), is a mixture of polysulphides and thiosulphides, often containing sulphate of potassium; irregular brownish or greenish pieces soluble in water and possessing an unpleasant saline taste, and an odor of hydrogen sulphide.

Sulphurated potassium is used to a very limited extent as an external application in certain skin diseases, particularly in acne, and to destroy skin parasites, such as that of scabies. It is used as an ointment (1 part to 10 parts), and is somewhat irritant.

Sulphides, especially barium sulphide, are used occasionally to remove hair. They cause destruction of the hairs but not of the follicles, so that the hair continues to grow.

Many mineral springs contain hydrogen sulphide in small amount, and these have obtained wide celebrity in the treatment of various chronic respiratory and skin diseases and in syphilis, gout, rheumatism, and chronic metallic poisoning (lead, mercury). Most of these springs are hot, and it is open to question whether the small amount of the gas contained in the water is of any efficacy, and whether the heat of the water and the hygienic conditions are not the true cause of the improvement observed in these cases. Sulphur baths are also formed artificially by the addition of sulphurated potassium (2–8 oz.) to an ordinary hot bath; a small quantity of acid is sometimes added, in order to free the hydrogen sulphide more rapidly.

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3. **Iodides.**—Although the iodides have been more largely used in medicine than any of the other salts of the alkalies, their mode of action is still in many ways obscure. The attention of investigators has been drawn to the symptoms of poisoning rather than to the therapeutic

action, and the effects seem to vary considerably not only in different individuals, but also in the same person at different times.

Symptoms.—Large quantities of the iodides cause irritation of the stomach from their salt-action and induce nausea and vomiting, more rarely diarrhœa; but these symptoms are quite distinct from those known as **Iodism,** which may arise from comparatively small quantities, and which are most commonly seen when the remedy has been administered repeatedly.

The commonest symptom of iodism is catarrh of the **Respiratory Passages,** more especially of the nose, which betrays itself in some swelling and discomfort in the nasal mucous membrane, in a profuse water secretion, and in sneezing. The catarrh spreads upward to the conjunctiva, which often becomes swollen and congested. There may be marked lacrimation and œdema of the eyelids. The frontal sinuses are involved, inducing a feeling of dulness or violent headache; and the condition may progress downward to the tonsils, which become swollen and inflamed in some cases. Still lower it occasionally causes some swelling and œdema or small ulcers in the larynx, and has thus caused dyspnœa, which has necessitated tracheotomy, or very rarely has proved fatal. Bronchitis has also been observed in man, with a profuse watery secretion, and in animals œdema of the lungs and pleuritic effusion have been produced by the injection of iodides. Even small quantities injected intravenously increase the mucus secreted by the bronchi.

In the **Mouth** iodism is often betrayed by swelling and irritation of the throat and tonsils and by salivation, rarely by swelling of the salivary glands. The stomach is seldom affected, the appetite generally remaining good, but in some persons iodides induce nausea and gastric discomfort. A single dose of iodide increases the amount of gastric juice and prolongs the secretion aroused by the taste of food.

Skin Eruptions of different forms are also common results of the administration of iodides, but are less liable to occur in the beginning of the treatment than the catarrh of the respiratory passages. These eruptions may simulate almost all known skin diseases, but the most common forms are erythematous patches, or papular eruptions, which may pass into pustules or into larger inflamed areas. Eczema, bullæ, pemphigus and purpura arise less frequently from the use of iodides. In some cases a more or less defined area of œdema has been observed in the face, especially around the eyes.

The **Secretion of Urine** is generally increased by the administration of iodides, as of other salts of the alkalies, though they seem to have no specific action on the kidneys. In rare cases albuminuria has been observed, and some irritation of the bladder, urethra and vagina is said to have been induced by iodide treatment, but these statements require confirmation.

In abnormal conditions of the thyroid gland, the iodides and many other iodine compounds often give rise to a series of symptoms which are due to the excessive production of the specific secretion of the gland, which itself contains iodine; these symptoms are quite distinct

from those described as iodism and may rather be referred to as thyroidism. Among these symptoms are acceleration and palpitation of the heart, tremors, nervousness, sleeplessness and disorders of sensation, such as localized anæsthesia or neuralgic pains. Sometimes some fever or accelerated metabolism leading to loss of weight has occurred, and occasionally extreme emaciation and cachexia with mental depression, which only abated slowly on the abandonment of the treatment, or which in rare cases were permanent.

In many instances small doses of iodide may be given repeatedly without any noticeable disturbance, but in others the smallest quantity (0.2 G.) induces severe poisoning. Some authorities consider that these small doses are more liable to cause iodism than larger ones, but the action of the drug is so capricious that the statistics of different observers show great discrepancies, even when approximately the same dose has been given. Thus, Haslund, treating patients with at first 3 G. (45 grs.) and then 5 G. (75 grs.) daily, observed iodism in only 12 per cent of his cases during the first few days, while others have found iodism induced in 60 per cent of their cases after a single dose of 3 G. Snodgrass found that iodism occurred much more frequently with doses of 5 grs. or less than with doses of 10–30 grs., and that it could usually be stopped by increasing the dose to 30 grs. An attempt has been made to explain these discrepancies by supposing that iodism is only produced by impure iodides, but this is not correct, for it has been observed in numerous cases in which the drug was absolutely pure. Among other conditions which favor the onset of symptoms is a slow excretion of the iodide such as is observed in some forms of renal irritation. Children seem less liable to suffer from the iodides than adults. The dose administered has, of course, some relation to the onset of symptoms; thus, very large doses are more likely to induce them than very small ones, but it seems that a tolerance is soon established in some cases, for after iodism has been induced, and the daily dose lessened accordingly, it is sometimes found that it may be gradually increased until a quantity considerably greater than that originally given may be taken with impunity. In other instances, a definite quantity may be given for a long time without inducing symptoms, but these may suddenly set in without any apparent change in the treatment and without any appreciable cause. Very often it is found that the symptoms disappear while the treatment is continued, and recovery invariably sets in when the drug is abandoned. The iodides all induce iodism, the symptoms being apparently unaffected by the basic ion. The condition is seldom dangerous, but a few cases are recorded in which œdema of the larynx resulted and proved fatal.

The iodides are not **Absorbed** from watery solutions applied to the skin, but are rapidly taken up by all the mucous membranes. When given by the mouth they are absorbed unchanged by the intestine, and appear in the secretions within five to ten minutes. The greater part of the iodide is **Excreted** in the urine, in which it appears as salts. Some escapes by the salivary glands, however, and small quantities are excreted by the stomach as hydriodic acid, from which free iodine may

be formed; iodide has also been found in the tears, perspiration, milk, sebum, and in the secretion of the nasal mucous membranes. More iodide is found in the blood than in any of the fixed tissues; the skin is also rich in iodide, while the lungs, kidneys and lymph glands contain smaller quantities; the brain and fatty tissues have merely traces; necrotic tissues take up more than sound ones because the dying cells no longer oppose resistance to the diffusion of the salts.

By histological methods Stieglitz has demonstrated that iodides are to be found in the parenchymatous cells such as in the secreting cells of the kidney, in the cells of Henle's loop. They are also found in the hepatic cells and in the free border of the epithelial cells lining the air passages at the secretory pole apparently being excreted.

Iodides are much more rapidly excreted than bromides, for 65–80 per cent of the iodide appears in the urine within twenty-four hours after its administration, and no iodide reaction is obtained from any of the secretions a week after the treatment has ceased. Some of the iodide

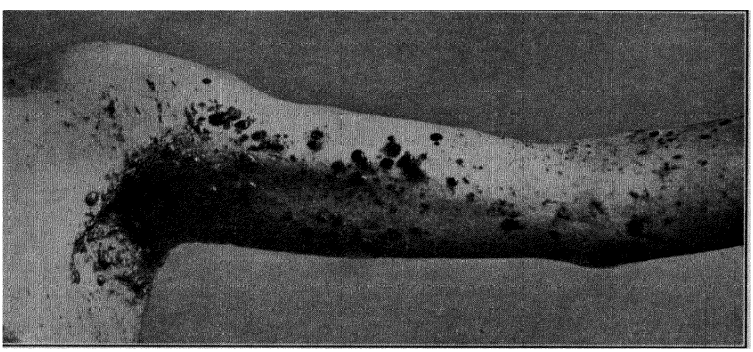

FIG. 1.—Eruption due to potassium iodide.

does not appear in the urine, however, and its fate in the body has not been very clearly traced. Different individuals vary in the amount that thus disappears, which seems to be fairly constant for each person; thus one patient receiving 0.5 G. of potassium iodide may retain 0.1 G., while another after the same dose may retain 0.2 G. or more, the same proportions appearing on different occasions.

The greater part of the iodide administered therefore passes through the tissues and is excreted in the urine in the form of salts. Some of the iodide undergoes decomposition in the body, however, for free iodine has been found in the stomach, and an organic compound of iodine exists in the hair and in various internal organs after iodide treatment. The successful treatment of goitre with iodide of potassium is also a strong argument in favor of the presence of free iodine, and the iodine of the thyroid glands has been shown to be increased by potassium iodide. When iodine is thus liberated in the body, it does not circulate as such, but at once combines with the proteins, and its presence can no longer be demonstrated by the ordinary tests.

Campbell and Snodgrass found that after the administration of single doses of potassium iodide by mouth, small amounts of iodine could be demonstrated in the cerebrospinal fluid. If the salt was given three times a day the amount found in the fluid was much greater. With intravenous injections of large doses the amount of iodine found was greater than by the oral method of administration.

The formation of free iodine from iodides (which is, of course, quite distinct from their dissociation into potassium and iodide ions) has been the subject of several ingenious theories, none of which have been established and which are now chiefly of historical interest and need not be entered on here.

It is often said to be set free along the mucous membrane of the respiratory passages and in the skin; and in this way the coryza of the former, and the eruptions on the latter are explained. It must be noted that free iodine has not yet been clearly demonstrated on either of these surfaces, and that the theory has been formulated only to explain the symptoms of iodism. Iodides have been found in the nasal secretion, saliva and perspiration, but no free iodine.

The central nervous system and the circulation scarcely seem to be affected by iodides. Very large quantities of potassium iodide injected into a vein are found to weaken and paralyze the heart in animals, but do not seem to be more poisonous than other potassium salts, and depression of the central nervous system may also be elicited in the same way by the potassium action. Barbera states that very large quantities of iodides paralyze the depressor nerve terminations in the medulla oblongata and weaken the peripheral inhibitory mechanism of the heart, while Hunt found the accelerator fibres less easily fatigued after iodide. The metabolism of the body seems little affected by iodides in most cases, but a further examination of the excretions of patients who lose weight under the treatment is desirable. Grabfield and Prentiss have found that the various iodides increase the urinary nitrogen excretion of subjects whose intake is constant. With most of the iodides the effect is immediate but in the case of the calcium and potassium salts the effect is considerably delayed, indicating an action of the cations of these salts upon the nitrogen excreting mechanism. Hesse found an increase in uric acid in hens and in total nitrogen in dogs and cats. He concludes that the iodides increase those chemical and enzyme processes which are concerned in protein breakdown. Fatty degeneration of the liver is stated to occur in some animals. The action of the iodides in therapeutics has been ascribed by some authors to their rendering the movement of the leucocytes (diapedesis) more active, but no satisfactory evidence has been adduced in support of this. Solutions of iodide of sodium are found to be more poisonous to muscle, cilia and unicellular organisms exposed to them than are similar solutions of the chloride or bromide, so that the iodide ion appears to be more fatal to protoplasm than the bromide and chloride ion, while it is less poisonous than the fluoride. In the frog stiffness and awkwardness in the movements are elicited by comparatively small doses of iodide of sodium and these symptoms have been shown to be due to rigor occurring in the muscles.

Therapeutic Uses.—The iodides are used very extensively in the treatment of tertiary *syphilis*, in which they have proved invaluable. They have also been administered in the earlier stages of the disease, but have proved to be of little service here. In syphilitic bone disease and ulcers, and in the gummata of the brain and other internal organs, however, a remarkable improvement very often occurs after the iodide treatment has been adopted. The iodide of potassium or of sodium is almost invariably used, and is often given in large doses, up to 5 G. (75 grs.) daily. Snodgrass, however, found that a dosage of 15 grs. three times a day was as effective as twice that amount. The iodide is often prescribed along with mercury, and this combination is found more efficient than the iodide alone. In actinomycosis iodide treatment has

proved of value, and in a rare infection known as sporotrichosis, which arises from a fungus nearly related to actinomyces, the effects are even more striking than in tertiary syphilis.

In *syphilis* and in these other diseases, the iodide does not act as a parasiticide; the spirocheta of syphilis, for example, is not killed by the application of iodide of potassium to a syphilitic lesion, and the fungus of sporotrichosis grows readily in a culture medium containing high concentrations of iodide. The specific effects of iodide in tertiary syphilis are exerted not on the parasite but upon the tissues in which it lives and which have reacted to its presence by the formation of tumors; these lowly organized tumors dissolve under the action of iodides, while the parasite remains unaffected, but is now more readily accessible to the parasiticide drugs, mercury and arsenic. It is important to recognize that iodide does not destroy the cause of the infection but only removes some of the results.

It is unknown how iodide removes the gummatous tissue; it accumulates in poorly nourished, necrotic tissues in greater concentration than elsewhere, because these have lost their power of resisting the permeation of salts which therefore diffuse into the cells freely. This is not specific for syphilis, and probably other salts would also be found in higher concentration in these tissues than in others. Kepinow found that iodide injected intravenously in animals accelerates the autolysis of the liver, and an analogous observation has been made by Jobling and Petersen, who found that serum no longer inhibits the trypsin action in the presence of iodides, and that in patients treated with iodide the antitryptic action of the serum is lowered; it is possible that it similarly promotes the autolytic solution of the gumma by removing the antagonistic substances.

In many diseases which are not directly attributed to syphilis, but in which there is a history of syphilis, iodides are of value; thus, *neuralgia* and other nervous disturbances are often relieved by them in persons of a syphilitic taint, and in fact, improvement is often observed in the most diverse conditions in persons who have formerly suffered from this complaint.

Another series of symptoms, or of diseases, which is often treated with iodides is *rheumatism* in its various manifestations. The treatment is of little value in acute rheumatism, and in fact, often fails in the chronic disease, but is occasionally attended with improvement, although the exact conditions in which this occurs are still unknown.

The iodides have long enjoyed some reputation in the treatment of *goitre*, but the thyroid extract has proved much superior to them and promises to supplant them entirely, as their effects are due to their action on the thyroid secretion. The same may be said regarding their use in obesity, which was found to be successful in some cases, presumably of thyroid insufficiency. When thyroid insufficiency is due to the absence of iodine, while the gland cells are capable of normal action, iodides and iodine give good results; but when the symptoms arise from absence or atrophy of the secretory cells, iodides are valueless, and relief is given only by the administration of the specific secretion.

The increase in the iodine of the thyroid gland under iodide treatment has been studied by Marine and his associates, who point out that the iodine is first taken up by the gland in an inactive form and is then slowly changed into the physiologically active combination. In some districts in which goitre is prevalent, good results have been obtained by giving iodide as a preventive measure; the children being given ten doses of 0.2 G. each during ten days twice a year. Iodide is also administered for such purposes in the form of iodized salt. This salt should not contain more than 1 part of sodium or potassium iodide for each 5000 parts of salt, or its equivalent in iodine in any other suitable iodine compound. This form of medication may be quite useful for the prevention of goitre in the pre-adolescent period but the use of such salt by adults is believed by some to be distinctly dangerous as it is not unlikely that its use in adults may be responsible for symptoms of hyperthyroidism. For the same reason self-medication by "goitre cures" containing iodine or over iodinization by a physician may also be dangerous to adults

Some *skin eruptions* have been found to be benefited by the iodide treatment even when no suspicion of syphilis could be entertained.

The success attending the treatment of *goitre* with iodides seems to have been the basis of their use in cases of enlarged lymphatic glands, scrofula, and lupus, but here the results are very doubtful, although some authorities allege that the iodide treatment is of value. There is a general consensus of opinion that the old treatment of malignant tumors, such as cancer and sarcoma, with iodides is hopeless.

These salts are sometimes credited with promoting the absorption of serous effusions, and the removal of hypertrophy of connective tissue in the body, as in the various forms of sclerosis and cirrhosis. Their efficacy in removing the syphilitic gumma was evidently the origin of their use here, but while the resolution of gummata under the iodides is beyond question, no satisfactory evidence of improvement in these non-syphilitic affections is available.

Aneurism and *arteriosclerosis* have often been treated with iodide, and improvement is undoubtedly observed in some cases, in which there is probably a syphilitic taint; but there seems no reason to suppose that the iodides have any special action on the vessels apart from their action on poorly organized tissue, such as is formed in syphilitic infection, for no change in the heart, pulse or blood-pressure can be observed even after prolonged treatment.[1]

Iodides are often prescribed along with other remedies in *expectorant* mixtures, the object being to render the bronchial mucus more watery and less tenacious, and thus to facilitate its removal. In some cases of asthma they have been found of value, perhaps from the same action, for they do not appear to affect the bronchial muscle.

Iodide of potassium is generally prescribed in *chronic poisoning* from lead or mercury, and it has been shown that it exerts a definite

[1] The supposed action in arteriosclerosis has sometimes been ascribed to iodides lessening the viscosity of the blood; but the experiments on which this explanation is based are not convincing.

influence in increasing the rate of excretion of lead in chronic poisoning from that metal, approximately doubling the output but even so it is not as effective as are some other agents such as acids and to a lesser degree alkalies (Aub). The belief in the efficacy of the iodides in mercury poisoning has suggested that they act in tertiary syphilis only by aiding in the mobilization of the mercury stored in the tissues from the treatment of the earlier stages, but this is incorrect, for the iodides are of value in cases of tertiary syphilis in which mercury has not been previously used. It is stated that when iodide is given along with mercury, the latter does not accumulate in the liver, but the statement requires confirmation.

Finally, iodide of potassium is sometimes added to other drugs in cases of *malingering*, or in which it is suspected that the patient is not taking the remedy as directed. If the iodide is swallowed it can be detected in the urine by the addition of a few drops of chlorine water and of starch solution, which assumes the well-known blue color.

Iodides have to be used with care in cases of pulmonary phthisis, in which they often increase the cough and expectoration, and in some cases, it is alleged, cause hæmoptysis and promote the infection of fresh tissue. If the tuberculous nodule is broken down by the iodides in the same way as the gumma, the bacillus may be freed, and many clinicians deprecate the use of iodide in all forms of tuberculosis. Children have sometimes been found to suffer from iodism from being nursed by a person under iodide treatment.

Iodism very often proves a disagreeable accompaniment of the treatment, and is sometimes so severe as to preclude the use of the salts, so that many attempts have been made to discover some expedient by which these symptoms may be avoided, but as yet no success has been obtained. Iodism occurs less readily under the organic preparations iodipin and sajodin, but it is not yet satisfactorily established that the specific action in syphilis is induced as certainly by these as by the inorganic iodides; in grave cases the latter should certainly be employed in preference.

PREPARATIONS.

U. S. P.

POTASSII IODIDUM, 0.3 G. (5 grs.).
SODII IODIDUM, 0.3 G. (5 grs.).
CALCII IODOBEHENAS, 0.5 G. (8 grs.).

B. P.

POTASSII IODIDUM, 0.3–2 G. (5–30 grs.).
SODII IODIDUM, 0.3–2 G. (5–30 grs.).

The iodides form colorless crystals when pure, a yellowish tint indicating the presence of free iodine. They are very soluble in water, less so in alcohol, and are always prescribed in watery solutions, and often along with carbonate of sodium or potassium, in order to prevent decomposition as far as possible. The iodide of potassium is the one most frequently used and is less liable to contain free iodine than the others, but iodide of sodium is preferred by some. The iodide of ammonium is said to be more liable to cause skin eruptions and

disturbance of the digestion than the others. Some iodide effects may also be obtained by the use of iodide of lead or mercury, but here they are complicated by the action of the metal, and these will be discussed along with the other salts of lead and mercury. The external application of iodides is not attended by any general effect, though some irritation may be induced by iodine being liberated by the decomposition of the fats; small quantities of iodine are absorbed and changed to iodides in the tissues.

Iodipin (unofficial) is an iodine addition produced of sesame oil and forms a yellow oily liquid with an oily taste. It is prepared in two strengths containing 10 per cent and 25 per cent of iodine, respectively. Dose 4–8 cc. (1–2 drs.) of iodipin 10 per cent. Hypodermically 2–6 cc. (30-90 mins.) of iodipin 25 per cent.

Calcii Iodobehenas, Sajodin ($(C_{21}H_{42}ICOO)_2Ca$, the monoiodobehenate of calcium, is a colorless and tasteless powder insoluble in water.

The rapid elimination of iodide by the kidney necessitates frequent large doses if the action is to be maintained, and these large doses in turn tend to induce iodism. An attempt has therefore been made to introduce iodine combinations which are slowly decomposed in the tissues and thus free iodide continuously. For this purpose protein compounds with iodine have not proved successful, as they tend to free the iodine in the alimentary tract and the resulting iodide is eliminated almost as quickly as when inorganic iodide is administered. Combinations of iodine with oil (*Iodipin*) or with fatty acids (*Sajodin*) are absorbed, stored in the fat depots of the body and gradually decomposed with the liberation of iodides. No iodine is found in the urine in the first hour after the administration of these organic compounds and the maximum excretion takes place after ten hours; the iodide reaction disappears from the urine after eighty-four hours.

An iodine compound of tariric acid has been introduced under the name of *Iodostarine* ($C_{18}H_{32}I_2O_2$). It is being used as a substitute for the inorganic iodides and in small doses is perhaps used most largely as a prophylactic against simple goitre. Closely allied compounds are *Oridine*, the calcium salt of iodized fatty acids of cotton seed oil and containing about 24 per cent of iodine, and *Riodine*, a solution in oil of an iodine addition product of castor oil. It contains about 17 per cent of iodine. It should be noted that the iodine content of both Oridine and Riodine is only from a third to a quarter that of the inorganic iodides.

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4. **Iodine.**—Iodine possesses a local irritant action similar to, though less intense than, that of chlorine and bromine (page 822). It is much less volatile, and therefore comes into contact with the tissues more slowly than these, but the chemical change is analogous, and iodides and iodo-protein compounds result.

Action.—When applied to the **Skin**, it dyes it a yellow-brown or dark brown color, and acts as an irritant, producing a sensation of heat and itching. In very concentrated solution or in the solid form it may cause blistering or even corrosion, but it acts more slowly than most other irritants, and at the same time the irritation is more prolonged. It penetrates into the deeper layers of the skin, and small quantities are absorbed.

The **Mucous Membranes** are more strongly affected by contact with it; thus when its vapor is inhaled for some time, smarting, swelling and increased secretion are caused in the nasal mucous membranes, conjunctiva, throat and lower respiratory passages, resembling exactly the symptoms known as iodism. In the stomach small quantities may cause slight irritation and improved appetite, but as a general rule nausea, discomfort and vomiting follow its administration in any save minute doses, and occasionally diarrhœa has been observed after it from irritation of the bowel. In cases of poisoning, the irritation of the alimentary canal may prove fatal by inducing collapse and failure of the heart and respiration, and iodine may be recognized in the vomited matter and in the stools.

Solutions of iodine **Injected Subcutaneously** or into tumors or cysts, formerly a common method of treatment, cause intense pain and irritation, which may induce collapse and which have been followed in some instances by suppuration and gangrene.

Iodine is **Absorbed** in the form of iodides, and perhaps in combination with proteins. Its fate in the body is precisely similar to that of the iodides—it is excreted in the form of iodides, chiefly by the kidneys, to a less extent in the saliva, perspiration, milk and secretions of the respiratory passages. The administration of iodine leads to an increase in the iodine of the thyroid gland.

Small quantities of iodine may be given internally to many persons without eliciting any symptoms except those which are clearly due to the local action. Repeated doses, however, sometimes cause symptoms resembling those observed after iodides (**Iodism**), although these have been much less often induced by iodine. Many other symptoms which have been observed under iodine treatment, obviously arise from the excessive activity of the thyroid gland, are especially noticeable in goitre.

The preoperative use of iodine in the form of Lugol's solution in cases of exophthalmic goiter produces histological changes in the thyroid gland which are quite remarkable. The epithelial hypertrophy resolves into the appearance of normal acinar epithelium, colloid appears in abundance, although it is rather thin and watery. The hyperplasia of the primitive lymph follicles, on the contrary, seems to be increased. If the treatment is extended over a period greater than that of ten days

or two weeks the amount of thin, watery colloid increases and a certain degree of enlargement of the acinary cells with lipid and vacuolar degeneration results, accompanied by marked lymphoid hyperplasia. When iodine treatment is persisted in for several months a peculiar hypertrophy of the acinar cells often occurs—"iodine hypertrophy"—shown particularly in adenomas. An undoubted proliferation of adenomas is excited by this treatment (Warthin). In patients having adenomas of the thyroid the administration of iodine is likely to increase metabolism by converting the condition into an adenoma with hyperthyroidism.

Some **Cases of Poisoning** from the injection of large quantities of iodine into cysts have been recorded. In Rose's well-known case, the chief symptoms were thirst, constant vomiting (the vomited matter containing iodine), cyanosis and coldness of the skin, a small, weak pulse, anuria and skin eruptions after a few days; and death occurred on the tenth day. In such cases of poisoning in man the mucous membrane of the stomach and intestine has been found swollen and loosened, and in animals fatty degeneration of the liver, heart, and kidney has been described.

Injected into the veins of animals, iodine causes œdema of the lungs, which v. Zeissl considers to be due in part to changes in the left ventricle, in part to contraction of the pulmonary arterioles.

Therapeutic Uses.—Iodine has been used internally in a variety of chronic conditions, such as syphilis and goitre, and in tuberculous disease of the glands, bones and other organs, but it has been almost entirely superseded by the iodides, and in goitre by the thyroid preparations.

Iodine, usually in the form of Lugol's solution, is being extensively used before operations for exophthalmic goitre and the discovery of its value has done much to decrease the dangers associated with the surgical treatment of this condition. It is usually administered in milk in doses of about 10 minims three times a day after meals. The patients improve rapidly under its effects—the nervousness lessens, sleep and appetite improve, the heart becomes slower and the basal metabolism decreases. The patient is protected against post-operative crisis. The drug is not by any means a cure for the disease but is only to be regarded as a temporary measure to prepare a patient for the surgical treatment of the condition. The beneficial effects usually reach their maximum between ten days and three weeks after the drug is started and operation is best done during this period. Following the favorable second and third week of iodine administration if the patient has not been operated upon the symptoms of hyperthyroidism gradually recur, the heart increases gradually in rate, the nervousness returns and the basal metabolism increases so that the condition of the patient is not so favorable for an operation as at the earlier period. Following the operation the administration of the iodine is usually continued for a few days.

It has been applied locally by painting on the skin in a variety of chronic inflammatory processes, such as tuberculous glands, pleuritic effusion, and tuberculous or rheumatic joint disease. Its action here consists simply of a mild lasting irritation of the skin, which induces

some congestion in the subcutaneous tissues and may thus aid in the absorption of exudates in them and may also influence the deeper lying tissues and organs in the same way as other irritants (see p. 224). There is, however, nothing specific in its action, and it differs from the other skin irritants only in being milder in action and more enduring in its effects. It seems unlikely that the small quantity absorbed can have any appreciable action. Some benefit often follows from this use of iodine in chronic inflammations, but there is no question that it is very often applied where more active surgical measures are really required.

Iodine was formerly injected into cysts in order to induce inflammation and adhesion of their walls, and thus to obliterate the cavity. It is used extensively to disinfect the skin before operation (see p. 798).

PREPARATIONS.

U. S. P.

IODUM, iodine, grayish-black plates, with a metallic lustre and a characteristic odor. Soluble about 1 in 3000 of water, 1 in 12 alcohol, freely in chloroform; is dissolved by aqueous solutions of iodides. 0.01 G. ($\frac{1}{6}$ gr.). Not administered as such.

TINCTURA IODI, contains about 7 per cent of I and 5 per cent of KI, 0.1 cc. ($1\frac{1}{2}$ mins.).

TINCTURA IODI MITIS contains about 2 per cent of I and 2.3 per cent of KI.

LIQUOR IODI COMPOSITUS, Lugol's solution, contains 5 per cent I dissolved in 10 per cent potassium iodide solution. (0.2 cc. 3 mins.).

UNGUENTUM IODI, 4 per cent.

OLEUM IODATUM. An iodine addition product of vegetable oils containing about 40 per cent of organically combined iodine.

B. P.

IODUM, iodine.

LIQUOR IODI FORTIS, strong solution of iodine, strong tincture of iodine. Contains 10 per cent of iodine and 6 per cent of potassium iodide in 90 per cent alcohol.

LIQUOR IODI MITIS, weak solution of iodine, weak tincture of iodine. Contains $2\frac{1}{2}$ per cent of iodine, $1\frac{1}{2}$ per cent of potassium iodide in 90 per cent alcohol. 0.3–2 mils. (5–30 mins.).

LIQUOR IODI SIMPLEX, simple solution of iodine, contains 9 per cent of iodine in 95 per cent alcohol. 0.2–1 mil. (3–15 mins.).

SYRUPUS FERRI IODIDI, syrup of ferrous iodide, contains 5 per cent of FeI_2. 2–8 mils. (30–120 mins.).

OLEUM IODISATUM (Iodized oil).

Unofficial Preparations of Iodine Used for Diagnostic Purposes.

In recent years iodine and certain other roentgen-ray opaque substances have been introduced into medical practice as an aid to diagnosis. They have been used, for instance, as an aid to diagnosis in pathological condition in the lungs or in suspected disease of the gall-bladder or of the genito-urinary tract. Several preparations are in use at the present time, those containing iodine being discussed here while the phthalein compounds used especially to permit visualization of the gall-bladder will be mentioned elsewhere.

In pulmonary conditions other than those due to tuberculosis iodized oils are sometimes employed. *Oleum Iodatum* (U. S. P.), *Oleum Iodisatum* (B. P.) (lipiodol), contains about 40 per cent of iodine in organic combination with poppy-seed oil. After the pharynx and base of the tongue have been anæsthetized, the oil may be administered by dropping it through the glottis as the

patient inspires, or it may be injected into the trachea by mean of a curved cannula inserted between the cocainized vocal cords. It may be given also through a bronchoscope. More commonly it is given through a curved cannula inserted through the cricothyroid membrane, the required amount being injected into the anæsthetized trachea, roentgenograms being taken immediately after the injection has been completed. Usually no symptoms follow immediately upon the administration of the oil, but in about fifteen minutes coughing may occur with ejection of most of it. The oil which is retained usually disappears in a week or two but it may be retained in the lungs for a considerable period. Iodism rarely follows from this use of iodized oil unless some of the oil is swallowed, when symptoms may occur.

The ethyl ester of diiodobrassidic acid under the name *Lipoiodine* is also used as an aid in the diagnosis of pulmonary conditions. It contains 41 per cent of iodine and it is usually employed for diagnostic work in a 60 per cent solution in sesame oil in a dosage of from 5 to 20 cc.

The iodine solutions have also been employed as diagnostic agents for injection into the subarachnoid space in cases of suspected diseases of the spinal cord. However, slight irritant effects have produced changes in the spinal fluid and in their experimental use animals have shown signs of leptomeningeal involvement so that these compounds should not be employed for subarachnoid injection unless it is absolutely unavoidable.

For renal pyelography oils should not be used except in the form of emulsions and recently iodine compounds which are soluble in water have been introduced for this purpose. One of these is sodium iodopyridon acetate, or *Iopax*, which was introduced under the name of *Uroselectan*. This compound, which contains about 43 per cent of iodine, is very soluble in water and is administered intravenously in doses of about 30 G. dissolved in 100 cc. of distilled water. During and immediately after the injection the patient may complain of a feeling of warmth, of palpitation of the heart, and of pain in the arm near the shoulder, or of dryness of the mouth and of thirst, but these symptoms usually pass off in about ten minutes. Occasionally symptoms of delayed poisoning such as high temperature and increased heart-rate with pulmonary râles have been reported. Roentgenograms are taken about fifteen minutes after the drug has been injected and again in about one-half hour, during which time the drug is being excreted most actively. Iopax is also injected by means of a ureteral catheter into the pelvis of the kidney, using a solution of the same strength as is employed for intravenous injection. A newer compound, *Neo-iopax* (uroselectan B), the disodium salt of N-methyl 3·5 diiodochelidamic acid, has advantages over iopax in that a smaller dose is required and the volume of the injected solution is less. It contains about 51 per cent of iodine.

The sodium salt of iodomethane sulphonic acid under the name of *Skiodan* (Abrodil) is also used to permit visualization of the urinary tract. Skiodan contains about 52 per cent of iodine and is freely soluble in water. For intravenous urography it is given in doses of from 20 to 40 G. dissolved in distilled water, the average dose for an adult being about 2 G. for each 15 pounds of body weight. The drug is rapidly excreted, about 75 per cent being eliminated in three hours and 90 per cent in ten hours. The maximum concentration in the urine of from 4 to 6 per cent is found within a few minutes after the drug is injected. For intraureteral injection a solution containing from 10 to 20 G. of the drug to 100 cc. of water is injected into the pelvis of the kidney. *Diodrast* (perabrodil), another compound containing about 50 per cent of iodine, is used in the same way, 20 cc. of a solution containing 7 G. of the substance being injected slowly into the cubital vein. *Hippuran*, sodium iodohippurate, containing about 39 per cent of iodine is also used for urography.

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V. ALKALIES.

1. **Hydrates and Carbonates of the Fixed Alkalies.**—The hydrates and carbonates of potassium, sodium and lithium owe their pharmacological action entirely to the non-metallic ion, which is so much more powerful than the metal that the latter may be discounted. In the hydrates the active constituent, then, is —OH. The carbonates and bicarbonates dissociate into K- or Na-ions and $-CO_3$, but the latter rapidly combines with the hydrogen of the water to form HCO_3 ions and thus frees —OH, so that the final effect is the same as if a hydrate had been administered, except that the carbonates are less rapidly dissociated than the hydrates, and, less —OH being formed, are less violent in their action. This hydroxyl ion, then, is what induces the alkaline reaction of the solutions and their pharmacological effect, the metallic ion only serving as a means of applying the hydroxyl ion, but not affecting the pharmacological action.

Action.—The pharmacological action of this group is due to their powers of neutralizing acids and of dissolving proteins and changing them to alkali-proteins, and in a less degree to their saponifying fat. They have in addition the ordinary salt-action, and in concentrated solutions withdraw fluid from the tissues.

The solution of proteins by the alkalies and the characters of the compounds thus formed outside the body are well known and need not be entered into here. The same solvent action is observed in the living tissues whenever the hydrates and carbonates come in contact with them in sufficient concentration. The hydrates are, of course, much more powerful solvents than the carbonates, and these than the bicarbonates. In very dilute solutions this solvent action is exercised only on the superficial tissues, but when stronger solutions are used, or when even weak solutions remain long in contact with the tissues, they tend to penetrate more deeply and cause widespread destruction or corrosion. These bodies form soluble compounds with the proteins and are only slowly neutralized by the tissues, so that no such barrier is raised against their penetration as is met by some other corrosives.

Applied to the **Skin**, weak solutions dissolve the superficial layer of horny matter and the oily secretions of the glands, and thus cleanse the surface more thoroughly than water or solutions of neutral salts. When applied for some time, they penetrate more deeply and cause some slight irritation and redness. Concentrated solutions dissolve the skin and cause necrosis of the deeper tissues, generally covered by a semitransparent crust which falls off in the course of a few days, leaving an ulcer. The solutions of the carbonates are much less corrosive than those of the hydrates, and induce actual lesion of the skin only under exceptional circumstances, such as very prolonged application.

In the **Mouth** the hydrates and carbonates have a characteristic "alkaline" taste, and dissolve the superficial layers of the lining membrane and the mucus of the secretions. The lips, tongue, and gums assume a bright red color from the irritation and feel soapy to the touch. Concentrated solutions may cause deep corrosion, as in the skin, while

very weak solutions have no effect except the characteristic taste and a reflex flow of saliva. The corrosion caused by strong solutions extends to the throat and œsophagus, and may either prove immediately fatal or may subsequently give rise to cicatrices.

The effect of the hydrates and carbonates in the **Stomach** has been much disputed, and perhaps this is not surprising, as they may produce somewhat different effects according to the dose given and the state of digestion at the time. They act chiefly in two ways, by directly modifying the reaction of the stomach contents, and, secondarily, by affecting the pyloric reflexes. Small quantities are undoubtedly neutralized by the hydrochloric acid of the gastric juice and act no longer from their alkalinity, but merely from their effects as salts, if at all. Larger quantities render the contents of the stomach neutral or alkaline and thus prevent gastric digestion. Very concentrated solutions corrode the walls of the stomach and may prove immediately fatal from causing perforation into the peritoneal cavity, while if the corrosion is not so severe, and the patient recovers from the shock and collapse, gastric ulcer and cicatrices may result.

In hyperacidity of the stomach, the alkalies may be of benefit by lessening the amount of free acid present. They have been supposed also to stimulate gastric secretion, especially if given in small quantities before meals, but this has not been satisfactorily proved.

Dilute solutions of the alkalies may act as slight irritants to the stomach wall and thus improve its circulation, and lessen pain, eructation and distention, very much in the same way as other slight gastric irritants, such as the volatile oils. In the case of the carbonates and bicarbonates, this carminative action may be strengthened by the carbonic acid liberated by the hydrochloric acid. In addition, they tend to render the mucus less tenacious, or may dissolve it completely, and thus improve the condition of the stomach.

The movements of the stomach are not much affected by the reaction of its contents until these pass into the duodenum. An excessive acidity or alkalinity of the gastric contents entering the duodenum tends reflexly to cause spasmodic contraction of the pyloric sphincter. Alkalies tend to hasten the emptying of the stomach if they alter the reaction in the direction of neutrality, that is especially in cases of hyperacidity.

In the small **Intestine** the alkalies have been shown to have an indirect effect, through their diminishing the acidity of the gastric juice. The secretion of the pancreas is normally augmented on the passage of an acid fluid through the pylorus, and if the acidity of this fluid be reduced by the administration of alkalies, a smaller quantity of pancreatic juice is thrown into the intestine. This may again render the digestion less complete, although the greater alkalinity of the intestinal contents tends to increase the efficiency of the pancreatic juice already secreted. On the other hand, in cases of hyperacidity of the stomach, the administration of alkalies may render the contents of the intestine less irritant, and thus tend to allay catarrh.

The alkalies administered in medicinal doses seem to have no effect

on the intestinal putrefaction. Kast states that very large quantities (15 G., ½ oz.) increase the putrefaction, probably through neutralizing the disinfectant gastric juice.

The alkalies have been believed to have some special action on the **Secretion of Bile**; but it has been shown that alkaline salts do not increase the secretion of bile, are not excreted in it, and do not cause any change in its reaction. Any effect which the alkaline carbonates or hydrates may possess in hepatic diseases would therefore seem due to their effects in the duodenum.

The prolonged administration of very large doses of the alkaline carbonates and bicarbonates causes chronic gastro-enteritis in animals, and may thus prove fatal to them.

Absorption. Both hydrates and carbonates disappear rapidly from the stomach and intestine, although the bicarbonate of sodium is sometimes credited with some laxative action; this may not, however, be due to the same causes as in the case of the saline cathartics. All alkalies are neutralized by the carbonic acid of the tissues, and circulate in the blood in the form of neutral bicarbonates. This does not alter the reaction of the blood as ordinarily understood; thus if the reaction with litmus be taken before and after the administration of alkali, it is found to be unaltered. On the other hand if the plasma be titrated with an acid, more is required after an alkali has been administered, provided the carbonic acid is driven off during the titration. After alkali treatment the reaction of the blood is unchanged but the alkali available for the neutralization of acid is augmented. Even when the alkali administered has been neutralized by the gastric juice, the reserve of alkali available is augmented because a certain amount of the carbonate of the blood and tissues is spared, which would normally have been used to neutralize the hydrochloric acid before it could be reabsorbed. This condition of augmented alkali can only last a short time, however, as the excretory glands at once proceed to remove the excess. While it is present, the tension of CO_2 in the blood may be lower and the respiratory centre is less active, while the alveolar air contains a higher percentage of CO_2.

It was formerly supposed that the alkalinity (hydroxyl concentration) was actually increased by alkali taken by the mouth and this was believed to influence the **Metabolism**, because many oxidative processes are accelerated outside the body when the reaction is rendered alkaline. But, as has been stated, the alkalinity is not increased in the tissues, but only the available alkali, so that the analogy does not hold, and examination of the metabolism under alkali shows that the tissue change is very little altered. The investigators of the subject have generally confined their attention to the effects of alkalies on the products of metabolism excreted in the urine, and have found the total nitrogen excreted to be unchanged in a considerable number of instances, to be slightly increased in others, and to be diminished in a few individuals. Even in those cases in which an increase is observed in the nitrogen of the urine, it does not always indicate an increase in the nitrogenous metabolism, for the urine is often increased considerably and it is

evident that the interchange of the fluids of the tissues and blood is augmented; so that the increased nitrogen of the urine is accounted for by the tissues being more thoroughly flushed out than usual by the alkalies, which act in the same way as the neutral salts.

Although the total nitrogen may be little affected by the administration of the alkalies, the form in which it is combined in the urine and in the blood may be changed. The ammonia of the urine is often diminished in amount, while the urea excretion is correspondingly augmented. This is especially marked in cases in which excess of acid is formed in the tissues or absorbed in any way, and is explained by the fact that this acid is ordinarily neutralized by the formation of ammonia in the tissues (see Acids). When, however, fixed alkali is present in sufficient amount, as when the carbonates are given, the nitrogen which would otherwise have been excreted as ammonium salts, is formed into urea.

The **Uric Acid Excretion** under the alkalies has been the subject of numerous researches, but, in the great majority of these, very imperfect methods of estimation have been used. In the few cases in which satisfactory methods have been employed, the results have been divergent, the uric acid being sometimes decreased and sometimes increased by the alkalies. In any case the change is trifling in extent, and no inference can be drawn as to the uric acid metabolism from it.

As regards the **Oxidation in the Tissues**, the only conclusion which seems admissible from many laborious investigations is that the tissue waste is but little affected in amount by the administration of alkalies, and the slight changes observed may vary not only in different species, but in different individuals, and even in the same individual at different times. The cause of this individual variation may be differences in the amount of acid formed in the tissues, but may also be differences in the local effect of the alkalies in the alimentary tract.

The organism rapidly frees itself from the excess of alkali by **Excreting** alkaline salts. This excretion occurs chiefly in the urine, which becomes less acid, or even alkaline in reaction, and in the latter event contains bicarbonate of potassium or sodium. As a general rule, the urine soon regains its acidity, but when fairly large doses are given repeatedly, its reaction may be kept alkaline constantly. This is almost always accomplished in man by the administration of about 10-15 G. (160-240 grs.) of sodium carbonate in twenty-four hours, but some persons require a still larger quantity, while others require less. A temporary alkaline reaction lasting two to three hours may often be induced by a single dose of 2-3 G. The alkalies have the same effect on the excretion of the salts in the urine as the neutral salts—large doses increase the sodium, potassium, and chlorides of the urine.

Dilute alkaline solutions applied to **Isolated Organs** generally increase their activity for a time, but subsequently weaken it, while strong solutions are immediately poisonous. Thus the ciliary movement of epithelium is accelerated by dilute alkalies, the sodium salts acting more strongly than the potassium because of the poisonous K-ion of the latter. The developing ova of sea urchins divide more rapidly in very dilute alkaline media, but the resulting cells are

often irregular in shape. The heart also contracts longer and more strongly when it is perfused with a chloride of sodium solution rendered alkaline by carbonate of soda than when the solution is neutral. Somewhat stronger solutions increase its tonus and eventually cause systolic standstill. The arteries are contracted in the same way by contact with alkaline solutions, and are dilated when acids are perfused through them. Some of the secretions have also been found to be increased by the presence of alkalies, thus the glands of the frog's skin are stimulated by very dilute alkaline solutions.

Strong alkaline solutions destroy all living tissues with which they come in contact.

Therapeutic Uses.—The caustic alkalies are used **Externally** to a limited extent to remove growths, such as warts, from the skin. For this purpose the potash pencils are employed, but they are very deliquescent and it is therefore difficult to limit their action to one spot, and to the superficial tissues. When the desired extent of cauterization has been obtained, the part should be washed with water, or with vinegar or some other dilute acid. The carbonates are also used externally to some extent, chiefly in baths, which they render more irritant to the skin, and in which they tend to soften and remove the superficial horny layers of the epithelium more than ordinary water or solutions of the neutral salts. The carbonates are also applied in strong solution or as a paste in itching skin diseases, and often give relief.

Internally the alkaline carbonates are used for their effect on the *stomach*, and in cases of hyperacidity relieve the pain and eructation almost instantly. As the concentration of the acid secreted by the stomach seems to be fairly constant, the acidity of the stomach depends upon the relation between the quantity of the secretion and the volume and nature of the stomach contents. Normally the acidity rises to a maximum about one hour and a half after a meal and then declines rapidly; but in *hyperchlorhydria* the acidity may remain high for hours. In this condition alkalies are usually given after meals, and oxide of magnesium is preferable to a carbonate as the carbonic acid liberated from a carbonate seems to stimulate gastric secretion and to increase the acidity after a temporary diminution. Small repeated doses (*e. g.*, 5 grs. MgO) are more effective for this purpose than single large doses. The proportionate amounts of the more commonly used antacids necessary to neutralize a given quantity of hydrochloric acid were found by Clark to be as follows: magnesium oxide, 3; magnesium carbonate, 7; calcium carbonate, 7; sodium bicarbonate, 12; bismuth subcarbonate, 136. Weight for weight, therefore, magnesium oxide has a fourfold greater antacid effect than sodium bicarbonate, while bismuth subcarbonate has a relatively feeble effect in this direction. When magnesium oxide is used as a stomach antacid, the resulting magnesium chloride acts as a mild purgative, whereas if calcium carbonate be used the calcium chloride formed acts as a mild astringent. In the treatment of hyperacidity or of gastric ulcer, disturbance of intestinal functions can be prevented by alternating magnesium oxide and calcium carbonate or by other combinations of antacids. Tribasic magnesium phosphate has been used as an antacid with the intention that, while it is a mod-

erately effective antacid, it does not produce systemic alkalosis. Magnesium trisilicate has antacid and adsorbent properties useful in the treatment of gastric ulcer and hyperacid gastritis. Its neutralizing action continues for several hours and it does not cause alkylosis or toxic symptoms even in large doses (Mutch). Even where no excessive acidity exists, the alkalies are often beneficial in small quantities, removing distention and discomfort without apparently altering the digestion to any marked extent. The bicarbonate of potassium is more frequently used for this purpose than the others, and the carbonic acid liberated in the stomach may be of importance in the action. Whatever preparation is used, it ought to be well diluted to avoid the irritant action on the stomach wall. When the secretion does not seem to contain an excessive amount of acid they are advised before meals, and may then be combined with other stomachics, such as bitters or volatile oils.

The alkalies are also administered for their effects after absorption, and here the bicarbonate of potassium is most frequently prescribed. *Diabetes* was formerly treated in this way, in the hope that the oxidation in the tissues would be increased, but there is little reason to suppose that the alkalies have any such effect on the metabolism. When, however, diabetes induces an increased acid formation in the tissues, as is almost invariably the case in its later stages, the alkalies are of undoubted benefit in neutralizing the oxybutyric acid formed and thus economizing the alkalies of the blood. In diabetic coma, temporary improvement may often be attained by the use of large doses of alkalies.

In *gout, rheumatism* and the "uric acid diathesis" generally, the alkalies have been used extensively, partly in the hope that the supposed increased combustion in the tissues would destroy a larger amount of the uric acid, and partly with the idea that the uric acid being neutralized in the tissues would be excreted more easily and would have less tendency to be deposited. There are some grounds for believing that the alkaline carbonates are of benefit in gout and rheumatism, but neither of these theories seems sufficient to explain their effects, for no increase in the oxidation has been shown to occur, and on the other hand the uric acid is not rendered more soluble in the blood or urine by the quantities of alkali used in therapeutics. In the present position of the uric acid question and of the pathology of these diseases, however, it is futile to attempt to explain their therapeutics, though it may be surmised that the alkalies may influence the formation of the uric acid rather than its excretion. The sodium and potassium salts have been used very largely. More benefit is derived from the treatment of gout and rheumatism by the alkaline mineral waters than by artificial preparations, and this is especially marked when patients are sent to the mineral springs. The alkalinity of most of the waters is very slight, and the conclusion is inevitable that the curative agency is not the alkalinity, but the large amount of fluid taken, together with the dietetic and other hygienic conditions.

The alkaline preparations are also largely used for their effects on the urine. The acetates, citrates, etc., may also be used for this purpose. In cases of *excessive acidity of the urine* leading to pain and strain-

ing during micturition, the symptoms are relieved by these drugs rendering the fluid less irritating, and this relief is especially marked in irritated conditions of the bladder and urethra. They may also be of value in those cases by rendering the mucus more soluble in the bladder. In the acute stage of *pyelitis* and *cystitis*, especially when due to Bacillus coli infection and when the acidity of the urine is high, the symptoms may be relieved, and occasionally the condition cured, by keeping the urine temporarily alkaline by administration of sodium bicarbonate or of potassium citrate. In *gravel* the alkalies also give relief, and this has been attributed to their dissolving the uric acid in the urine, or rather to their keeping it in solution in the form of salts. In order to attain this, the urine would have to be rendered alkaline, or at least neutral, and relief is given by quantities of the alkalies which are quite insufficient to do this; this relief in gravel results from the amount of the urine being increased while its acidity is lessened; the inflamed surface of the bladder is thus bathed in a less irritant fluid and the pain is diminished. Attempts have even been made to dissolve calculi in the bladder or in the kidney by treatment with the alkalies, but there is no question that this is hopeless. The solution of the alkalies formed in the urine is extremely dilute, and in fact, except under large doses, the reaction is not even constantly neutral. On the other hand, even the alkaline urates are by no means very soluble bodies, and are formed only with difficulty except in strong alkaline solutions. Again, alkaline urine is very liable to deposit phosphates in the bladder, and thus rather to increase the calculus than to diminish it. Experience has shown conclusively that the alkaline treatment does not remove calculi, although in one or two cases it is stated that soft calculi broke down into fragments under it, from the mucus which held the fragments together being dissolved. The pain and irritation of calculi may be relieved to some extent, however, from the acidity of the urine being lessened.

The alkaline carbonates are also prescribed in cases of *jaundice and gall-stone*, often with benefit. This is not due to their acting on the bile directly in all probability, for it has been shown that they do not affect it in the normal animal; the improvement may rather be ascribed to their lessening duodenal irritation.

The bicarbonate of potassium is often added to other *expectorant* remedies in the treatment of bronchial catarrh and bronchitis, and is believed to increase the excretion and render it more fluid and more easily expectorated.

The alkaline carbonates may be given as antidotes in poisoning with the corrosive acids, although magnesia is preferable, because it is less irritating to the stomach. Alkaline solutions should not be injected hypodermically, as sloughing has been observed repeatedly from this procedure.

In cases of **Poisoning** with the caustic alkalies, the treatment consists in the administration of dilute acids, of which the organic—acetic, citric or tartaric—are the best. The first is most readily obtained in the form of vinegar. No attempt should be made to pass the stomach

tube, as it is liable to pass through the corroded wall of the œsophagus or stomach. General measures, such as central nervous stimulants, warmth, etc., may be taken.

In patients taking alkalies for hyperacidity or gastric ulcer, occasional toxic symptoms may occur, especially loss of appetite, irritability and drowsiness. The urine may be of low chloride concentration with albumin and casts. All these symptoms disappear when alkalies are withdrawn (Cope).

Preparations.

Potassii Hydroxidum (U. S. P., B. P.) (KOH), potassium hydrate, caustic potash—dry, white pencils or fused masses, deliquescent in the air and very caustic.

Potassii Carbonas (U. S. P., B. P.) (K_2CO_3), a white granular powder of alkaline reaction, soluble in one part of water, very deliquescent. 1 G. (15 grs.); B. P., 0.12–0.3 G. (2–5 grs.).

Sodii Carbonas (B. P.) ($Na_2CO_3+10H_2O$), colorless crystals with an alkaline reaction and taste, soluble in about 2 parts of water. 0.3–1 G. (5–15 grs.).

Sodii Carbonas Monohydratus (U. S. P.) ($Na_2CO_3+H_2O$), a white crystalline powder without odor and strongly alkaline. Dose, 0.25 G. (4 grs.).

Sodii Carbonas Exsiccatus (B. P.) Na_2CO_3. 0.12–0.3 G. (2–5 grs.).

Potassii Bicarbonas (U. S. P., B. P.) ($KHCO_3$), colorless, transparent crystals with a saline, slightly alkaline taste and soluble in 4 parts of water. 1 G. (15 grs.); B. P., 1–4 G. (15–60 grs.).

Sodii Bicarbonas (U. S. P., B. P.) ($NaHCO_3$), a white, opaque powder, with a cool, alkaline taste, soluble in 11 parts of water. 1. G. (15 grs.); B. P., 1–4 G. (15–60 grs.).

Magnesii Oxidum (U. S. P., B. P.), magnesia (MgO). 2 G. (30 grs.); B. P., 0.6–4 G. (10–60 grs.).

Magnesii Carbonas (B. P., U. S. P.), 3 G. (45 grs.); B. P., 0 6 4 G. (10–60 grs.).

These two act as aperients in large doses (p. 279) but are largely used as antacids. They are amorphous powders with an earthy taste, insoluble in water. The B. P. contains both a light and a heavy carbonate and oxide.

Magma Magnesiæ (U. S. P.), milk of magnesia, a suspension of magnesium hydroxide in water containing 7 per cent of $Mg(OH)_2$. Dose, 10 cc. (2½ fl. drs.).

Mistura Magnesii Hydroxidi (B. P.) is a similar preparation containing 8.25 per cent of $Mg(OH)_2$. 4–16 mils. (60–240 mins.).

Magnesii Phosphas Tribasicus (U. S. P.), $Mg_3(PO_4)_2.5H_2O$. 1 G. (15 grs.).

Numerous alkaline mineral waters are used instead of the pharmacopœial preparations, but as a general rule they contain only very small quantities of the carbonates.

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2. **Acetates and Citrates.**—As far as their local effects are concerned, the acetates and citrates of the fixed alkalies resemble the chlorides, owing any effect they possess to the salt-action. In the tissues, however, they are oxidized and form carbonates, so that the effects are those of the chloride before absorption, and those of the carbonate subsequently. The oxidation seems to proceed rapidly, and is very complete, over 95 per cent of the acetate or citrate disappearing, and only some 2-3 per cent being excreted unchanged in the urine. The available alkali of the blood is increased by the acetates as by the carbonates, and the urine is increased in amount and is less acid or may be alkaline.

The **Acetates** seem almost devoid of specific action—they act only as salts by changing the physical properties of the body fluids, or as alkalies after absorption. The other members of the acetate series have some action, however, for the formate, propionate, butyrate and valerianate of sodium have been shown to be very weak narcotics when they are injected hypodermically or intravenously; this is especially marked in the case of the butyrate. Rather more of the formate escapes unchanged in the urine than of the acetate, while the others are apparently entirely oxidized. The butyrate differs from the acetate in being capable of taking the place of the carbohydrates and fats more completely, and in thus leading to an economy of the nitrogenous tissues of the body. All of the simpler salts of this series are equally rapidly absorbed from the intestine, but the œnanthylate and the caprylate resemble the saline cathartics in being very slowly absorbed.

Lactates resemble the acetates in being almost entirely inactive, but they are rather more slowly absorbed. They are oxidized in the tissues for the most part, and resemble butyrates in limiting the nitrogenous waste, at any rate when they are given in moderate quantities. Lactates are also excreted in the urine, however, in small quantity.

The **Citrates** are absorbed more slowly than the acetates or chlorides and in sufficient quantity act as saline purgatives. The doses ordinarily prescribed, however, are too small to have this effect, and are also insufficient to induce any action after absorption except from that of the carbonate formed. Citrates form indissociable calcium salts and when they are injected intravenously they arrest the clotting of the blood and weaken the heart by throwing the calcium out of action (see Calcium, Oxalate).

Therapeutic Uses.—Acetate and citrate of potassium have been largely used as diuretics and for increasing the alkalinity of the urine. They act here exactly as the alkaline carbonates and bicarbonates, but have the advantage of not neutralizing the gastric juice, or in any way affecting the digestion except from their salt-action, which may be minimized by exhibiting them in dilute solution.

Preparations.

Potassii Acetas (U. S. P., B. P.), a crytalline salt of pleasant, saline taste and very soluble in water. 1 G. (15 grs.); B. P., 1–4 G. (15–60 grs.).

Potassii Citras (U. S. P., B. P.) ($C_3H_4OH(COOK)_3$). 1 G. (15 grs.); B. P., 1 4 G. (15–60 grs.).

Sodii Citras (U. S. P., B. P.) ($Na_3C_6H_5O_7+2H_2O$), 1 G. (15 grs.); B. P. 1-4 G. (15–60 grs.). Crystalline salts with a cool saline taste, readily soluble in water.

Potassii Citras Effervescens (U. S. P.), 4 G. (60 grs.).

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3. **Ammonia and Carbonate of Ammonia.**—Ammonia solution and carbonate of ammonia differ considerably from the corresponding

hydrates or carbonates of the fixed alkalies in their effects. Solutions of ammonia and of the carbonate give off ammonia freely, so that the effects are very similar, although the solution of ammonia is much the more powerful. Owing to its volatility, ammonia penetrates more rapidly and deeply than the fixed alkalies, and at the same time is less corrosive and less enduring in its effects. Applied to the skin in concentrated solution, it may corrode to some extent, but ordinary dilute preparations act merely as rubefacients, like the volatile oils. Even concentrated solutions do not dissolve the epidermis like the fixed alkaline hydroxides, but tend to penetrate through it and raise blisters. When inhaled, the irritation of the nasal mucous membrane causes a reflex stimulation of the vasomotor centre, and consequent contraction of the arterioles and augmented blood-pressure, while the respiration is first arrested, and then becomes deeper and fuller. The heart may be temporarily slowed by inhibitory reflexes. Three parts of ammonia in 10,000 of air cause sneezing, pain in the nose, and tears, when inspired by man, and 5 parts in 10,000 are dangerous when inhaled for some time (Lehmann); the symptoms arise only from the local irritation and subsequent inflammation for any ammonia absorbed from the lungs is immediately neutralized.

Concentrated solutions cause corrosion of the mouth, œsophagus and stomach similar to that seen in poisoning with the fixed alkalies, but some of the vapor, passing into the respiratory passages, often sets up spasm of the glottis, or such swelling of the mucous membrane of the larynx and trachea as to induce asphyxia. In cases of ammonia poisoning, therefore, the symptoms often arise, not so much from the gastric corrosion as from asphyxia, and death may occur very suddenly from this cause. The carbonate of ammonia, when swallowed, also causes slight gastric irritation, and in larger quantities nausea and vomiting.

After absorption ammonia and its carbonates are rapidly changed to urea, and thus differ from the fixed alkalies in not increasing the available alkali of the blood, and in having no effect on the urine except to increase the urea and thereby cause some diuresis.

The carbonate of ammonia stimulates the central nervous system when it is injected into the blood in some quantity, but it has no such effect when absorbed from the stomach. (Cf. Ammonium Chloride, page 56.)

Therapeutic Uses. –The aqueous solutions of ammonia are comparatively rarely employed, although the strong solution has been advised as a vesicant in cases of renal disease, in which cantharides is contraindicated. The ammonia solution has to be covered by a watch-glass in order to prevent its evaporation, and is said to be more painful than other vesicants. The liniment is used as a *rubefacient* in bruises and in other similar conditions. The gas arising from ammonium carbonate is often inhaled in cases of *fainting* or collapse, in order to elicit reflex stimulation of the medullary centres. The ordinary "smelling salts" used for this purpose consist of the carbonate reinforced with some of the strong solution and flavored with oil of lavender.

The aromatic spirits of ammonia and the carbonate (in solution)

are used as mild *gastric stimulants* in debility, flatulence and alcoholism, and are very efficient for a short time. Large doses of the carbonate (2 G.) have been used as *emetics*, and do not cause such prolonged nausea as tartar emetic or ipecacuanha.

The carbonate of ammonia and the spirits or even the ordinary water of ammonia are often given in cases of collapse or sudden *heart failure*. They are generally administered by the mouth and probably act here not directly on the heart and respiratory centre, as has been supposed, but reflexly from gastric irritation. The action lasts only a very short time, but may be sufficient to tide the patient over an acute collapse. In depression from many different causes the aromatic spirits of ammonia is a favorite remedy, and probably owes its value to its gastric action, and not to any changes in the central nervous system. The carbonate is often added to other expectorant remedies to render the bronchial mucus excretion more fluid. This effect is mainly due to irritation of the stomach causing reflexly an increase in bronchial secretion. (See Ammonium Chloride, page 58.)

Strong water of ammonia is applied locally in snake-bite and is popularly believed to be very efficacious. It has no effect on the toxalbumins of snake poison, and probably is of little or no value in these cases.

PREPARATIONS.

AQUA AMMONIÆ (U. S. P.), LIQUOR AMMONIÆ DILUTUS (B. P.), an aqueous solution of ammonia of 10 per cent strength by weight. 1 cc. (15 mins.).

AQUA AMMONIÆ FORTIOR (U. S. P.), 28 per cent, and LIQUOR AMMONIÆ FORTIS (B. P.), 32.5 per cent, are strongly caustic irritating liquids.

SPIRITUS AMMONIÆ AROMATICUS (U. S. P., B. P.), spirit of sal volatile, contains ammonia and ammonium carbonate along with several volatile oils dissolved in alcohol. 2 cc. (30 mins.); B. P., 1–4 mils. (15–60 mins.) in a glass of water.

AMMONII CARBONAS (U. S. P., B. P.) is not the pure carbonate, but a mixture of somewhat varying composition, consisting of bicarbonate (NH_4HCO_3) and carbamate of ammonia ($NH_4NH_2CO_2$). It releases ammonia in the air and has therefore its pungent taste and smell. It forms translucent, crystalline masses, is very soluble in water and is contained in the aromatic spirit of ammonia. 0.3 G. (5 grs.); B. P., 0.3–0.6 G. (5–10 grs.) in dilute solution.

AMMONII BICARBONAS (B. P.), a white crystalline powder with a pungent taste and slightly ammoniacal odor, is given in the same doses as the carbonate.

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See Ammonium Chloride, page 58.

LEHMANN Arch. f Hyg., vol. 5, p. 1.

VI. ACIDS.

Some acids owe their activity in the organism almost entirely to their acidity, *i. e.*, to the hydrogen ion, and may therefore be treated of together. In the case of many other acids, such as prussic or salicylic acid, the effects of the acidity or hydrogen ion are insignificant in comparison with those of the rest of the molecule or the negative ion, and these are treated along with their salts.

Action.—The acids owe their action on living tissues to their neutralizing alkalies, to their withdrawing water when in concentrated

form, and to their precipitating some of the proteins, more especially the globulins.

Most living matter is neutral or slightly alkaline in reaction, and seems to be incapable of existing in acid media. Exceptions are met with in some of the moulds and in other vegetable organisms which live in somewhat acid solutions, but even these are destroyed by more concentrated solutions, perhaps because the acids precipitate their proteins. Acids are therefore **Protoplasm Poisons** and antiseptics of some power. Hydrochloric acid is found to delay the growth of organisms, and even to destroy the great majority of the less resistant forms in 0.2–0.3 per cent solution, or in the percentage in which it exists in the gastric juice. The others vary in strength largely according to their acidity, that is, according to the number of hydrogen ions, or the amount of dissociation. The inorganic acids are therefore more powerful as a general rule than the organic, which are less dissociated, and among the latter the simpler compounds are generally more active than those of larger molecule.

When sulphuric or nitric acid is applied to the **Skin** in concentrated form, it acts as a powerful caustic, destroying the epidermis and penetrating some distance into the skin and subcutaneous tissues, in which it causes necrosis. This is of course accompanied by great pain, and if much of the skin is attacked, by shock and collapse and symptoms similar to those seen in severe burns. Sulphuric acid causes a white, later a brown or black eschar, nitric acid a yellow. Hydrochloric acid is less liable to cause wholesale destruction of the skin, but penetrates the epidermis and raises blisters. The organic acids and phosphoric acid are still less irritant, but cause redness and even blistering when applied in concentrated solution. Dilute solutions of the acids may act as slight irritants to the skin, and often cause a feeling of stiffness and numbness, perhaps from precipitating the proteins.

The corrosive action of the acids is much more marked when they are applied to the less resistant **Mucous Membranes.** Even small quantities of strong sulphuric acid striking the eye are sufficient to destroy the sight.

In the **Mouth, Œsophagus, and Stomach,** the corrosive action is evidenced by complete destruction of the mucous membranes which come in contact with the strong acid. The œsophagus and stomach may be perforated, and this, along with the shock and collapse, often proves immediately fatal, or if the patient recovers temporarily, the erosions may give rise to cicatricial contractions and death from inanition. Hydrochloric acid and the stronger organic acids are capable of causing corrosion of the mucous membranes, but this is generally not so extensive as that following nitric and sulphuric acid. The corrosion produced by acids differs from that produced by alkalies in that the tissues become shrunken, hard and brittle, while after a caustic alkali they are soft and swollen, and have a slimy, soapy appearance.

The symptoms of corrosive acid poisoning are intense pain in the mouth, throat and stomach, vomiting, and often diarrhœa, shock and

collapse, with rapid, weak pulse and shallow respiration. The temperature is often subnormal and death occurs in the course of a few hours. When fuming acids are swallowed, and especially in poisoning with hydrochloric acid, the irritant vapor passing into the respiratory passages may cause spasm of the glottis, or œdema of the larynx, and prove immediately fatal from asphyxia. Even one part of hydrochloric acid vapor in 20,000 of air causes sneezing and pain in the throat and chest.

Dilute solutions of the acids have a characteristic taste, and induce a reflex flow of saliva and an astringent feeling in the mouth and throat, from their causing a coagulation of the superficial layers of proteins. In the stomach they displace any weaker acids from their combinations with bases, and may have some antiseptic action, but do not influence the amount of secretion in any way. The gastric juice is normally acid, containing about 0.2 per cent of free hydrochloric acid, and this acid reaction is essential to the action of pepsin. Other acids may replace the hydrochloric acid in digestion, but both clinical experience and experiment point to hydrochloric acid as the most suitable acid for use in the stomach. In cases of deficient gastric secretion, the administration of acids increases the acidity of the food as it passes into the duodenum and may thus promote the formation of secretin and consequently the secretion of the pancreas. When the food in the stomach is rendered strongly acid, it is found to leave the stomach more slowly, though the movements of the organ appear to be more rapid and stronger than normally.

The acids are absorbed from the alimentary canal fairly rapidly in most cases. In the **Blood and Tissues** they do not exist as acids but as salts, for the reaction of the blood must remain slightly alkaline throughout life, and if sufficient acid be given to neutralize the alkalies of the body, the animal dies before the blood becomes neutral, although after death it may be found to be acid. The means provided by the economy to neutralize acids differ in different animals; in the herbivora the fixed alkalies of the blood and tissues are called upon chiefly, and if more acid be absorbed than can be neutralized by these, the animal dies; in the carnivorous animals and in man, a further protective mechanism exists, for in these ammonia is liberated by the tissues, and serves to neutralize the acid, and thus saves the fixed alkalies. The difference is relative and not absolute, however, for the herbivora also develop some ammonia, and the carnivora employ some of the fixed alkalies to preserve the normal reaction of the tissues. Man seems to stand midway between the two classes, for while ammonia appears in the urine after acid absorption, the fixed alkalies are also present in excess. Much larger amounts of dilute acids may therefore be absorbed without serious symptoms by man and by the carnivora than by the herbivora. The explanation of this difference between the flesh-eating and the plant-eating animals is to be found in the nature of their food. The flesh-eaters are accustomed to the formation of some acid in their tissues, because the alkalies of their food are insufficient to neutralize the acids formed by the oxidation of the organic matter,

and they would gradually be deprived of all their alkaline salts, therefore, were they not protected by the formation of ammonia. On the other hand, the herbivorous animals absorb much larger quantities of the organic salts of the alkalies in their food, and these, forming carbonates in the body, serve to neutralize what acid is formed in the tissues. In ordinary circumstances, therefore, they have no need to protect the fixed alkalies, and are unprovided with any mechanism for this purpose. When an excess of acid is absorbed, they neutralize it by means of the fixed alkali of the tissues and blood, and the slight change in the reaction reduces the power of the hæmoglobin to transport carbonic acid from the tissues to the lungs. Thus in acid poisoning in rabbits, the alkali of the blood has been found to be so greatly reduced that the blood instead of containing some twenty-five volumes per cent of carbonic acid, carried only two volumes per cent or very little more than could be dissolved in the same amount of water. When this occurs, the tissues are unable to rid themselves of their carbonic acid, and a series of symptoms follow, commencing in deep, labored, rapid, afterward shallow, respiration; the heart is weak, a condition of collapse follows, and eventually the respiration ceases, the heart continuing to beat for some time longer. The injection of sodium carbonate, even in the last stage of intoxication, is followed by rapid recovery, from the restoration of the normal reaction of the blood and tissues, while other carbonates are not so useful, owing to the action of the basic ion. In carnivora and man, the absorption of dilute acids does not alter the available alkali of the blood so much, but here also the transport of CO_2 is delayed, and slight exertion causes breathlessness and exhaustion.

Acidosis.—When small quantities of acid are absorbed the acid is at once neutralized by the alkali bicarbonate of the blood, the resulting CO_2 stimulates the respiratory centre and is got rid of by the increased ventilation of the lungs. A smaller amount of alkali remains in reserve in the blood, but this is remedied by the excretion of acid salts by the urine, so that the reserve quickly rises again. The only important symptom arising from a considerable reduction of the alkali reserve is breathlessness on exertion. If the alkali is further drawn upon by very large amounts of acid, death follows as has been described above.

The salts formed in the blood and tissues after the absorption of acids are rapidly **Excreted** by the kidneys, which, however, retain as much alkali as possible in the body and thus excrete the salts in an acid form. Hence there arises in some cases irritation of the kidneys, with albumin, and even blood, in the urine, which is rendered more acid than usual and causes a sensation of heat and smarting in the bladder and urethra. In the herbivora the reaction changes from alkaline to strongly acid, and large quantities of the salts of the alkalies appear, while in the carnivora some increase in the sodium and potassium of the urine occurs along with a much greater increase in the ammonia. The total nitrogen is somewhat increased from the large amount of ammonia, but the urea is slightly decreased.

Not infrequently fatty degeneration of the heart, liver, muscles or kidney has been observed in corrosive acid poisoning, when the patient survived for a few days, and Fraenkel and Reiche found a form of necrosis of the renal cells in these cases. These changes are not due to free acid in the blood, but to the impaired tissue respiration probably.

The prolonged treatment of animals with acids has been found to be followed by anæmia and loss of flesh and strength, which are probably attributable to the disturbance of the digestion and not to any specific action of the acids.

The limits within which tissues live and grow are given as between pH-4 on the acid and pH-10 on the alkaline side, and acids applied directly to them lessen their vitality, and unless there is sufficient alkali present to neutralize them, soon destroy it entirely. In some cases they tend to cause a temporary increase in activity at first; thus the cilia of ciliated epithelium have been found to move more rapidly at first in very dilute acids and then to cease all movement, while muscle seems to be rendered weaker and less irritable at once. As in the case of alkalies, Loeb finds that dilute acid causes muscle to imbibe more water than salt solution does, and Hamburger finds that the red blood cells are increased in size by the addition of small quantities of acid to the blood outside the body. The frog's heart is weakened and dilated by the addition of acid to a perfusing solution, and the muscular wall of the vessels and other organs are first contracted and then dilated but the results seem to vary with the other constituents of the fluid (Heymann). The addition of acids to the blood tends to agglutinate the red cells and to form acid hæmatin.

Therapeutic Uses.—The acids are used in medicine only to a limited extent, and most of the official preparations might well be dispensed with.

They may be employed to give flavor to draughts in fever and in the thirst of diabetes, the most popular forms being those formed from fruits, such as lemons, limes, or grapes. The taste is due to the sugars, acids and volatile oils of the fruits, and is modified by the presence of inert colloid substances, such as the pectins. The acids, of which citric, tartaric and malic are the chief, are very important factors in the effect, for if these be neutralized, the fruit juices become insipid, and do not quench thirst so thoroughly. The so-called grape cure, in which very large quantities of grapes are eaten, owes most of its value to the large amount of water taken, although the acids and salts may act as aperients in the same way as the saline cathartics. Instead of the fruit juices, carbonic acid waters may be advised, and occasionally other acids, such as phosphoric or sulphuric, are prescribed to give flavor.

Acids are also used in certain forms of *dyspepsia* in which the hydrochloric acid of the stomach is deficient. Hydrochloric acid is most frequently prescribed for this purpose, and is certainly more efficient than the others in test-tube experiments on digestion. In *achylia gastrica*, which may be congenital, there may be a total absence of hydrochloric acid in the stomach. In *pernicious anæmia* and malignant disease of the stomach, hydrochloric acid may be greatly reduced or absent. Grave lack of acid not only prevents gastric digestion but also deprives the stomach of the antiseptic action of the acid. Also food tends to leave the stomach too soon because the reflex closure of the pylorus which is induced by high acidity of the duodenum fails to take place. The acid stimulus to secretin formation is also wanting. Improvement of digestion and of the general condition is often produced in these diseases by administration of dilute hydrochloric acid. In forms of

dyspepsia arising from a sedentary life or in the course of convalescence, acid is often prescribed along with the bitter stomachics and is to be taken about one-half hour before meals. Irritation of the stomach or hyperacidity of the gastric juice, is, of course, a contra-indication.

Acid may also be used to make the urine acid, and thus to render it less favorable to the growth of microbes. For this purpose the acid sodium phosphate is used; this salt is very often given along with methenamine (hexamine), which acts only in acid urine (p. 814).

In cases of alkaline poisoning, the acids are the natural treatment; the organic acids should be preferred for this purpose, as they are less liable to cause additional corrosion, and acetic acid in the form of vinegar is more likely to be at hand than any other.

In every case in which acids are prescribed internally, they have to be given largely diluted, as otherwise they irritate the throat and stomach. They are taken through a glass tube, in order to prevent as far as possible their action on the teeth.

Strong acids have some effect in arresting hæmorrhage (styptics) when applied directly to the bleeding point, but are much inferior to some of the metallic salts, such as ferric chloride.

Externally, the acids are used to some extent as corrosives, strong nitric acid being used not infrequently to destroy small tumors, to cauterize the os uteri and for similar objects. Its action is more easily localized than that of potash and on the other hand is more powerful than the metallic salts, such as silver nitrate and zinc chloride. In dilute solution, they are sometimes applied to the skin to lessen excessive local sweating and diluted vinegar is often used to sponge fever patients.

In cases of corrosive **Poisoning** with acids, the first indication is to neutralize the acids as far as possible by giving alkalies. These ought not to be in themselves corrosive, and the best antidote is therefore the insoluble magnesia and magnesium carbonate. Lacking these, the most readily accessible alkali is the best, and the lime may be scraped from the walls or ceilings, or chalk, soap, or wood ashes may be given. The walls of the stomach and œsophagus may also be protected by giving milk or white of egg, or the acid may be rendered less corrosive by diluting it with large quantities of water.

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Compare Alkaline Hydrates and Carbonates. For the specific effects of the anions of the acids, see chlorides, phosphates, acetates, oxalates, etc.

Sulphuric Acid is one of the most corrosive acids when it is applied in concentrated form, and often induces complete charring of the tissues, and a coal-black slough.

Acidum Sulphuricum (U. S. P., B. P.), 95 per cent.

Acidum Sulphuricum Dilutum (U. S. P., B. P.) contains 10 per cent of absolute sulphuric acid. 1 cc. (15 mins.); B. P., 0.3–4 mils. (5–60 mins.).

Acidum Sulphuricum Aromaticum (U. S. P.), an alcoholic solution flavored with ginger and cinnamon, contains 20 per cent of sulphuric acid. 0.5 cc. (8 mins.) in a glass of water.

The sulphuric acid preparations are not largely used. The aromatic acid is sometimes given as a prophylactic and remedy in lead poisoning, but it is probably of little value here.

Nitric Acid is equal or superior to sulphuric in its corrosive action. It stains the skin and tissues a bright yellow or yellowish-brown, and this serves to distinguish cases of poisoning under the two acids.

Acidum Nitricum (U. S. P., B. P.) contains 68 per cent of absolute nitric acid (HNO_3) (B. P., 70 per cent).

A glass rod dipped in concentrated nitric acid is used as a corrosive.

Hydrochloric Acid is less corrosive than the two preceding acids, and tends to cause blistering on the skin rather than necrosis. It may cause actual loss of substance, however, when applied to the mucous membranes in concentrated form, and stains the mouth a whitish color.

Acidum Hydrochloricum (U. S. P., 36 per cent, B. P., 32 per cent).

Acidum Hydrochloricum Dilutum (U. S. P., B. P.), contains 10 per cent of hydrochloric acid gas. 2 cc. (30 mins.); B. P., 0.3 4 mils. (5–60 mins.) in a glass of water.

The diluted acid is prescribed in dyspepsia in which there seems a deficiency of the natural acid secretion. In cases of diarrhœa in which excessive putrefaction of the intestinal contents is present, it may be of benefit when prescribed along with other drugs; this action is probably explained by its disinfecting the stomach contents, as the hydrochloric acid of the gastric secretion normally does. It is said that hydrochloric acid prevents the lactic fermentation in 1:1000 dilution, and that in addition to its action on the digestive ferments it increases the peristalsis of the stomach.

Phosphoric Acid is much less corrosive and irritant than the other mineral acids, but in large, concentrated doses may cause gastro-enteritis. It has been used to some extent to form cooling draughts in fever.

Acidum Phosphoricum 89 per cent U. S. P., 87 per cent B. P.

Acidum Phosphoricum Dilutum 10 per cent U. S. P., 1 cc. (15 mins.); B. P. 0.3–4 mils. (5–60 mins.).

The acidity of the urine arises from the excretion of acid phosphates for the most part, and may be increased by the administration of *Sodii Biphosphas* (U. S. P.); *Sodii Phosphas Acidus* (B. P.), NaH_2PO_4. This consists of colorless crystals with an acid saline taste, readily soluble in water. Dose, 2–4 G. (30–60 grs.).

The **Organic Acids** have a much less marked local action than the inorganic, causing little or no corrosion unless when applied to mucous surfaces in very concentrated form. They are absorbed as salts of the alkalies, but do not as a general rule reduce the available alkali of the blood or render the urine more acid, because they are oxidized to carbonates in the tissues. Those which are not burned in the tissues, such as oxalic acid and the aromatic acids, have the same effects as the inorganic acids on the alkali reserve and the urine.

Acetic Acid applied in concentrated solution to the skin causes irritation and congestion and eventually blistering, but does not induce necrosis except of the most superficial layers. The congestion is often followed by marked pallor instead of by blistering; and this has been explained by contraction of the vessels, but may be due to a precipitation of the proteins of the skin. In the mouth and stomach it acts as an irritant, causing vomiting, great pain, collapse and even death; the epithelium is found thickened and occasionally contains hæmorrhages. Dilute acetic acid (vinegar) has little effect apart from its acid taste, and is used largely as a flavoring agent and condiment. The prolonged use of large quantities may, however, give rise to gastric irritation and to loss of appetite and weight.

Acidum Aceticum Glaciale (U. S. P., B. P.) contains 99 per cent of acetic acid.

Acidum Aceticum (U. S. P., B. P.) contains 36 per cent of absolute acetic acid U. S. P., 33 per cent B. P.

Acidum Aceticum Dilutum (U. S. P., B. P.) contains 6 per cent of absolute acetic acid. 2 cc. (30 mins.); B. P., 2–4 mils. (30–60 mins.).

Acetic acid is sometimes applied to the skin as a slight local irritant in contusions, and in very dilute solutions to cool the surface and to prevent excessive local perspiration. It has been used as a styptic in slight hæmorrhage, and may be inhaled for this purpose in epistaxis. Vinegar is also inhaled in cases of fainting, in order to induce reflex stimulation of the vasomotor centre through irritation of the nostrils. In cases of poisoning with alkalies vinegar is often the most convenient acid, and in addition is less likely to do harm than the inorganic acids. Glacial acetic acid is a powerful caustic.

Acetic acid itself is not used as a corrosive, but one of its derivatives, trichloracetic acid (CCl_3COOH), U. S. P. and B. P., has been employed with good results.

Formic Acid resembles acetic acid in most points, except that it is more volatile and more irritant, that less of it is oxidized in the tissues, and that given in large quantities it is said to induce nephritis. It is quite useless in therapeutics.

The other acids of the acetic acid series resemble it in their effects, but become less irritant as they become more complex and less easily dissociated.

Lactic Acid resembles acetic acid in its behavior in the organism.

Acidum Lacticum (U. S. P., B. P.), containing 87 per cent of lactic acid, has been used as a caustic application to malignant ulcers and diphtheritic membranes.

Oxalic Acid is frequently used as a poison by suicides, either as such or the acid potassium salt (salt of sorrel or essential salt of lemons). Poisoning has repeatedly occurred from oxalic acid having been mistaken for magnesium sulphate, which it resembles in appearance. The symptoms are those of acid poisoning, along with the specific effects of the oxalates. Oxalic acid is not used in therapeutics.

Tartaric Acid induces symptoms of gastric irritation when taken in large doses, and has been the cause of fatal poisoning in a few cases. It is slowly absorbed, and some of it escapes combustion in the tissues and is excreted in the urine in the form of acid tartrate. (See Tartrates, page 279.)

Acidum Tartaricum (U. S. P., B. P.) ($H_2C_4H_4O_6$), colorless crystals, very soluble in water. B. P., 0.3–2 G. (5–30 grs.).

Tartaric acid is prescribed with the carbonates and bicarbonates to form effervescent draughts; the tartaric acid ought to be slightly in excess in order to lend its pleasant acid taste, the usual proportion being about eight parts of acid to seven parts of sodium bicarbonate. These effervescent mixtures formed with the tartrates act as saline cathartics in large doses (see page 281). Tartaric acid may be prescribed in dilute solution with sugar and a drop of volatile oil as a lemonade, which is cheaper than that formed with citric acid.

Citric Acid resembles tartaric acid in its action, but appears less irritant, and no case of serious poisoning is recorded from its use. It is slowly absorbed like tartaric, but seems to be almost entirely oxidized in the tissues.

Acidum Citricum (U. S. P., B. P.) ($H_3C_6H_5O_7+H_2O$) resembles tartaric acid in its properties for the most part. B. P., 0.3–2 G. (5–30 grs.).

Syrupus Acidi Citrici (U. S. P.) is ordinary syrup to which 1 per cent of citric acid and tincture of lemon-peel have been added, and is used only as a flavor.

Citric acid and the citrates when added to drawn blood prevent clotting by combining with the calcium in a practically non-dissociating salt. When administered by the mouth it has no such effect on the circulating blood, and its use to lessen clot formation in the body is based on erroneous observation.

Citric acid is used to form lemonades and effervescent draughts. For lemonade 2–4 parts of citric acid may be dissolved in 1000 parts of water, some sugar and a few drops of volatile oil being added. For effervescent solutions about 8 parts of the acid may be prescribed along with 7 parts of bicarbonate of soda, with directions to dissolve the two powders separately, mix the solutions and drink while effervescing. In large quantities this mixture acts as a saline cathartic; in smaller quantities it may be used to increase the alkali of the blood, and to render the urine less acid.

Lime juice and lemon juice, which contain considerable amounts of free citric acid, are generally preferred to the pure acid for lemonades to quench the thirst. Lime juice has been found of great benefit as a prophylactic in the treatment of scurvy, but this is not due to the citric acid, but to the vitamin of the fruit juices (p. 615).

VII. OXYGEN.

Ever since the discovery of the relation of oxygen to the respiration, attempts have been made to use it in therapeutics especially in cases where the blood seems to be insufficiently oxygenated. Air contains about 20 per cent of oxygen, and normally the alveolar air contains 14 per cent of oxygen, which, at ordinary barometric pressures, is equivalent to an oxygen pressure of approximately 100 mm. of mercury. At this pressure the amount of oxygen in simple solution in the blood is 0.3 volume per cent, while the amount of oxygen in combination with hæmoglobin will be 18.5 per cent. As the hæmoglobin is under these conditions already 95 per cent saturated with oxygen, increase in the percentage of oxygen in the alveolar air cannot materially alter this; but the amount of oxygen in solution can be increased from 0.3 to a maximum of 2.2 volumes per cent when pure oxygen is respired. Under normal conditions, therefore, only an insignificant increase in the oxygen-carrying capacity of the blood can be attained even by the inspiration of pure oxygen. At first sight this would seem to be discouraging to the use of oxygen as a therapeutic measure, but in abnormal conditions of oxygen want, other factors come in which materially affect the improvement which can be produced by increasing the percentage of oxygen in the inspired air. Recent investigations have not only elucidated more clearly how the undoubted improvement produced in certain abnormal conditions by increase in percentage of inspired oxygen is brought about, but also have in part determined in what particular conditions such an increased supply of oxygen can be expected to be of value. It is necessary first to consider what are the more important conditions in which the tissues suffer from oxygen lack.

The normal functioning of all the tissues in the body is dependent upon their receiving a sufficient supply of oxygen. This supply may be inadequate owing either to the blood receiving or absorbing insufficient

oxygen or to the circulation in the tissues being defective. Conditions of oxygen lack may be conveniently arranged under the following groups.

1. *Anoxic Conditions.*—In these, owing to alteration in the atmospheric environment or to impairment of the gaseous exchanges in the lungs, the arterial blood does not contain its normal amount of oxygen. This may occur, for example, where there is an insufficient partial pressure of oxygen in the inspired air, as in mountain sickness. It may occur when for any reason there is an impediment to the normal entry of air into the lungs, *e. g.*, in laryngeal or bronchial obstruction, or when an area of the lung is partially or totally unventilated. One of the most important pathological conditions which may produce this condition is an inflammatory or œdematous thickening of the alveolar epithelium, which may necessitate an increased partial pressure of oxygen in the alveolar air in order that normal amounts of oxygen may reach the blood. This condition may be present, for example, in pneumonia or pulmonary œdema.

2. *Anæmic Conditions.*—The supply of oxygen to the blood may be normal, but the oxygen-carrying capacity of the blood may be deficient. This will happen when there is a deficiency in the actual quantity of hæmoglobin (*e. g.*, in certain anæmias) or in the available hæmoglobin (*e. g.*, in carbon monoxide poisoning).

3. *Circulatory Conditions.*—In some conditions of circulatory failure, though the amount of oxygen in the arterial blood may be within normal limits, the blood passes so slowly through the capillaries that the blood becomes unduly desaturated as regards oxygen. The anoxæmia of circulatory failure is primarily a stagnation anoxæmia.

4. *Tissue Conditions.*—In certain types of poisoning, notably with cyanides, the tissues are relatively incapable of taking up oxygen even if it is supplied to them in normal amounts by the blood.

Full descriptions of the symptoms of oxygen lack can be found in the published works of Haldane and others. Those symptoms vary greatly according to the degree of oxygen lack and the rapidity with which it is induced, but among the important symptoms are hyperpnœa, cyanosis, increased pulse-rate and fall of blood-pressure.

Those symptoms are always present more or less in *acute lobar pneumonia*, and this is one of the diseases in which oxygen therapy has proved most successful, abolishing the cyanosis and dyspnœa, lowering the pulse-rate and producing a marked improvement in the subjective condition of the patient. It is important to remember that cyanosis does not commence to be apparent until the oxygen saturation of the arterial blood has fallen to 80 or 85 per cent, and that even before this stage is reached damage may be done to the myocardium or central nervous system. Oxygen ought therefore to be given, if possible, before cyanosis develops, and to be given in larger quantities than will merely remove the cyanosis if that is present. The ideal would be to administer just sufficient oxygen to restore the oxygen saturation to the normal level. Blood-gas estimations are necessary to determine this accurately, but these are not always practicable, and the value of oxygen administration must usually be judged by the relief of symptoms of oxygen lack.

Anoxæmia is of course only one of several toxic factors at work in pneumonia, but administration of oxygen can remove this one and, in so doing, strengthen the patient's resistance to the others.

Oxygen is of less value in acute bronchopneumonia, and of little value in anæmia. In the later stages of circulatory failure with persistent dyspnœa even at rest, orthopnœa, cyanosis and œdema of the lungs, oxygen is often of service in tiding over a crisis. It is of little permanent value in the cyanosis of congenital heart disease, though the cyanosis may be transiently removed.

Though any good effect derived from oxygen therapy is, as a rule, evanescent, it is important to realize that often a permanent effect may be obtained from its breaking a vicious circle. Usually it should be given as continuously as possible and the benefit to be obtained from it depends largely upon the efficiency of the method of its administration.

Methods of Administration.—Oxygen is stored in steel cylinders at high pressure. For private use those cylinders may be of 20–40 cubic feet capacity; for hospital use of 100 feet capacity. It is difficult to devise a method of administering it which will provide an adequate raising of the oxygen in the alveolar air, without an expensive wastage of oxygen and without employing an apparatus which will be cumbrous, expensive and in practice disagreeable to the patient. The chief methods at present in use can only be indicated here.

The most primitive, wasteful and useless method of giving oxygen is the so-called "*tube and funnel.*" As usually employed, oxygen is bubbled at a slow rate through water and delivered by a funnel in more or less close proximity to the patient's face. Davies and Gilchrist found that, with a rate of flow of 2 litres a minute and with the funnel touching the nose and chin, the percentage of oxygen in the alveolar air was raised only to 26.7. They conclude that this method has no value in practical therapeutics.

Administration of oxygen by a *nasal catheter* is a much better method. This method was first used in France on "gassed" men, and had the advantage that several cases could be treated at once from the same cylinder; it has subsequently been widely used clinically with considerable success. One disadvantage is that the rate of oxygen flow necessary to produce a satisfactory increase in the alveolar oxygen percentage is so large that great discomfort is caused, except in subjects where the respiratory minute volume is small and the necessary rate of oxygen flow is therefore less, as, for example, in children. In the latter it has been found (Bourne) to give excellent results if the anoxæmia is treated early, before the arterial oxygen saturation has had time to fall greatly. As an emergency method it has the advantage of simplicity and moderate efficiency when used for adults.

In both those methods the oxygen passing during the expiratory phase is wasted, and only exceptionally is it possible to raise the oxygen percentage in the alveolar air to the optimum point. To obviate these drawbacks, a more complicated apparatus is necessary such as that devised by Haldane or the modification of it by Davies and Gilchrist. These methods involve the use of a mask and valves for conserving the

oxygen during expiration and raising the available percentage of oxygen. While Haldane's apparatus is much more efficient than the nasal catheter, it has the serious drawback that many patients cannot tolerate the mask.

Oxygen chambers are in use in some large hospitals. The patient may be placed in a specially constructed chamber or in some type of bed-tent, where the oxygen percentage can be raised to any desired degree. In practice however it is difficult to attain an oxygen percentage of more than 60, and, in any case, the high initial cost, the imperative need for elaborate precautions against fire, and the necessity for skilled supervision restrict the employment of this method to a few institutions.

The use of carbon dioxide combined with oxygen is referred to later.

Oxygenium (U. S. P., B. P.) contains not less than 98 per cent by volume of O_2. A colorless, odorless, tasteless gas. For convenience in use it is compressed in metal cylinders.

Ozone, or active oxygen (O_3), is a much more powerful oxidizing body than ordinary oxygen, but is more easily reduced than peroxide of hydrogen. It has a curious phosphorous odor and is distinctly irritant to the respiratory membranes; it is almost always accompanied by nitrogen oxides, and these may further aggravate this local irritation. It is rapidly decomposed by living matter, and is certainly not absorbed into the blood unchanged; in fact it is immediately destroyed on the pulmonary surfaces. In man its inhalation in a dilution of 2–3 per million of air causes drowsiness and headache from irritation of the frontal sinus. In animals 15 20 parts of ozone per million of air sometimes proves fatal in a few hours from respiratory irritation; a condition of weakness and drowsiness precedes death, apparently as a result of the local irritation, and the lessened movement is accompanied by a fall in the CO_2 eliminated. Ozone injures most enzymes and the fermentation of yeast is hindered, but the lactic fermentation does not seem to be affected and some others are merely delayed. Ozone applied to the seeds or leaves of the higher plants also delays their development and injures them.

Ozone has undoubtedly disinfectant properties, but these are only apparent when air contains 15 mg. or more per litre. Even this disinfects only the air itself and the surfaces of objects, as the ozone loses its oxidizing properties whenever it comes in contact with organic matter and therefore fails to penetrate. It has recently been advocated to disinfect drinking water, but is efficient only in fairly pure waters, as any organic matter is oxidized and thus absorbs the ozone and the microbes escape. For this reason it cannot be used to sterilize milk or food. Comparatively low dilutions are sufficient to lessen the perception of odors, partly owing to the smell of ozone itself and partly by its action on the nasal mucous membrane.

Ozone inhalation has been recommended as an antiseptic in pulmonary phthisis, but its irritant properties preclude its use here, and it has been generally discarded. Ozone is of no value as a substitute for oxygen, and this applies equally to other oxidizing agents; oxygen must be supplied in the molecular form to combine with hæmoglobin.

Many so-called solutions of ozone contain only small percentages of hydrogen peroxide and no ozone proper, as, though the latter is soluble in water, it decomposes very rapidly, only traces of it being found in the solution after ten to fifteen days. It breaks up into oxygen, and does not form hydrogen peroxide.

The ozone of the air has been appealed to, in order to explain and advertise the benefits induced by many watering places and forest resorts, but it has never been satisfactorily proved that the air in these localities contains more ozone than in other less favored places. The curative agency is generally the change of scene and interests and the dietary.

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VIII. CARBON DIOXIDE.

Carbonic acid is contained in considerable quantity in many therapeutic preparations, notably in the effervescent cathartics and antacids, and also in many beverages, such as soda water, potash water, champagne and other sparkling wines. In some of these it is formed by the action of an acid such as citric or tartaric acid on carbonates, in others it is liberated in the course of fermentation, while in the artificial aërated waters it is forced into solution under high pressure. The last are therefore simple solutions of carbonic acid, while in the others more powerful agencies—cathartic salts or alcohol—are contained in addition.

Carbonic acid has a weak irritating action when applied in quantity; thus in baths charged with carbonic acid, a slight reddening of the skin has been observed, and some irritation and prickling of denuded surfaces is produced; a stream of carbonic acid directed against a wound or burn causes considerable heat and pain. Pure carbonic acid gas causes spasm of the glottis when inhaled, and even when it is much diluted, some irritation in the respiratory passages may follow at first. Solutions of carbonic acid induce reddening of the mucous membrane of the mouth and stomach, and are very rapidly absorbed, owing to the congestion and increased blood flow in the stomach wall which follows their administration. Much of the carbonic acid is thrown up by eructation, but some of it is absorbed and is excreted by the lungs. The absorbed acid has no effect on the organism, but the slight irritation of the stomach may cause increased appetite and a feeling of well-being. The rapid absorption of the water in which it is dissolved is followed by an augmented secretion of urine, and the carbonic acid waters are therefore used in preference to ordinary waters where a rapid flushing of the tissues and a profuse secretion of urine is desired. In addition, the slight irritation of the mouth and stomach renders them more acceptable than ordinary waters in fever and in other diseases accompanied by intense thirst; a mixture of milk and aërated water is often very grateful. The presence of carbonic acid in the sparkling wines leads to the rapid absorption of the alcohol also, and this action on the stomach may explain their being more exhilarating than other

50 per cent, 5 per cent CO_2 by as much as 500 per cent, the increase in the former case being due to greater depth of respiration, in the latter case also to increased frequency. With higher percentages toxic effects may appear.

The stimulating effect of CO_2 inhalations will occur to the degree mentioned above only when the respiratory centre is normally excitable. When the respiratory centre is depressed, *e. g.*, by narcotics or prolonged defective blood supply, the effects will be less dramatic.

The inhalation of oxygen containing 5 to 7 per cent of CO_2 has been used in a variety of conditions to stimulate the respiratory centre and to prevent collapse of the lungs, especially in asphyxia due to drowning or in asphyxia of the newborn, and in poisoning by carbon monoxide, morphine, etc. In some forms of Cheyne-Stokes respiration it has been found that carbon dioxide restores regular breathing (Fig. 2). Inhala-

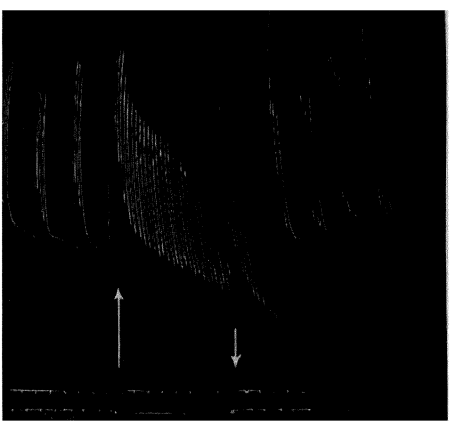

FIG. 2.—Periodic respiration in a rabbit. Between the arrows, 6 per cent CO_2 in air was inhaled and the respiration became regular, but relapsed again soon afterward.

tions of CO_2 have been strongly recommended for the prevention of lung complications following the use of anæsthetics, especially ether. During unconsciousness produced by ether or arising from any other cause, the stoppage of voluntary movement, the cessation of changes of posture and especially the suppression of coughing tend to prevent the natural removal of mucus from the bronchi. This accumulation of mucus may block the smaller bronchi, leading to collapse of areas of the lung, and so favor bacterial infection. The increased respiratory movements produced by CO_2 tend to prevent this collapse of the lung. It also accelerates the excretion of the anæsthetic by the lungs. For these reasons, short periods of inhalation of CO_2 administered during recovery from anæsthesia are believed to be of value in preventing lung complications. When respirations are arrested, inhalation of CO_2 must of course be effected by some form of artificial respiration.

Mineral waters containing large quantities of carbonic acid in solution are often recommended as baths in various chronic diseases, such as rheumatism. The effects may be due to the carbonic acid in part, but these waters also contain salts in solution.

Solid carbonic acid (carbonic acid snow) has been applied as an irritant in various external conditions (page 227) and has also been used to induce local anæsthesia by cold (page 345).

Carbonei Dioxidum (U. S. P., B. P.), contains not less than 99 per cent of CO_2 and for convenience in use is usually compressed in metal cylinders.

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IX. THE HEAVY METALS AND METALLOIDS.

A. HEAVY METALS.

A large number of important drugs belonging to the chemical series of heavy metals resemble each other so closely in their action in living organisms that they may be readily grouped together in a division of the pharmacological system. There is both chemical and pharmacological justification for separating the group of the heavy metals proper from their near relatives the metalloids, though the transition from the former, through bismuth and antimony, to arsenic and phosphorus, is a gradual one. Bismuth might almost equally well be grouped with the heavy metals and even antimony is sometimes included in that group; but there are at least reasons of convenience for the subdivision here adopted.

The metals as such do not induce any symptoms except from their mechanical properties. Thus mercury may be swallowed in large quantities without causing mercurial poisoning, and silver or copper coins are equally devoid of effect as poisons. They are active only when they are capable of dissociation into ions of the metal or of an oxide. Thus potassium ferrocyanide does not cause any symptoms of iron poisoning when it is injected into a vein, because the iron passes through the body undissociated, and any effects are due to the ferrocyanide ion and not to the iron. In the same way compounds of the metals with ethyl and methyl, such as lead triethyl, have an action quite different from that of lead, as long as they remain undecomposed in the tissues, but eventually induce metallic poisoning, as they are broken up into bodies from which the lead or lead oxide ion can be dissociated.

The action of the heavy metals consists of two parts, the local effects induced at the point of application, and the general effects which follow the absorption of the poison into the blood and tissues. Either of these may be produced alone by suitable preparations and modes of administration, and they are to be regarded as entirely independent of each other.

The Local Action of the heavy metal series is due to their precipitating proteins in very dilute solutions; the nature of this action is not quite established, but it is considered by most authorities that no true chemical compound is formed between the metal and the protein, but that the precipitate is of the nature of an adsorption complex. Proteins are also thrown out of solution by salts of the alkalies and alkaline earths, but only when these are present in much higher concentration than is necessary in the case of the heavy metals; and the precipitate formed by the salts of the alkalies is reversible, that is, it can be redissolved by the addition of water.

When a salt of a heavy metal is added to a solution of egg albumin, or similar protein, a precipitate is formed consisting of proteins and a variable amount of the metal or its oxide, while free acid remains in solution. The precipitate is insoluble in water but is dissolved by neutral salts, including those of the heavy metals, so that the addition of more metallic salt may redissolve it; similarly the addition of more protein solution may redissolve it by increasing the supply of neutral salts. The precipitate contains the metal in an insoluble form, and the latter may be detected by the ordinary reactions; thus the protein precipitate from iron salts is blackened by ammonium sulphide in the same way as ordinary iron.

On subjecting these precipitates to certain chemical manipulations, however, the metal seems to become more firmly attached to the protein, for ammonium sulphide acts on it much more slowly. The metal is then said to be masked, because its presence is not so readily detected as in ordinary combinations. Partially masked preparations have been formed artificially, but in the body the process is carried much further, for in many of their protein compounds the metals cannot be detected by any of the ordinary tests, however long the reagents may remain in contact with them, and their presence is recognized only when the protein is destroyed by heat or other similar agencies.

When a solution of a metallic salt comes in contact with a living tissue, such as the mucous membrane of the mouth or stomach, the same precipitation of protein and metal occurs and the acid is liberated; the local action appears to be determined by the combined effects of these factors. The more completely dissociated the ions of the salt are, the more rapid is the reaction with protein, and the more intense the local action. Thus the more readily ionized inorganic salts act more strongly than the organic ones, which are slowly dissociated, and these in turn are more liable to cause marked local changes than the double salts, which are dissociated with difficulty. The activity of the acid liberated also varies with the extent to which it is dissociated into ions; it therefore exercises the same astringent or corrosive effects as if it had been applied uncombined, but its action may be modified by the presence of a layer of precipitate protecting the surface. Thus when a weak solution of lead acetate is applied to a mucous membrane, a precipitate is formed in the proteins lying on the surface, and protects the cells from the action of the very dilute acetic acid which is set at liberty. If a stronger solution be applied, however, the

metallic precipitate extends into the cell, while the acetic acid, being more concentrated, exercises some irritant action. As the concentration increases, the deeper parts of the epithelial cells are coagulated, and at the same time the acid becomes more destructive, so that eventually the superficial layer of the epithelium is killed and the deeper layers are attacked. The acetate of lead may thus act as an astringent, covering a mucous surface with a protective pellicle of insoluble precipitate, or as an irritant, which induces an increase in the circulation of the part, a more rapid division of the cells and an effusion of liquid, or as a corrosive, involving the superficial layer of cells, and sometimes even the deeper ones, in its destructive effects.

When the nitrate of lead is applied, the astringent effect is much less evident, the irritant and corrosive more marked, because the salt is more readily dissociated and the reaction is therefore more rapid, and, in addition, the nitric acid is much more corrosive than acetic acid. The same metal attached to different acids may therefore induce very different effects, in the one case acting chiefly as an astringent, in the other as an irritant and corrosive.

The character of the metal which is carried down in the precipitate also influences the local effect; thus mercury is intensely poisonous and destroys the cells in which it is deposited, while lead is a less powerful poison and the cells may recover even if lead has been deposited on them.

In addition, salts which have a very strong affinity for water withdraw fluid from the cells, and thus act more strongly on them than others which have not this character; for example, dried alum is much more destructive to the tissues with which it comes in contact than alum containing its ordinary water of crystallization.

The different metallic salts therefore vary in their local action within wide limits—from the formation of mildly astringent membranes to the production of widespread necrosis and destruction of tissue.

The most powerful corrosive salts of any metal are those which are most rapidly dissociated into ions, that is, the chlorides and nitrates, provided they are soluble. The sulphates are much less irritant, because they are less readily dissociated, and perhaps because the sulphuric acid may fail to penetrate the cells, owing to its being less volatile and its anion having less permeating power than that of hydrochloric or nitric acid. The iodides and bromides are generally regarded as less irritant than the chlorides, but are less frequently used and less well known.

The least corrosive of the salts of the metals are those formed with the slowly dissociated organic acids, such as the acetates, tartrates or citrates. When these are united with a metal which in itself is not a very active poison, such as lead, they are almost purely astringent. On the other hand, the acetate of silver or of mercury tends to be irritant and corrosive, from the poisonous action of these metals on the tissues. In any case, the acetates are less irritant than the corresponding chlorides and nitrates, provided they are equally soluble.

The local action also varies in the same salt of different metals.

Lead is the most astringent of the metals ordinarily used in solution, while mercury salts have little or no astringent action, owing to their specific poisonous action on the cells. Iron and aluminium approach most nearly to lead, then copper, zinc and silver, and at a longer interval, mercury.

It is impossible to arrange the metallic salts as either astringents or irritants, because in every instance the effect varies with the concentration, and with many other features, such as the condition of the surface to which they are applied, and the quantity of protein with which they come in contact before they reach the living membrane.

The insoluble salts come into less intimate contact with the tissues, and have much less effect; but many of them are slowly taken up and may then act as irritants or astringents. The insoluble preparations of mercury tend to irritate and corrode the surfaces to which they are applied, but the insoluble salts of the other metals are generally astringent. It is difficult to determine how far the so-called astringent and protective action of these insoluble substances is due to the formation of precipitates, and how far to their acting mechanically as protective coverings over irritated surfaces, but the latter factor is undoubtedly the more important in many instances.

If the metal is applied in the form of an "albuminate," that is, in the protein precipitate, the effects are the same as if it were used in any other insoluble form; for example, the "albuminate" of lead and most metals cause no irritation, but that of mercury acts as an irritant.

The precipitation induced by the astringents involves only the surface layer of cells, but the membrane formed protects the part from mechanical and chemical irritation, and thus lessens congestion and inflammation. It also renders the surface less permeable and so may check exudation. Some authors maintain that the astringents contract the vessels by direct action on their coats, or lessen secretion by direct action on the secretory cells, but these statements are not satisfactorily established, and the changes may be the indirect results of the protection afforded to the surface cells. When irritation is induced, the vessels of course dilate, and congestion and exudation follow.

Many of the metallic salts are powerful disinfectants, partly no doubt from their coagulating the proteins of the microbes, but also from a specific poisonous action on them, which is quite distinct from their precipitating action. As a general rule the disinfectant power varies with the degree of dissociation of the salt, that is, with the number of metallic ions present in the solutions, although the undissociated molecule also seems to have some influence, and a salt which is dissociated with difficulty may in some instances make up for this drawback by the more intense toxicity of the metal.[1] The most widely used metallic antiseptics are the mercurial salts, but silver, copper, zinc and other metals are also used as antiseptics.

Almost incredibly small quantities of some of the metals have been found to be rapidly fatal to some of the algæ, the bacteria, and the infusoria. Thus one part of the perchloride of mercury in one million

[1] Trans. Assn. Am. Phys., vol. 12, p. 488.

parts of water kills spirogyra, one of the simpler algæ, and water distilled from copper vessels or in which small pieces of copper foil have been suspended[1] is rapidly destructive to many lower organisms. Silver is less active and lead still less so. The amount of copper in the solution is too small to be recognized by any chemical test. This so-called "oligodynamic" action of metals, which was first obtained by Naegeli, and which has been confirmed by other observers, indicates that certain lower organisms are much more sensitive to the action of copper, and probably of other metals, than the more highly organized plants and animals. Further examination of their effects as disinfectants in medicine and surgery is certainly desirable. Other curious effects on the growth of bacteria have been observed by Bolton and Brown, who found that a piece of metal placed on a culture of microbes in gelatin causes curious alternating zones of intense growth and of sterility. These observations have been extended by Thiele and Wolff, who state that silver, mercury, or copper plates prevent the growth of microbes owing to minute traces of these metals being dissolved in the medium. Several other heavy metals—iron, lead, zinc, tin, gold, platinum and aluminum—proved devoid of action.

The salts of the heavy metals are often only slowly **Absorbed.** Mercury is again an exception, but even mercury does not induce general symptoms until many hours after its administration. The other metals given by the mouth pass through the alimentary canal for the most part unabsorbed, but it seems probable that a small proportion of most of the metals finds its way into the blood. At the same time there is no question that the great proportion of most of the metals passes through unabsorbed, and is devoid of any effect except from its local action. Little is known regarding the form in which the metals are absorbed, but it is not unlikely that they are taken up in insoluble forms by the leucocytes and thus carried into the tissues. Iron seems to be the only metal which is absorbed intracellularly. When there is any lesion of the stomach and intestine, and particularly when the salt itself induces irritation and congestion, much more of the metal is taken up than by the normal epithelium. But even in the most favorable circumstances little of the metal is absorbed, and in acute poisoning the symptoms arise from the local irritation and corrosion and only to a smaller extent from the general action.

If the absorption of the metals is slow, their **Excretion** progresses even more gradually, and repeated administration leads to their accumulation in the tissues and thus to chronic poisoning. The metal seems to leave the blood very rapidly, and to become stored up in various organs, chiefly the liver, to a less extent the spleen, kidney, and bone marrow. While some of the metal is deposited in the liver and other organs, another part is excreted, for the most part along the alimentary tract. Thus it is found in the saliva and the secretions of the stomach and small intestine and, to a much larger extent, in the cæcum and in the large bowel; in some cases the excretion is limited to the large

[1] Arch. f. Hyg., vol. **34**, p. 43. *Foa and Aggazotti.* Biochem. Ztschr., vol. **19**. *Moore and Hawk.* Biochem. Jour., vol. **3**, p. 313.

bowel, a strict line of demarcation being formed by the ileo-cæcal valve. A comparatively small amount escapes with the urine except in the case of mercury. Some metals have been detected in very small quantity in the milk, and there is reason to suppose that traces are eliminated by the other cutaneous secretions.

The **General Action** of the heavy metals in man is often elicited only by their prolonged ingestion, but it has been studied in animals by the intravenous or subcutaneous injection of such preparations as the double salts, which do not precipitate the proteins and slowly liberate the metal or its oxide. The ordinary salts cannot be used, because the precipitated albumin of the blood causes embolism, and this obscures the symptoms. The symptoms of acute metallic poisoning elicited thus in animals generally resemble fairly closely those of chronic poisoning in man.

Even when the heavy metals are injected into the blood in considerable quantity, the symptoms are often late in appearing, in the case of aluminium only after several days, so that the slowness of the absorption from the intestine is not the only factor in the delay in the onset of the intoxication.

The general symptoms of metallic poisoning, as distinguished from those due to the local action at the point of application, arise chiefly from the central nervous system, and from the excretory passages—the alimentary canal and the kidney. Metallic poisoning always induces disturbance of the **Stomach and Intestine**, manifested by loss of appetite, pain and discomfort in the abdomen, nausea, vomiting, and purging. In some cases no lesion of the canal is observed post mortem, but in the great majority congestion and swelling of the mucous membranes of the stomach and intestine are seen, or the whole surface may be covered by a diphtheritic membrane composed of necrosed cells and inflammatory exudate. Beneath this, hæmorrhages occur, and if the animal lives long enough, ulcers are formed, so that the whole condition can scarcely be distinguished from that of dysentery. Some metals act strongly on the mouth and induce salivation, which is one of the earliest features of mercury poisoning. The lining membrane of the mouth becomes congested and inflamed, and numerous shallow ulcers are formed in it.

The heavy metals thus seem to have a specific action along the alimentary tract quite independent of the local action induced when they are swallowed, and apparently arising from their excretion along it. One or two metals, notably lead, cause constipation and colic when they are absorbed into the blood, but under certain circumstances they too induce purgation.

Another organ which suffers from the circulation of metals in the blood is the **Kidney**. Comparatively little of the metal is excreted in the urine, but it is found that most of this class acts as diuretics in small quantities. Somewhat larger doses irritate the renal epithelium, and albumin appears in the urine, along with casts, and, in severe cases, blood cells and hæmoglobin. If this irritation of the secretory

cells be long continued, it sets up a secondary inflammation of the interstitial tissue, and cirrhosis of the kidney results.

The **Circulation** is differently affected by different metals. The heart is often weakened only in the last stages, and it is impossible to determine how far its failure is due to direct action, and how far to the disorder of the nutrition. The blood-pressure invariably falls toward the fatal issue of the intoxication, and as a general rule, a slow fall is observed from the beginning. This fall in blood-pressure may doubtless be induced by different factors in the different forms of intoxication, but there is no question that it is partly due to the dilatation of the vessels of the intestines and stomach from the inflammation of these organs. In acute general poisoning in animals, many of the metals cause a great fall of blood-pressure, which is ascribed to their paralyzing the walls of the capillaries.

The general malnutrition from the gastro-intestinal action renders it impossible to determine whether the metals alter the metabolism of the body through directly affecting the cells, but it is not improbable that this is the case, for the loss of weight is often too rapid to be explained by the starvation alone.

The **Central Nervous System** is always affected more or less by the presence of the metals in the blood. As a general rule, the symptoms are a mixture of those of stimulation of certain divisions with those of paralysis of others. Several metals induce disturbance of the psychical centres, manifested in delirium, hallucinations and mania, or in stupor and coma. Convulsions of all forms indicate that the motor areas of the brain, the basal ganglia and the spinal cord are affected; thus epileptiform convulsions, chorea, clonic and tonic spasms occur from metallic poisoning. In several instances actual lesions of the brain cells have been shown to be caused by the ingestion of the metals. They often cause general weakness, or paresis of certain groups of muscles, and in addition to their specific action on the nervous centres, they may induce peripheral neuritis (lead).

Therapeutic Uses.— In therapeutics only mercury and iron are largely employed for their effects after absorption, while the others have a more or less extensive use for their local effects as astringents, irritants, caustics or styptics. Iron is not prescribed for its general action on the organs, but to supply the place of food-iron in the formation of hæmoglobin. Mercury is used for its specific effect in syphilis, and some of its preparations have been advised as diuretics. Not infrequently the local action of the heavy metals is supposed to be induced after absorption, and prescriptions are met with containing lead or iron which are intended to stay hæmorrhage from the lungs or from the kidneys. It ought to be recognized, however, that lead or iron is absorbed only in minute quantities, and that they have no predilection for the bleeding points. If they were capable of coagulating the blood after absorption, and thus stopping hæmorrhage, they would certainly do so in the portal circulation and would not be carried to the lungs or kidney before they acted. As a matter of fact, however, they never reach the blood except in forms in which they have no astringent or styptic action.

Metallic compounds are widely used by local application as astringents and antiseptics. Their various uses for these purposes will be considered under individual metals.

In regard to the arrangement of the metals, no strictly scientific order is perhaps possible yet. Iron will be considered first, as it stands in a class by itself owing to its physiological importance. Copper, zinc and aluminum resemble one another in being used therapeutically mainly for external application or as emetics. Lead and silver have close similarities in their local actions and to some extent in their liability to produce chronic poisoning. By leaving mercury to the last of the more important heavy metals, the trypanocidal remedies, mercury, bismuth, antimony and arsenic are brought into juxtaposition.

I. IRON.

Iron differs from the other heavy metals in being essential to the life of many, probably all, forms of protoplasm. In the vertebrates most of the iron is contained in the hæmoglobin of the blood, a fact which, until recent years, has tended to obscure the importance of it in other tissues. Apart from the hæmoglobin in the circulating red blood corpuscles, iron occurs in greater or lesser amounts in the organs concerned with the formation and destruction of red cells. Traces of iron found in the blood plasma are concerned with the transport of iron to and from organs. Warburg has shown that traces of iron exert a very marked catalytic activity upon biological oxidations and the traces of iron found in all tissue cells are doubtless concerned with this function. Cytochrome, which may play an important part in oxidative processes, contains iron. From its presence both in hæmoglobin and in other compounds, iron appears to play a part of the first importance in the oxidative processes of the body. In the invertebrates, in many of which no corresponding compound exists in the blood, considerable amounts of iron are found in the tissues, and there is no question that throughout the animal kingdom iron is essential to living matter, quite apart from its special relation to the blood in the vertebrates. Molisch has shown that it is also necessary for the development of the lower vegetable forms, and it has been found that in its absence the higher plants fail to form chlorophyll, although iron is not actually contained in the latter, as it is in hæmoglobin.

The iron combinations vary in the readiness with which they liberate the iron ion and therefore in the facility with which they react with such reagents as ammonium sulphide or potassium ferrocyanide; the more dissociable salts, such as the chloride or acetate, are sometimes known as "inorganic iron" while compounds such as hæmoglobin, which do not dissociate the iron ion, are termed masked or "organic" iron; between these two extremes there lie many intermediate forms, which react slowly to the sulphides and other tests.

The dissociable iron salts precipitate proteins from solution and thus act as astringents or irritants (page 111) according to the concentration in which they are applied; but iron has no specific poisonous action

on living matter such as is possessed by mercury or antimony, and the irritation induced by such salts as the perchloride arises from the acid constituent and not from the metal. The less dissociable compounds, such as the double salts and "organic" iron, do not precipitate proteins, and are therefore neither irritant nor astringent as long as they maintain their original form and are not decomposed into simple salts.

Pharmacological Actions.—So far as is known, the therapeutic uses of iron salts do not depend upon pharmacological actions in the usual sense, for the available evidence goes to show that they do not act otherwise than food iron. Only a brief account is therefore necessary of the pharmacological actions of iron.

Inorganic iron compounds, of which the perchloride may be taken as a type, have an astringent, metallic, or often acid taste, but in ordinary doses induce no further symptoms. If swallowed in large quantities, they cause pain and uneasiness in the stomach, nausea, vomiting and often purging, with all the ordinary symptoms of acute gastro-intestinal irritation. General weakness and even collapse may be induced, but are manifestly secondary to the gastric and intestinal effects, and no symptoms which can in any way be attributed to the absorption of iron have been observed in either man or animals.

The prolonged use of inorganic iron is frequently followed by some dyspepsia and by constipation and colic, which are obviously due to the continued astringent action on the stomach and bowel. Other symptoms observed occasionally are blackness of the teeth and tenderness in the gums, which may be due to the acid contained in many iron preparations; the blackening of the teeth has been supposed to be due to the tannic acid of the food precipitating the inky black tannate of iron, or to the sulphide of iron being formed by the action of the hydrogen sulphide present in carious teeth. According to Buzdygan, the iron preparations increase the secretion of hydrochloric acid in the stomach, and may thus lead to hyperacidity, or aggravate it if already present. In artificial digestion, the salts of iron with organic acids are said to hinder the process more than those with inorganic acids, the ferric salts more than the ferrous, and the insoluble preparations least of all. The digestion of starch is almost unaffected by the presence of iron.

Iron given by the mouth induces leucocytosis (Pohl) and does not affect the amount of double sulphates excreted in the urine, so that it has no antiseptic action in the bowel (Mörner).

Some symptoms from the circulation are sometimes said to arise, but are for the most part subjective, and seem to be handed down by tradition rather than really observed. These are a feeling of congestion, fullness and heat in the head and hæmorrhages from the nose, throat and lungs, especially in phthisis. If these symptoms are not entirely imaginary, they are to be attributed to some reflex from the stomach and intestine and not to any direct action of iron on the heart or vessels.

When the astringent preparations are injected into the blood-vessels in animals, they coagulate the proteins and cause thrombosis but no real symptoms of iron poisoning. Fatal thrombosis has been observed in patients from the injection of the perchloride into the uterus and also into nævi. The hypo-

dermic injection of these salts causes some pain and swelling, but no further symptoms follow, and the iron is found for the most part deposited in an insoluble form at the point of injection.

The **General Action** of iron is obtained only by the intravenous injection of double salts, such as the tartrate of iron and sodium, which do not coagulate the blood and at the same time are capable of freeing the iron ion in the tissues. Such salts as the ferrocyanides or ferricyanides, on the other hand, leave the body unchanged, and the iron ion is not liberated, so that no iron symptoms are induced. Meyer and Williams found that the double tartrate caused in the frog slowness and clumsiness in movement, which gradually developed into complete paralysis of the central nervous system. The heart seemed to be little affected, but the skeletal muscles were somewhat less irritable than usual. In mammals the symptoms of iron poisoning were often very late in appearing, and began with some acceleration of the breathing, which later became slow and dyspnœic; vomiting and diarrhœa often followed and blood was sometimes seen in the evacuations of the stomach and bowel. Increasing weakness was followed by central paralysis and death, accompanied by weak convulsive movements. The heart seemed little affected, although the blood-pressure fell rapidly toward the end. Postmortem, the mucous membranes of the stomach and intestine were found swollen and congested, and often contained numerous small blood extravasations. Kobert found that repeated injection of small quantities of the citrate of iron induces congestion of the kidney and the appearance of casts and albumin in the urine.

Iron, like the other heavy metals, would therefore seem to have a specific irritant effect on the intestinal and gastric mucous membrane, and to a less extent on the kidney. In addition, it depresses and eventually paralyzes the central nervous system, but it is impossible to state how far this is due to direct action and how far it is secondary to the action in the alimentary canal.

Amount and Distribution of Iron in the Body.—An approximate estimate of the total amount of iron in the body can be obtained in the following way. Assuming the blood volume to be $\frac{1}{14}$ of the body weight, an adult man weighing 70 kilograms will possess 5 litres of blood. Of that blood, hæmoglobin has been estimated to form 14 per cent, which would make the total amount of hæmoglobin in the blood to be about 700 G. The amount of iron in different forms of hæmoglobin has the remarkably constant value of 0.33 per cent. The total blood would, therefore, contain 2.3 G. of iron. As only about two-thirds of the total iron in the body is contained in the hæmoglobin, the total iron content of the body would be about 3.5 G. This figure, which is very near that which has been arrived at by other evidence, is of importance in connection with the use of iron in the treatment of anæmia. In the meantime it may be of interest to observe that, in spite of its great physiological importance in the body, the total amount of iron is small, comprising only about 0.005 per cent of the body weight.

The iron content of organs, other than blood, varies considerably. The liver, kidneys and especially the spleen contain it in relatively large amounts.

Iron in the Food.—Apart from the endowment of iron which the child receives at birth, all the iron in the body must be derived from the food. And as the proportion of iron to the body weight, especially after the first year of life, remains under normal conditions of health remarkably constant, it is clear that iron must be absorbed from the food in amounts sufficient to keep place with growth. Plants take up iron from the soil

and build it up into highly complex organic compounds. Iron is necessary for the development of lower vegetable forms and for the formation of chlorophyll in higher plants, though iron is not actually contained in the latter as it is in hæmoglobin. All natural vegetable foods, therefore, contain more or less iron. Parsley, watercress, spinach and beans contain relatively high amounts; potatoes, wheat and most fruits contain relatively little. Animals derive their iron from the complex iron compounds of vegetables, and animal tissues contain iron in varying amounts. Liver, spleen, and kidney contain a relatively high percentage of iron, muscle contains less. Milk contains about 1 mg. per litre.

The iron in the food is required chiefly for the formation of hæmoglobin. Red blood corpuscles are continually being removed from circulating blood and destroyed while new red cells, made in the bone-marrow, replace them. No completely satisfactory method has yet been devised for estimating the rapidity with which this destruction of red blood corpuscles takes place. From such experiments as have been made, however, the average life of a red blood corpuscle has been variously computed to be from three to six weeks. On this estimate about $\frac{1}{20}$ to $\frac{1}{40}$ of the total hæmoglobin is removed from the blood in the course of a day. According to the estimate given above, the total iron-content of the blood is about 2.3 Gm. Consequently about 0.05 to 0.1 G. of iron is removed from the circulating blood in twenty-four hours; and as, under normal conditions, the iron content of the blood remains very constant, the blood-forming organs must find an equivalent amount of iron for the daily formation of the hæmoglobin of new red cells. When this amount is compared with the quantity of iron in the food, it becomes at once apparent that only a part of the iron required for the formation of hæmoglobin can come from the food iron. The total amount of iron in the food naturally varies very much with the amount and nature of the diet, but it is generally agreed that the normal iron intake of an adult man is about 10 to 30 mg. per day. According to these figures, less than one-fourth of the iron necessary for the formation of hæmoglobin can come from the iron in food; the remainder is obtained from hæmoglobin of destroyed corpuscles which is used again.

Absorption of Iron.—Iron in the food exists as more or less complex organic compounds, which do not give the reactions of free iron ions. Apart from occasional traces of iron in drinking water, the iron in the diet consists entirely of non-ionizable iron. There is every reason to believe that the large-molecule compounds containing iron which are present in the food have to be reduced by digestive processes into smaller and more diffusible molecules before they can be absorbed. As to the degree to which this reduction of iron-containing compounds is necessary before absorption is possible, opinions have differed.

Though at one time it was suggested that iron can only be absorbed in organic combination and not as inorganic ionized compounds, recent investigations have proved conclusively that inorganic iron compounds, *e. g.*, ferrous chloride, can be readily absorbed. Indeed, recent opinion is tending rather to the view that even the food iron may first have to

be changed largely if not entirely into ionized iron before it can be absorbed.

The site of absorption of iron from the alimentary canal has been determined by histological methods, reagents being used which color most forms of iron but leave the hæmoglobin unaffected. When animals are given iron preparations, and are then killed and the mucous membrane stained by these reagents, the mucous membrane of the stomach and of the greater part of the small intestine gives no coloration, but the epithelium of the duodenum and of the upper part of the jejunum is found to contain numerous granules of iron. Lintzel has emphasized the fact that it is exactly this part of the intestine the contents of which are acid in reaction. Various investigators have found that food substances, both vegetable and animal, are in part reduced to ionized iron compounds by digestion. In the presence of easily oxidizable substances and especially in the presence of acid, ferric ions are readily reduced to ferrous. As these conditions obtain in the stomach the probability is that part of the food iron is reduced to simple ferrous compounds. All the recent evidence goes to show that such compounds are readily absorbed in the duodenum and upper part of the small intestine. It is not yet known whether this is the sole form in which food iron can be absorbed. In the more distant parts of the intestine where the reaction becomes neutral or alkaline, the iron forms insoluble phosphates, carbonates or more complex salts, which may easily be presumed to be less readily absorbed. This view lays especial importance upon the acidity of the intestinal contents in connection with the absorption of iron. Hober has shown that iron, alone of the heavy metals, is absorbed intracellularly by the cells of the intestinal mucous membrane, other metals being only absorbed intercellularly. This absorption of iron cannot be explained by solubility in the lipids of the surface membrane of the cells of the mucous membrane. It has been suggested that this vital activity of the intestinal epithelial cells may govern the degree of absorption of iron. When there is very little iron in the food, the body is extraordinarily conservative of its iron and picks up the slightest traces of iron from the food (Cloetta). On the other hand, if excessive amounts of iron are given in the food, and provided that this does not damage the intestinal epithelium, the intestine soon ceases to absorb it (Lintzel). There must, therefore, be some mechanism which regulates the absorption of iron in accordance with the needs of the body, and the suggestion is that, when the body is plentifully supplied with iron, the epithelial cells of the intestine share in the richness and refuse to absorb iron; but when the body is poorly supplied, these cells, being also deficient in iron, absorb the metal more readily.

The amount of iron absorbed cannot be accurately gauged by subtracting the amount excreted from the total amount of iron ingested, because iron is both absorbed and excreted by the intestinal epithelium. The least equivocal type of experiment for this purpose is the comparison of the total amount of iron in the body in animals fed on iron-poor and iron-rich diets, respectively. Thus Lintzel estimated the total iron and the hæmoglobin iron in young rats at the end of the suckling period.

Rats of the same litters were then divided into two groups, one of which was fed on an iron-free diet while the other received the same diet plus ferric chloride. The rats were killed at the end of six weeks, and it was found that the animals which had received iron had not only a much larger amount of total iron but also a much larger amount of iron in the form of hæmoglobin. This experiment proves conclusively not only that inorganic iron can be absorbed but that it can be utilized for the synthesis of hæmoglobin. While during growth or in iron deficiency iron may be rapidly absorbed, recent experiments suggest that, in the adult, only minute traces of iron are taken up from the food. The iron obtained from the destruction of red blood corpuscles is used over again for the formation of new hæmoglobin.

Excretion of Iron.—The estimation of iron in the urine has presented great difficulties. While some have found as much as 8 mgs. excreted daily in the urine, recent experiments with reliable methods of estimation show much smaller quantities. Lintzel goes so far as to say that the amount of iron normally excreted in the urine is negligible. All investigators agree that iron is excreted mainly by the intestinal epithelium, chiefly of the large intestine. If iron is withheld from the diet, most observers have found that the intestine still excretes 7 to 11 mgs. a day, but Lintzel found that if the iron in the food is reduced to about 1 mg. per day, the excretion of iron in the intestine soon goes down to that amount. When iron is injected parenterally, the amount excreted in the intestine is increased but not that in the urine

Fate of Iron in the Body.—Iron absorbed from the food probably undergoes changes in the intestinal epithelium, and the resulting combinations are given off gradually into the blood, and taken up by the liver. Blood destruction takes place principally in the spleen and the iron-containing compounds derived from hæmoglobin are given off gradually from the spleen and taken up and stored in the liver. From this organ iron compounds are again given up to the blood and utilized over again by the bone-marrow in the formation of hæmoglobin of new cells. Unwanted iron is excreted by the large intestine. The store of iron in the liver is in such a form that it can be rapidly mobilized when necessary to form hæmoglobin. Lintzel and Radeff found that when rats having a normal iron reserve were brought into a low-pressure chamber and kept on an iron-free diet, the total amount of hæmoglobin increased while the iron in the spleen and liver diminished correspondingly. The sum of the iron in the blood, spleen and liver remained practically constant. Obviously the iron necessary for the manufacture of hæmoglobin had come from the iron stored in the spleen and liver.

To sum up the main facts of iron metabolism, so far as they are known, iron occurs in the food in the form of more or less complex organic compounds which have to be disintegrated into smaller molecules, possibly even to inorganic compounds, by the digestive processes before they can be absorbed. The value of a particular food as a source of iron depends upon its iron content and upon the ease with which it can be disintegrated. These simpler compounds, as well as iron salts like ferrous chloride, are taken up by the epithelial cells of the upper part of the

small intestine, probably as ferrous ions. They undergo some changes in these cells and are then gradually given off into the blood and stored in the liver and spleen. The fate of iron compounds liberated from the liver and spleen into the blood depends upon the needs of the body. What iron is required for the formation of the hæmoglobin is taken up by the bone-marrow; what is not required is excreted by the mucous membrane of the large intestine. The body readily absorbs iron when necessary, *e. g.*, during growth. In the healthy adult, however, under normal conditions, only minute amounts of iron are absorbed and excreted; practically all the iron liberated by the breakdown of hæmoglobin is retained in the body and used over again for the manufacture of hæmoglobin.

Iron in Experimental Anæmias.—A large number of observations have been made on animals rendered anæmic in various ways with a view to observing the factors concerned in blood regeneration and the best methods of treatment of anæmias. Whipple and his colleagues instituted careful and elaborate researches on dogs reduced to a constant state of anæmia by repeated bleedings and kept on an iron-poor diet, so that the effects of remedies in provoking blood regeneration could be measured. They found that under such conditions inorganic iron hastened hæmoglobin formation only after lengthy intervals. They found, however, that of the various articles of diet tried, liver had the most striking effect. An aftermath of this was the discovery of the remarkable curative effects of liver diet and of liver extracts in pernicious anæmia (see p. 593). Hart, Steenbock and their colleagues found that young rats rendered anæmic by iron-poor diet were not cured by pure iron salts but that the addition of the ash of certain plant and animal substances effected a cure. They came to the conclusion that the copper content of the ash was responsible for this beneficial action (see p. 131). It is now agreed that the results obtained from the study of experimental anæmias in the lower animals can only be tentatively applied to the treatment of idiopathic anæmias in man, but nevertheless experiments of the former type have already thrown much light on the whole problem of the etiology and treatment of human anæmias.

Therapeutic Uses.—It is convenient to consider, first, the diseases in which iron is of value and, second, the best methods of administering it.

Iron is generally useful, and often strikingly successful, in the treatment of all forms of anæmia which are characterized by a low hæmoglobin content of the red cells. Until recent years iron found its chief sphere of utility in the treatment of *chlorosis*, in which its reputation is attested by the old saying, "qui nescit Martem, nescit artem," a survival of the astrological association of iron with the planet Mars. Owing to more hygienic methods of living and more judicious dieting, chlorosis has become an increasingly rare disease in nearly all countries during the last quarter of a century. Chlorosis is characterized by a relatively slight reduction in the number of red cells but by a marked reduction in the amount of hæmoglobin in each. The effects of iron are seen in an increase of the hæmoglobin in the blood, while the number of corpuscles may also show a considerable increase. A number of symptoms which

are secondary to chlorosis, and which are often more prominent than the original disease, are also relieved or entirely removed by iron. Thus gastric catarrh, amenorrhœa, breathlessness or œdema may disappear under it, but in these cases the improvement is due to the increased hæmoglobin and not to the direct action on the stomach, uterus or the circulation.

Many cases of chlorosis recover without inorganic iron under hygienic conditions, such as rest, and particularly when foods rich in iron are prescribed, this being exactly what is to be expected on the theory that inorganic iron merely takes the place of the deficient food-iron. But many chlorotic patients show little or no improvement when treated with foods containing iron, even when there is no question that the iron supplied daily in food form is sufficient for the needs of the economy, and chlorosis even appears in individuals who have never suffered from any deficiencies of food-iron. Yet many of these cases recover rapidly under inorganic iron, and this has led to the suggestion that inorganic iron when absorbed acts as a stimulant to the blood-forming organs, while food iron has no such property. This view has been ably criticized by Zahn, who shows it to be untenable. He found that in animals rendered anæmic by hæmorrhage and then treated with foods rich in iron, the recovery is not accelerated by iron salts as would be expected if the blood formation were actually stimulated by iron; he therefore believes that the curative action of the iron preparations in anæmia may be explained by the abundance of the material offered to the blood-forming organs rather than by their being stimulated in the ordinary sense. The difference in the effects of the iron of the food and of the inorganic preparations may be due to the fact that food-iron is always accompanied by a large amount of colloid material, which may materially delay its absorption, while inorganic iron, on the other hand, is much less completely enveloped and may be more easily absorbed. In addition, the iron preparations are given in much larger amounts than the food-iron. When 10 mgs. of food-iron are taken per day, only a small proportion (*e. g.*, 5 mgs.) may be absorbed, and this may be insufficient to supply the needs of the body, but if some hundreds of milligrams of inorganic iron be added, the proportion absorbed will be amply sufficient. The same effect might be obtained by the same amount of food-iron, but this is only to be obtained by giving more food than can be digested.

Iron is not absorbed from the unbroken skin, and the iron and steel baths are therefore of no value in themselves in the treatment of anæmia.

No account of the action of iron would be complete without reference to Bunge's view which formerly attracted a large amount of attention, though it has now been abandoned. His theory was that in ordinary conditions a certain amount of iron is lost by the body constantly through the excretions, and this loss is made up by the absorption of the iron contained in the food. This food-iron consists wholly of organic iron, that is, of iron combined in such a way that sulphides attack it with difficulty; an example of such organic iron is the hæmatogen of the yolk of egg. In normal individuals the food-iron is sufficient to replace that lost by excretion, but in chlorosis the presence of large amounts of sulphides in the intestine causes the food-irons to be decomposed to ferric sulphide, which is insoluble and unabsorbable. When the ordinary inorganic

iron preparations are administered in these cases, they are not taken up in place of the food-iron; but, by forming sulphide in the intestine, they remove the sulphuretted hydrogen and prevent the decomposition of the food-irons, which thus remain capable of being absorbed. Bunge and his followers went on to state that inorganic iron is never under any circumstances absorbed by the normal epithelium, but that when large quantities are administered, they tend to corrode the walls of the stomach and intestine, and are thus absorbed to some extent. Even then, however, they are incapable of being formed to hæmoglobin, the animal body being able to perform only the last steps of this synthesis after the plants have formed the simpler types of organic iron. This theory now possess only historical interest, so that it is unnecessary to enumerate the arguments brought against it. It may be sufficient to state that if the ordinary preparations of iron acted only by binding the sulphides of the intestine, various other metals would be equally efficient in chlorosis; iron would not be beneficial injected hypodermically, and iron sulphide given so as to escape the action of the gastric juice would be equally useless. It is found, however, that no other metal can replace iron in chlorosis, that iron injected hypodermically is curative in chlorosis, and that the sulphide administered so as to reach the intestine unchanged acts as well as other preparations (Stockman). Finally, it has been shown that ordinary preparations of iron are absorbed.

Though chlorosis has become in recent years an increasingly rare disease, minor forms of anæmia remain, in many of which iron is of value. Animals on normal diet store up iron in the liver and spleen. This reserve iron is utilized when there are special demands upon it, *e. g.*, after profuse hæmorrhage or during pregnancy. In these conditions it is not uncommon to prescribe iron to supplement these natural stores. It is commonly prescribed in anæmia following both acute diseases, such as typhoid or influenza, and chronic diseases, such as malaria and syphilis.

In simple achlorhydric anæmia, a not uncommon disease of middle and later life, and in the rarer chlorotic anæmia of young males, iron is usually curative if given in large enough quantities (Witts). Infants and young children, especially if fed chiefly on milk, which is poor in iron, and requiring, as they do, to absorb more iron to meet the demands of growth, often suffer from anæmia which is cured by iron. An injudicious dietary may easily fail to furnish in an assimilable form even that small amount of iron which is necessary and it has become usual in recent years to revert to an older practice of prescribing iron whenever a mild degree of anæmia is evidenced.

In all these conditions it must be remembered that the improvement in the blood occurs slowly. The formed red cell is of course incapable of synthesizing hæmoglobin. The increase of hæmoglobin in the blood in anæmia is therefore due to new red cells with a higher percentage of hæmoglobin gradually replacing the cells which are regularly being destroyed. This replacement takes time and a complete cure usually requires months. The improvement in the first month is often small and it may be wrongly concluded that iron is proving ineffective.

Arsenic is also used in many forms of anæmia, but appears to differ from iron in accelerating the growth and renewal of the corpuscles rather than increasing their content of hæmoglobin. Both arsenic and iron may be advisable in some anæmias. Iron was formerly considered to be contraindicated in fever, plethora, heart disease and pulmonary phthisis from an apprehension that it tended to cause hæmor-

rhage. But there seems no basis for this view. In phthisis it should be given with caution in order to avoid irritation of the stomach and dyspepsia, and in the presence of gastric catarrh from any cause, its effects have to be watched carefully.

Administration of Iron.—Iron has been administered, both by mouth and parenterally, in a great variety of combinations but it is highly probable that in the near future the number of iron preparations will be drastically reduced.

Complex organic preparations, such as albuminates or hæmoglobin itself, have not proved so effective as inorganic iron either in experimental or human anæmias. Probably the larger molecules must be broken down by the digestive juices before absorption, and as sources of iron they do not seem to provide a short cut to hæmoglobin formation. Owing to the close resemblance in structure between chlorophyll and hæmatin, the former has been advocated, especially by Bürgi, as a potent remedy for anæmias, but his claims have not been adequately substantiated by other observers. Soluble ferric salts are more astringent and irritant than the corresponding ferrous salts. They are more liable to produce dyspepsia and constipation and moreover they must probably be reduced to ferrous compounds before they are absorbed. Though they will act efficiently, they possess disadvantages compared with ferrous salts, and clinical opinion has steadily shown a preference for ferrous salts, apart from any theoretical considerations.

Of insoluble ferrous compounds, the carbonate has been chiefly used. It is unstable, being slowly transformed into ferric hydroxide. Oxidation is to a certain extent prevented by the addition of sugar as in the Ferri Carbonas Saccharatus. In Pilula Ferri Carbonatis, ferrous carbonate is formed in the pill mass and is to a considerable extent thus prevented from oxidation. Being insoluble, the carbonate is less irritant to the stomach, where it is converted into the soluble chloride. In chlorosis, fresh ferrous carbonate has been amply proved to be a reliable and effective preparation of iron. The fact that it has to be converted into a soluble chloride before absorption suggests that it would be less effective in anæmias complicated by achlorhydria, though even then it may be rendered soluble by organic acids in the stomach.

The same remarks apply to reduced iron, which consists mainly of metallic iron with a varying amount of iron oxide. It is partly converted in the stomach into ferrous chloride, a conversion which is probably necessary for absorption.

As iron is probably absorbed in the form of ferrous chloride and as this salt undergoes no change in the stomach, it would appear to be the most suitable salt for administration. It acts more rapidly and in smaller dosage than other preparations. It was long ago used and advocated by Fraser as the best iron compound for routine use in anæmia, an opinion which recent experiments confirm. The double salts of iron, such as the Ferri et Ammonii Citras, are soluble but do not give free iron ions. They are therefore not astringent or irritating and do not disturb digestion. They are effective in anæmia if given in sufficient doses.

The following table, adapted from Witts, gives the minimum effective

dose by mouth and the iron content in grams of different preparations of iron.

Preparation	Minimum daily dose in grams	Iron content in grams
Reduced iron	1 5 –6 0	1 2–5 0
Iron and ammonium citrate	4 0 –8 0	0 8 1 6
Pill of iron carbonate	3 0 – 4 0	0 3 0 4
Ferrous chloride	0 25 0 5	0 1 0 2

Iron is occasionally injected hypodermically, with the object of avoiding the irritation of the stomach, but this procedure is painful and causes some swelling and irritation, which lasts twenty-four hours or more. Witts has shown that to cure an anæmia of ordinary severity, it would be necessary to inject the maximum official dose of Injectio Ferri, B.P., every day for four months. Doses of iron large enough to be therapeutically effective in a reasonable time when given parenterally are too near the toxic dose. Except for very rare instances the administration of iron by injection should be avoided. Fortunately, cases which do not respond well to oral treatment are very exceptional.

The perchloride was formerly employed as a **Styptic** and acted by precipitating the proteins of the blood and thus forming an obstruction to the flow of blood from the wounded vessel. The treatment is of value only for oozing from capillaries or small arterioles and the iron must be brought into immediate contact with the bleeding point. It has been injected into the uterus in hæmorrhage, into nævi in order to cause coagulation and subsequent cicatrization of the tissue, and into aneurisms. This is a very dangerous treatment, however, for several cases of fatal embolism have arisen from the precipitated protein being carried off in the veins. The perchloride is, of course, valueless in hæmorrhage from internal organs.

The sulfate of iron is used as a disinfectant for sewage because it is cheaper than the other salts of the heavy metals. It acts here merely by precipitating the proteins, which carry down the bacteria mechanically.

Preparations.

U. S. P.

Ferri Sulfas, ferrous sulfate ($FeSO_4+7H_2O$), large, pale, bluish-green crystals with a saline, astringent taste, soluble in water, insoluble in alcohol, and unstable in moist air. 0.2 G. (3 grs.).

The sulfate of iron is very astringent, though less so than the ferric salts.

Ferrum Reductum, reduced iron, a very fine, grayish-black, lustreless powder, without taste, insoluble in water or alcohol, soluble in acid. It consists of metallic iron, with a small amount of the magnetic oxide. 0.5 G. (8 grs.).

Pilulæ Ferri Carbonatis, ferruginous or chalybeate pills, Blaud's pills, are prepared by the action of ferrous sulfate and carbonate of potash. Sugar, tragacanth, and glycerin are added; they ought to be freshly prepared in order to avoid the formation of the hydroxide. Dose, 2 pills.

Ferri et Ammonii Citrates Virides; contains about 15 per cent of Fe. Dose by parenteral injection 0.06 G. (1 gr.).

Ferri et Ammonii Citrates, thin garnet-red scales with a salt, iron taste, soluble in water and containing 16 per cent of iron. 2 G. (30 grs.).

Syrupus Ferri Iodidi contains about 7 per cent of the iodide. Dose, 1 cc. (15 mins.).

Liquor Ferri Chloridi, a strongly acid solution of ferric chloride containing 10 per cent of iron. 0.1 cc. ($1\frac{1}{2}$ mins.)

Tinctura Ferri Chloridi contains 4.5 per cent of iron. 0.6 cc. (10 mins.).

Magma Ferri Hydroxidi, 120 cc. (4 fl. ounces).

B. P.

FERRI SULPHAS, as in U. S. P. 0.06–0.3 G. (1–5 grs.). The exsiccated form is used for making pills, ½–3 grs.

FERRUM REDUCTUM, a fine grayish-black powder, insoluble in water, and containing not less than 80 per cent of metallic iron. 0.06–0.6 G. (1–10 grs.).

FERRI CARBONAS SACCHARATUS, an olive-brown, slightly hygroscopic powder, partially soluble in water and containing not less than 50 per cent of $FeCO_3$. 0.6–2 G. (10–30 grs.).

PILULA FERRI CARBONATIS, prepared by action of ferrous sulphate and sodium carbonate, with tragacanth, acacia and liquid glucose as excipients. 0.3–2 G. (5–30 grs.).

FERRI SUBCHLORIDUM CITRATUM, a buff-colored powder with an acid astringent taste, freely soluble in water. 0.2–0.3 G. (3–5 grs.).

SYRUPUS FERRI PHOSPHATIS COMPOSITUS, Parrish's food, chemical food, contains phosphates of iron, calcium, sodium and potassium. 2–8 mils. (30–120 mins.).

SYRUPUS FERRI PHOSPHATIS CUM QUININA ET STRYCHNINA, Easton's syrup. 60 mins. contain about ½ gr. of iron, ¼ gr. of quinine sulphate and $\frac{1}{60}$ gr. of strychnine hydrochloride. 2–4 mils. (30–60 mins.).

FERRI ET AMMONII CITRAS, dark-red transparent scales, with an astringent taste, deliquescent in moist air, freely soluble in water. Contains about 21 per cent of iron. 0.3–1 G. (5–15 grs.).

FERRI ET QUININÆ CITRAS, thin, greenish-yellow scales, with a bitter, chalybeate taste, deliquescent in moist air, freely soluble in water. Contains about 15 per cent of anhydrous quinine and about 13 per cent of iron. 0.3–1 G. (5–15 grs.).

SYRUPUS FERRI IODIDI contains 5 per cent of FeI_2. 2–8 mils. (30–120 mins.).

LIQUOR FERRI PERCHLORIDI, contains 15 per cent of $FeCl_3$. 0.3–1 mil. (5–15 mins.).

PILULA ALOES ET FERRI, contains about ¼ gr. iron in 8 grs. 0.25–0.5 G. (4–8 grs.).

Iron is contained in many *mineral waters*, which are therefore advised in cases of anæmia. It is generally in the form of the carbonate, which is dissolved by the excess of carbonic acid present, but becomes oxidized to the insoluble ferric hydrate in the air. The amount of iron contained is small, seldom being more than 0.1 G. per litre, but the treatment of chlorosis is unquestionably aided by change of scene and in particular by the high elevations at which many of these springs are situated.

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II. COPPER.

Copper seldom gives rise to poisoning, and has been less frequently used in medicine than many of the other heavy metals, though recent researches have indicated that it may in future have an important use in the treatment of certain anæmias. The soluble salts precipitate proteins from solution, and are therefore astringent when applied to the mucous membranes and to wounded surfaces. In larger quantities they are somewhat irritant and corrosive, although less so than mercury.

Symptoms.—The copper salts have a harsh, metallic, astringent taste, and when swallowed in some quantity cause nausea, salivation, and vomiting. The most of the salt is thus removed, and no further symptoms are observed. Large quantities, however, induce corrosion of the walls of the stomach and intestine, and give rise to violent vomiting and purging, the copper giving a blue or green color to the vomited matter and the stools, and blood appearing in them later from the corrosion of the mucous membrane. Violent pain in the abdomen is complained of, and the usual symptoms of acute corrosive poisoning may follow: collapse, with weak pulse and respiration, headache, giddiness, unconsciousness, delirium, coma, convulsions, and paralysis. These may prove fatal in a few hours, but more frequently the patient lives for several days to sink eventually from exhaustion.

The nausea, vomiting and purging of acute copper poisoning are due to the local effect on the mucous membranes of the stomach and intestine. In fact, although some copper is absorbed in these cases, there is no reason to suppose that any of the acute symptoms are due to it, for they are all induced by other poisons which act only as gastro-intestinal irritants.

The occurrence of **Chronic Copper Poisoning** in man has not been established. In copper- and brassworkers, gastro-intestinal catarrh, or colic and diarrhœa, occur occasionally and are ascribed to the copper swallowed or inhaled in the course of their occupation. The dust inhaled may similarly cause laryngeal irritation and bronchitis. The skin and hair often have a greenish tint, and a green line on the teeth, just where they enter the gums, is known as the copper line; but it is believed that these are due largely to the copper dust deposited on the skin, hair and teeth, and not to the excretion of the metal. Local paralysis, anæmia, tremor, emaciation and cutaneous eruptions are said to have followed these symptoms in some cases, but it may fairly be doubted whether these symptoms are really due to the copper or to the lead, arsenic and other poisons often associated with it. Furthermore, copper has been taken in the form of the metal, or of its soluble salts, for prolonged periods without any symptoms being elicited except those of slight intestinal catarrh and some nausea.

In animals the general action may be elicited by the injection of slowly dis-

sociated salts, such as sodium-copper tartrate, into the blood or subcutaneously. In the frog copper induces great weakness and eventually complete paralysis of the spontaneous movements and of the heart. This appears to arise from a depressant action on the central nervous system, but the muscles are also weakened and finally completely paralyzed; often fibrillary contractions are observed early in the frog, but it is unknown whether these are of central or of peripheral origin. The heart is somewhat accelerated at first by very small quantities, but later becomes slow and weak, and finally ceases in diastole before the skeletal muscles are paralyzed; the changes in the heart are due to direct action on the muscle.

In mammals the intravenous injection of copper does not cause vomiting, but the locomotion soon becomes slow, clumsy and weak, and later complete paralysis of the spontaneous movements follows. The heart and respiration seem equally involved, but the respiration ceases somewhat earlier than the heart. The blood-pressure rises slightly after the intravenous injection of copper, but afterward falls, partly on account of the weakness of the heart, and partly from dilatation of the blood-vessels. When an animal survives longer, violent, sometimes bloody, diarrhœa is generally induced by copper, as by most of the other heavy metals. The animals lose flesh rapidly, and refuse food, and the urine often contains albumin, and according to some authors, hæmoglobin and blood. In the rabbit some icterus and anæmia are said to occur from the destruction of the red blood cells, and fatty degeneration of the liver, kidney and heart has been observed. Others have found ecchymoses and congestion along the intestine and in the kidney to be the chief lesions. Similar results are obtained in rabbits when copper is given by the mouth, as this animal is incapable of rejecting the poison by vomiting. In the dog, on the other hand, poisonous doses are removed by vomiting when they are given by the mouth.

Copper is absorbed from the intestine, for large quantities have been found in animals fed on it for some time; a large proportion of the metal is absorbed when small doses are given, but the proportion lessens as the dose is increased. It also passes into the blood from other mucous surfaces and from wounds. The copper absorbed from the intestine is lodged chiefly in the liver, less in the spleen, kidney, and thyroid. It is excreted especially by the intestinal tract, to a less extent in the urine. Traces have been found in saliva, bile and milk and it is said to pass from the mother to the fœtus in utero. Copper is found in small quantities in these organs and secretions in man and in animals that have not been treated with it, but in a much larger amount after prolonged administration.

Copper is found as a normal constituent of the blood in many of the invertebrates, in which it performs the same function as the iron of the hæmoglobin in the vertebrates. It has been detected in one of the pigments of birds' feathers, and, as has been stated, is so frequently found in the tissues of mammals, both wild and domesticated, that it may be regarded as a normal constituent. Oysters and other animals take it up in large quantities when they live in water rich in copper, and apparently are not injured by it, while on the other hand Locke found that the traces of copper contained in the water distilled in copper vessels is sufficient to destroy tadpoles and tubifex, one of the annelid worms. Traces of copper, added to the water in which they live, destroy some of the simpler algæ, and the parasites of the grape vine, potato, apple and other plants are killed by spraying the plants with copper; yeast ceases growing in a 0.02 per cent solution, while the moulds seem to be almost immune to its action. Bucholtz stated that the development of bacteria is stopped by a solution of copper sulfate under 1 per cent in strength, but others find that tubercle bacilli may

be suspended for days in a 1 per cent solution of copper chloride without any impairment of their virulence. Voegtlin and Dyer found that the oligodynamic action of copper on spirogyra can be antagonized by glutathione and suggest that this action is due to a combination between copper and glutathione in the protoplasm.

Therapeutic Uses.—Copper sulfate is used internally as an *emetic*, and for this purpose ought to be given in about 1 per cent solution. It acts promptly, and does not leave much depression and nausea, and for this reason is unsuitable as an expectorant. In *phosphorus poisoning* it is especially valuable, as in addition to causing evacuation of the stomach, the metal is deposited on the particles of phosphorus and prevents their absorption. As an emetic in other conditions, zinc sulfate is preferable, as it causes less irritation of the stomach should vomiting not take place.

Externally copper sulfate is used as an *astringent* injection in gonorrhœa, and occasionally as a lotion in ulcers and wounds; for this purpose it is employed in 1 per cent solution. The solid crystals are sometimes used to touch exuberant granulations for their astringent and corrosive effect.

Small quantities of copper sulfate have recently been used to destroy the algæ which grow in reservoirs and often give the water a disagreeable odor and taste. The proportion of copper required for this purpose is about one part in a million or sometimes in fifty millions; this treatment does not render the water deleterious to man, for much larger quantities of copper have been taken constantly without injury.

A new physiological function for copper has been elucidated by recent researches on experimental anæmias. Waddell and his associates found that the anæmia produced in young rats by a diet of cow's milk was cured by iron plus copper but not by iron alone. This important fact was emphasized almost simultaneously by McHargue and his colleagues. It was concluded that copper may play an important function in the formation of hæmoglobin. Subsequently much work has been done upon the relation of copper and other metals to hæmoglobin formation, and the general opinion is that, as a supplement to iron, no metal other than copper is of value, with the doubtful exception of manganese. It was suggested that the necessity for large doses of iron in the treatment of certain anæmias was due to the fact that iron salts may contain small but variable amounts of copper and that the large doses of iron were indirectly needed in order to supply the requisite amount of copper. This possibility has, however, not been established. Experiments on induced anæmias in laboratory mammals indicate that copper does not affect the absorption or storage of iron but facilitates the formation of hæmoglobin, in spite of the fact that copper is not itself a constituent of hæmoglobin.

How far these results are applicable to the treatment of human anæmias is not yet fully determined. Copper is widely distributed in food material, green vegetables and liver being especially rich in it. On the analogy of experimental anæmias the amounts of copper needed is very small, only a few milligrams per day, which would be amply sup-

plied by an adult mixed diet. On the other hand, milk, especially cow's milk, is deficient in copper as well as in iron and it is possible that children fed on cow's milk may suffer from a deficiency of both copper and iron. Indeed results have already been published to show that anæmia in children may be cured by simultaneous administration of iron and copper more rapidly than by iron alone, and that in a certain proportion of cases copper is necessary for the cure.

Copper forms a very stable compound with chlorophyll, and traces of copper salts are sometimes used to give a bright green color to preserved green vegetables. No harmful results have been proved to occur from this practice so long as the copper is in organic combination and the amount added is small.

The chloride of copper is a much more irritant and disinfectant substance than the sulfate.

In cases of **Poisoning** with copper salts, the stomach generally rejects the metal by vomiting and no emetic is required. Non-corrosive compounds may be formed by giving milk, egg, or other forms of albumin, tannic acid, magnesia, or ferrocyanide of potassium. Morphine may be required for the pain, ice to stop the vomiting.

Cupri Sulfas (U. S. P., B. P.) ($CuSO_4+5H_2O$), large, transparent, deep blue crystals, without odor, but with a nauseous, metallic taste, soluble in water, scarcely so in alcohol. Dose as an emetic, 0.25 G. (4 grs.); B. P., 5-10 grs. Suggested dose in anæmia, $\frac{1}{50}$–$\frac{1}{10}$ gr.

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III. ZINC.

The effects of zinc resemble those of copper so closely that they need only brief mention. Like copper, the soluble salts precipitate proteins and therefore possess an astringent action, or in large quantities act as irritants and corrosives. The sulfate is the soluble salt most commonly used in medicine, but the chloride, which is used only as a caustic and disinfectant, has frequently given rise to corrosive poisoning.

Symptoms.—The sulfate of zinc has a harsh, metallic taste, and in small doses causes nausea and vomiting, in larger quantities, violent

vomiting and purging, pain in the abdomen and collapse; these symptoms are due to the local action on the stomach and intestine. The insoluble zinc oxide and carbonate are not liable to cause acute irritation, but their prolonged ingestion has given rise to dyspepsia and constipation or diarrhœa in some cases. The continued administration of zinc salts has no effects in man, except those of disordered digestion and constipation, and Lehmann could detect no effects in the dog after the administration of 155 G. of the carbonate in the course of three hundred and thirty-five days, although a considerable amount of the metal had been absorbed.

In workers exposed to zinc fumes a condition known as "*brassfounders' ague*" is occasionally met with. It is ushered in by dryness of the throat, hard cough, metallic taste, constriction of the chest, lassitude and weakness, sometimes with nausea and vomiting; muscle cramps and joint pains are often present, and later prolonged rigors and shivering are followed by a rapid acceleration of the pulse, coughing and soreness of the chest, and headache. These symptoms give place to profuse perspiration, and the patient sinks into a sleep from which he awakes in ordinary health. The attack has been attributed to the absorption of decomposition products of the proteins destroyed by the fumes of zinc inhaled; it is held that the same symptoms would arise from the fumes of other metals, but these are less volatile than zinc and are therefore seldom inhaled. A number of obscure nervous conditions have also been described as arising from zinc in workmen in brass factories and bronze-works, but it is questionable whether they are really due to the zinc or to its impurities, such as arsenic and lead.

Action.—The general action of zinc can be observed only when a double salt is injected intravenously or hypodermically, as the ordinary salts precipitate the proteins of the blood when injected into a vein, and cause acute irritation when applied subcutaneously. In the frog, zinc is found to cause weakness and lessened reflex excitability, and the heart becomes weak and inefficient, irregular and slow, and eventually ceases in diastole; the voluntary muscles respond more weakly to the electric current in life and lose their irritability entirely soon after death.

In mammals, the intravenous injection of zinc causes vomiting and diarrhœa, weakness, tremor and paralysis of the extremities; and the stomach, intestines and heart contain small hæmorrhages. The blood-pressure seems to be but little affected, until just before death, but the pulse is slowed. Helpup found that the subcutaneous injection of zinc salts induced congestion and parenchymatous inflammation of the kidney.

Zinc seems therefore to depress the central nervous system and to a less extent the heart and voluntary muscles, and to cause irritation and congestion of the mucous membrane of the stomach and intestine and inflammation of the kidney. The fact that vomiting occurs from the intravenous injection of zinc salts is explained by the metal inducing inflammation in the stomach.

Lehmann found that of the zinc absorbed from the stomach and intestine, most is contained in the liver and bile, less in the spleen, kidney, thyroid and pancreas, and very little in the other tissues. Zinc is excreted by the stomach and intestinal walls, and in much smaller amounts in the bile and urine.

Locke found zinc to possess a poisonous action on the tadpole and tubifex when present in traces in the water in which they lived, but this effect was weaker than that of copper. Richter states that zinc is less poisonous to fungi than copper, and very weak solutions seem to promote their growth. The zinc salts seem to be in general much weaker than those of copper, which they resemble closely in other respects.

Therapeutic Uses.—Zinc sulfate is used internally as an *emetic*. The sulfate, the oxide and the carbonate have been advised in the treatment of various brain diseases, from the erroneous belief that zinc is a sedative.

Externally the zinc preparations, with the exception of the chloride, are used as *astringents* and *antiseptics*, the sulfate being applied in solution, the oxide and carbonate as powders, lotions, or ointments. The oxide is especially useful as an application in many skin diseases. Calamine (B. P. C.), an impure carbonate of zinc, is used in ointments and lotions as an astringent and to impart a pink color. Solutions of the sulfate are used as an eye wash (0.5 per cent) and as an injection (1–4 per cent) in gonorrhœa, leucorrhœa and otitis. The stearate is used as a soothing and mildly antiseptic preparation for acne, eczema and other skin diseases.

The chloride of zinc differs from the other salts in being a powerful caustic, and is used as a paste or in pencil form to destroy malignant growths, or in chancres and gangrenous sores. It produces a white eschar and is said to be less liable to spread over the surface than potash, but penetrates the epidermis with difficulty, and it is therefore advisable to destroy this with potash or a blister before applying the caustic. It is sometimes mixed with flour or dried gypsum and water to a paste (Canquoin's paste), when a less active caustic is desired. Its use is much more restricted at the present time than formerly. Burnett's disinfecting solution (a somewhat stronger solution than the official liquor) is used to disinfect fæces and urinals, and the liquor of the pharmacopœia may be employed for the same purpose. It has frequently given rise to severe corrosive poisoning from being swallowed accidentally or suicidally.

Preparations.

U. S. P.

Zinci Sulfas ($ZnSO_4+7H_2O$), colorless, transparent, odorless crystals, with a harsh, astringent, metallic taste, soluble in water, not in alcohol. 1 G. (15 grs.).

Zinci Acetas, pearly crystals, efflorescent, soluble 1 part in 2–3 of water.

Zinci Chloridum ($ZnCl_2$), a white powder, or porcelain-like mass, irregular or moulded into pencils, odorless and strongly caustic, very deliquescent and soluble in water and alcohol.

Zinci Oxidum (ZnO), an amorphous white powder without odor or taste, insoluble in water.

Unguentum Zinci Oxidi, 20 per cent, in paraffin or petroleum jelly.

Zinci Stearas, a white impalpable powder, insoluble in water.

The acetate, phenolsulphonate or sulphocarbolate, and the valerianate of zinc are superfluous soluble salts.

B. P.

Zinci Sulphas, 0.06–0.2 G. (1–3 grs.); as emetic, 0.6–2 G. (10–30 grs.).

Zinci Oxidum.

Unguentum Zinci Oxidi, 15 per cent in simple ointment.

Gelatinum Zinci (Unna's Paste), 15 per cent in gelatine, glycerin and water.

Pasta Zinci Oxidi Composita, 25 per cent in starch and soft paraffin.

Zinci Stearas.

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IV. ALUMINIUM AND ALUM.

The chief pharmacopœial preparation of aluminium is the sulfate of aluminium and potassium, or alum, which has been largely used for its astringent properties. Alum solutions precipitate proteins in the same way as the salts of the other heavy metals, and dilute solutions have thus an astringent action, while larger quantities and more concentrated solutions act as irritants. This is more especially the case when dried alum is applied, for, in addition to its coagulating effect on the proteins, this preparation has a great avidity for water.

Symptoms. -Alum solutions have a sweetish, astringent taste, and in small quantities induce no symptoms except a feeling of dryness and astringency of the mouth and throat, and some constipation. Larger doses act as gastric irritants and cause nausea and vomiting, and, in extreme cases, purging. Even the largest quantities, however, are followed by no symptoms except those of gastro-intestinal irritation and inflammation, and the long-continued use of alum does not elicit any symptoms of chronic poisoning. The aluminium salts are only absorbed in small quantity from the stomach and intestine, so that no symptoms of general poisoning arise from the internal use of the salt. The small amount of aluminium absorbed is stored up in the liver, kidney, muscles and pancreas and slowly excreted in the bile and urine.

The suggestion that toxic effects may result from the ingestion of food cooked in aluminium vessels has given rise to much controversy and experiment. The evidence on the whole is that the amount of aluminium so introduced into the system is too small to produce any deleterious effects, and Burn, who has recently made a critical survey of the literature, concludes that the use of aluminium cooking-vessels is devoid of danger. Alum has been used extensively in baking powders. With any ordinary diet this could hardly lead to the ingestion of more than 1 gr. of aluminium per day, a quantity which appears to be quite innocuous. Very large amounts of aluminium taken experimentally with foods in the form of baking powders were found to produce diarrhœa, but no symptoms of general poisoning have been proved to result from the ordinary use of such powders.

Aluminium salts, especially the acetate, chloride, and some more recent preparations, have considerable antiseptic power, much more than some of the more generally used antiseptics, such as boric acid.

Action.—Aluminium has a very remarkable general action when it obtains access to the blood. In Siem's experiments on animals, the sodium-aluminium lactate or tartrate induced a very slow intoxication, mammals never dying from the effects sooner than one or two weeks after the intravenous injection of the salts. In frogs the symptoms were those of a descending paralysis of

the central nervous system, the heart and the peripheral nerves and muscles being little affected. In mammals the first symptoms appeared only after three to five days, and consisted of constipation, rapid loss of weight, weakness, torpor and vomiting; marked abnormalities in movement and sensation were observed later, such as tremor, jerking movements, clonic convulsions, paresis of the hind legs, anæsthesia of the mouth and throat, and lessened sensation all over the body. Before death, diarrhœa often set in, and albuminuria was generally present. The mucous membrane of the stomach and bowel was found swollen and congested, the kidney and liver had often undergone fatty degeneration, and hæmorrhages were found in the renal cortex. Aluminium was found in the urine.

Like the other members of the heavy metal series, aluminium therefore acts on the bowel and kidney in general poisoning, while many of the symptoms point to a direct action on the brain. Dollken confirmed Siem's results and showed that the nerve cells and fibres of the cord and medulla undergo degeneration, particularly those of the lower cranial nerves.

Uses.—Alum is used chiefly externally for its astringent properties. It has been employed as an *emetic*, but is less reliable than the sulfate of copper or tartar emetic, and very large doses (4–8 G., 1–2 drs.) are required. In *diarrhœa* alum is sometimes advised.

Alum solution is useful as an *astringent* gargle (1–5 per cent), as an injection in gonorrhœa ($\frac{1}{2}$–1 per cent), as an astringent lotion in skin diseases (1 per cent), and for other similar purposes. A solution (1 per cent) has been injected into the rectum in chronic dysentery, but is inferior to the nitrate of silver. Dried alum is more caustic, from its withdrawing fluid from the tissues; it has been used as an application to exuberant granulations, hæmorrhoids, or condylomata, and as a styptic in bleeding from the nose or teeth.

Preparations.

Alumen (U. S. P., B. P.), alum, potassium or ammonium alum ($AlK(SO_4)_2+12H_2O$, or $AlNH_4(SO_4)_2+12H_2O$), large, colorless octahedral crystals, with a sweetish, strongly astringent taste, soluble in water but not in alcohol. B. P., 0.3–0.6 G. (5–10 grs.).

Glycerinum Aluminis (B. P.), 13 per cent.

Alumen Exsiccatum (U. S. P.), burnt alum, dried alum ($AlK(SO_4)_2$, or $AlNH_4(SO_4)_2$), a white, granular powder, attracting moisture on exposure to air, soluble in water.

A large number of aluminium preparations have been introduced as antiseptic astringents. Among these may be mentioned *alumnol* (naphthol sulphonate of aluminium), *salumin* (salicylate), *tannal* (tannate), *gallol* (gallate), *boral* (borotartrate), *cutol* (borotannate), *alsol* (acetate), *alkasal* (salicylate of potassium and aluminium). They are used partly in solution, chiefly as dusting powders.

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V. LEAD.

Lead is used to some extent in therapeutics, but its chief interest from a medical point of view lies in the frequency with which it gives rise to chronic poisoning, and in the diversity of the symptoms presented in that condition.

Solutions of lead salts precipitate proteins, and this precipitate is formed when lead solutions are applied to the mucous membranes and protects them. The metal contained in the precipitate is not destructive to the cells as in the case of mercury, so that the lead salts are less corrosive; and the salt chiefly used is the acetate, whose acid is only slightly active, so that the astringent action of the protein precipitate is the chief feature of the action. Solutions of lead nitrate are irritating and corrosive, however, because it is more readily dissociated and the nitric acid freed is itself corrosive.

Symptoms.—Lead acetate solutions applied to the skin have no effect, but mucous membranes, or exposed tissues, such as ulcers, are covered with a thin pellicle of precipitate, which serves to protect them from irritation, and thus promotes their healing. In ordinary therapeutic doses, the acetate of lead (sugar of lead) has a sweetish, metallic taste followed by a feeling of astringency, and induces no symptoms except constipation. The stools after lead are often said to be dark in color from the sulfide formed in the intestine, but this does not seem to be the general rule. Probably little lead is absorbed from an ordinary dose of the acetate; at any rate no symptoms arise from the general action of the metal absorbed.

When very large quantities of acetate are swallowed, particularly if in a concentrated form, they give rise to the ordinary symptoms of irritant poisoning, nausea, vomiting, pain in the abdomen, violent purging or sometimes constipation, blood in the vomited matter and stools, great thirst, weakness, and collapse. In some instances in which the patients recovered from these symptoms, they subsequently suffered from chronic lead poisoning, but apart from these, nothing in the course of acute lead poisoning suggests the absorption of the metal, all the symptoms being obviously due to the local effects on the stomach and bowel, and to the consequent collapse. In fact, the effects of a sudden absorption of lead are unknown in man or animals.

Continued ingestion of small quantities by way of the stomach, or by inhalation by the lungs, induces chronic poisoning, which can be explained only by its absorption. There seems some reason to believe that lead is absorbed from the unbroken skin, though it is possible that some of the metal was carried to the mouth and swallowed with the food in the cases on which the statement is founded. Lead is apparently **Absorbed** more rapidly than most of the metals except mercury, and remains lodged in the tissues a long time, the excretion taking place only very slowly. It is found in most organs and tissues in cases of poisoning, particularly in the bones, liver and kidney. In the blood 90 per cent is said to be carried in the red cells. Lead has also been found in the cerebrospinal fluid in cases of poisoning. It is

Excreted in the urine, the bile, the secretion of the intestinal epithelium, in the milk and saliva, and in traces in the perspiration. The average ratio of excretion of lead between the urine and fæces in cases of chronic poisoning is 1: 2.5 (Aub)

Chronic Lead Poisoning is the commonest of all forms of metallic poisoning and, at the same time one of the most insidious. It is always accidental and, although it is most common in workers in lead, may occur in persons who are not apparently liable to come in contact with the metal. There is no question that some people are more susceptible to lead than others and that sometimes persons who have suffered from the early symptoms recover and prove resistant to the further action of the metal. Anæmia and weakness from any cause are generally believed to predispose to the disease; women and children are more liable to it than men, and alcoholism and previous lead intoxication increase the tendency to the attack. Relapses are very common, and may occur years after the first symptoms, even though there has been no further exposure in the interval. Lead smelters and refiners, workers in white lead factories, painters, plumbers, electricians, and typesetters are liable to lead poisoning from continually handling the metal; but other trades are not exempt from it, and sometimes the channels by which it gains entrance to the body are very obscure. Trades which have recently yielded a considerable number of cases are pottery, from the use of a lead glaze, and coach-painting from the rubbing down of the layers of paint. Some of the more common industries in which lead poisoning is found are among the makers of lead wire, sheet lead, pipe, picture frames, car and can seals, stoppers for bottles and basins and other industries involving the handling of solid or molten metallic lead. The making of storage batteries involves the use of lead oxide and from the great growth of this industry it is proving an important source of cases of chronic poisoning (Hamilton). The painters' trade still furnishes the highest incidence of poisoning and the introduction of the "spray gun" to paint all sorts of objects as well as the interior of buildings is likely to increase the number of cases of plumbism unless a specially constructed mask is worn to hold back the droplets containing minute quantities of lead. Formerly a common source of poisoning was wine and cider to which lead had been added to reduce the acidity. A considerable number of cases of poisoning have been recorded from the use of lead preparations as abortifacients. Chronic lead poisoning has been induced experimentally in animals by the inhalation of lead carbonate dust and in birds by passing lead shot into the crop. Young animals are much more susceptible to lead poisoning than older animals.

The symptoms of chronic lead poisoning vary greatly in different cases, sometimes only one or two organs being attacked, in others the whole economy appearing involved in the disorder. The symptoms may be divided into groups for convenience, but it is to be noted that many of these appear to be closely interconnected, and that in many cases it is impossible to decide whether a set of symptoms is due to direct action upon a single organ, or to the simultaneous involvement of several.

The **Mouth, Stomach, and Digestion** very often give early indications of lead poisoning. The patient complains of loss of appetite, nausea, constipation, wasting, a metallic taste and fœtid breath, and a blue-black line is seen along the margin of the gums close to where the teeth enter. This "lead line" is due to the precipitation of lead sulphide by the hydrogen sulfide arising from septic processes in the teeth and gums; it is often absent if the teeth and mouth are kept clean and healthy, and its presence does not indicate lead poisoning, but only contact with lead. The lead is not deposited on the surface but in the subepithelial tissue, as it cannot be removed by rubbing. The metallic taste seems due to the excretion of lead in the saliva, and the loss of appetite may arise from the same cause. These symptoms may be produced in animals also.

Another early symptom is **Anæmia,** which may be due in part to malnutrition, but is attributed mainly to an abnormal destruction of the red cells of the blood; the white corpuscles are increased in many cases but not in all. It is often accompanied by jaundice, with the highly pigmented urine and other symptoms which usually follow the liberation of large quantities of hæmoglobin from the breaking up of red cells. The red blood cells often contain granules staining with basophile dyes (stipple cells) and indicating incomplete disappearance of the nucleus; this change may present itself before any other symptom and is an important diagnostic sign of lead poisoning; it may, however, occur also in other forms of anæmia. The anæmia is often very marked, and is sometimes the chief or only symptom of lead poisoning; according to some authorities, it is present in a greater or less degree in the majority of white lead workers, and it leads to weakness, languor, and in young women often to amenorrhœa. Lead is also said to alter the surface of the red blood cells, causing them to shrink and rendering them relatively impermeable to water; they lose their stickiness and are not agglutinated by sera. Being less elastic than normal and more brittle, they cannot withstand trauma and therefore break up easily, explaining the anæmia. The loss is partially compensated for by new young erythrocytes, but these are affected by the lead also, so that the basophilic material is clumped together, giving the stippled appearance (Aub). Kaplan and McDonald found an average of 0.031 mg. of lead per 100 G. of blood in normal people and from 0.1 to 0.6 mg. in cases of clinical lead poisoning.

Abortion is very often met with in lead poisoning, and in women employed in lead-works who do not show any marked symptoms of disease. In animal experiments it is found that the offsprings of a male suffering from lead poisoning are undersized, delicate and of slow growth; in most cases the spermatogenesis in the parent is not affected but some become sterile and the germinal epithelium atrophies (Weller).

One of the commonest symptoms is **Lead Colic,** painters' colic, colica saturnina or colica Pictonum. This generally sets in suddenly, and is accompanied in most cases by obstinate constipation, in a very small proportion by diarrhœa. Paroxysms of the most acute agony are followed by intervals of comparative freedom from pain, but in these

intervals some tenderness of the abdomen may be complained of, while during the attack pressure generally relieves the pain. The colic lasts for several days, or a week, and then disappears, but is liable to return at intervals. The abdomen is generally hollow, retracted and hard, and during the acute spasms the patient often gains some relief by lying on his face with the fists pressed against the umbilical region, to which the pain is usually referred. Vomiting is frequently present, the pulse is slow and very hard, especially during the acute crises, while the respiration may be accelerated. The urine is scanty and often contains hæmatoporphyrin.

The cause of lead colic is evidently spasm of the intestine, but it is uncertain whether it arises from action on the muscle or on the ganglionic plexus. It can be induced in animals, and is relieved by atropine. The blood-pressure is raised in man, not only during the spasms, but also in the intervals. This contraction of the vessels, like the slowing of the pulse, is often said to be reflex from the pain, but this seems to

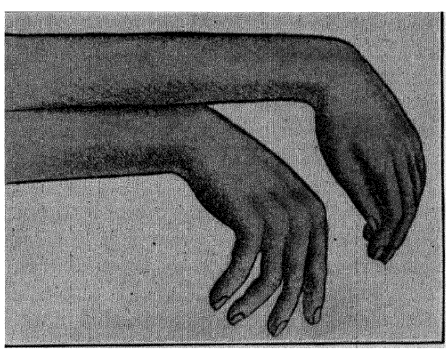

FIG. 3.—Lead palsy of the forearm extensors. (After Oliver.)

be disproved by the fact that it remains during the intervals. Some writers have therefore regarded the colic and its attendant symptoms as due to a vascular spasm, and have supported this by showing that nitrite of amyl, which dilates the vessels, also relieves the colic.

Another common result of chronic lead poisoning is **Paralysis,** lead or painters' palsy, paralysis saturnina, which is almost invariably limited to certain groups of muscles, the extensors of the forearm. It is bilateral in many cases, but sometimes involves only one arm. The affection generally begins in the middle and ring fingers, which cannot be extended, then spreads to the index and little finger, and afterward to the thumb and wrist. The fingers remain flexed and later the wrist is similarly affected, so that the condition is often known as wrist-drop. Even after all the other muscles of the extensor surface of the forearm are involved, the supinator longus remains normal as a general rule. The muscles affected atrophy rapidly, and in old cases contracture of the flexor muscles sets in, when the limb becomes immovable and has a characteristic claw-like appearance. More rarely

other regions are affected, such as the laryngeal muscles, the external rectus of the eye, or the muscles of the leg. In animals several observers have succeeded in inducing paralysis of the hind limbs, and the legs are said to be affected very often in young children. When paralysis is complete, the reaction of degeneration is given by the muscles on electric stimulation, and even muscles which are not completely paralyzed are said to give it in some cases. The cause of lead palsy is peripheral neuritis and degeneration of the nerves, which sometimes involves secondarily the cells of the anterior horn of the spinal cord. Not infrequently the onset of palsy is very sudden, and this has been ascribed to small hæmorrhages in the nerve trunk. Peripheral neuritis and paralysis have been elicited repeatedly in animals. According to Edinger's view, the nerves of those muscles are selected by lead, which are least developed in proportion to the work they have to perform. Aub and his co-workers believe the primary lesion is in the muscle. The afferent fibres are also involved in the action, as is shown by local **Anæsthesia**, which is generally sudden in its onset, but may be preceded by numbness or tickling of the skin, and generally lasts only one or two weeks when sensation returns again to the part.

Lead **Arthralgia**, which arises from the same action on the peripheral nerves, consists in sharp lancinating or boring pains around the joints, the intensity of the pain being comparable only to that of lead colic. It sets in suddenly, usually in the night, and generally disappears as suddenly.

Lead **Amblyopia**, or blindness, is one of the rarer affections. The sight may be lost completely, or may only be dim, and the onset may be sudden or gradual. It arises from neuritis of the optic nerve and degeneration of the retinal nerve cells, or in some cases may be the result of the changes in the kidney occasioning albuminuric retinitis or effusion into the optic sheath. In early cases of neuritis, the disease can generally be arrested and even complete restitution may take place, but if it is neglected, optic atrophy follows.

Under saturnine **Encephalopathia**, a number of disorders of the brain are classed together. They are comparatively rare at the present time, and their onset generally indicates long standing and neglected lead intoxication, although in some cases the patient has been exposed to the poison for only a short period. One of the most characteristic features is the rapidity with which the disease changes from one type to another, and the diversity of the symptoms present at one time. These cerebral symptoms sometimes appear suddenly, while in other cases they are heralded by violent headache, giddiness and sleeplessness, or by amblyopia, deafness, great depression, stupor, weakness, and tremor. Later, sudden mania and delirium, with convulsions resembling chorea or epilepsy, hallucinations and illusions indistinguishable from those of alcoholic delirium, sudden apoplectic paralysis, ataxia, partial analgesia, hyperæsthesia, or coma may occur separately or in succession. Oliver states that the encephalopathic symptoms are especially liable to occur in persons addicted to alcohol.

In animals cerebral symptoms are readily induced by lead in chronic

poisoning. Chorea, tremors and general convulsions have been caused in this way in dogs.

The encephalopathia is obviously of cerebral origin, and at autopsy atrophy of parts of the cerebrum, or hæmorrhages and very frequently disease of the brain vessels have been met with. In other cases of undoubted encephalopathia in man, no such lesions have been observed; and many of the symptoms are obviously not due to these gross lesions, for the suddenness of their onset and of the recovery precludes any such explanation, and shows that lead has also a direct action on the brain cells.

Another organ acted on by lead, especially in prolonged poisoning, is the **Kidney,** which is often found to present a typical red granular nephritis. During life the urine presents the ordinary appearances of this disease, being copious in amount and of low specific gravity, and containing comparatively small quantities of albumin or casts. In some cases in man, the kidney has presented a mixture of parenchymatous and interstitial disease, while in animals the parenchyma alone is affected, perhaps because the experiments have not lasted long enough. The disease of the kidney from lead poisoning, as from other sources, may cause dropsy, uræmia and amblyopia, but the brain and eye may be affected in cases in which there is no nephritis. Fairley has recently associated the frequency of nephritis in children in Queensland with lead poisoning. The poisoning was attributed to the weathering of lead paint on wooden buildings which subsequently washed off when heavy tropical rain occurred.

Another condition in which lead poisoning may act as a predisposing factor is **Arteriosclerosis** and **High Blood-pressure**; the malnutrition, anæmia, and renal changes induced by the metal would in themselves tend to induce changes in the vessels throughout the body, and degeneration of their walls is met with in a considerable proportion of cases of very prolonged exposure to it.

Gout is said to be common in lead poisoning, which may predispose to this disease, for Garrod stated that in one-fourth of the cases of gout treated by him there was a history of lead poisoning; more recently the relationship is less obvious. The purine substances of the urine are augmented in chronic lead poisoning in animals.

Lead poisoning runs no definite course. As a general rule the anæmia, wasting, constipation and weakness appear early, and then colic may follow, or paralysis, or arthralgia. Nephritis, encephalopathia, anæsthesia and gout are rarer, and as a rule occur only in very prolonged poisoning. Any one of these symptoms may be present alone, and the diagnosis is then very difficult. In doubtful cases the urine or the stools may be tested for lead. Every case in which lead is found in the urine is not necessarily one of lead intoxication, however, for it has been detected in a number of perfectly healthy individuals.

It is impossible at present to give any general explanation for the diversity of the forms of chronic lead poisoning. The central nervous system is certainly acted on, both in its higher and lower divisions The lead line, metallic taste and nausea, and perhaps the constipation, would seem to be connected with the excretion of the metal along the

alimentary canal, while the renal action is probably of the same nature as that inducing periarteritis in the brain and, as is alleged, in the lungs under some conditions. Some authorities are disposed to regard the action on the vessels as the fundamental feature in lead poisoning which leads to all the other symptoms; thus the colic is said to be a vascular spasm and the encephalopathia and palsy to arise from capillary hæmorrhages. The anæmia indicates an action on the red cells of the blood, and the gout, some disturbance of the general nutrition. Attempts have been made to elucidate the nature of this action on metabolism by estimating the urea and other constituents of the urine, but no important light has been thrown on it by this means, nor in fact are significant results to be hoped for in a disease which offers so many and so diverse types as lead poisoning. In chronic poisoning lead is found deposited in the bones and other organs, but the quantity actually in circulation at any one time may be so small as to escape estimation; the symptoms and lesions of chronic lead poisoning are thus not due to the accumulation of lead in the affected organs but to the cumulation of injury from its continually renewed passage in infinitesimal dilution (Straub). Aub and his co-workers believe that lead exists in the blood in the form of colloidal lead phosphate and is deposited in the bones as tertiary lead phosphate. This compound is sensitive to changes in acidity (especially as caused by lactic acid) and this may explain the not infrequent development of symptoms of acute poisoning following acute infections or acidosis.

Lead acts upon so many tissues that it might be expected to have some distinctive action upon the simpler organisms, but, as a matter of fact, it seems less poisonous to them than most other heavy metals.

Organic Lead combinations have been investigated in the hope that their action might throw light upon that of the metal. *Triethyl lead* ($Pb_2(C_2H_5)_6$) has been examined by Harnack and more recently by Mason, in the hope that it might be decomposed in the tissues to simpler lead compounds, but the effects seem to arise from the unaltered molecule, and cannot be brought into analogy with those of the metal. In the frog it induces paralysis, apparently from action on the central nervous system. In the dog small doses cause a marked fall in blood-pressure, with marked disturbance or failure of the respiration, but a second dose increases the blood-pressure by constriction of the vessels, and accelerates the respiration. The intestinal movements are increased, perhaps from central action. Tremors and convulsions may occur from stimulation of the brain.

Lead tetraethyl, Pb $(C_2H_5)_4$, is of considerable importance from its industrial use especially as an addition to petrol, whereby poisoning by it may arise. It is a clear heavy oily liquid, insoluble in water, soluble in alcohol and oils, and somewhat volatile at ordinary temperatures. Poisoning in man occurs mainly by absorption from the skin and lungs, and the chief symptoms, as described by Kehoe, are insomnia, nausea, pallor, low blood-pressure and temperature, loss of weight, tremor and sometimes delirium or mania. In acute poisoning, symptoms may come on in a few hours. Colic is frequent, but neuritis and the lead line are rare and the stippling of the red cells does not appear until very late.

Therapeutic Uses.—Lead is used in therapeutics only for its astringent action. The acetate was formerly, but now rarely, prescribed internally in diarrhœa, generally along with opium, and always in pill form, as the solution would act on the stomach and have less effect on the bowel.

It has been tried in dysentery and cholera, but has proved of little value. Lead has also been advised in cases of hæmorrhage from the lungs, kidneys and uterus, but is quite valueless here, as it acts as a styptic only when applied locally. Still less reason is there for its use in nephritis, cystitis, and similar conditions.

Externally, a solution of the acetate or the dilute solution of the subacetate is used as an *astringent* lotion in burns and as an injection in gonorrhœa.

Lead ought not to be employed externally or internally except for a short time, as otherwise symptoms of poisoning may arise. Blair Bell has recently employed intravenous injections of colloidal lead in the treatment of cancer, with apparent success in a certain percentage of cases. Great care is required in the preparation of the colloidal injection and in the dosage of it. With all precautions, the treatment is not without danger and is still to be regarded as on trial.

Prevention of Chronic Poisoning.—The most important factor in the prevention of chronic poisoning is the avoidance of dust, as absorption of lead from the respiratory tract is quite rapid. Wet processes of manufacture should be substituted for dry wherever possible and suction draft should also be employed to draw the dust from the workers. Workers should not wear the same clothes when at work as at their homes Separate rooms should be provided for eating purposes and the hands should be carefully washed before handling food. Frequent careful medical examinations should be made of all persons exposed to lead to determine their fitness for the work and to detect early signs of poisoning.

Treatment of Poisoning.- During the acute symptoms it is recommended that milk should be given for its calcium content to favor the deposit of the lead in the bones. Calcium lactate may be given at the same time. After the acute symptoms are past the excretion may be aided by maintaining a negative calcium balance and changing the hydrogen-ion concentration of the blood. For this reason acids are effective in hastening the elimination of the lead. Dilute phosphoric acid in doses of 20 cc. is recommended to be given in a glass of water every hour or ammonium chloride may be given in 1 G. doses every hour. Sodium bicarbonate is also effective in large doses (20–40 G. daily), doubling the rate of elimination. Potassium iodide has been long used and it has been recently shown that it too will double the rate of excretion. Magnesium sulfate is often used in the treatment, and the improvement is attributed to its purgative effect, at any rate in part. Diuretics may be prescribed, and hot baths; sulfur baths are especially recommended, and massage is said to hasten the elimination of the poison. As the storage of lead and calcium is closely analogous, parathyroid extract has been tried to hasten the excretion of lead. It may at first cause a rapid excretion of lead from the bones, but this action slows down. With any method of treatment care must be taken not to convert a chronic lead toxæmia into an acute one by too rapid mobilization of lead.

In colic, morphine or opium is often necessary to allay the pain.

Belladonna or atropine is used less frequently, and nitrite of amyl is said to be efficient for a short time. In the intervals between the paroxysms, a saline cathartic is often indicated to relieve the constipation, or if the vomiting prevents this, a large enema may be thrown into the bowel.

In arthralgia, the pain may necessitate the giving of opiates. In anæsthesia and encephalopathy, the treatment is expectant and symptomatic; for instance, in mania, or violent delirium, the hypnotics may be necessary.

In paralysis, strychnine may be used along with the general treatment, but the chief reliance is to be placed on the electrical stimulation of the paralyzed muscles, first with the galvanic current, and, as recovery sets in, with the induction coil. Massage of the muscles is also of benefit.

Preparations.

U. S. P.

Plumbi Acetas, lead acetate, sugar of lead ($Pb(C_2H_3O_2)_2+3H_2O$), forms colorless crystals, with a sweetish, astringent, afterward metallic taste, very soluble in water, less so in alcohol.

B. P.

Plumbi Acetas, 0.03–0.12 G. ($\frac{1}{2}$–2 grs.).

Liquor Plumbi Subacetatis Fortis, contains about 20 per cent of lead.

Liquor Plumbi Subacetatis Dilutus, 1 in 80 of the above.

Suppositorium Plumbi cum Opio, each contains about 3 grs. of lead acetate and about 1 gr. of opium.

Plumbi Monoxidum, orange scales or powder, almost insoluble in water.

Emplastrum Plumbi.

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VI. SILVER.

The only salt of silver used at all extensively in medicine is the nitrate, which is caustic, astringent, and disinfectant. Added to solutions of proteins, it forms a heavy precipitate, which is at first white in color, but turns darker in the light as the silver is reduced.

Symptoms.—In dilute solution silver is a slight irritant to the skin, and causes redness and itching only, but more concentrated solutions blister, and the solid nitrate of silver causes an eschar, which is at first white, but later turns black from the reduction of the silver in light. On the mucous membranes, dilute solutions act as astringents, but concentrated cause irritation and corrosion. The caustic action of silver does not extend so deeply as that of some other metals, such as mercury, because the penetration of the metal is limited by the formation of the insoluble chloride. On the other hand, the silver salts are more irritant than those of lead.

The astringent action is due to the formation of a protective layer of coagulated albumin. If irritation is induced the vessels are dilated, and there is no evidence that they are ever contracted in the practical use of silver.

In acute silver poisoning from the ingestion of silver nitrate, the symptoms are those of severe gastro-intestinal irritation and corrosion. Burning pain is felt in the throat and abdomen, and is followed by nausea and vomiting and often by purging. The mouth is covered with a grayish-white membrane, which turns darker after a time, but this is absent if the poison is swallowed in the solid form, as has happened sometimes. The corrosion of the stomach and intestine causes collapse, with weak pulse, shallow respiration and pinched features and this may be followed by coma, convulsions, and death. The throat, stomach and intestine presented the ordinary appearances of acute corrosive poisoning in one case in which an autopsy was performed.

Action.—The symptoms of acute poisoning are due to the local action, and present no features suggesting that silver is absorbed and causes general poisoning. The action of silver after absorption has, however, been investigated in animals poisoned by subcutaneous or intravenous injection. The nitrate, owing to its coagulating properties, is unsuitable for this purpose, and the hyposulfite of sodium and silver, or a solution of the albuminate has therefore been used. In mammals the central nervous system is the chief seat of action, especially the medulla oblongata, which seems to be stimulated at first, for the blood-pressure rises and the pulse is somewhat slow, owing to increased activity of the vasomotor and vagus centres. Later the blood-pressure falls and the respiration becomes slow and labored, and eventually ceases from paralysis of the centre. Gaethgens asserts that the diaphragm, and eventually the other striated muscles are paralyzed soon afterwards. The heart is comparatively little affected and often continues to beat some time after the respiration has

stopped. In less acute poisoning, when the animal survives the injection for several hours or days, a marked increase in the bronchial secretion, culminating in œdema of the lungs, has been noted; no satisfactory explanation of this has been advanced, but it does not seem due to cardiac inefficiency. Congestion and ecchymoses are found in the stomach and intestine, and some authors mention ulceration of these mucous membranes. Cohnstein found that small quantities of silver salts injected intravenously cause some increase in the urine for a time, but that larger quantities are followed by albuminuria.

In cold-blooded animals and in invertebrates, silver preparations are said to cause violent convulsions resembling those of strychnine and followed by general paralysis.

The general action of silver is thus apparently directed first of all against the medulla oblongata, the rest of the central nervous system being affected to a less extent. The mucous membrane of the stomach and intestine is acted on, as by most heavy metals, and the kidney is also liable to irritation. Œdema of the lungs occurs frequently.

Chronic Poisoning.—There is no evidence that in acute poisoning in man any considerable amount of the metal is absorbed from the stomach and intestine. When silver is given for prolonged periods, however, some is absorbed, although probably only a minute fraction of that actually swallowed. None of it is found in the epithelium of the stomach and intestine, and some of it may circulate in the blood in a soluble form for a short time. But the greater proportion is very soon thrown down in the form of minute granules, which are found chiefly in the connective tissues of the body, and when present in quantity, give a dark color to the skin and mucous membranes. This pigmentation (Argyria) was much commoner formerly, when the nitrate was used in the treatment of epilepsy. More recently it has occurred in the makers of artificial pearls, who use silver as a pigment. Local argyria is sometimes met with from the prolonged application of silver nitrate to the eye or throat, when it tints the eyelids and mouth, and from working with silver, when the hands are permanently blackened from the granules being forced into the skin.

The deposit of the silver in the skin gives it a darker color, varying from light gray in mild cases to a darker slate shade after more prolonged use. It is generally distributed all over the body, but in some cases has been especially marked in the face, and it is said to begin in the gums, where it causes a dark, slate-colored line somewhat resembling the lead line. In the skin it is found in the corium, not in the epidermis. The deposit and the dark color extend throughout the alimentary canal and the respiratory passages, the granules occurring in the connective tissue, particularly in the intestinal villi, and not in the epithelium. The glomeruli of the kidneys, the connective tissue of the liver and spleen, the choroid plexus, the tunica intima of the aorta, the serous membranes, and the mesenteric lymph glands contain more of the deposit than other organs. The pigmentation is not accompanied by any other symptoms of importance, and the victims may live to old age without suffering from the chronic poisoning in any way, except from the annoyance induced by the change in color.

Argyria is quite incurable, although many attempts have been made to remove it. Iodide has been tried, for the most part without effect,

and blistering is equally valueless, as the pigment lies deeper than the epidermis. The only known solvent of the granules is cyanide of potassium, and of course this is inadmissible, owing to its powerful poisonous action.

Argyria has been induced in animals by prolonged treatment with small doses of silver salts, though here the pigment is not found in the skin, but in the connective tissue of the internal organs.

In man it seems likely that most of the silver passes through the alimentary canal unabsorbed and that the small proportion taken up by the tissues is precipitated and remains embedded in them indefinitely, for the pigmentation remains unchanging in its depth, and there is therefore no reason to suppose that any of the silver is eliminated.

In animals, however, some of the silver injected hypodermically or intravenously is excreted by the epithelium of the alimentary canal. None appears in the urine. In the frog silver injected hypodermically is all excreted by the epithelium of the tongue, is swallowed, and passes out in the feces. No other poison is known to be eliminated by this channel.

Silver nitrate is a powerful disinfectant, partly from its action in coagulating the proteins of the microörganisms, partly from the specific effects of the metal.

Therapeutic Uses.— Silver nitrate pills have been recommended in some forms of *dyspepsia* and *vomiting*, and in *gastric ulcer*, and have also been used as astringents in *diarrhœa*, but generally with little benefit. A very ancient use of silver oxide, and more recently of the nitrate, is that in the treatment of epilepsy, chorea, tabes and various other nervous diseases. This dates from the Arabs, and is said to have originated from the astrological medicine of that period, which taught that nervous diseases were especially affected by the phases of the moon, which was associated with silver in their system (hence lunar caustic, lunacy). Clinical experience shows that silver is of no benefit in epilepsy, and, in fact, it is improbable that silver reaches the central nervous system in any other form than inert granules. This use of silver often gave rise to argyria without benefiting the patient, about 15–30 G. proving sufficient to cause marked pigmentation.

Externally silver nitrate is employed very extensively, the sticks of lunar *caustic* being used to destroy warts and other small skin growths, to arrest capillary hæmorrhage, to destroy the false membranes of diphtheria and for other similar purposes. A solution of 2–5 per cent may also be applied to cauterize chancres and indolent *ulcers*, and weaker solutions are employed for their astringent-antiseptic action for fissures of the lips, impetigo, etc. A solution of common salt may be used to wash the part to remove the excess of silver as insoluble chloride.

Silver has a wide use for application to mucous membranes, as it is not only a good astringent but a powerful antiseptic, being especially valuable for gonorrhœal infections, *e. g.*, of the eye or urethra. For ophthalmia it is extremely valuable. For the prevention of *ophthalmia neonatorum* a routine treatment in some lying-in hospitals is to wash the eyes of the infant with a solution of silver nitrate. Credé's method,

which was once the accepted practice, consisted of the instillation of 1 drop of a 2 per cent solution of silver nitrate into each eye after the conjunctiva and lids had been carefully cleaned. This is, however, not without danger and many cases are on record where this procedure had resulted in permanent corneal opacity with gross diminution in vision. It is stated to be as efficient and much safer to employ a solution of one of the organic silver compounds. Silver is also used for other types of conjunctivitis and for trachoma.

In gonorrhœal urethritis and proctitis silver is widely used, in the form of weak solutions of the nitrate (1 in 200–500) or of protargol (1 in 100–1000). For pyelitis lavage of the renal pelvis, through a ureteral catheter, has been practised with success, using 1 per cent of silver nitrate or stronger solutions of protein or colloid compounds. Solutions are used in a similar way for cystitis and have been injected into the rectum for chronic dysentery. Generally for more sensitive mucous membranes, such as the eye and urethra, the milder protein compounds are tending to replace silver nitrate itself, as they achieve the same effect with less irritation.

For *silver arsphenamine*, see p. 207.

Protein Compounds of Silver.—The antiseptic action of silver nitrate depends upon its combining with the proteins of the microorganisms, but it combines also, and possibly with no less readiness, with the proteins of the tissues. Owing to the latter action it causes irritation and sometimes pain, and these effects are all the more noticeable as silver is so often applied to delicate mucous membranes, as the eye or urethra. Also its precipitation by proteins and by chlorides limits the antiseptic action of silver nitrate. To circumvent these drawbacks, compounds of silver have been introduced in which the metal is less easily dissociated. These compounds produce less local irritation, but their antiseptic action is likewise, though not necessarily correspondingly, reduced. Various protein compounds, for example, have been introduced on this principle.

Such compounds differ from one another not only in their percentage composition of silver but also in the degree to which their contained silver is ionizable. Generally speaking, the less ionized they are, the less irritant they are, but also the less antiseptic. Compounds of the strong silver protein (Protargol) type may contain about 8 per cent of silver, a considerable amount of which is in an ionizable form, and they are used in concentrations of from 1 to 10 per cent.

Compounds like Mild Silver Protein (Argyrol) which contain from 20 to 25 per cent of silver, almost entirely nonionizable, are used in stronger solutions, up to 25 per cent. The antiseptic action of these compounds is usually, compared with that of silver nitrate, less rapid but more lasting, and for inflammatory conditions of the eye and urethra they have established themselves as of value.

Colloidal silver (Collargol) differs from silver nitrate much in the same way as the previous compounds, its antiseptic action depending largely upon the small amount of ionizable silver.

Numerous other compounds, also less dissociable than silver nitrate, have also been used as antiseptics.

In cases of poisoning with silver nitrate, eggs, milk and, above all, common salt solution are indicated to form insoluble compounds. In argyria no improvement can be expected, though the iodide of potassium may be tried.

Preparations.

Argenti Nitras (U. S. P., B. P.) ($AgNO_3$), colorless crystals which become gray or grayish-black on exposure to light in the presence of organic matter, with a bitter, caustic, strongly metallic taste, very soluble in water, less so in alcohol. 0.01 G. ($\frac{1}{6}$ gr.); B. P., 0.008–0.016 G. ($\frac{1}{8}$–$\frac{1}{4}$ gr.).

ARGENTI NITRAS INDURATUS (U. S. P., B. P.), moulded nitrate of silver, lunar caustic—a white, hard solid, generally cast in the form of pencils, and containing about 95 per cent of silver nitrate.

The silver preparations ought to be kept in dark amber-colored bottles, in order to prevent their being reduced by light, and ought not to be prescribed with organic matter, which rapidly reduces them.

ARGENTO-PROTEINICUM FORTE, STRONG SILVER PROTEIN, STRONG PROTARGIN (U. S. P.). A compound of silver and protein containing about 8 per cent of silver.

ARGENTO-PROTEINICUM MITE, MILD SILVER PROTEIN, MILD PROTARGIN (U. S. P.). Silver rendered colloidal by the presence of or combination with protein and containing between 19 and 25 per cent of silver.

ARGENTOPROTEINUM (B. P.). Strong silver protein, containing about 8 per cent of Ag. A brown powder, somewhat hygroscopic, slowly soluble in about 2 parts of water.

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VII. MERCURY.

Mercury, one of the most powerful inorganic poisons, has been used in medicine for a long time and in a large variety of forms. Some differences are observed in the action of these, but all of them induce the same general results, the differences existing only in their local effects, and being due to the salts differing in solubility and dissociability. A soluble salt, such as the perchloride, comes into more intimate contact with the tissues, and therefore acts more powerfully locally and is also absorbed more rapidly and in larger amount than calomel, which is entirely insoluble in water. Both the local and the general effects of the perchloride are more marked than those of calomel, therefore, but when sufficient mercury in the form of calomel is absorbed into the tissues, the general effects are the same as if an equal quantity had been taken up as perchloride.

The corrosive action of the soluble mercury salts is doubtless due in part to their precipitation of the proteins, but in addition to this there is a specific toxic action on all living cells. It is unknown in what form mercury is absorbed and circulates in the blood, but there is no evidence that the insoluble preparations, such as calomel, are changed to the soluble perchloride before absorption; on the contrary, the mercury of the perchloride is precipitated in contact with proteins and must be taken up in this insoluble form. When mercury is injected hypodermically in an insoluble form, the leucocytes take it up and carry it off as they do any other foreign insoluble body, and it is quite possible

that they may take it up in the same way from the alimentary canal. Less of the insoluble preparations are absorbed merely because they come into less intimate contact with the tissues than the soluble perchloride; but even the metal may be oxidized and absorbed when it is applied to the living surfaces or injected into the blood in a state of fine division. Thus the inhalation of mercury vapor by the lungs leads to general poisoning, often of a very malignant type, and mercury rubbed into very fine globules, and applied in ointment to the skin, passes into the gland ducts and along the roots of the hairs, and is absorbed into the tissues, in which it causes the typical mercurial effects.

Symptoms.– **Acute Mercurial Poisoning** occurs only from the use of soluble preparations, and in particular from the perchloride of mercury, or corrosive sublimate. Many cases have arisen from this poison being swallowed accidentally or with suicidal intent, or from its use as a disinfectant wash for large cavities. Fatal cases have occurred from the use of mercury solutions as a vaginal douche. When corrosive sublimate is swallowed in poisonous quantity, the patient complains at once of the harsh metallic taste, which is followed by burning pain in the mouth, throat, and stomach. Nausea and vomiting set in very soon, and the vomited matter may contain shreds of mucous membrane and blood. Diarrhœa and violent tenesmus, with watery or bloody stools, often containing shreds of membrane, may be among the early symptoms, or may only occur after twenty-four hours. These symptoms from the alimentary canal are accompanied by collapse, with a small, thready, sometimes irregular, pulse; shallow, irregular, rapid respirations; cold, clammy skin; pinched features, and sunken eyes. The temperature is often subnormal, but sometimes fever is observed, although this is attributed by many to concurrent disease. The consciousness is usually unaffected, but in some cases somnolence, giddiness, or more rarely anxiety and restlessness have been observed. The urine is much diminished and complete anuria often occurs in a few hours. If the urine is not completely suppressed, it generally contains albumin, renal epithelium, casts and more rarely sugar. Death may occur within an hour from shock, but more frequently the patient survives several days or even one or two weeks, the symptoms of intestinal corrosion and of renal irritation continuing, until he finally sinks from exhaustion. Complete suppression of urine may exist for several days before death. Gangrenous colitis may occur, usually in six to twelve days, possibly the result of an attempt to excrete mercury by that channel when the kidney has ceased functioning. Corrosive sublimate has induced fatal poisoning in doses of 3 grs. or even less, but other cases have recovered from much larger doses, depending upon the rapidity of vomiting and the degree of absorption.

When acute poisoning occurs from the absorption of corrosive sublimate from wounds, the symptoms of corrosion of the mouth and stomach are absent at first, but the dysenteric symptoms and the renal inflammation are produced in the same way as when the poison is swallowed. Here again the patient may die within a few hours, but

more frequently survives for several days, and in the latter case the symptoms toward the end partake of the character of chronic poisoning. In particular, salivation and stomatitis set in in the course of a few days. These also occur when the poison is swallowed, although they are more liable to be overlooked, from the cauterization produced in the mouth by the local action.

Chronic Poisoning.—A much more frequently observed form of poisoning is that induced by the prolonged medicinal use of mercury. It may arise from any of the preparations, and from any form of application, although some methods of administration are credited with being less liable to induce it than others. Thus inunction with mercurial ointment and the use of calomel internally are both more liable to cause the severer forms of stomatitis than is corrosive sublimate. A single hypodermic injection of an insoluble preparation may induce it in susceptible persons, because the mercury is only slowly absorbed, and passes into the tissues as gradually as if it were given by the mouth regularly for several days. Thus chronic poisoning, or **Mercurialism,** is due, not to the local action, but to the effects of the drug after absorption. It may follow the abuse of mercury in any case, but some individuals exhibit a special susceptibility from some unknown cause. Formerly it was believed that the earlier symptoms of mercurial poisoning had to be induced in the cure of syphilis, but in modern therapeutics every effort is made to avoid them. The first symptoms generally arise from the *mouth and throat,* the patient complaining of a metallic taste, and of a feeling of numbness or soreness of the tongue and gums. The breath has an unpleasant fœtid odor, the tongue is swollen and thickly coated, the gums are soft, swollen and often of a dark bluish-red or gray color and the flow of saliva is augmented. If the medication be continued, as was often done formerly, ulcers appear on the gums and on the sides of the tongue where it comes in contact with the teeth, especially if these are carious, and on the mucous membrane of the cheeks; the salivation increases and irritates the lips and the skin where it is exposed to the secretion. If the administration of mercury be still persisted in, the teeth become loose and fall out, gangrene of the gums, lips and throat, and necrosis of part or even of the whole jaw may follow. The milder forms of stomatitis and salivation are observed in a large proportion of cases of syphilis treated with mercury, according to some authors, in 30 per cent or more. It may be avoided, to some extent at least, by scrupulous cleanliness of the mouth and teeth, by attention to carious teeth, and by using a 2-4 per cent solution of chlorate of potassium as a mouth wash.

The *stomach and intestine* also suffer in chronic mercury poisoning. The patient often complains of loss of appetite, and occasionally of a feeling of weight and discomfort in the stomach, nausea and vomiting, general weakness and loss of flesh. Colic and diarrhœa are frequently observed, or diarrhœa and constipation may alternate. These symptoms are naturally more liable to occur from the administration of mercury by the mouth than by other channels, as here the action after absorption is reinforced by the direct local effects. Some *fever* is some-

times noted, but this is secondary to the affection of the mouth, bowel or skin, and is not directly attributable to the mercury.

Occasionally *skin eruptions* are seen when mercury is given by the mouth, but much more frequently when it is applied to the skin. In the latter case they are not limited to the point of application, although they often begin from it and spread over a large surface of the body. They vary greatly in form, consisting of small reddish spots, large red erythematous surfaces, urticaria, or eczema, each of these occurring alone or in succession, and being usually followed by desquamation. The eruption generally lasts only one to three weeks, but in some cases has not entirely disappeared until three months after its appearance, and in others has returned repeatedly afterwards. It is said to have been induced occasionally by a single dose of calomel.

The *urine* is often somewhat increased, but may be decreased afterwards, and it not infrequently contains albumin, although the proportion of cases in which this occurs is much disputed, and the amount in the urine is generally very small. Glycosuria is much rarer in man, but has been frequently observed in rabbits after prolonged treatment with mercury.

It is still a matter of doubt how far the *sexual organs* are involved in mercury poisoning. According to some authorities disturbances of the menstruation and even complete amenorrhœa have been observed, and abortion is also stated to have been caused by it.

A general condition of *cachexia* may be induced by these disorders, and is marked by pallor, anæmia, emaciation, weakness and restlessness, with a tendency to fainting and disturbed sleep. The pulse is small, weak and quick, and the patient often complains of breathlessness.

Affections of the *central nervous system* are rarely induced now by the abuse of mercury in therapeutics, but still occur in the case of workers in mercury mines, in mirror, barometer, thermometer, and other manufactories, in which mercury is used and its fumes are inhaled by the workmen for prolonged periods. One of these affections is the mercurial *erethism*, a condition of abnormal irritability, timidity or shyness, accompanied by great muscular weakness, and sometimes developing into sleeplessness, delirium and transitory hallucinations. Another well-known form is the mercurial *tremor*, which affects the hands and arms first, later the legs, and sometimes extends over all the muscles of the body. Shooting pains along the nerves or in the joints are sometimes complained of, circumscribed areas of partial anæsthesia, amblyopia, anosmia or deafness have been described, and in some cases localized paralysis of the muscles of the arm or leg has been induced.

The symptoms of mercurial poisoning, both acute and chronic, in animals, resemble those in man so closely that it is unnecessary to describe them further.

Action.—Lower Forms of Life.—Mercury is destructive to living matter wherever it comes in contact with it in sufficient concentration. This poisonous action is naturally much more evident when soluble

preparations are used than when the oxides or calomel are in question. Thus corrosive sublimate in a solution of one part in 50,000 destroys infusoria in some twenty minutes, and even one part in one million kills algæ in the course of a few days. The effects of mercury in syphilis arise from its affecting the specific organism in a similar way, for mercury in a dilution of 1 in 200,000 destroys spirochætes in the test-tube. The exact amount of mercury present in an active form in the tissues cannot be estimated, but it probably is effective in very great dilution in cases of syphilis. Here, as in the case of other specifics (quinine, arsenic, antimony, etc.), mercury seems to have a stronger affinity for the parasite than for the tissues of the host, and even than for nearly related organisms; for mercury has little effect in malaria or trypanosomiasis, that is, it does not injure the organisms of these diseases in the same degree as it does that of syphilis. The bacteria are somewhat more resistant than these forms, but corrosive sublimate is said to delay the development of some of these in a solution of 1 part in 1,000,000, and the anthrax bacillus fails to grow in blood which contains 1 part in 8000. A solution of 1 part in 1000 is generally regarded as capable of disinfecting fluids completely in the course of a few hours. Much lower concentrations act as antiseptics if given sufficient time, time being necessary for the absorption and subsequent penetration of the metal. The presence of organic matter reduces the antiseptic action, so that mercury is not generally suitable for rapid disinfectant action, especially in the presence of excess of proteins. There is no doubt, however, that corrosive sublimate and the other soluble salts of mercury are among the most powerful antiseptics at present available. The insoluble preparations are less poisonous, owing to the difficulty in bringing them into intimate contact with the microbes.

In the **Higher Animals and in Man** the same destructive effects are induced by the mercury preparations. The corrosion of the mouth, throat and stomach when the perchloride is swallowed, has already been mentioned. When it is applied to the other mucous membranes, similar effects are obtained, and when it is injected hypodermically, even in dilute solution, it induces intense pain, swelling and inflammation, which is rarely followed by suppuration, but which may result in the formation of cicatrices.

When solutions of corrosive sublimate are applied to the skin, they cause a feeling of numbness very often; but when very strong solutions come in contact with tender parts of the skin, and in particular, when the salt itself is allowed to lie in contact with it for any length of time, deep corrosion, necrosis, and sloughing may follow. Even the insoluble preparations are liable to set up irritation when they are rubbed into the skin, especially if there is any preëxisting tendency to cutaneous eruption.

After absorption, mercury acts more especially on the alimentary tract and on the kidneys, although other organs are not exempt from its effects.

The Salivation and Stomatitis, which are so frequently seen under mercurial medication, are obviously not due to the local action of the

drug on its way to the stomach, for they occur equally readily when it is applied by hypodermic injection or by inunction. The saliva is sometimes excreted in enormous amounts, many litres of it being poured out in the course of twenty-four hours. It contains mercury, and has therefore a metallic taste, and tends to irritate the lips and skin where it comes in contact with them. In extreme cases it leads to sleeplessness from its accumulating in the back of the throat and awakening the patient with a feeling of suffocation. The stomatitis is due to the excretion of mercury by the glands of the mouth and throat. The irritation caused by the metal leads to excoriations, and these to the formation of ulcers, particularly where microbes are present in large numbers, as around carious teeth. The necrosis of the jaws arises from these ulcers penetrating to the bone and setting up periostitis, for mercury in itself has no specific action on bone.

Mercury has less direct effect on the **Stomach,** though congestion and even small hæmorrhages in cases of poisoning indicate that it is not entirely immune; the loss of appetite and malnutrition in chronic poisoning are ascribed to the presence of mercury in the saliva rather than to its affecting the gastric functions directly. In the **Intestine,** on the other hand, mercury is excreted in larger amount, and induces very distinct lesions. The parts affected are the cæcum and colon, while the small intestine often escapes almost entirely. The action of mercury is evidenced by hyperæmia, redness and swelling of the mucous membrane, which later develop into necrotic surfaces and ulcers along the folds; these lend it an appearance almost indistinguishable from that of chronic dysentery and may eventually end in perforation. The symptoms from the intestine are in accordance with the lesions, consisting of constant purging with very fluid, sometimes rice-water, stools, intense pain and tenesmus, blood and fragments of mucous membrane in the fæces.

The **Purgative Action** of mercury may be described here. The soluble preparations and even those which are insoluble but are readily changed to soluble forms are too irritant to the stomach to be employed for their action on the bowel. But certain preparations pass through the stomach in an insoluble form and slowly unfold a mild irritant action on the bowel mucous membrane, and, rendering it more sensitive to the presence of its contents, increase the peristalsis in the same way as the vegetable purgatives. Calomel is more widely used as a purgative now than any other mercurial, but the metallic preparations have also a certain vogue for this purpose.

These preparations pass through the stomach unchanged, and presumably form some protein combination in the mucous membranes of the intestine, but its nature is quite unknown. Only a limited proportion of the calomel administered seems to enter into this combination, for much can be regained from the stool in an organic form. And though the action on the bowel is greater after large doses, it never becomes excessive, no marked poisoning occurring from calomel, such as arises from the souble salts of mercury. A certain amount is absorbed into the tissues and is finally excreted in the urine, but in ordinary con-

ditions this is small. But when calomel fails to evacuate the bowel, absorption may occur in larger measure, and severe poisoning is said to have followed.

Small doses generally cause a soft stool without pain or straining, but after larger amounts there may be a considerable amount of fluid. In some people nausea and griping occur with calomel. Purgation usually takes place in eight to ten hours. The stools are often of a gray-green color and this has been attributed to the putrefaction of the bowel being lessened, so that the bile retains its original tint. But mercury acts when no bile reaches the intestine and the stools are of the same greenish color, so that it seems likely that this arises from the presence of some mixture of mercury sulphides in the stool.

Mercury is generally believed to act mostly on the small intestine, increasing the secretions and accelerating the passage of its contents.

The mercurial purges, and in particular calomel, have often been credited with increasing the secretion of the **Bile**, but they have not been found to have any effect on the secretion escaping from a biliary fistula. It is still possible, however, that the gall bladder may share in the increased persistalsis shown by the small intestine and that consequently there may be an accelerated evacuation of the gall bladder. There is no sufficient experimental or clinical evidence that the liver is in any way affected directly by mercury. The "biliousness" which is so often relieved by calomel or blue pill, is due, not to the liver, but to disorder of the alimentary tract.

Mercury has no such powerful effect on the **Unorganized** ferments of digestion as it has upon the microbes, for though large amounts of the soluble preparations precipitate the pepsin in artificial digestion experiments, smaller quantities have little effect. Calomel has no action on the digestive ferments, but may retard the putrefaction in the intestine, and thus limit the decomposition of the food. Its antiseptic action is aided by the increased persistalsis which follows its use, and which removes the decomposing mass from the canal.

The **Kidney** is excited by mercury, a moderate dose of calomel inducing marked diuresis, particularly in cases in which there is a large accumulation of fluid in the body, as in dropsy from heart disease. When purging follows the administration of the mercurial, less diuretic effect is observed. In normal individuals and in animals the diuretic action is generally weaker; the kidney is affected directly and not through changes in the circulation.

In acute mercurial poisoning, when death does not follow in the course of a few hours, anuria is often observed with inflammation and necrosis of the epithelium of the tubules. The whole organ is congested and the glomeruli are in a state of acute inflammation, but the necrosed tubules are the most prominent feature. Very generally in the rabbit, less often in the dog and in man, these are filled with a deposit of phosphate of calcium, which is thrown out in the necrosed cells, and as these break up, passes into the tubules. It may be remarked in passing that several other poisons, such as bismuth, and aloin, occasionally induce this deposit of lime in the kidneys.

This renal necrosis occurs chiefly in corrosive sublimate poisoning, as the more slowly absorbed, insoluble preparations apparently do not often accumulate in sufficient quantity in the blood to induce such severe effects. At the same time, albumin or casts are often observed in the urine from the treatment of syphilitic patients with mercury in any form. The more marked the action on the intestine, the less destruction of the kidney is observed in cases of severe poisoning.

The lime deposited in the kidney has suggested the idea that mercury causes the absorption of the calcium in the **Bones** through a specific action on them, but the lime deposited in the kidney is drawn from that normally circulating in the blood; in necrosed tissue from other causes lime is very often deposited, although not so rapidly as in mercury poisoning. Large doses given repeatedly lead to an increase in the size and number of the vessels of the bone-marrow, and the fat cells atrophy rapidly; later gelatinous degeneration follows and the cellular elements of the marrow disappear.

Mercury seems to have comparatively little direct action on the **Circulation** in cases of poisoning, and most of the changes in the pulse are to be ascribed rather to the shock and collapse, or in chronic poisoning to the cachexia and malnutrition, than to any direct effects on the heart and vessels; in some cases of acute poisoning, however, patches of fatty degeneration have been found in the heart. In the frog large doses of soluble salts slow and weaken the heart, and mercury salts injected into the blood-vessels of mammals have been found to cause a sudden descent of the blood-pressure and paralysis of the heart. Subcutaneously injected into animals, the soluble salts reduce the blood-pressure more gradually, but at the end a very sudden descent to zero occurs. The action is in part on the heart, in part on the vessels (capillary poisoning).

The **Respiration** is also only affected indirectly. In chronic mercury poisoning marked breathlessness is sometimes observed and was ascribed by Kussmaul to the general muscular weakness but may arise from acid being developed in the tissues.

The action of mercury on the **Nervous System** is very obscure. In acute poisoning the intellect often remains clear to the end, and no symptoms pointing to any direct affection of the central nervous system are observed. In chronic poisoning, however, the higher centres are undoubtedly involved in the effects, as is shown by the erethism and occasional hallucinations. The tremor also is probably of cerebral origin though this is not yet certain, and the general muscular weakness is not due to the peripheral muscles and nerves being affected, but to the alterations in the centres. The paralysis sometimes observed in the arms or legs in workers in mercury, and the areas of partial anæsthesia and the pains in joints probably arise from peripheral neuritis. In some cases, especially where the tremor is marked, the reflex excitability of the spinal cord has been found to be exaggerated but it is generally unaffected. The muscles do not seem to be acted on directly in either acute or chronic poisoning in man, and even when paralysis is developed, they maintain their irritability and do not atrophy.

A good deal of interest has been manifested in the question whether mercury affects the **Nutrition** in any way except through its action on the alimentary canal. It is sometimes stated that the protein metabolism is accelerated, but the subject is a difficult one to investigate, for when any save the smallest doses are given, the kidney and bowel

are involved in the effects, and the prolonged use of mercury is restricted to experiments on animals and on syphilitics. The cachexia of chronic poisoning may be due in part to a specific action on the metabolism, but it is impossible to determine this point, because the alterations in the alimentary tract are in themselves sufficient to cause such symptoms.

Changes in the **Blood Corpuscles** have been observed under mercurial treatment in a number of instances, but there is as yet no general agreement as to wherein these consist, and it seems not unlikely that the blood reaction in health is different from that in syphilis and that it may vary in the successive stages of the disease. In health the red corpuscles and the hæmoglobin are said to be augmented at first but afterward diminished, while in syphilis a sharp fall in the amount of hæmoglobin is succeeded by an increase to beyond that present before the treatment. Kuperwasser states that in healthy persons mercury increases the number of newly formed leucocytes but that this is more than counterbalanced by the fall in the older cells; in syphilis he found fewer recently formed leucocytes and more mature ones after mercury.

Mercury has no effect on the **Temperature** in itself, but when stomatitis or skin eruptions are developed, some fever generally accompanies them, while in collapse the temperature may fall several degrees below the normal.

Distribution.—After its prolonged use mercury is found in almost every organ of the body, but larger quantities are found in the kidney, intestinal wall and especially in the liver. In cases of acute poisoning through absorption from the subcutaneous tissue or from wounded surfaces, the distribution is the same. The statement that mercury is stored up in the bones has been recently reaffirmed and traces are certainly found here, as in the muscles, brain, lungs, intestine, and spleen.

Mercury is **Eliminated** by almost all the excretory organs, but most largely by the intestine and kidney. It has been found in small quantities in the perspiration, milk, saliva, gastric juice and bile, and has been shown to pass to the fœtus in utero through the placental circulation. The excretion in the urine begins within an hour when mercury is injected intravenously, but more slowly by the ordinary methods of administration; for example, after inunction, none may be found for twenty-four hours. The quantity eliminated daily rises slowly during the treatment and then falls gradually. The excretion is very slow and varies according to the method of administration; there is no question, however, that after the usual methods of administration in syphilis mercury is found in the urine for months and in some cases for years after the last dose. No accurate estimation of the mercury excreted in the fæces has been made, but it is believed that less is excreted here than in the urine at first, but that later the greater part may pass out by the intestine. The administration of potassium iodide does not accelerate the elimination of mercury. In the urine the mercury probably exists for the most part in the form of a salt, although some of it may be in organic combination.

Therapeutic Uses.—The chief purpose for which mercury is used internally is the treatment of **Syphilis.** Its curative effects in this disease are due to its specific destructive action on the *Treponema pallidum*, the organism of syphilis. Long a subject of discussion, its usefulness in this infection is now acknowledged by all who have studied the subject. It is true that mild cases sometimes recover without the use of mercury, but even these run a shorter course if mercury is administered. And in many others, in which the symptoms show no signs of abating under hygienic measures, mercury causes a rapid and permanent improvement. A certain number of relapses undoubtedly occur after the mercurial treatment has been stopped, but it seems probable that many of these would not have had even temporary relief without mercury. In a certain proportion of malignant forms mercury is unable to arrest the progress of the disease. And when the organism has invaded the central nervous system, mercury does not seem to be able to reach it, for little or no improvement is obtained from its use in tabes or in general paralysis of the insane.

The effects of mercury in syphilis present many analogies to that of arsenic and antimony in trypanosomiasis; in each a protozoal parasite in the tissues is in some cases destroyed by the specific remedy, and this is fortunately often complete in syphilis; but in other cases a relapse occurs from some of the organisms surviving the first treatment. In the case of the trypanosomes these survivors are more resistant to the specific than the original infection, and this appears to hold for the organisms of syphilis also; but these organisms do not acquire so high or so permanent a tolerance for mercury as they do for arsenic.

The recent introduction of the organic arsenic compounds has not led to the mercurial treatment being abandoned, for it is found necessary to combine the action of both parasiticides to obtain the best results in the treatment of syphilis. The injection of arsphenamine ought to be supplemented by a vigorous use of mercury or bismuth until the specific Wassermann reaction disappears and remains absent.

The study of the arsenic treatment seems to have finally determined a long debated question, whether mercury should be exhibited in the primary stage of syphilis. The danger of a widespread infection, possibly involving the central nervous system, is now recognized to be so great that no delay is permissible; vigorous treatment with arsphenamine and mercury should be instituted as soon as the disease is diagnosed and should be continued as long as there is any risk of a relapse. The treatment with mercury is not so heroic now as a century ago, and all are agreed that it ought not to be allowed to induce any but the earliest symptoms of chronic poisoning. In tertiary syphilis mercury is generally associated with the iodides, as it is found that the resolution of the new-grown tissue by the latter facilitates the destruction of the spirochæte by the mercury. In animals mercury in large doses has been found to prevent infection with syphilis.

Mercury has been used in syphilis in a large number of forms, and of late years many new preparations and new methods of administration have been proposed. Mercury cures syphilis by destroying the

organism, and this object is to be attained by introducing enough of the metal to act on the spirochæte without inducing symptoms from its action on the tissues. The estimation of the metal absorbed by the different forms of treatment is thus of much interest, and a fairly accurate idea of the amount absorbed appears to be given by that excreted. The best clinical results appear to follow from a rapid absorption and prolonged excretion, as, if the stay of the mercury in the tissues is short, relapses are liable to occur. Each method of administering mercury has its own advantages and disadvantages, the chief methods being by mouth, by inunction and by injection. Administration *by mouth* has the advantage of being less troublesome and the preparations generally used are corrosive sublimate, calomel, or the metallic preparations—blue pill and gray powder—the last being used most widely in England. Calomel and the metallic preparations are, however, very liable to induce diarrhœa, from their being insoluble and thus passing far down the intestine before being absorbed, and opium is therefore often prescribed along with them. Calomel is also credited with causing salivation and stomatitis more readily than the other preparations, perhaps because it is more difficult to gauge how much of it is absorbed than in the case of the soluble perchloride. Large amounts of mercury have been shown to be absorbed when calomel and other salts are taken, but the concentration in the blood appears to vary more irregularly from day to day than when other methods are employed. And mercury administered by the mouth is in all cases more liable to derange the digestion than when administered by other channels, and on the whole is less certain and less satisfactory in its results.

Inunction was introduced to avoid the disturbance of the stomach and intestine caused by the local action of the mercury, while that due to its excretion along the alimentary tract remained unchanged. Mercury ointment is rubbed into the skin and is absorbed in part from the ducts of the glands and in part by the lungs as vapor. For this purpose 2–4 G. ($\frac{1}{2}$–1 dr.) is rubbed in daily in different parts of the body, in order to avoid the irritation induced by applying it repeatedly to one spot. A warm bath is taken first, and the patient then rubs in the ointment on the inside of the thighs, next day on the inside of the arms, on the following days on the forearms, legs, abdomen and back, returning to the thighs on the seventh day and repeating the series. The treatment is continued for a fortnight or three weeks. The absorption is slower than by internal administration, but is more regular and lasts longer and there is less disturbance of digestion. Salivation is not so readily produced as by oral administration but, when it occurs, it lasts longer and may become severe. The objection to the method is that it is inconvenient and uncleanly, and that it is even less possible to estimate the amount of mercury actually absorbed than when it is given by the mouth. Instead of mercury ointment being rubbed into the skin, one of the plasters, or lint containing mercurial ointment (Weylander) may be applied to it, permitting of the continuous absorption of small quantities by the skin and by inhalation of the vapor.

Lewin, in 1867, introduced the method of administering mercury by

injection, employing a dilute solution of mercuric chloride for this purpose; and since then an extensive trial has been given to injection methods. Mercury has been given subcutaneously, intramuscularly, and intravenously, the general advantage being the avoidance of digestive disturbances, cleanliness, and a more accurate estimation of the amount of mercury administered. *Subcutaneous injection* has been almost abandoned because of the pain caused and of the relatively imperfect absorption. *Intravenous injection* has also had little vogue. It is liable to injure the vein and to produce emboli; excretion is too rapid and it causes the maximum injury to the kidney. *Intramuscular injection*, however, has steadily increased in popularity and it is now a favorite method of administering mercury in syphilis. Various preparations have been used for intramuscular injection. A soluble salt like the bichloride, given in water solution, is most rapidly absorbed but is also relatively rapidly excreted, so that injections have to be repeated every one or two days. Such a solution also causes much pain, so that the tendency has been to employ for intramuscular injection less soluble preparations. Thus the benzoate or succinimide cause less pain than the bichloride. Also the local actions can be diminished, and absorption retarded, by administering the mercurial in some form of vegetable oil. The salicylate of mercury, which is almost insoluble in water but rendered soluble by the presence of other salts, is often used as a 10 per cent suspension in a vegetable oil, injection of 1 cc. being given once a week.

Insoluble compounds like calomel or metallic mercury itself, suspended in oil have been widely used. The B. P. contains two such injections. The injection is usually given once a week deep into the gluteal muscles. The injection is only slowly absorbed and forms a depot from which mercury is gradually taken up.

Suppositories of mercury have been used to some extent and are said to disturb the digestion less than the administration per os.

Mercury *fumigations* have also been practised to a limited extent, the vapor of mercury being freed by heating calomel or the sulphide. The patient sits in a tent up to his neck, and the mercury deposited on the skin is absorbed. The method is very cumbrous and the quantity of mercury taken up cannot be controlled.

The **Other Protozoal Infections** are not so amenable to mercurial treatment as syphilis, and it has proved of little value in malaria or trypanosomiasis. Some spirillar infections in animals are said to react to mercury in the same way as syphilis, however.

Mercury was recommended by Hamilton in the beginning of the last century in the treatment of **Acute Febrile Affections,** and the greatest abuse unquestionably prevailed in the earlier decades. Later its sphere of usefulness was restricted to the treatment of inflammation of the serous membranes—pleurisy, meningitis, pericarditis, peritonitis—but its usefulness in these conditions has never been established and its employment is now more limited; in acute iritis it is still used widely. In these cases it is always administered by the mouth in the form of calomel, blue pill, or gray powder.

Mercurochrome, a compound of mercury and fluorescein, has been used in a variety of **Septicæmic Conditions**—in erysipelas, cellulitis and similar infections. Good results have been described in many cases, but the value of remedies in these conditions is often difficult to estimate and this remedy, like so many others, has not lived up to its first recommendations.

The mercurials are largely used as occasional **Purgatives** for acute constipation, not so frequently in chronic constipation. In "biliousness" and in the diarrhœa of putrefaction they have a high reputation, but their action here is not materially different from that of other purgatives. There is no evidence that they are of value when the intestinal wall itself is the seat of infection. They may therefore be given where preëxisting irritation contra-indicates the use of most other purgatives. They are often advised in affections of the liver but it is a question whether they have any effect here except as purges. Calomel and gray powder are especially adapted for children and are of value in summer diarrhœa and similar affections. They are quite tasteless and are easily taken in sugar or jam. Very often a mercurial is taken at night and is followed in the morning with a saline purgative such as Seidlitz powder. There is a marked variation in individual response to calomel; $\frac{1}{2}$ gr. may produce as free purgation in one individual as 5 grs. in another. It occasionally produces nausea and griping.

Calomel should be avoided in nephritis and is said to be dangerous when iodides are being given since the poisonous periodide of mercury may be formed.

Calomel and other mercurials have long been known to be of value in cases of **Dropsy.** One of the best preparations is calomel, given in 0.2 G. (3 grs.) doses three times a day or in 0.1 G. ($1\frac{1}{2}$ grs.) doses five times a day. It is of great value in certain cases of cardiac dropsy, but is less reliable in the accumulations of fluid met with in hepatic or renal disease, although here too its administration is sometimes followed by the rapid excretion of the fluid. It does not seem to be contra-indicated in chronic nephritis, although its action has to be carefully controlled. It has no effect in removing the exudations of acute inflammation such as pleurisy. Blue pill is also given in cardiac dropsy, often with squill or digitalis, but is inferior to calomel as a diuretic.

More recently *Merbaphenum* (*Novasurol*) has been widely used as a diuretic. It is a complicated compound of mercury with barbital, containing 34 per cent of mercury, and is prepared for use as a 10 per cent solution which is given intravenously or intramuscularly in doses of 0.5 to 2 cc. Novasurol is a very powerful diuretic especially in cardiac œdemas and is sometimes successful when other remedies fail. Diuresis commences in one to three hours and reaches its height in six to eight hours. It is characterized by a marked increase in the chlorides of the urine.

Another complex aromatic mercury compound, *Mersalyl* (*Salyrgan*), has been introduced more recently. It contains about 40 per cent of mercury in a non-ionizable form and is given by intravenous or intramuscular injection. It has been used especially in œdema or ascites of

cardiac origin in which the results are sometimes good and profuse diuresis may follow a single injection. It is claimed that toxic effects with it are rare, and that in this respect it is superior to Novasurol. The diuretic effect of these compounds is often enhanced by the simultaneous administration of ammonium chloride or nitrate by mouth. Other proprietary compounds of mercury have been used as diuretics, *e. g.*, neptol and novurit.

Mercury is used **Externally** as a **Disinfectant** wash in surgical operations, chiefly in the form of the perchloride, but also as the cyanide and oxycyanide. (See page 787.)

Numerous ointments have been applied externally in the treatment of **Skin Diseases**, particularly those of a parasitic nature, such as itch, and in condylomata, ulcers, and skin diseases of syphilitic origin. These preparations combine a disinfectant with a more or less irritant action, and unlike carbolic acid and its allies, are equally powerful antiseptics in ointments and in water. Other external applications are the plasters and the black wash. Ointments containing calomel, corrosive sublimate and other preparations are sometimes prescribed, or calomel may be used as a dusting powder in syphilitic ulcers and as a prophylactic against infection. The mercury ointments are frequently applied to the eye, the milder ones as antiseptics and slight irritants, citrine ointment to destroy granulations.

The nitrate of mercury and its ointment (citrine) are sometimes used as caustics for application to the os uteri, condylomata, and elsewhere.

Mercury treatment is **Contraindicated,** or requires special caution in cases of profound cachexia, weakness or anæmia, unless these arise from syphilis. Where the digestion is weak and in cases of tuberculosis, it ought to be avoided if possible. In severe nephritis it is also to be used with caution, although it is beneficial in some cases, and although some authorities deny that it is injurious even when it has no diuretic action. In pregnancy mercury is not absolutely contraindicated, at any rate up to the sixth month. Later it is liable to injure the patient by its action on the digestion, and in some cases has induced abortion; the child may also suffer from mercurial poisoning. Mercurial ointments or dusting powders have to be used with care when iodides are being administered internally, as the iodide of mercury may be formed and may cause violent corrosion. Thus in the eye, severe effects have been induced by the application of calomel to the cornea while iodide of potassium was being given.

In cases of **Acute Corrosive Poisoning**, the indications are the evacuation of the stomach, preferably by the stomach tube. Tannic acid, or eggs, milk and other albuminous substances may be given to precipitate the metal and protect the mucous membrane. Rosenthal has recently advocated the use of sodium formaldehyde sulphoxalate in acute mercury poisoning, the stomach being first washed out with a 5 per cent solution, and about 200 cc. left in the stomach. Immediately afterwards 10 G. of the drug dissolved in 100–200 cc. of distilled water is slowly injected intravenously, from twenty to thirty minutes being

allowed for the injection. This treatment is the more effective the sooner it is given after poisoning. Decapsulation of the kidney should be tried in cases of acute mercury poisoning which are not yielding to appropriate medical treatment but operative treatment is not defensible if the patient is moribund or if gangrenous colitis is present (Brenner). The treatment of the later symptoms is the same as that of the chronic form.

In **Chronic Poisoning** the salivation and stomatitis are treated by the use of potassium chlorate solution as a mouth wash, and its free application during mercurial treatment, along with careful brushing of the teeth, is believed by most physicians to hinder the onset of the symptoms. Tannic acid solution is also recommended as a mouth wash. The diarrhœa may be treated with opium, the other symptoms on general principles. In any case the drug ought to be abandoned or the dose much reduced, as soon as the salivation becomes marked. Iodide of potassium and hot baths or sulphur baths are often advised in chronic poisoning with the view of accelerating the elimination of the metal, but careful estimations have shown that they have no such effect.

Preparations.

U. S. P.

Hydrargyri Bichloridum, Corrosive Sublimate ($HgCl_2$), forms heavy, colorless crystals without odor, but possessing an acrid, metallic taste, soluble in 16 parts of cold water, in 2 parts of boiling water, in 3 parts of alcohol. Dose, 0.003 G. ($\frac{1}{20}$ gr.).

Toxitabellæ Hydrargyri Bichloridi, Magnæ and Parvæ. The large tablets contain about 0.5 G. of $HgCl_2$, the small, 0.125 G.

Hydrargyri Chloridum Mite, mild mercurous chloride, Calomel (Hg_2Cl_2), a heavy white powder, without odor or taste, insoluble in water, alcohol and ether. 0.15 G. ($2\frac{1}{2}$ grs.); in powder or tablets, less suitably in pill form.

Hydrargyri Salicylas, a white or yellowish powder, practically insoluble in water. 0.06 G. (1 gr.) intramuscularly.

Hydrargyri Succinimidum, white crystals or powder, soluble 1 in 20 in water. 0.015 G. ($\frac{1}{4}$ gr.).

Hydrargyrum cum Creta, mercury with chalk, Gray Powder, is formed by rubbing up metallic mercury with chalk and honey until the mercury is divided into very fine globules, each encased in chalk. It forms a light-gray, somewhat damp powder, without odor and with a sweetish taste from the honey. The mercury (38 per cent) remains in the metallic state, very little oxide being formed. It is insoluble in water, alcohol and ether, and is always prescribed in powder form. 0.25 G. (4 grs.).

Massa Hydrargyri, mass of mercury, Blue Mass, Blue Pill, is formed from metallic mercury by rubbing it with honey, glycerin, althæa and liquorice until the globules are invisible under a lens magnifying ten diameters. The blue mass contains about 33 per cent of mercury, almost entirely in the metallic form. It is of the consistency of pills and is always prescribed in this form. 0.2 G. (3 grs.).

Unguentum Hydrargyri Forte, mercurial ointment, is formed by triturating metallic mercury with wool-fat and petrolatum until the globules are invisible when magnified 10 diameters. The ointment contains about 50 per cent of metallic mercury.

Unguentum Hydrargyri Mite, Blue Ointment, contains 33 per cent of mercury.

OLEATUM HYDRARGYRI, oleate of mercury, has been used for the same purposes as mercury ointment, but is somewhat more irritant and possesses no compensating virtues.

HYDRARGYRI OXIDUM FLAVUM, yellow mercuric oxide, an orange-yellow, impalpable powder, almost insoluble in water.

UNGUENTUM HYDRARGYRI OXIDI FLAVI, 1 per cent.

HYDRARGYRUM AMMONIATUM, mercuric ammonium chloride, white precipitate (NH_2HgCl), is formed by precipitating corrosive sublimate with ammonia, and is a white, amorphous powder, without odor and with an earthy, metallic taste, almost insoluble in water and alcohol.

UNGUENTUM HYDRARGYRI AMMONIATI, 10 per cent.

MERBAPHENUM (NOVASUROL), a double salt of sodium mercurichlorphenyl oxyacetate with barbital, containing 34 per cent of mercury, forms a white crystalline powder soluble in water. Dose as a diuretic, 0.5 to 2 cc. of 10 per cent solution intravenously or intramuscularly once or twice a week. U. S. P. 0.15 G. ($2\frac{1}{2}$ grs.) by hypodermic injection.

B. P.

HYDRARGYRI PERCHLORIDUM, mercuric chloride, corrosive sublimate. 0.002–0.004 G.; $\frac{1}{32}$–$\frac{1}{16}$ gr.

LIQUOR HYDRARGYRI PERCHLORIDI, 0.1 per cent in distilled water. 2–4 mils. (30–60 mins.).

HYDRARGYRI SUBCHLORIDUM, calomel. 0.03 0.2 G. ($\frac{1}{2}$–3 grs.). By intramuscular injection, 0.03–0.06 G. ($\frac{1}{2}$–1 gr.).

INJECTIO HYDRARGYRI SUBCHLORIDI, 5 per cent in wool-fat, olive oil, etc. By intramuscular injection, 0.6–1.2 mils. (10–20 mins.).

UNGUENTUM HYDRARGYRI SUBCHLORIDI, 20 per cent in simple ointment.

LOTIO HYDRARGYRI NIGRA, contains black mercurous oxide from interaction of calomel with calcium hydroxide. Used as a local remedy in syphilitic lesions.

HYDRARGYRUM, quicksilver, Hg; the liquid metal. 0.03–0.2 G. ($\frac{1}{2}$ 3 grs.). (One-third of that dosage by intramuscular injection.)

INJECTIO HYDRARGYRI, 10 per cent in wool-fat, olive oil, camphor and creosote. 0.3–0.6 mil. (5–10 mins.) by intramuscular injection.

PILULA HYDRARGYRI, blue pill, 33 per cent. 0.25 0.5 G. (4–8 grs.).

HYDRARGYRUM CUM CRETA, gray powder, 1 part of mercury with 2 of chalk. 0.06–0.3 G. (1–5 grs.).

UNGUENTUM HYDRARGYRI, blue ointment, 30 per cent.

UNGUENTUM HYDRARGYRI COMPOSITUM, 12 per cent.

UNGUENTUM HYDRARGYRI NITRATIS FORTE, citrine ointment is used, diluted with oil or lard, in conjunctivitis, and also as an application to syphilitic sores and gangrenous ulcers; it is acid and strongly irritant. 6.7 per cent.

UNGUENTUM HYDRARGYRI NITRATIS DILUTUM, citrine ointment diluted to one part in five.

HYDRARGYRUM OLEATUM, mercuric oleate, contains the equivalent of 20 per cent of mercuric oxide.

UNGUENTUM HYDRARGYRI OLEATI, 25 per cent in simple ointment.

HYDRARGYRI OXYCYANIDUM, a white powder, soluble in about 18 parts of water. By intramuscular injection, 0.005–0.01 G. ($\frac{1}{12}$–$\frac{1}{6}$ gr.); by intravenous injection, 0.01 G. ($\frac{1}{6}$ gr.).

HYDRARGYRI IODIDUM RUBRUM, 0.002–0.004 G. ($\frac{1}{32}$–$\frac{1}{16}$ gr.).

LIQUOR ARSENI ET HYDRARGYRI IODIDI, Donovan's solution. 0.3–1 mil. (5–15 mins.).

HYDRARGYRI OXIDUM FLAVUM, yellow mercuric oxide, an orange-yellow amorphous powder, insoluble in water.

OCULENTUM HYDRARGYRI OXIDI, 1 per cent.

HYDRARGYRUM AMMONIATUM, white precipitate, a white powder insoluble in water.

UNGUENTUM HYDRARGYRI AMMONIATI, 5 per cent in simple ointment.

A large number of new preparations of mercury have been introduced of late years and have received a more or less extensive trial, but have seldom

been found to be superior to the older forms. Among these may be mentioned the *tannate*, which was introduced in the hope that it would cause less purgation than calomel, and might therefore be better adapted for the treatment of syphilis. 0.1–0.3 G. (2–5 grs.) in powder. The *carbolate, salicylate* (*either neutral or basic*), *benzoate, sozoiodolate, thymol-acetate* and many other similar compounds have been used instead of calomel for hypodermic or intramuscular injection, and have each in succession been advocated as the best preparation. The salicylate is said to be excreted more rapidly than the inorganic salts. Several amino-acid salts of mercury such as the *formamide*, the *amino-propionate* (alanin mercury) and the *succinimide* have been proposed as substitutes for corrosive sublimate in hypodermic injection. It was believed that the affinity of mercury for nitrogen being satisfied in these compounds, it would attack the proteins less, and as a matter of fact, the injections are said to be less painful than those of corrosive sublimate. *Colloid mercury* (*Hyrgol*) has been injected intramuscularly, but has no advantage over the older preparations.

MERCUROCHROME, the disodium salt of dibromohydroxy-mercurifluorescein, containing 26 per cent of mercury, is in the form of iridescent green scales, freely soluble in water. Used locally as an antiseptic in 1 to 4 per cent solution; intravenously, 5 mg. per kilogram as 1 per cent solution.

MERSALYLUM (B. P.). Mersalyl (Salyrgan) contains 39·6 per cent of mercury. It is very soluble in water. *Injectio mersalyli* (B. P.) is a 10 per cent solution. Dose, 0·5–2 mils. (8–30 mins.) by intramuscular or intravenous injection.

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VIII. MINOR METALS.

Gold.

Gold has been used at various times as a therapeutic agent generally for fantastic reasons. In recent years, however, it has been subjected to more scientific scrutiny, especially as a possible remedy for tuberculosis and syphilis.

In experimental syphilis it has been found to have a definite effect, but is inferior in activity to mercury, while producing more undesirable effects. It had been tried in tuberculosis over fifty years ago but was reintroduced by Mollgaard. He employs a thio-sulphate of sodium and gold (sanocrysin), containing about 40 per cent of the latter metal, which is very soluble and is given intravenously. The dosage varies according to the condition and reaction of the patient but a common dosage is 0.5 G at the beginning followed by 4 to 10 doses of 1 G given at weekly intervals. It is notoriously difficult to estimate the value of a remedy in tuberculosis and the merits of sanocrysin are not yet decided. Gold has certainly nothing like the remedial effect in tuberculosis that arsenic has in syphilis.

On the other hand, a great many cases have been recorded in which at least temporary improvement has been produced by sanocrysin, as estimated by alleviation of fever, diminution of sputum, reduction of the number of bacilli in the sputum and improvement in the general condition of the patient. Some cases are not improved and, unless dosage is carefully watched, some may even be made worse. Good results have been claimed in lupus erythematosus. In rheumatoid arthritis gold compounds have been widely used in the last few years and improvement has been recorded in over half of the treated cases. Injections are usually given intramuscularly at intervals of five days or more, and should be given as early in the disease as possible.

Of the disagreeable effects observed in human beings after sanocrysin injections, the more common are rise of temperature, nausea, and vomiting, rashes, ulceration of the mouth, rectal spasm, and albuminuria. The dermatitis may be severe. Toxic hepatitis, purpura, and agranulocytosis have occurred from the use of gold compounds in rheumatoid arthritis. The major part of an injection is excreted very slowly.

When given by mouth, soluble gold salts act as gastro-intestinal irritants and readily produce vomiting. Intravenously given they produce a fall in blood-pressure, due especially to dilatation of the mesenteric vessels. In chronic poisoning, loss of weight with ulceration of the stomach and intestine are the most conspicuous effects.

Platinum.

Platinum resembles gold in its action, but is more poisonous. In the frog it paralyzes the central nervous system and later the striated muscles. Kebler observed a stage of convulsions precede that of paralysis, the spasms evidently arising from the spinal cord or medulla oblongata. In mammals the symptoms resemble those of gold poisoning in almost every detail. Small quantities of platinum double salts injected intravenously increase the urine to some extent; larger injections cause albuminuria.

Platinum, like gold, was at one time advised in syphilis, but has never been widely used.

Chromium.

Chromium is used in medicine in the form of chromic acid and the bichromate of potassium, which are both powerful oxidizing bodies in addition to their poisonous action as metallic oxides. The former property renders them more irritant and corrosive than most of the salts of the heavy metals. Chromic acid in particular is a powerful caustic, combining the action of a metallic oxide, an acid and a strongly oxidizing agent. Applied to the skin in substance it corrodes it, but is said to cause less pain than the more penetrating caustic

potash. Even in dilute solution, the chromic salts and the acid act as skin irritants. In industrial poisoning by chromium, the chief symptoms are diffuse dermatitis, usually on the hands or forearms, frequently with deep perforating ulcers. These ulcers arise from any abrasion of the skin, and the cartilaginous septum of the nose is also a common seat of ulceration which eventually leads to perforation. They are due to the local action of the poison and not to its absorption; they are said to be almost painless. The inhalation of the dust leads to chronic bronchitis, while that swallowed and absorbed may give rise to nephritis.

Symptoms.—In acute poisoning, when a large quantity of the acid or of a salt is swallowed, the symptoms are those of gastro-intestinal corrosion, intense pain in the throat and stomach, vomiting and purging, with blood in the vomited matter and the stools, collapse, and frequently death. The mouth and throat are stained yellow, and the stomach and intestine exhibit the usual appearance of violent corrosive poisoning.

The general action of chromic preparations may be elicited in animals by subcutaneous or intravenous injection, or by the administration of smaller quantities by the mouth. The symptoms resemble those caused by the general action of other metals. In the frog increasing weakness, tremor, and eventually paralysis of the central nervous system are induced. In the mammal weakness and slowness in the movements is followed by albuminuria, glycosuria, diarrhœa, and vomiting. Sometimes twitching of the muscles or even convulsions are seen, and then the weakness passes into general paralysis. The heart seems little affected by chromium, but the blood-pressure falls. After death the stomach and bowel are found congested, and the mucous membrane is necrosed and ulcerated in some parts, covered with ecchymoses in others. Hæmorrhages are also found in other organs of the body, notably in the heart wall. The kidney is in a state of acute parenchymatous nephritis and may contain deposits of uric acid; albumin, casts, and often blood cells appear in the urine. In chronic poisoning interstitial nephritis is said to occur.

Chromic acid and its salts are readily absorbed from the stomach and intestine. They seem to be excreted for the most part through the kidney, to a less extent probably by the intestinal epithelium. In the urine the metal occurs in part in organic combination.

Chromii Trioxidum (U. S. P., B. P.), chromic acid or anhydride (CrO_3), forms crystals of dark purplish-red color and metallic lustre, odorless, very soluble in water. When brought in contact with organic substances, such as alcohol, glycerin or sugar, it oxidizes them rapidly and often violently with explosion.

Chromic acid is used as a caustic application to malignant growths, condylomata, lupus and diphtheritic membranes, to a less extent as an irritant disinfectant. It has generally been applied by dipping a glass rod into a solution formed by allowing the crystals to deliquesce, or it may be fused on the end of a wire. It has also been advised in 5 per cent solution as an application to prevent perspiration of the feet and to harden the skin. Weaker solutions (0.1–1 per cent) may be used in ozæna, leucorrhœa, etc.

Manganese.

Traces of manganese are found in the blood and tissues of man and animals very frequently, but this metal is not an essential constituent of the body, but is apparently absorbed accidentally with the food. The salts of manganese in large quantities cause acute irritation of the stomach and intestine, like those of the other heavy metals, and a form of chronic poisoning has been described in workmen exposed to manganese dust; the symptoms are chiefly stolid mask-like features, hysterical laughter or grief, languor and sleepiness and similar psychical manifestations, and later motor disturbances which are exhibited in a spastic gait, tremor and twitching of muscles, or cramps and stiffness and increased tendon reflexes. These symptoms are ascribed to lesions of the basal ganglia of the brain and when they are developed, no recovery occurs, although

the patient may live many years. Manganese is absorbed from the alimentary tract only in very small quantity, and it appears to resemble iron closely in its course through the tissues. Its general action has been elicited by the hypodermic or intravenous injection of double salts. In frogs manganese injected hypodermically causes a descending paralysis of the brain and spinal cord, and later weakens and arrests the heart while the peripheral muscles and nerves seem unaffected. In mammals large injections induce epileptiform convulsions, particularly in the rabbit and guinea-pig. Smaller quantities, which cause a less acute intoxication, induce in the dog nausea and vomiting, diarrhœa, weakness, somnolence, stupor, and death from arrest of the respiration. The urine is often increased, and contains bile pigment, and, toward death, albumin and casts. The stomach and bowel present no congestion or ulceration in these cases. Manganese is found in the vomited matter and the stools, in the liver, kidney, and intestinal wall, to a less extent in the other organs. In acute poisoning in mammals the blood-pressure falls, from depression and paralysis of the vasomotor centre, while the heart is affected only much later. In subacute poisoning the darker color of the urine indicates icterus, but this is much more marked when small quantities are repeatedly injected into the subcutaneous tissues, and chronic poisoning induced. In chronic cases the nephritis, which is shown in the acute poisoning by albuminuria, is also more developed, the inflammation commencing in the cells of the tubules but later involving the interstitial tissue, if the animal lives long enough. Manganese injected hypodermically is excreted chiefly by the intestinal epithelium, bile and to a less extent by the kidney. In small repeated doses it causes liver cirrhosis.

Traces of manganese are found in most plants and animals, including man, and its occurrence in the blood led to its use in the treatment of chlorosis, in which it was formerly credited with the power of completing the cure when given along with iron. Stockman found that it had no effect in this disease when given alone. Recently Titus and Hughes have claimed that, in experimental anæmias in rats, it assists the utilization of iron in hæmoglobin formation in a manner similar to copper, but there is still no convincing evidence of its value in human anæmias. The use of potassium permanganate as an antiseptic, etc., is referred to later (page 792).

Cadmium resembles zinc very closely in its effects, but is more toxic. The chloride is a powerful emetic. According to Hessel, cadmium behaves in some ways like mercury in the system. After absorption it is found chiefly in the liver and kidneys. It may produce nephritis. It has been suggested that the illness which may occur in spelter workers is due to cadmium, which is always present as an impurity in zinc, and which is found in the liver in these cases.

Nickel and **Cobalt** salts, administered to the frog, cause a curious dark color in the skin, followed by convulsive movements, which at first arise apparently from the medulla oblongata and higher centres, and resemble those of picrotoxin, but later are reflex, from excessive irritability of the spinal cord. In mammals the usual symptoms arising from the action on the intestine and kidney are accompanied by tremors and chorea-like movements, later by tetanus, and finally by paralysis. These metals also cause a profound fall in blood-pressure resembling that from arsenic and apparently arising from direct action on the walls of the arterioles and capillaries. Waltner found that cobalt given in the food of rats increased their hæmoglobin but destroyed fertility. The doses given were too large. Le Goff found that cobalt, given intravenously in man, produced a marked dilatation of the blood-vessels of the face with a slight fall of blood-pressure. Strongly acid food may form nickel salts when it is cooked in vessels made of this metal, but no poisoning results, either because the quantity ingested is too small or because it is too slowly absorbed from the stomach and intestine.

In recent years a form of nutritional anæmia, "hive" disease, has been described which occurs in cattle and especially in sheep, in Australia, New Zealand and Great Britain. The blood shows a diminution in red cell count and in hæmoglobin value. The disease is curable by large doses of iron, though the evidence goes to show that there is no lack of iron in the food or tissues. Filmer and Underwood believe that the beneficial effect of iron compounds is due

to traces of cobalt and the use of this metal alone has proved highly successful in the treatment of this disease. It is possible that cobalt may find a place also in the treatment of some human anæmias (Cronin). The value of cobalt in anæmias has recently been reviewed by Corner.

The gas, nickel carbonyl, $Ni(CO)_4$, formed when CO is passed over finely divided nickel, has produced poisonous effects when inhaled, the chief symptoms in man being cyanosis, dyspnœa with bloody sputum, œdema of the lungs and later involvement of the nervous system.

Tin salts paralyze the central nervous system in the frog, and later the heart. In mammals diarrhœa, colic, vomiting and general weakness are observed, along with paralysis of some parts of the central nervous system and stimulation of others, leading to ataxia, stiffness and irregularity of the movements and occasionally convulsions. The sulphide is said to be deposited in the lymph spaces of the intestines in the same way as in bismuth poisoning. General poisoning may be induced by the administration of the salts by the mouth, even when there is no corrosion of the mucous membrane. Tin is often present in preserved foods containing acids, from being dissolved off the vessels, and is certainly absorbed, for it has been detected in the urine after the use of such articles. Apparently it is not often present in sufficient quantities to induce poisoning, for although some cases of "tin poisoning" are met with in medical literature, in none of them has it been satisfactorily established that tin was the cause. Chronic poisoning from this cause is unknown, and animals present no symptoms from prolonged treatment with larger quantities of tin than are contained in any preserved foods.

Thallium.—Thallium salts produce no immediate effects beyond a relaxation of plain muscle, *e. g.*, of the bronchi and uterus, but have remote and delayed effects that are unique, as when injected or ingested they cause shedding of the hair in all animals. This action was discovered by Richet, and thallium was tried by Sabouraud for ringworm about thirty years ago and revived recently by Buschke. It has now had a fairly thorough trial as a depilatory in ringworm, especially for children, for whom roentgen-ray treatment is difficult.

Accuracy of dosage is essential. The dose recommended is 8 to 9 mgs. per kilo, as a single dose by mouth, in 2 ozs. of sweetened water. Hair of the scalp begins to loosen about the seventh day, and to fall out dramatically on the fourteenth. It is complete by the nineteenth, and soon begins to grow again. Hair on regions other than the scalp is more resistant and does not fall out with this dosage. There is no doubt that the therapeutic dose is dangerously near the toxic dose.

Experiments on sheep show that both the pilotrophic and toxic doses of thallium are enhanced by starvation or by a dry diet. All monovalent thallium compounds are active in proportion to their thallium content. In angora rabbits the threshold pilotrophic dose was found to be about half the minimum lethal dose, indicating a small margin of safety for therapeutics.

Toxic symptoms which may occur are joint pains, especially in the lower limbs, peripheral neuritis, albuminuria, mental symptoms and hypochlorhydria; and some fatal cases of poisoning have occurred through overdosage. Retrobulbar neuritis has been described due to the use of a depilatory cream containing a high percentage of thallium. Several observers have described destructive changes in the endocrine glands, especially the testes, adrenals and thyroid in experimental poisoning with thallium.

Dixon stated that thallium stimulates the autonomic reflexes, especially of the sympathetic, much in the same way as strychnine facilitates spinal reflexes.

Vanadium is said to induce symptoms in workmen in various industries in which it is used. These consist in diarrhœa followed by severe constipation, anæmia, emaciation and some indefinite nervous disturbances; albumin, casts, and blood often appear in the urine. Hæmorrhage from the lungs is not infrequent and lesions are found in the lungs, kidneys, liver, and intestinal tract. The symptoms observed in acute poisoning in animals resemble those induced by the other irritant metallic poisons. Jackson states that the intravenous injection of the vanadates in animals causes a sharp rise in the arterial pressure

from constriction of the peripheral vessels; this arises from an action on the muscle wall of the arterioles for the most part, though the myoneural junctions may also be involved. The intestinal walls and the bronchioles are similarly aroused to contraction by vanadates.

Molybdenum and **Tungsten** resemble each other closely and induce typical metallic poisoning.

Uranium, in addition to the ordinary features of metallic intoxication, causes nephritis, œdema and some glycosuria, the sugar often amounting to 1 per cent in the urine. In addition, dropsy occurs in animals poisoned with this metal, partly from the changes in the renal tubules, but chiefly, it is said, from a destructive effect on the smaller vessels. Uranium also exerts a toxic action on the liver (MacNider).

Selenium and **Tellurium** are classed along with sulfur in chemical systems, but the salts of telluric, selenious, and selenic acid induce symptoms resembling those of the heavy metals and arsenic in many points, and may be inserted in this series. In the frog the symptoms are those of central nervous paralysis, and later of heart failure. In mammals vomiting, purging, somnolence, dyspnœa, tonic and clonic convulsions have been noted, and the stomach is found somewhat reddened, the mucous membrane of the intestine swollen and dysenteric, while the kidneys seem less affected. The perspiration is prevented by tellurates, apparently from paralysis of the terminations of the secretory nerves similar to that induced by atropine. Loss of hair occurs in rats receiving tellurium in their diet. An early symptom of poisoning with these bodies is a garlic odor in the breath, and many of the organs are found of a grayish color after death, and possess this odor. Hofmeister has shown that these salts are reduced to metallic selenium and tellurium in the body, and that afterward methyl compounds ($Te(CH_3)_2$, $Se(CH_3)_2$) are formed. These are volatile, and, excreted by the lungs, urine and fæces, give the disagreeable odor. The synthesis of methyl-tellurium is one of the few known cases in which a compound with methyl is formed in the animal body, and is of some biological importance. All the selenium and tellurium is not excreted in this form, for some of it appears in the urine, and probably in the fæces, in other combinations.

Selenium causes a disease in livestock, "alkali disease," in Dakota and "blind staggers" in Wyoming. Selenium as it occurs in cereals is more toxic than in the form of inorganic selenates or selenites. Selenium in the food of rats causes a fall of weight and diminution of hæmoglobin. It is stored especially in the liver and kidneys. Franke and Moxon found the following sequence of toxicities for rats: Selenium > vanadium > tellurium > molybdenum = arsenic.

Tellurates have been advised in therapeutics to prevent excessive sweating, and certainly have this effect, but are not to be recommended, as the strong garlic odor of the breath persists for days or even weeks after one dose.

Osmic Acid has been recommended as an injection into the nerves in neuralgia. It is an intensely irritant substance, and seems to induce nephritis and diarrhœa when absorbed. The greater part of the poison is, however, deposited as a black powder at the point of injection, owing to its being reduced by the tissues.

Germanium, on account of its close chemical relationship with arsenic, has been tried in experimental and human anæmias. Hammett and Muller found that germanium dioxide produced in rats an increase in the number of erythrocytes with an apparent stimulation of the bone-marrow. Good results have been claimed in pernicious anæmia by some, but denied by others.

Beryllium resembles aluminium in its effects but is more poisonous. It is absorbed from the alimentary canal and excreted by the kidneys and intestine. A type of poisoning with fever and rigors has been described in workers who inhale the vapor of beryllium fluoride.

Cerium was formerly used in therapeutics in the sickness of pregnancy and similar conditions, but is valueless. The cerium double salts injected into the blood-vessels of animals are said to depress the heart and cause ecchymoses

in the stomach and bowel, and nephritis. The oxalate is insoluble and is not absorbed from the alimentary tract.

Thorium.—The soluble thorium salts resemble those of aluminium in their local and irritant properties. Salts like the nitrate coagulate proteins, cause local sloughing when injected hypodermically, and intravascular clotting intravenously. The addition of sodium citrate prevents clotting. Hepatitis and cirrhosis of the liver have been described in rabbits after intravenous injection of thorium oxide. Late deposition of thorium may occur in the bones.

Thorium salts are radioactive and have been tried therapeutically for a variety of purposes. Mesothorium has been recommended by local application for lupus and superficial epitheliomas. Thorium X has been given for obesity, psoriasis, and chronic rheumatism. Its therapeutic value is not still established. Thorium X given by mouth has produced hæmorrhagic diarrhœa and, by injection, hæmorrhages from the mucous surfaces. Thorium salts have also been used to cast an opaque shadow to roentgen-rays, especially in radiography of the kidney and arteries. Hepatitis and cirrhosis of the liver occur in rabbits after intravenous injection of thorium oxide.

Niekirk found that **zirconium** and **haffnium** resembled one another in action and produced a fall of blood-pressure, stimulation, followed by paralysis of respiration and relaxation of the isolated rabbit's intestine.

Yttrium resembles aluminium in action. The chloride precipitates proteins. It produces paralysis in frogs, and excitement, dyspnœa and later paralysis in mice.

Vincke and Oelkers have found that salts of the rare earths, *e. g.*, neodym, lantharum, praseodym, yttrium and cerium, when injected into the blood stream, cause an incoagulability of the blood that may last several hours. Large doses of these metals cause necrosis of the liver and hypoglycemia (Fischler and Roecke).

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B. THE METALLOIDS.

I. BISMUTH.

The insoluble salts of bismuth have long enjoyed a reputation in the treatment of gastric and intestinal irritation, and have more recently been advised in surgery as applications to granulating wounds. In the last few years intramuscular injections of bismuth have been widely used in the treatment of syphilis.

Symptoms.—The official bismuth salts are almost completely insoluble in water and consequently do not immediately precipitate proteins as do the soluble salts of the heavy metals. Indeed what local action they exert seems to be due almost entirely to the mechanical effect of a fine insoluble powder. They are used externally as dusting powders, when they absorb moisture and possibly toxins and have a sedative and protective action. Applied to ulcers or wounds, they have a slight antiseptic action, again largely mechanical, though possibly, under certain circumstances, small amounts of insoluble bismuth salts may go into solution when allowed prolonged contact with the body tissues, and they may thus have an antiseptic action similar to that produced by the insoluble salts of the heavy metals. When ingested in therapeutic doses, they induce no marked symptoms, even after prolonged use.

They have little or no taste, and pass through the stomach and intestine for the most part unabsorbed, as both the oxychloride which is formed in the stomach and the sulfide formed in the intestine are likewise insoluble. So given, they coat the internal surface of the stomach and intestine and act as sedatives and allay gastric and intestinal irritation. They do not seem to affect the passage of food through the stomach in most cases. In the intestine they often cause some constipation. They give the stools a black color, due to the formation of the sulphide of bismuth, which, by the removal of soluble sulphides, also tends to check diarrhœa.

Very little of the bismuth swallowed is absorbed, but several authorities have found traces in the urine of patients treated with it internally, so that some evidently passes into the blood under certain unknown conditions. Enormous quantities have been administered internally, especially in roentgen-ray examination of the stomach and intestine, without any symptoms of poisoning being elicited, but in one or two cases some stomatitis has occurred, while in other instances large concretions of bismuth have been found in the stomach and bowel. In a few cases fatal poisoning has occurred from nitrites being formed from the nitrate and leading to the formation of methæmoglobin in the blood cells. This danger may be avoided by using the carbonate instead of the subnitrate. Some of the older writers describe serious poisoning from bismuth, but this was not due to the drug itself, but to the lead, arsenic, or antimony with which it was contaminated. A symptom formerly noted in cases treated with bismuth was an extremely disagreeable odor in the breath, but this has been shown to be due to the presence of tellurium in the preparation. Since its use was extended to wounded surfaces, several cases of serious intoxication have occurred. The symptoms are salivation, stomatitis, swelling of the gums, tongue, and throat, pain and difficulty in swallowing, a black line along the gums or black patches in the mouth and throat, and gangrene of the soft palate and other parts of the mucous membrane of the mouth. Vomiting, diarrhœa and albuminuria follow, but the patients generally recover when the dressing is removed from the wound. In these cases much less bismuth is applied than is often prescribed for internal use, so that it would appear that it is absorbed more rapidly from granulating surfaces than from the mucous membranes, or that what is absorbed from the stomach and intestine is prevented by the liver from reaching the general circulation.

Action.—The general action of bismuth has been studied in animals by the subcutaneous or intravenous injection of the double salts, such as the tartrate of bismuth and sodium. In frogs the symptoms are those of stimulation of the spinal cord and medulla oblongata, followed by depression and paralysis.

In mammals also large doses act chiefly on the central nervous system. The respiration is accelerated, the heart slowed, and violent clonic and tonic convulsions follow at short intervals, during which the movements are weak and incoördinated. Towards the fatal issue of the injection the heart often ceases entirely for some time and then regains its former rhythm quite suddenly. The blood-pressure falls, partly owing to the weakness of the heart, partly from depression of the vasomotor centre. The cardiac effects—mainly a direct

depressant action on the heart, with irregularities of which heart block is the commonest—have been described by Masson.

Smaller quantities injected intravenously or subcutaneously into mammals induce a more chronic form of intoxication, which resembles that seen in man. The earliest symptoms are loss of appetite, vomiting and diarrhœa, salivation and stomatitis with ulceration of the gums, tongue, and buccal mucous membrane. Weakness, slowness and incoordination of the movements follow, and except in very few chronic cases, tetanic convulsions occur at intervals. The urine contains albumin and casts. The weakness gradually deepens into complete paralysis and the animal dies, generally without convulsions. The heart seems little affected in the chronic intoxication, but the blood-pressure is low from the intestinal irritation and general collapse.

Besides the stomatitis and ulceration of the mouth, the post-mortem appearances of chronic bismuth poisoning in animals consist of some congestion, inflammation and necrosis in the kidney, and an intense black coloration of the cæcum and the upper part of the large intestine. This pigmentation is limited very exactly by the ileocæcal valve, and extends throughout the thickness of the bowel wall. The mucous membrane may also be necrosed in places and ulcers and hæmorrhages are met with in it. The black coloration is due to a deposit of bismuth sulphide on the mucous membrane and in the capillary vessels and lymph spaces. Meyer and Steinfeld found that bismuth is excreted all along the alimentary canal, but in larger quantities in the cæcum and large intestine than elsewhere, and they ascribe the ulceration to the precipitation of the sulphide in the vessels and the consequent arrest of the blood current.

Bismuth is stored in the liver, kidneys, spleen, intestine and other organs, and is excreted by the urine, stomach, and intestine, but especially by the cæcum and large bowel. It has been found in the saliva, sweat, milk and other secretions. It may pass through the placental circulation.

The action of bismuth in acute poisoning in animal experiments seems therefore to be exerted on the medulla and spinal cord, to a less extent on the heart, while in chronic intoxication the organs affected are those by which it is excreted —the mouth, kidney, and large intestine, especially the cæcum.

Therapeutic Uses.—Bismuth salts are employed as dusting powders or ointments in the treatment of ulcers and skin diseases, when they act as protectives and mild astringents and antiseptics. McKenna recommends a 10 per cent ointment of bismuth oxychloride as an efficient remedy in subacute impetigo, pustular folliculitis and sycosis. The subnitrate has been advised in surgery as an antiseptic and astringent powder to replace iodoform. It is true that it is devoid of the disagreeable odor of the latter, but it is not a harmless remedy, as was at first supposed, for several cases of bismuth poisoning have been recorded from its surgical use.

A paste consisting of bismuth subnitrate, iodoform and liquid paraffin, "bipp," was used extensively in the treatment of wounds during the World War. Toxic effects may result from absorption of the bismuth or especially of the iodoform, and it is possible that the healing effect of bismuth paste is due largely to the mechanical effect of liquid paraffin alone.

Bismuth has been used in *gastric catarrh and ulcer*, and has often been looked upon as a specific in the last affection, though it acts simply as a protective powder with perhaps some astringent properties. It has been found that when swallowed it is at first deposited in the most dependent part of the stomach, but is later distributed evenly over the surface and forms a continuous sheet over any ulceration, which it thus

protects from mechanical injury from the food, and also from the chemical action of the gastric juice. The subnitrate has been largely used for this purpose, but the carbonate is to be preferred if an antacid action is desired. Bismuth has also been used in *diarrhœa* for its astringent and protective action on the intestine, which is again due to its being deposited on the mucous membrane and acting as a mechanical coating over irritated surfaces. If bismuth is prescribed with alkalies, the carbonate should be used, as the subnitrate is slightly acid in reaction. When bismuth salicylate is given, salicylic acid is freed in the stomach and exerts an added antiseptic action on the stomach and small intestine. It is a valued remedy in infantile diarrhœas and in cholera.

Following the discovery in 1921 by Sazerac and Levaditi that bismuth has antisyphilitic properties similar to arsenic and mercury, bismuth has been extensively used in the treatment of syphilis, the value of this treatment being now well beyond the experimental stage. Most bismuth compounds have little or no effect in syphilis when given by mouth; subcutaneous injections produce local irritation and are inadequately absorbed; intravenous injections are too toxic and too rapidly excreted; so that intramuscular injection is at present the only reliable method of giving bismuth in syphilis. When so given, small amounts pass into the circulation and tissues, and destroy the spirochætes or inhibit their multiplication. It is not possible to get into the blood a concentration of bismuth sufficient to produce immediate and complete destruction of the organisms; and treatment aims rather at the prolonged maintenance of maximum tolerated concentration. With a view to attaining this, a variety of compounds and preparations have been tried, including aqueous solutions of water-soluble compounds, aqueous suspensions, and solutions or suspensions in oils. As a rule soluble preparations are more rapidly absorbed, but are more liable to produce severe local reactions and toxic effects. The B. P. preparations, Injectio Bismuthi, which is a suspension of finely divided metallic bismuth in a solution of glucose, and Injectio Bismuthi Salicylatis, which contains a suspension of bismuth salicylate in olive oil, may be taken as among the most convenient and reliable of the many preparations which have been used. Bismuthi et Potassii Tartras (U. S. P.) as well as the corresponding sodium salt and the oxychloride are also used for intramuscular injection. Such injections form local depots of bismuth which are gradually absorbed. They are as a rule given weekly into the gluteal muscles for six to ten weeks. Sollmann and his co-workers, who have studied the absorption and excretion of various bismuth compounds, suggest that, when a rapid but prolonged effect of bismuth is called for, the best results may be obtained by combining injections of a rapidly absorbed compound with injections of a more slowly absorbed compound. Though insoluble bismuth compounds, when administered by mouth, are absorbed too sparingly to give a therapeutically effective concentration in the blood, some of the soluble compounds, *e. g.*, sodium bismuthate, are fairly readily absorbed from the alimentary canal (Hanzlik).

A good deal of agreement has been reached as to the relative values of arsenic, mercury and bismuth in syphilis. The organic arsenicals

are most rapid in action and are generally preferable in the primary stages of the disease, though most authorities believe that they must be supplemented by either mercury or bismuth and Harrison advocates giving one of the latter metals from the commencement of treatment. Bismuth seems to be more rapid in action than mercury and less liable to produce toxic effects, so that in some countries it has largely displaced mercury in routine treatment. It is believed by many to be superior to mercury in tertiary and congenital syphilis. It has been proved to have a definite prophylactic value against syphilitic infection. Like mercury it is of less value in neurosyphilis, though in locomotor ataxia it may produce definite subjective improvement. Bismuth in the basic form does not readily penetrate the cerebrospinal fluid, but Hanzlik has shown that, in the form of an anion, *e. g.*, as sodium iodobismuthite, it penetrates more readily. He states that the electropositive compounds of bismuth are rendered slowly soluble and changed into electronegative complexes by the action of salts in the body, while the electronegative compounds which are soluble require no such change and are directly available in the tissues. Most of the bismuth in the blood is in plasma solution. In the tissues by far the largest proportion is found in the kidneys, liver and muscle containing the next highest amounts.

Bismuth is, therefore, now chiefly used in syphilis as an adjuvant to arsenicals and as a substitute for mercury It may be used alone in cases where the latter are contraindicated, *e. g.*, when syphilis is complicated by cardiovascular disease, nephritis or jaundice. Bismuth compounds are also effective in yaws.

Preparations.

U. S. P.

Bismuthi Subnitras, white bismuth, Magisterium Bismuthi, bismuth oxynitrate, a heavy, white, insoluble powder, odorless and almost tasteless, with a slightly acid reaction. It consists of a mixture of the hydrate and subnitrate of bismuth in varying proportions. 1 G. (15 grs.) in powder or suspended in water.

Bismuthi Subcarbonas, bismuth oxycarbonate, a white or pale yellowish-white powder, varying in composition; odorless, tasteless, insoluble in water or alcohol. Dose as for subnitrate.

Bismuthi Subsalicylas, the salicylate or oxysalicylate of bismuth, is a white, amorphous powder, insoluble in water. 1 G. (15 grs.), by mouth; 0.125 G. (2 grs.) by parenteral injection.

Bismuthi Subgallas, an amorphous, bright yellow powder, odorless, tasteless and practically insoluble in water. 1 G. (15 grs.).

Bismuthi et Potassii Tartras, a granular white powder, which darkens on exposure to light. Soluble 1 in 2 of water. Dose, 0.15 G. ($2\frac{1}{2}$ grs.) by parenteral injection.

B. P.

Bismuthi Carbonas, the oxycarbonate or subcarbonate, a white powder, odorless, tasteless, insoluble in water. 0.6–2 G. (10–30 grs.).

Trochiscus Bismuthi Compositus. Each contains about $2\frac{1}{4}$ grs. of bismuth carbonate, with carbonates of magnesium and calcium.

BISMUTHI SALICYLAS, the subsalicylate. 0.6–2 G. (10–30 grs.); by intramuscular injection, 0.06–0.12 G. (1–2 grs.).

INJECTIO BISMUTHI SALICYLATIS, a 10 per cent suspension in olive oil, with some camphor and phenol. 0.6–1.2 mils. (10–20 mins.).

BISMUTHUM PRECIPITATUM, a dull gray powder, easily diffusible in water. 0.1–0.2 G. (1½–3 grs.).

INJECTIO BISMUTHI, 20 per cent of precipitated bismuth, in very fine powder, in a solution of dextrose, with some cresol. By intramuscular injection, 0.5–1 mil. (8–15 mins.).

BISMUTHI ET SODII TARTRAS, a white powder freely soluble in water. By intramuscular injection, 0.06–0.2 G. (1–3 grs.).

BISMUTHI OXYCHLORIDUM, a white powder, insoluble in water. By mouth, 0.6–2 G. (10–30 grs.); by intramuscular injection, 0.1–0.2 G. (1½–3 grs.).

INJECTIO BISMUTHI OXYCHLORIDI, 10 per cent suspension in water solution of dextrose. By intramuscular injection, 1–2 mils. (15–30 mins.).

Several new compounds of bismuth have been introduced in therapeutics, chiefly with the intention of combining the astringent properties of bismuth with the antiseptic action of benzol preparations. These have been used chiefly as dusting powders in various forms of skin disease, in burns and ulcers, in some ophthalmic conditions and after operations.

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II. ANTIMONY.

Preparations of antimony had a great vogue in therapeutics in the seventeenth and eighteenth centuries, being used empirically in a great variety of diseases. In many of these it was of doubtful utility, and its popularity declined until about thirty years ago when it was found to possess powerful trypanocidal properties. It has recently been used with success in a variety of tropical and other diseases, and is now scientifically established as one of the most important of remedies. The salt most commonly used is *tartar emetic*, or the double tartrate of antimony and potassium ($K(SbO)C_4H_4O_6$). As a double salt it is not readily dissociated and is therefore not so corrosive as the chloride, which is a powerful caustic when applied to the skin or the mucous membranes.

When rubbed on the **Skin**, however, tartar emetic causes redness and a papular eruption, which later passes into vesicles and pustules. If the application be further persisted in, these pustules may become confluent and form small abscesses, and later cause extensive necrosis and ulceration of the skin. The points of origin of the papules are the openings of the cutaneous glands and the hair follicles. When injected hypodermically, tartar emetic causes intense and lasting pain

and very often suppuration and sloughing, which may involve the underlying muscles.

Symptoms.—Tartar emetic has a slight acrid taste, and in very small quantities causes no symptoms, except some perspiration. In somewhat larger doses its ingestion is followed by nausea and vomiting, with very marked depression and the usual accompaniments of emesis, such as salivation, profuse perspiration and acceleration of the pulse (see Apomorphine, page 403). In antimonial poisoning the vomiting is violent and continuous, the ordinary contents of the stomach being first evacuated, and then a slimy mucous fluid, which may later contain blood. In some cases it is said that no gastric symptoms are observed, but these must be exceedingly rare. The vomiting is accompanied by profuse watery diarrhœa, resembling that of arsenical poisoning, and by great muscular weakness and collapse. The pulse may be somewhat accelerated at first, but is weak, and later becomes slow and irregular. The skin is cold and covered with clammy perspiration, and cyanosis of the face and extremities is generally marked. The respiration is slow and may be irregular, the voice weak and husky, the temperature is depressed, and the patient falls into a comatose condition, which deepens, until after a few weak convulsive movements the respiration ceases. The urine is sometimes increased in the beginning of the poisoning, but later may become scanty or entirely suppressed. It often contains albumin.

The minimum fatal dose of tartar emetic is doubtful, as the greater part of the poison is generally removed by vomiting. Recovery has been observed after very large quantities, while in other cases 0.1 G. (2 grs.) has proved fatal.

Industrial poisoning from antimony is of rare occurrence, but in recent years there have been several outbreaks of poisoning from the use of enamelled vessels of inferior quality as containers for acid drinks, such as lemonade. Antimony oxide is sometimes used in the enamelling of hardware and is dissolved out by the tartaric or citric acid. Enamelled hollow-ware vessels obviously intended for other purposes may be dangerous if used for the preparation or storage of food or drink.

Chronic antimonial poisoning is very rare and difficult to diagnose. The symptoms are depression, headache, giddiness and confusion, drowsiness and indistinct sight. The appetite is bad, and the patient complains of heaviness, discomfort or pain in the region of the stomach, general weakness and exhaustion. Profuse diarrhœa may be present, rapid loss of flesh, albuminuria, and finally collapse. Pustular eruptions have been observed from the prolonged internal use of tartar emetic. There is some reason to suppose that printers occasionally suffer from antimony poisoning arising from the presence of antimony in the type. In rabbits poisoned with tartar emetic, Franz found especially degenerative changes in the liver and kidney which were independent of capillary injury.

Action.—Many of the symptoms of antimonial poisoning, the profuse perspiration, salivation and, to some extent at least, the collapse, are manifestly secondary to the **Emetic Action**, and the cause of the vomiting has, accordingly, been repeatedly investigated. The older writers regarded it as arising from some central action, but there can

be no question that it is the result of local irritation of the stomach; small quantities cause vomiting without any obvious lesion, but larger doses induce hyperæmia and swelling of the gastric mucous membrane. Large quantities of antimony injected intravenously or subcutaneously also cause vomiting and purging, and this is apparently not due to its excretion into the stomach and bowel, for the movements occur in eviscerated animals; but much smaller quantities suffice to cause vomiting when given by the mouth.

In the stomach the antimony is slowly dissociated from the double salt and acts as an irritant; this liberation of the antimony ion may be aided by the acid reaction, but it also occurs when the reaction is rendered neutral, and in the intestine and skin, where the reaction is not acid. It is more irritant than arsenic and is absorbed more slowly, so that its action remains confined to the stomach, and as the vomiting removes much the greater part of the poison, the intestine remains unharmed except when large quantities have been swallowed and the emesis is insufficient from any cause. In chronic poisoning, ulceration of the small intestine is said to occur, especially around the solitary follicles and Peyer's patches.

The acceleration of the **Pulse** seen after tartar emetic is due to the emetic action and not to the absorption of the drug. When injected into a vein in animals, antimony acts directly on the cardiac muscle and causes a slow and weak pulse, although this is preceded in some cases by slight acceleration.

The **Blood-pressure** falls at first from central stimulation of the vagus (Oelkers), later owing to the weakness of the heart. There may be also an action on the vascular mechanism similar to that described under arsenic.

The **Respiration** is often slightly accelerated at first, and may be shallow and irregular from the nausea; but in cases of poisoning it becomes slow and labored, and eventually ceases along with the heart. Marked congestion and œdema of the lungs is often found in fatal poisoning.

The **Central Nervous System** is depressed by antimony in the frog, while its effects in mammals are more obscure, for it is impossible to ascertain how far the changes are due to direct action and how far they are attributable to the disturbance of the circulation and the alimentary canal.

Many of the **Secretions** are increased by tartar emetic, such as the perspiration, the saliva, and the mucous secretion of the respiratory tract. This is not due to any direct action on the glands, for the same effect is induced by anything which causes vomiting. (See Apomorphine, page 403.) The urine is sometimes increased by antimony, at other times it is diminished or suppressed. This indicates that antimony, like most of the heavy metals, irritates the kidneys and thus increases their activity in small doses, while larger amounts cause inflammation and albuminuria or anuria; acute nephritis with hæmorrhages is often found in fatal poisoning, and in chronic poisoning the chief symptoms arise from the renal changes.

The irritant action of tartar emetic on the **Skin** when it is applied to it in ointment arises from the liberation of the antimony from the double salt; this apparently fails to penetrate through the horny epidermal layer and thus causes irritation only where it reaches the unprotected living cells at the mouths of the glands. The inflammation thus occurs as discrete points which may suppurate and form pustules.

Antimony is much less poisonous than arsenic to most of the protozoa, but is found to possess the same extraordinary affinity for certain pathogenic organisms, notably the trypanosomes of the blood, which it destroys in solutions as weak as 1 in 500,000.

The effects of antimony on the **Nutrition** are very imperfectly known; fatty

degeneration of many organs is induced by its prolonged use, the nitrogen of the urine is found to be increased and the glycogen disappears from the liver. Very small quantities of antimony given repeatedly are said to increase the glycogen and fat of the liver, without apparently altering the nitrogen of the urine.

The fall in **Temperature** after antimony is often very considerable, amounting in animals to 6° C. in the course of a few hours. It is explained by the slowness of the circulation and by the general depression and collapse and profuse perspiration.

Antimony is **Absorbed** from the skin very slowly, and from the stomach and intestine. It passes into the tissues much more gradually than arsenic, however, and its action on the stomach can, therefore, be elicited without danger of its causing general symptoms. After absorption antimony is found in considerable quantity in the liver, which stores it up for some time. It is excreted into the stomach and intestine, in the urine, and, it is said, in the bile and milk. No such tolerance is acquired for antimony as is said to occur under arsenic.

Therapeutic Uses.—In the seventeenth century antimony was prescribed so widely and was believed to do so much harm, that the graduates in medicine of Heidelberg were required to take an oath never to use it. At present it is used to a limited extent as an emetic, but is slow in action and induces greater depression and more prolonged nausea than the other drugs which are prescribed for this purpose, such as apomorphine, ipecacuanha, or sulfate of copper. It is therefore seldom used to evacuate the stomach in cases of poisoning or of foreign bodies in the stomach or œsophagus. Its expectorant action is taken advantage of in acute bronchitis in which the secretion of the bronchial mucous membrane is insufficient, but is of less value when the secretion is abundant. In commencing bronchitis tartar emetic is sometimes given until vomiting occurs, and then continued in smaller doses and at longer intervals.

In the last twenty years antimony has been used with success in several protozoal and other parasitic diseases. It was found to have a trypanocidal action very similar to that of arsenic and was first used in trypanosomiasis. It is of some value in *sleeping sickness* and in syphilis. Good results have been obtained with it in *filariasis*. It seems to be of little value in malaria.

It has proved strikingly successful in *kala azar*, "converting a disease with a 90 per cent mortality into one with a 90 per cent rate of cure." It is equally effective in other forms of leishmaniasis, such as *oriental sore*, and also in *granuloma inguinale*. It has become the standard remedy for *bilharziasis* since its introduction by Christopherson for this purpose. It kills both the eggs and the parent worm.

Many compounds of antimony have been investigated with a view to obtaining something superior to tartar emetic, but in the treatment of bilharziasis, no compound has so far been found more generally suitable than the antimony-tartrate of potassium or sodium. The latter is more soluble, less toxic and equally efficient, and is now chiefly used.

The tartrates of antimony are too irritating for subcutaneous injection, and they are now given intravenously. For bilharzia disease the dosage recommended by Christopherson is ½ gr., rising by ½ gr. at each injection to 2 grs. This dose is continued every second day until a total of

25 to 30 grs. has been given. A 1 to 2 per cent solution is generally used; too strong solutions may produce coughing and retching. The ova of the parasite may be killed by a few injections, but prolonged treatment is usually necessary to destroy the adult worms (the infection is usually multiple). Though the antimony-tartrates of potassium and sodium, owing to their cheapness and efficacy, remain the usual form of giving antimony in bilharziasis, many other compounds have been tried. A trivalent antimony compound of pyrocatechin sodium disulphonate, "*Fouadin*," has been used by Khalil and his associates, who find that it cures the disease more rapidly than does tartar emetic and with less toxic symptoms. For the treatment of leishmaniasis the tartrates of antimony may be used in the same way as in bilharziasis but more prolonged treatment and a larger total dosage is needed to cure the former disease, a total amount of 60 grs. of tartar emetic being often necessary. Many organic compounds, chiefly pentavalent, have been used in the treatment of leishmaniasis and the best of these seem to be superior to tartar emetic. They are less toxic and fewer injections are required. Of these compounds may be mentioned *Neostibosan* which is highly recommended by Napier, Rogers, and others. *Urea Stibamine* (introduced by Brahmachari), and Stibamine Glucoside.

Following therapeutic intravenous injections of antimony salts, the following symptoms may occur: dry cough, frequently; more rarely, dryness of the mouth, a feeling of constriction of the throat or tightness of the chest, colicky pains in the abdomen and pains in the shoulder. The occurrence of giddiness, vomiting, or diarrhœa calls for care with subsequent doses.

In cases of **Antimonial Poisoning**, emetics are seldom required, but the stomach may be washed out by means of the stomach tube if vomiting is not present, and a purge may be given to remove the poison in the bowel. Tannic acid, lime or magnesia may be used to precipitate the antimony in the stomach, and potassium hexatantalate has recently been advised for this purpose.

PREPARATIONS.

ANTIMONII ET POTASSII TARTRAS (U. S. P., B. P.), tartar emetic, tartrated antimony ($(KSbOC_4H_4O_6)_2+H_2O$), forms colorless, transparent crystals, or a white granulated powder, without odor, and having a sweet, afterward disagreeable, metallic taste, soluble in 17 parts of cold water, insoluble in alcohol. Dose as an expectorant, 0.003 G. ($\frac{1}{20}$ gr.); B. P., 0.002–0.008 G. ($\frac{1}{30}$–$\frac{1}{8}$ gr.); emetic, 0.03–0.06 G. ($\frac{1}{2}$–1 gr.); by intravenous injection, 0.03–0.12 G. ($\frac{1}{2}$–2 grs.).

ANTIMONII ET SODII TARTRAS (B. P.), whitish scales or powder, hygroscopic, soluble in 1.5 parts of water. Doses as of tartar emetic above.

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III. ARSENIC.

Some of the less active preparations of arsenic, such as the sulphides, Realgar (As_2S_2) and Orpiment (As_2S_3), have been known in therapeutics since the beginning of the Christian era, but this metal was brought into especial prominence in later times through the frequent use of the more dangerous oxides in criminal poisoning. Thus the notorious Aqua Tofana of the sixteenth and seventeenth centuries owed its activity to the presence of arsenic, and various arsenical compounds have been used up to the last few years more largely than almost any other poison in suicide and homicide. This is to be explained by their having been widely employed in the arts and for such purposes as weed-killers, and thus being readily accessible to all, and by the general recognition of their poisonous nature. Of late years intentional arsenic poisoning has become somewhat less common, though on the other hand, accidental poisoning is still met with not infrequently, especially in the chronic forms. Many of these chronic cases are extremely difficult to diagnose, and probably often pass unrecognized by the attending physician. In view of this fact, it seems desirable that more stringent measures should be taken to reduce the use of arsenic in the arts, and especially to prevent its being brought in contact with food. The danger of the use of the green arsenical dyes, such as Scheele's Green (arsenite of copper), and Schweinfurt's Green, or Paris Green (arsenite and acetate of copper), is now generally recognized, but arsenic is still used in the preparation of other colors, and these may give rise to poisoning from the imperfect removal of the metal. It has also been used in dilute solution to preserve food, and a solution is often sprayed upon grape vines and other plants to preserve them from the attacks of insects. Poisoning has occurred from these sources and is difficult to diagnose, as it is in some cases impossible to find the means by which the arsenic enters the system. A widespread epidemic of poisoning in England in 1900 drew attention to a source of arsenic which up to that time had not received the attention it merited. Several thousands of persons suffered from arsenic being contained in cheap beers made from glucose, in the manufacture of which sulphuric acid had been employed. The sulphuric acid was formed from iron pyrites containing arsenic, and the poison was carried from the sulphuric acid with the glucose into the beer. Sulphuric acid is used in the manufacture of so many drugs, foods and other substances in constant use, that this intimation that it may convey arsenic into articles where its existence has not hitherto been suspected, is of the gravest importance.

Metallic arsenic is insoluble in water, and passes through the alimentary canal for the most part unchanged and without action, but it is possible that small quantities may be oxidized to arsenious acid in the stomach and intestine under some conditions. Some symptoms have been observed when it is rubbed on the skin in a state of fine division, and these are probably due to its absorption in the form of an oxide. The characteristic "arsenic" action is induced by the salts of trivalent arsenious acid (H_3AsO_3), and by its anhydride (As_2O_3), which is often known as arsenic, and which exists in the tissues as arsenites. Arsenic action is therefore due, not to the element, but to the ion of arsenious acid. The anhydride and salts of the pentavalent arsenic acid (H_3AsO_4) cause similar symptoms, but are less poisonous and act more slowly than those of arsenious acid, and probably owe their effects to their being changed to arsenites in the tissues. The action being due to the ion and not to the element, it necessarily follows that compounds from which the ion is not liberated do not induce the arsenic action, or do so only when they are changed to bodies which can dissociate the arsenious acid ion. Thus organic arsenic combinations in which the metallic atom is directly attached to carbon are only feebly poisonous, but in course of time seem to be changed to arsenious acid in the tissues, and then cause typical poisoning.

Arsenious acid, which in the following pages will be taken as the representative of "arsenic" action, has a faint sweetish taste, and is therefore not so likely to be detected by the victim as many of the other poisons.

Symptoms.- In large quantities arsenic very often causes no symptoms for one-half hour or more, but then the patient complains of a feeling of constriction in the throat, of difficulty in swallowing, and of discomfort in the stomach region. This soon increases to violent pain, and is accompanied by vomiting, and later by watery diarrhœa. The stools are at first of ordinary diarrhœic appearance, but later resemble the "rice-water" stools of cholera, in that they consist almost entirely of minute shreds of disintegrated mucous membrane suspended in a serous fluid; sometimes, however, they are clear and gelatinous in appearance. In some cases, blood appears in the vomited matter and also in the stools, but this is not by any means an invariable feature. The urine is diminished, or entirely suppressed, from the great amount of fluid eliminated by the stomach and bowel. These symptoms from the alimentary tract are accompanied by giddiness, cramps in the muscles, headache, and soon by collapse, with cold damp skin, pallor, feeble pulse and weak, sighing respiration; this later passes into coma, and death follows with or without convulsions. In cases in which the dose is smaller than the fatal one, or in which much of the poison is eliminated by vomiting, the patient may recover without further symptoms than those already described. Frequently, however, he recovers from the acute symptoms only to develop those of chronic arsenical poisoning. In some instances it is said that no symptoms are present except those of collapse and coma. In acute poisoning death may occur within twenty-four hours, but more fre-

quently the patient lives for two to four days or longer, and then succumbs to exhaustion. The fatal dose is uncertain, because arsenic is very insoluble, especially when in coarse particles, and thus large amounts (2 G) have been swallowed in solid form with impunity and have been recovered from the stools unchanged; even when more soluble preparations are taken, much may be rejected by vomiting. Fatal poisoning has occurred from about 0.1 G. of arsenic in solution.

Chronic Arsenic Poisoning may arise from a single large dose, the effects persisting for weeks or months after the ingestion and new symptoms arising as the earlier ones disappear; more frequently, however, it is induced by the prolonged absorption of small quantities. The milder symptoms may arise from its therapeutic use, but typical cases are generally due to the presence of arsenic in the form of dyes in wall paper, carpets, or clothes, or in stuffed animals in the rooms inhabited by the victims, or to the constant handling of arsenical pigments and other compounds in mines and manufactories. Widespread poisoning has been observed from the use of wines containing arsenic at Hyeres in France, from milk diluted with arsenical water in London, and from beer in the Manchester district. In these last cases the arsenic was in solution, but it often seems to be inhaled in the form of fine dust, which falls from the walls or other objects.

The symptoms of chronic arsenic poisoning, which are often very obscure, may be divided into three phases. In the first of these, the patient complains of weakness and languor, loss of appetite, some nausea and occasionally vomiting, with a sense of heaviness and discomfort in the stomach. Diarrhœa may be present, but is often absent, and in fact some constipation may occur.

In the *second* phase the conjunctiva is often red and inflamed, and symptoms of coryza appear, with sneezing, hoarseness and coughing, from a catarrhal condition of the mucous membranes of the nose and larynx. Some swelling of the liver and jaundice may occur, but these are not generally well marked. Skin eruptions of various forms—papular, vesicular, or erythematous—are generally noted; very often the epidermis falls off in fine brownish scales, or, in the hands and feet, in large flakes (keratosis); a curious pigmentation is very common, the skin assuming a dark metallic color resembling in extreme forms that produced by rubbing a lead pencil upon it (arsenic melanosis). This pigmentation is much more marked in persons of dark complexion than in fair people, in whom it may be indistinguishable from ordinary freckles; it generally disappears when the patient is removed from the poisonous atmosphere, but has been permanent in some cases. In prolonged poisoning the eruptions may simulate almost any form of skin disease, and the hair and nails fall off. Herpes is not infrequently observed and points to nervous disturbances such as are prominent features in the next phase.

These phases are not always distinct in cases of poisoning, and very often some of the symptoms of the second phase may appear before any marked disorder of the digestive tract. In the prolonged therapeutic use of arsenic, the first indications of commencing poisoning

are redness, itching, suffusion and swelling of the conjunctiva and eyelids, and dryness of the nose and throat, as in coryza. On the other hand, in workmen exposed to arsenical dust, the first symptoms may arise from the skin or from bronchial irritation.

The *third phase* is marked by disturbance of sensation and motion in localized areas, generally in the hands and feet (peripheral neuritis). It is often ushered in by intense persistent headache or by acute pain located around the knee, ankle or foot, less frequently in the wrist and hand. The patient complains of formication in the extremities, and of the discomfort caused by the pressure of the bed-clothes on the feet and legs. The palms of the hands and the soles of the feet are often red, swollen and extremely sensitive to touch (erythromelalgia), and pressure on the muscles induces the most intense pain. Later, sensory paralysis may set in, especially in the extremities, and the less acute sense of touch in the feet and hands induces symptoms resembling those of locomotor ataxia. The sensitiveness to heat and cold may be exaggerated or dulled, or sometimes heat is not appreciated, while cold causes intense pain. The sense of pain varies in different cases, in some being abnormally acute, in others deadened. These sensory disturbances are followed in severe poisoning by motor paralysis, which generally appears in the extensor muscles of the toes, later in the peronei muscles. More rarely the flexor muscles of the leg and foot are involved, and in some cases the affection commences in the extensors of the hand and fingers. As a general rule the paralysis is confined to the extremities, but in some cases it has been found to invade the trunk. It is generally, but not invariably, symmetrical, and the muscles affected atrophy rapidly, and present the reaction of degeneration. There is sometimes some difficulty experienced in diagnosing arsenic from lead paralysis, but in the former there is often a history of acute poisoning, while the latter is almost invariably due to prolonged absorption. Disturbances of sensation are much more common in arsenic than in lead palsy, and in the latter the forearm muscles are generally affected first, in the former, those of the leg. In arsenic poisoning atrophy is said to occur more rapidly, and there is no line on the gums. Another condition which presents still greater difficulties in diagnosis is alcoholic neuritis. But in the latter skin eruptions are rare, coryza is not present, and there are generally more marked brain symptoms than in arsenical cases. In doubtful cases the urine and the hair of the patient should be tested for arsenic. Arsenic paralysis may appear as early as three days after an acute intoxication, but is commonly observed later, and may occur only after three or four weeks.

In very prolonged arsenic poisoning the patient may sink into an apathetic, semi-idiotic condition, or may become epileptic. In most cases the symptoms slowly disappear when the poison is removed, but even slight paralysis may last for many years before it is entirely cured, and after complete degeneration of the muscles little improvement is to be expected. The contractures which follow are generally due to the unopposed action of the sound muscles, but sometimes arise from the shortening of the paralyzed ones.

Arsenical poison occurs industrially from inhalation of, or contact with, the dust of compounds of arsenic, showing itself often in skin eruptions, or more rarely in cancer of the skin, especially where the dust alights on folds of skin or moist surfaces like the groin. Other symptoms of chronic arsenical poisoning may be present, due to absorption of arsenic, conjunctivitis and hoarseness being frequently early symptoms. Perforation of the septum of the nose is not uncommon. The frequency of poisoning from this source has been greatly diminished by measures taken to protect the workers, *e. g.*, by use of exhaust draughts.

Action.—Arsenites and arsenious acid do not coagulate proteins or change them in any way, except when applied in such enormous quantities as never reach the stomach, so that the action of arsenic on the **Alimentary Canal** cannot be explained as due to any ordinary form of corrosion, although the symptoms and the postmortem appearances resemble in many points those of the corrosive poisons. Thus the mucous membrane of the stomach is generally found red and swollen, and often contains hæmorrhages. The epithelial coat can be rubbed off very easily, and is found to be in a state of fatty infiltration, and sometimes resembles a false membrane; or the only lesion may be cloudy swelling and fatty infiltration of the gland-cells.

The intestine presents very similar appearances, the mucous membrane being swollen and congested, more especially around Peyer's patches. It contains a quantity of thin fluid with flakes of membrane, resembling exactly the rice-water stools of cholera, from which it is difficult to distinguish it.

The same symptoms arise when arsenic is absorbed from the subcutaneous tissue, or from the broken skin, though only traces of arsenic are found in the contents of the stomach and intestine when it is ingested in this way.

The failure to explain the gastro-intestinal action of arsenic by ordinary corrosion has led to the suggestion that it is due to the extreme dilatation of the intestinal vessels, which gives rise to the congestion and swelling, and this in turn to the destruction of the lining membrane, perhaps by the exudation of fluid beneath the epithelium. This transudation of fluid is certainly in accord with the watery character of the stools in arsenic poisoning, but the explanation does not seem entirely satisfactory, for it fails to account for the fatty infiltration and the cloudy swelling of the epithelium, which are in some cases the only lesions found here. The fatty infiltration is not confined to the stomach and bowel, but involves a number of other organs, although it is not as a general rule so widely distributed as in phosphorus poisoning. Arsenic then must be considered to have a specific action in causing fatty infiltration of the epithelium of the stomach and intestine. This in itself is sufficient to explain many of the symptoms from these organs, although it may well be that the vascular action is the cause of the excess of fluid in the intestine, and in fact, the fatty infiltration alone is insufficient to explain this feature, which is absent in phosphorus poisoning.

In therapeutic doses arsenic is said to increase the appetite and promote digestion, an effect which may perhaps be due to the specific action on the epithelium, this in its milder forms proving of advantage to the organ, though in excess it leads to its degeneration; it has been observed in dogs with gastric fistulæ that the gastric secretion is augmented by small quantities of arsenic.

Circulation.—In the frog the heart is slow, weak, and irregular, and ceases in diastole after comparatively small doses; the action seems to be a direct paralysis of the muscle. In the mammal the heart is little affected by arsenic, but a very marked fall of the blood-pressure follows the injection of large doses intravenously. This is due to dilation of the capillaries from a direct action on their walls; epinephrine and nicotine continue to raise the blood-pressure after arsenic, because the arterial wall can still respond to strong nervous impulses; the vessels of the splanchnic area seem more susceptible to this arsenic action than those of the rest of the body, and their dilation leads to very marked congestion of the stomach and bowel, and reduces the blood-pressure to zero. The dilated capillaries permit the passage of fluid into the tissues more readily than normally, and this explains the appearance of œdema in cases of poisoning and also the large amount of fluid in the stools and vomited matter. Arsenic is therefore often termed a capillary poison.

Respiration.—In cases of poisoning in man the respiration does not seem to be much affected until late, but it ceases before the heart, probably from the exhaustion and low blood-pressure, and not from any specific action on the centre.

The action of arsenic on the **Central Nervous System** has been repeatedly examined. A descending paralysis is elicited in the frog, the animal first losing its spontaneous movements, and then its reflexes, and the terminations of the motor nerves being involved only very late in the intoxication. In mammals there are generally no certain indications of direct action on the nervous system in acute poisoning, for the weakness and prostration, and the final loss of consciousness and coma may be attributed to the exhaustion from the gastro-intestinal effects rather than to the centres being immediately affected.

The pathology of the nervous disturbances observed in chronic poisoning, and often after a single large but not immediately fatal dose, bears no relation to the effects observed in animals in acute poisoning. The symptoms in chronic poisoning all point to peripheral neuritis as the cause, and the characteristic lesions in the nerve trunks have been shown to occur both in man and animals exposed to the prolonged action of arsenic. In severe cases the spinal cord may also be involved secondarily. The peripheral muscles and nerves are little affected in acute poisoning.

The unbroken **Skin** is not affected by arsenic, unless when it is applied repeatedly or allowed to remain in contact with it for some time, when it may give rise to redness, pustules or vesicles and later to violent erysipelatous inflammation. It has not, however, any such corrosive action on the skin as is possessed by strong acids, and the subcutaneous injection of arsenic is not painful at first. It is more active when applied

to denuded surfaces and to the mucous membranes, destroying them to some depth and causing acute pain, but even here it acts more slowly than ordinary caustics. According to Ellinger, the local "corrosive" action of arsenious acid is due to a primary injury to the capillaries, which leads to cell death by loss of circulation. The local effects of arsenic on the skin are seen only in workmen handling arsenic, as in color factories, in which affections of the skin of the face, hands and scrotum are by no means rare.

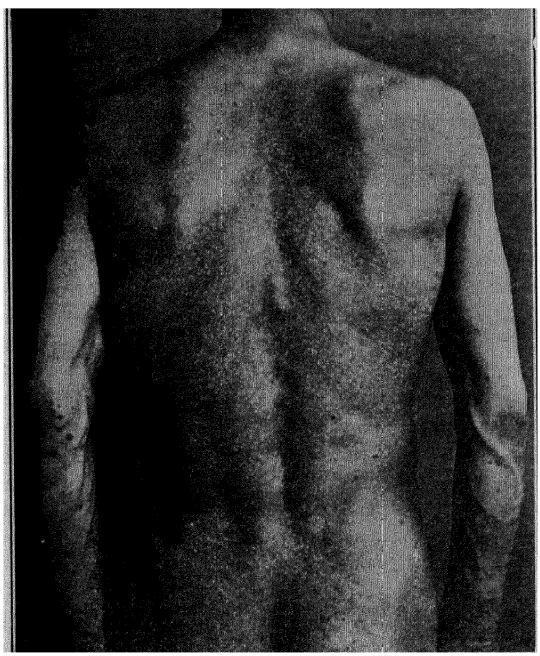

FIG. 4.—Generalized mottled hyperpigmentation following long-continued ingestion of arsenic.

In chronic arsenic poisoning skin eruptions are common, and are to be ascribed to the direct action of the drug on the skin. This appears to accelerate the growth and proliferation of the epithelium, which is found to be increased in thickness, but which in very severe cases shows signs of atrophy and degeneration. Arsenic has been found in appreciable amount in the hair and epidermal scales, and in the fluid of a blister in patients treated with it, and changes in the condition of the skin in animals have also been observed.

The melanosis of arsenic poisoning seems to be due to the deposition not of an arsenical compound, but of some organic product in the deeper layers of the corium. The symptoms of irritation of the mucous membranes of the eye, nose and larynx are analogous to the skin eruptions.

The action of arsenic on **The Blood** is still obscure, although it is frequently prescribed in various forms of anæmia. In chlorosis and in normal persons, it is said to diminish the number of the red corpuscles, but not to alter the total hæmoglobin of the blood. Stockmann and Greig found the blood cells and hæmoglobin unaltered by arsenic in normal animals, but describe the bone-marrow as evidently in a state of unusual activity, indicated by its increased vascularity, greater number of red blood corpuscles and lessened fat cells. In pernicious anæmia it has been stated that arsenic increases the number of young newly formed red cells while the number of more mature corpuscles is diminished. Gunn has shown that in shed blood small quantities of arsenite protect the red cells from various hæmolytic agents and suggests that this may occur in the therapeutic use of arsenic. After hæmorrhage the blood is said to regenerate more quickly if arsenic is given, and the number of red cells rises faster than the hæmoglobin. In spite of the long history of the use of arsenic in anæmias, there is still no real consensus of opinion as to its value in these diseases, in the treatment of which it has undoubtedly lost favor in recent years.

The **Metabolism** is affected by a poisonous dose of arsenic in the same way as by phosphorus, but the alteration is not generally so marked and is liable to be overlooked, owing to the more intense action on the alimentary canal. The nitrogen of the urine is considerably greater than that of inanition, but it is not quite clear whether this is due to an increase in the urea or to other nitrogenous substances. The ammonia is probably augmented, for a considerable amount of lactic acid has been obtained from the urine. The glycogen of the liver disappears entirely, and the liver seems incapable of forming it from the sugar of the food; it is said that under arsenic treatment quantities of sugar can be assimilated which would normally be sufficient to cause glycosuria. Lesion of the medulla oblongata (puncture diabetes) does not cause glycosuria after arsenic, but curare and other drugs are still capable of eliciting this symptom. The fatty degeneration of the epithelium of the stomach and intestine has been mentioned already, but this alteration is not confined to these tissues, being found in the liver and kidney, in the muscle cells of the heart, blood-vessels and striated muscles, and in the lining epithelium of the alveoli of the lungs. Small necrotic foci have been observed by Wolkow in the liver, along with signs of active division of the parenchymatous cells, as in phosphorus poisoning. Szent-Györgi ascribes the changes in metabolism produced by both arsenic and antimony to interference with tissue respiration and Oelkers finds that arsenic inhibits the action of ferments on protein and fat metabolism.

The fatty infiltration may have the same results as in phosphorus poisoning. The liver is somewhat enlarged and the pressure on the bile ducts prevents the escape of bile into the intestine, and thus induces jaundice and appearance of bile pigments and bile acids in the urine. Jaundice is seldom, however, a very marked feature in arsenic poisoning,

and is often entirely absent. The bile is said to contain albumin, red blood cells, and casts, as in phosphorus poisoning, but does not present other changes except immediately before death.

The prolonged administration of arsenic in quantities insufficient to produce chronic poisoning is reputed to have some effect on the **Growth and Nutrition,** but while improved nutrition is attested by a number of the older observers, other equally careful investigators have not been able to confirm their results. Thus Stockman and Greig observed no change in the growth of animals under prolonged treatment with arsenic, and found that the only tissues affected were the growing bones, which appeared denser than usual. Sollmann, feeding rats with very small quantities, far below the corresponding therapeutic dose in man, found that these tended to lessen appetite and retard the growth of the animals. The results of these careful researches are thus opposed to the popular view that arsenic is a "tonic" and exercises an invigorating action on the nutrition in man.

Attempts made to substantiate this view by measurement of the nitrogen metabolism have led to divergent results in the hands of different workers, and even in the more favorable cases, the change is so small that doubt may be entertained whether it may not have arisen from unavoidable error in these very long and tedious investigations. Several workers on the subject state that the bone formation may be altered, while denying any other influences on the metabolism.

Another widely held view is that the habitual use of small quantities of arsenic leads to **Tolerance,** and that the dose may be gradually increased until it far exceeds that which would be poisonous in ordinary persons. This is given as the explanation of arsenic-eating, a practice which has existed in different parts of the world, but which was most widespread and best known in Styria and the Tyrol. The peasants there believe that it enables them to work better, and in particularly to climb the mountains with less effort and less respiratory distress. Knapp administered 0.4 G. (7 grs.) of arsenious acid to one of the peasants at Graz without inducing any effects whatsoever. Arsenic-eating is said to be indulged in to a considerable extent in young women in some countries with the object of improving the complexion and figure, and cases of arsenic habit have been described in different parts of America and elsewhere. As far as can be observed, the habit is not deleterious, for the Styrian peasants live to old age, and no symptoms attributable to the poison have been noted. As a general rule large doses are taken once or twice a week, and no fluid is swallowed for some time afterwards.

It is also stated that large doses can be taken with impunity by animals previously treated with increasing quantities of dry arsenic by the mouth; on the other hand this has not been observed under arsenic given in solution hypodermically, and the statement is made that animals that tolerate large quantities by the mouth are killed by small quantities injected in this way. This has led to the view that in tolerance the intestinal cells fail to absorb the arsenic, and the poison thus does not reach the body cells, which remain susceptible to it. Thus Joachimoglu holds that tolerance is limited to the intestinal cells, which no longer

undergo inflammation and necrosis under arsenic. But considerable quantities of arsenic have been found in the urine of arsenic-eaters, showing that absorption occurs. Unfortunately these experiments and observations have not taken account of the great variation in the fatal dose of dry arsenic taken by the mouth; when coarse powder is taken, many times as much arsenic may be taken as when a fine powder is swallowed, and still less is dangerous when a solution is employed. And no tolerance has been definitely shown to be developed when the drug is given in solution; until this has been done, the development of tolerance to arsenic has not been demonstrated; the whole question requires further examination.

As a contrast to the Styrian peasants, the miners of Reichenstein may be mentioned, who are constantly exposed to arsenic owing to its being contained in large quantities in the ore. These people are described by Geyer as shortlived, very subject in childhood to severe rickets and in adult life to dropsies and respiratory diseases; they offer little resistance to microbial infection and frequently present the skin and nervous symptoms of arsenic poisoning. The difference in the reactions of these people may arise from the Styrians swallowing the dry crystals, which fail to be dissolved and absorbed, while the ore-workers may be exposed to a finer powder, which may perhaps reach the blood through the lungs. Differences in the general nutrition may also play a part, for Delepine and others have found that animals supplied with abundant food and in good hygienic conditions survive under chronic arsenic poisoning much longer than less well-nourished ones. This difference in the nutrition may also explain the fact that in epidemic poisoning, as in the Manchester cases, comparatively few of the persons exposed to the poison exhibited any symptoms from it.

Arsenic is **Excreted** very slowly, some appearing in the urine and fæces within twenty-four hours, but only about one-fifth of that absorbed being eliminated in this way. The rest is stored in the tissues for a long time and slowly got rid of in the hair and epidermis, in which arsenic may be found for many months after it has disappeared from the urine and fæces. Traces may be found in other secretions, and fatal intoxication has been observed in a child from the milk of its mother, who was suffering from acute poisoning. Arsenic is transmitted to the fœtus through the placental circulation. In the urine arsenic appears as arsenite and arsenate. It is probable that the effects, especially the paralysis, last long after the drug has been excreted, lesions having been induced which only recover slowly.

Arsenic disappears rapidly from the blood when injected, being taken up by the tissues in which it forms firm combinations with the nucleins; it is found chiefly in the liver, and is also deposited in the kidney, in the walls of the stomach and intestine, and in the spleen and lungs. Much smaller quantities are found in the muscles and in the nervous tissues, in which it is said to occur in larger proportion in the white than in the gray matter. It has been detected in the cancellous bones of the skull and vertebræ after it has disappeared from all the other organs.

Arsenic is poisonous to many of the lower forms of life, as well as to the vertebrates; thus it has been found that its presence in comparatively dilute solution (one part of arsenious acid in 30,000 parts of water) hinders the development of, and eventually kills, algæ and the seeds of the higher plants. On the other hand, moulds grow abundantly in a solution of potassium arsenite (1 per cent) containing some organic matter, and the alcoholic fermentation proceeds in the presence of arsenic, although it is somewhat retarded at first; very dilute solutions of arsenic even accelerate the fermentation, as is true of most other antiseptics. Arsenious acid is only about one-tenth as strong an antiseptic as perchloride of mercury, and the spores of anthrax are destroyed only after ten days in a 1 in 1000 solution. It has therefore a greater antiseptic power than many of the other acids, but compared with its action on the higher forms of life, it is but slightly poisonous to the fungi. Some pathogenic protozoa are extraordinarily susceptible to the action of arsenic; thus a concentration of arsenic in the blood of 1 in 200,000 is sufficient to destroy many of the trypanosomes, while other protozoa living in water may survive in a 1 in 5,000 solution. All the parasitic protozoa are not so readily destroyed, however, for that of malaria is found to be much more resistant. When an animal infected with trypanosomes is treated with arsenic, the parasites often disappear from the blood for some days or weeks and then reappear, but can again be expelled by arsenic, though for a shorter time; this phenomenon of developed tolerance is better seen when these organisms are treated with organic arsenic compounds and will be discussed later (p. 200). Apparently infusoria also acquire a certain tolerance to arsenic and other metallic poisons in water, but the very high resistance seen in the trypanosomes in the blood has not been observed in these non-parasitic protozoa.

The arsenates are much less harmful to lowly organized forms, for seeds and algæ as well as moulds grow in a neutral solution abundantly, and even the infusoria do not seem injured by it to any marked degree. Apparently these plants and animals are incapable of reducing the arsenates to arsenites, which are much more toxic.

The bodies of persons poisoned with arsenic are said to remain undecomposed for a remarkably long time, and tend to become mummified. The statement is still disputed, but is vouched for by a number of authorities. It is certainly not invariably the case, and little weight is to be laid upon mummification in determining whether arsenic poisoning was the cause of death in exhumed persons.

No account of the pharmacology of arsenic would be complete without mention of the theory advanced by Binz and Schulz to explain its action. They supposed that arsenious acid is oxidized to arsenic acid by the living tissues, and the arsenic acid again reduced to arsenious. In this way oxygen is alternately withdrawn from and supplied to the protoplasm, and this alternate reduction and oxidation they suppose to be the essential feature of the action of arsenic. The grounds on which this explanation is based must be sought in the numerous papers on the subject by these authors, and it may suffice here to state that while arsenic acid appears to be reduced and arsenious acid oxidized in the tissues, these processes are probably only gradual. Otherwise it would be difficult to explain how arsenious acid is so much more poisonous than arsenic acid, for if the latter were readily reduced to arsenious acid it would be equally toxic.

Arsenic and phosphorus are included in one group in chemistry and their effects on living organisms present sufficient resemblance to justify their association in the pharmacological system. The mucous membranes and the skin are more affected by arsenic, however, and the circulation is more rapidly depressed, while the fatty infiltration is much more prominent in phosphorus poisoning. The differences between their effects are more in degree than in kind, and there seems no ques-

tion that their ultimate action on protoplasm is of the same nature. It is to be noted, however, that there is no reason to suppose that phosphorus owes its action to any of its numerous compounds with oxygen, while it is probable that the oxides of arsenic alone are capable of modifying vital functions.

The **Sulfur Compounds** of arsenic are entirely insoluble and are therefore not absorbed as such, but it seems likely that small quantities of arsenious acid are formed from them in the intestine by microbes. Commercial orpiment often contains large amounts of arsenious acid.

Arseniuretted Hydrogen (AsH_3) is an exceedingly poisonous gas, which has caused a number of fatal accidents from being inhaled accidentally in chemical laboratories. Its action is quite different from that of the oxides of arsenic and there is no reason to suppose that arsenites give rise to appreciable amounts of the gas in the body, or that the effects of the latter are due to the formation of arsenites. Its action arises from its great affinity for hæmoglobin, which takes it up in large quantity and combines with it or with some product derived from it. This leads to hæmolysis, and the liberated hæmoglobin induces severe symptoms in the course of its excretion. In the test-tube arseniuretted hydrogen forms a combination with hæmoglobin which gives a characteristic spectrum but this has not been shown to occur in living animals. Most of the symptoms appear to arise from the hæmolysis, but there may be in addition some direct action on the central nervous system.

Arseniuretted hydrogen induces intense headache, nausea and vomiting, prostration and fainting fits, cyanosis and collapse. Hæmoglobin, methæmoglobin, hæmatin and occasionally blood are passed in the urine, and more rarely the stools contain blood. Sometimes the urine is entirely suppressed from the tubules being plugged with blood cells and débris, and intense icterus appears from the formation of excess of bile-pigment from the hæmoglobin of the disintegrated corpuscles. Œdema of the lungs or sudden failure of the heart is the cause of death. Some of the gas is excreted by the lungs, and may be recognized by its garlic odor, and some arsenic appears in the urine, but it is not known in what form. It is estimated that one part in 100,000 parts of air is injurious to man if breathed for a few hours.

Kiese investigated the effects in dogs of poisoning by small concentrations of AsH_3 for several weeks. He found a diminution in the number of red cells and a diminished osmotic resistance and an increase in reticulocytes. The liver, spleen and bone marrow were laden with an iron-containing pigment and, after long poisoning, a high concentration of arsenic was found in the hair.

Therapeutic Uses.—The action of arsenic as ascertained from experiments on the lower animals and from cases of poisoning in man throws little light on its use in therapeutics, and so little is known of the pathology of most of the conditions in which it is found of benefit, that no attempt can be made to bring the two series of observations into relation. The treatment of trypanosome infections, such as sleeping sickness, with arsenic and its compounds has given rise to the idea that many of the conditions in which arsenic is useful may arise from protozoal infection. But there is no question that arsenic acts in other ways than by destroying parasites, and such speculation is futile until the cause of these diseases has been determined.

Arsenious acid has been used externally as a *caustic*, formerly in various forms of malignant disease, more recently in lupus, in which it is said to destroy the diseased surface while leaving the healthy skin unaffected. It has been superseded, however, by the introduction of

surgical measures and treatment with light rays. Arsenous anhydride is still used in dentistry to destroy the pulp in decayed teeth; this destructive, caustic action proceeds more slowly than under more violent corrosives, so that there is little or no pain from it.

Internally arsenic is used in *malarial disease*, especially in inveterate cases in which there is much cachexia. In acute cases it is also of benefit, but is much less certain in its effects than quinine; it may act here by improving the general nutrition and lessening the cachexia and wasting, but in addition arsenic acts on the malarial parasite, though less powerfully than quinine. Many authorities, in fact, deprecate the use of arsenic in acute malaria, and would limit its use to the cachexia of old disease, while others advise its use with iron in ordinary cases, after the acute stage has been successfully treated with quinine. In obstinate cases it is probable that the quinine action may be reinforced by arsenic, and that parasites which have a low susceptibility to quinine may succumb to the arsenic. Thus while malaria generally does not require the use of arsenic, if the disease does not yield to quinine carefully administered, the patient may be treated with arsenic and quinine together.

Arsenic has also been used with benefit in *neuralgia* and in *chronic rheumatism*, but in many cases no definite improvement follows, and the conditions under which it is of value cannot be more accurately defined at the present time. It has long been used, and is still somewhat recommended in *Chorea*, especially when there is no fever and when the nervous, rather than the infective, element prevails. Fowler's solution, 5 mins. thrice daily, raised drop by drop to 10 or even 15 mins. is advised, the maximum dose being maintained for a week and the administration then abandoned. No satisfactory explanation has been given of its beneficial action in this disease. *Asthma* has also been treated with arsenic with benefit in some cases.

Small doses of arsenic are often of service in increasing the appetite and improving the general condition in diseases accompanied by cachexia, want of appetite, general weakness and apathy.

In *pernicious anæmia*, arsenic is sometimes beneficial, but the improvement is only temporary. It is also used in *erythræmia*, in which disease the treatment is very satisfactory in those who can tolerate the large doses of arsenic required and which may amount to 15 or even 20 mins. of Fowler's solution, thrice daily (Witts). The number of red cells begins to diminish about ten days after beginning treatment and a slow decrease may continue for many weeks. In *leucæmias*, especially of the chronic myeloid type, arsenic is often of value. Fowler's solution is prescribed in doses of 3–4 mins., increasing to 12–20 mins., thrice daily, and gradually withdrawn as the blood condition improves. Organic compounds of arsenic, like arsphenamine, have also been tried in blood disorders, but it is now generally admitted that they are not superior to inorganic arsenic for this purpose.

Many forms of *skin disease* are treated with arsenic, some of them with the happiest results. Thus in psoriasis, chronic eczema, and lichen

ruber, marked improvement or complete recovery often dates from the beginning of the arsenic treatment. It is generally advised only in the chronic forms, and is said to be positively deleterious during the earlier stages of rapid cell proliferation.

Arsenic has been used in syphilis in combination with mercury for over a century, and attention has again been drawn to this action through the efficacy of its new organic compounds. For this purpose Donovan's solution of the iodides of arsenic and mercury has generally been used. The quantity of iodide present in this solution is insufficient to have any specific iodide action and the improvement under it must thus be credited to the arsenic and mercury.

Arsenic has been used in some forms of *trypanosome infection* in animals, and has been found to improve similar conditions in man. The ordinary preparations have now been almost entirely replaced by the organic compounds.

Arsenic is in the great majority of cases prescribed in the form of Fowler's solution. It is generally advisable to commence with small doses, and to increase them slowly as long as no symptoms follow, but some authorities advise large doses from the outset. Arsenic is always prescribed to be taken after meals and well diluted, in order to avoid any possible action on the digestion. It is contraindicated in cases of irritation of the stomach and bowel, and is generally avoided during acute fever.

With continued administration of arsenic, watch must be kept for symptoms of chronic poisoning and, if they arise, the drug must be discontinued at once. The first symptoms are generally diarrhœa and disordered digestion, loss of appetite and discomfort in the stomach region, a feeling of constriction in the throat, and redness and swelling of the conjunctiva and eyelids. An early symptom of neuritis of the motor nerves is disappearance of the ankle-jerk.

In Acute Arsenic Poisoning the stomach ought to be emptied at once by means of the stomach tube or by an emetic (apomorphine). The stomach washing is to be continued for some time, as arsenic is very insoluble. Iron or magnesium preparations have been advised in order to form a loose chemical combination with the arsenic; a reputed antidote is freshly precipitated iron hydrate formed by adding magnesia to a solution of iron sulphate, as in the *Magma Ferri Hydroxidi* (U.S.P.). Experiments on animals throw doubt on the value of these antidotes and reliance is to be placed mainly on repeated and copious lavage.

The collapse is treated by the ordinary measures, warmth and stimulants, such as caffeine and digitalis. In chronic poisoning the paralysis is treated by stimulating the muscles with the galvanic current, the other symptoms, by suitable general treatment.

Preparations.

Arseni Trioxidum (U. S. P., B. P.), Acidum Arseniosum (As_2O_3), arsenous, or arsenious, acid anhydride, white arsenic, ratsbane, forms a white powder, or opaque, porcelain-like masses, or a transparent, amorphous surface like glass.

It dissolves slowly in cold water, the glassy variety requiring about 30, the porcelain about 80, parts of water. It is almost tasteless and has no odor. 0.002 G. ($\frac{1}{30}$ gr.); B. P., 0.001-0.005 G. ($\frac{1}{60}$–$\frac{1}{12}$ gr.).

LIQUOR ACIDI ARSENOSI (U. S. P.), a 1 per cent solution of arsenious anhydride acidulated with hydrochloric acid. 0.2 cc. (3 mins.).

LIQUOR POTASSII ARSENITIS (U. S. P.), Fowler's solution, contains 1 per cent of arsenious anhydride rendered alkaline with bicarbonate of potash. 0.2 cc. (3 mins.).

LIQUOR ARSENICALIS (B. P.), Fowler's solution, a 1 per cent, colorless, neutral solution of arsenic trioxide. 0.12-0.5 mil. (2-8 mins.).

LIQUOR ARSENI ET HYDRARGYRI IODIDI (B. P.), Donovan's solution, contains 1 per cent of arsenic iodide and 1 per cent of red mercuric iodide. This solution is clear and yellowish, without odor, but with a harsh metallic taste 0.3-1 mil. (5–15 mins.).

Some mineral waters contain arsenic, that of Levico as much as 8 mgs. per litre.

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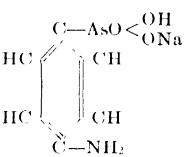
IV. ORGANIC ARSENIC COMBINATIONS.

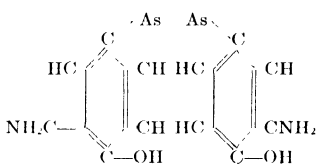
Inorganic arsenic has long had some reputation in the treatment of malaria and syphilis; in the latter disease it has been used along with mercury in the well-known Donovan's solution. These diseases have

been shown to arise from animal parasites living in the blood and tissues, and when the sleeping sickness of Africa was found to arise from trypanosomes, another protozoan parasite, inorganic arsenic was used to treat it. The results were disappointing, as the quantity of arsenic that could be given was limited owing to its poisonous action on the patient. For inorganic arsenic proved to have little specific affinity for the parasite; in Ehrlich's phraseology, it was not parasitotropic, while it was very poisonous to the tissues of the host, or strongly organotropic. In the test-tube inorganic arsenic preparations are very poisonous to trypanosomes, and they would doubtless be equally destructive in the tissues if they could be applied there without injuring the host.

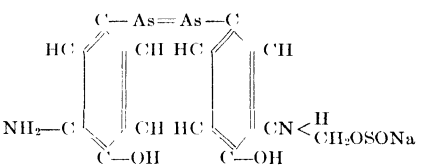
Some organic preparations of arsenic proved available for treatment, the first being *Atoxyl*, or sodium arsanilate. Later a modification of atoxyl



Atoxyl



Arsphenamine.



Neoarsphenamine.

known as *Arsacetin* (acetylatoxyl, $CH_3CONH—C_6H_4—AsO<\begin{matrix}OH\\ONa\end{matrix}$) was found more active in combating trypanosome infections. These combinations proved useful in syphilis also, but while destroying the parasites in these diseases, they were not devoid of deleterious action in man and have already almost disappeared from therapeutics. Ehrlich soon pointed out that atoxyl has practically no action on trypanosomes in test-tube experiments and only gains its parasiticidal action in the tissues. He explained this by the view that the pentavalent arsenic compounds, such as atoxyl and arsenic acid, are really inactive in themselves and only acquire activity when they are changed to the trivalent arsenic, such as exists in arsenites.

This led him to seek for organic compounds in which the arsenic is trivalent, and two of these were introduced by him, *Arsenophenylglycin* and *Arsphenamine* or *Salvarsan* $(AsC_6H_3OHNH_2)_2 2HCl$, of which the latter has been very widely used in the treatment of syphilis. More recently a modification of arsphenamine, *Neoarsphenamine* or *Neosalvarsan*, and several other organic arsenicals have been used instead of the parent substance. All of these organic compounds are much less poisonous to man and the higher animals than inorganic arsenic, while they maintain the poisonous action toward the protozoa that infest the

blood and tissues. In other words they are less organotropic and more parasitotropic. Ehrlich supposed that certain parts of the molecule in these compounds attach themselves to the parasites, and that these haptophoric groups then allow the poisonous part, or toxophoric groups, to act on the protozoa. The tissues of the mammals do not afford points of attachment for the haptophoric groups and therefore are not attacked by the toxophoric radical. This hypothesis of Ehrlich served a valuable purpose in stimulating and directing research on chemotherapy but new facts have come to light which render it untenable in its original form.

The treatment of trypanosome infections with arsenic preparations is complicated by the fact that the parasites rapidly develop *tolerance* to the drug. If an animal infected with trypanosomes receives an injection of atoxyl, the parasites disappear from the blood and none may be found in it for many days or weeks; then a few reappear and rapidly multiply but are again destroyed by a second dose; the interval before they are again seen in the blood is shorter, and becomes shorter with each succeeding injection until atoxyl no longer frees the blood from trypanosomes even in the maximal dose which can be given without injury to the host. If a second animal is now infected with the blood of the first containing these resistant trypanosomes, it is not improved by atoxyl, the descendants of the resistant type maintaining their tolerance of atoxyl through an indefinite series of generations. This form of resistance appears to arise, partly at least, from a process of selection by the survival of the most tolerant. The first dose of atoxyl destroys all but the most resistant of the trypanosomes, and these multiply and again the most resistant survive the second dose, and thus a strain is eventually reached which is as resistant to the atoxyl as the tissues of the host. This change in the character of the trypanosomes depends on their asexual generation and is readily intelligible when it is realized that successive generations are really only fragments of the original resistant individuals. Whenever a sexual cycle is interposed, all the resistance to atoxyl is lost. A strain of trypanosomes which has developed tolerance for one of the organic arsenical preparations (arsenic-fast) is generally tolerant to the others also, but not in such high degree to inorganic arsenic. To avoid the possibility of inducing tolerance in the parasites by repeated injections, Ehrlich hoped to find a substance a single dose of which would kill all the parasites. This hope has not been realized in regard to syphilis, though one dose of neosalvarsan may cure relapsing fever. Fortunately the organism of syphilis appears to acquire the tolerance to a less extent than most trypanosomes.

This tolerance acquired by the trypanosome may, however, hold good only for one particular host. It may be lost, for example, if the arsenic-resistant strain of trypanosomes is transferred from mice to rats, and may reappear again if these trypanosomes are again injected into mice. This points to the tissues of the host taking part in the trypanocidal action. Levaditi showed that both arsenic and bismuth compounds which are almost inactive toward trypanosomes *in vitro,* become actively trypanocidal when extracts of liver are added, and he suggested that it is

a compound formed by a reaction between arsphenamine and the tissue cells which really acts as the trypanocidal agent. Such a reaction might easily vary in different individuals and would explain the wide differences observed in the curability by arsphenamine of different species of mammals infected with the same strain of trypanosomes.

Voegtlin and Smith found that compounds of the type of R–As=O ("arsenoxide") produce a rapid trypanocidal action both *in vivo* and *in vitro*, and also produce more immediate toxic effects on the host. They suggest that arsphenamine undergoes partial oxidation in the body and that these oxidation compounds are responsible for the curative and toxic actions of arsphenamine. Voegtlin also found that arsenoxide combines readily with substances containing a sulphydryl grouping and the latter can inactivate the former. He suggests that combination with sulphydryl compounds, glutathione for example, may play an important part in explaining the toxic and curative action of arsenical derivatives. Though, as has been found by Ehrlich and others, the organic arsenicals have little immediate action on trypanosomes *in vitro*, Yorke and Murgatoyd find that trivalent compounds may be very actively trypanocidal if allowed twenty-four hours to act, and Reiner and Leonard have shown that, in contact with plasma plus arsenicals, trypanosomes may have their infective virulence decreased without being killed. Eagle, working with virulent S. pallida fresh from rabbit chancres, has recently found that arsphenamine and neoarsphenamine are antispirochætal *in vitro* in concentrations of about 1 in 200,000 and arsenoxide in a concentration of about 1 in 1,000,000. The organisms were immobilized and rendered non-infectious for other rabbits. These concentrations are of the same order as those attained *in vivo* after therapeutic administration. The idea originally held that compounds of the arsphenamine type are inactive outside the body is therefore no longer tenable, though it is still probable that they are converted in the body into some more active compound.

All these experiments suggest that the actions of arsphenamine and of its congeners do not admit of so simple an explanation as Ehrlich proposed and that coöperation of the tissues of the host is needed before the therapeutic virtues of these compounds are fully displayed. In the tissues they are changed into some more highly active organic compound of arsenic.

Only the more important of these remedies can be considered here and they will be discussed roughly in historical order.

1. **Cacodylates.**

The earliest of the organic arsenic compounds to be used in medicine was sodium cacodylate, $(CH_3)_2AsO\,ONa$, which is relatively feeble in action as it releases only small quantities of arsenic ion in the tissues. Most of the cacodylate is eliminated unchanged in the urine; some appears to be reduced to cacodyl, $(CH_3)_4As_2$, which is excreted in the breath and lends it an odor like garlic, while another small proportion is changed to the inorganic form and exercises the typical arsenic action. The amount which undergoes this transmutation is unknown and probably varies in different individuals and in different circumstances. Sodium cacodylate (Sodii Cacodylas, U. S. P.) is value-

less in syphilis. It is a white crystalline salt readily soluble in water. Dose, 0.06 G. (1 gr.). Another nearly related salt has been introduced as *Arrhenal* ($CH_3AsO(ONa)_2$), and resembles cacodylate in action.

2. Atoxyl.

Atoxyl, or sodium arsanilate ($NH_2C_6H_4AsOOH \cdot ONa$), was used extensively in trypanosome infections, in which it presented some advantages over the inorganic arsenic salts. It is absorbed rapidly and circulates in the blood longer than the arsenites, which are taken up by the tissues rapidly and thus can exert only a transient action on parasites living in the plasma. Atoxyl is excreted in the urine for the most part unchanged, but a small proportion undergoes decomposition and is believed to liberate the arsenious ions. Most of it is excreted within twenty-four hours.

In a number of cases atoxyl has given rise to *poisoning* in man, the symptoms being dryness of the throat, headache, giddiness, fever, colic, vomiting and diarrhœa, nephritis, and paresis of the lower limbs; the most serious effects, however, are disturbances of vision, which may advance to total and permanent blindness. In animals, ataxia and tremors are seen, especially in the cat, and renal hæmorrhages in the dog. Blindness has also been induced experimentally in animals, and is found to arise from degeneration of the ganglion cells of the retina and later of the fibres of the optic nerve. It seems likely that these symptoms are the result of the arsenic liberated from the atoxyl, and that they are different from those ordinarily seen under arsenic, because the arsenic is liberated in unusual parts of the body, owing to the atoxyl penetrating where the inorganic forms fail to reach.

A number of other arsenic compounds similar to atoxyl have been tested in trypanosomiasis and other diseases. Of these *Soamine* is practically identical with atoxyl, differing only in the amount of water of crystallization. *Arsacetin* is acetyl-atoxyl and resembles the parent substance closely in effects.

Atoxyl and its allies were introduced for the treatment of *trypanosomiasis*, in particular in sleeping sickness. But the hopes which were at first entertained that it would prove a cure for the disease are now dissipated; atoxyl appears to act efficiently on the parasites in the blood, but has less effect on those which have infected the lymph glands, and apparently does not reach those in the central nervous system in efficient concentrations. It clears the blood of the parasites, but the supply is constantly renewed from the foci in the nervous axis and eventually the parasites become resistant. In sleeping sickness atoxyl may alleviate the symptoms and prolong life but a cure of the disease from its use is very rare. It has been replaced by tryparsamide and Bayer-205, which are more effective in sleeping sickness and less toxic. It was also proposed to use it in syphilis, but fortunately before it attained popularity, the frequency with which it causes blindness and other toxic effects was recognized and since then this group of compounds has been regarded as too dangerous to use.

3. Arsphenamine or Salvarsan.[1]

Arsphenamine (p-dihydroxy-m-diamino-arsenobenzene) differs from the organic arsenic compounds so far discussed in the fact that it contains arsenic in the triad form, and thus corresponds to the arsenites, while in atoxyl the arsenic is pentad and corresponds to the arsenates.

Arsphenamine was at first injected into the muscles in man, but it tended to be deposited locally and to give rise to pain, swelling and infiltration, and was absorbed only slowly. The intravenous administration was therefore adopted and has become the ordinary method, and intramuscular administration has been practically abandoned.

[1] Other names introduced for this substance are *Kharsivan, Arsenobillon, Diarsenol, Arsenobenzol.*

When arsphenamine is injected intravenously, there are as a general rule no symptoms elicited, but in individual cases effects varying from comparatively trivial disturbance to grave and even fatal issues have been met with. Some of the more serious effects are definitely a variety of arsenical poisoning; others, less severe, are due to the bulk of fluid injected and the colloidal nature of the solution.

Immediately after the injection there may be a feeling of faintness, headache, flushing and heat in the head and face, giddiness and nausea, general malaise, profuse sweating, dyspnœa, or restlessness and tremor; vomiting and diarrhœa have occurred sometimes. There may be a fall in blood-pressure. Some fever followed in the earlier cases, from the use of water contaminated with the proteins of killed bacteria. These early symptoms are rarely of serious import, and have become rarer, as experience in the use of the drug has grown and suitable precautions have been taken to prepare the patient for what should be regarded as in the nature of a surgical operation. The faintness and syncope are sometimes due to fear of the injection and are rarely seen if the patient is in the recumbent position.

More alarming effects which are of the same nature as the flushing are the so-called "anaphylactoid" symptoms, marked by swelling of the lips and tongue, cyanosis and severe dyspnœa, urticarial and other skin eruptions, herpes labialis, stomatitis and albuminuria. When these symptoms arise in the later stages of a course of treatment, they suggest caution in the dosage and longer intervals between the injections. These effects seem due not to a toxic action of arsenic but to an alteration in the blood proteins, or perhaps agglutination of the red blood corpuscles, resulting from the colloidal nature of the arsphenamine injection. They do not occur after intramuscular injections. These reactions can generally be arrested by an intramuscular injection of epinephrine or prevented by previous administration of ephedrine by mouth.

Not infrequently swelling and œdema occur around the local manifestations of syphilis after arsphenamine has been injected; for example, when arsphenamine is administered in syphilitic skin eruptions, the skin lesions swell up, and the secretion from ulcers is increased (Herxheimer). This may perhaps arise from the poisonous action of the proteins freed from the dead spirochætes.

Severe symptoms have arisen in rare cases several days after the injection, and fatalities have followed either from cerebral symptoms (encephalitis hæmorrhagica) culminating in convulsions, coma and death, or from skin affections (dermatitis exfoliata), or from jaundice developing into acute yellow atrophy of the liver. These fatalities have become rarer in recent years and toxic effects of this nature are a variety of arsenical poisoning.

Toxic effects from arsphenamine may be due to impurity of the drug itself but misadventures from this cause have become less common since biological standardization of it has been adopted. The possibility of faulty technique, however, remains. Scrupulous attention is needed to every detail of administration and the solution must be freshly

prepared and correctly neutralized. Even when all precautions are taken, however, a small number of cases remain in which arsphenamine produces unusually toxic effects that can only be ascribed in the meantime to idiosyncrasy of the patient. Fortunately the number of accidents with arsphenamine is small in comparison with the frequency of its use.

In animals, the intravenous injection of arsphenamine in large quantities causes a marked fall in systemic blood-pressure, which is stated to resemble that seen under arsenic in arising in part from direct action on the walls of the arterioles and capillaries, in part from central action; but other observers regard it as due to arsphenamine weakening the heart. The pulmonary pressure in the dog is said to be increased from constriction of the arterioles, probably from obstruction from particles blocking the capillaries. In man a fall of blood-pressure sometimes follows the intravenous injection, but in other cases no change in the circulation is seen except a slight acceleration of the heart.

It is stated that in animals fatal encephalitis may be elicited by arsphenamine, with hæmorrhages and thrombosis of the vessels; necrosis and other lesions of the liver have also been observed. In rabbits large doses are found to induce nephritis, which, like that induced by inorganic arsenic, arises from the changes in the general circulation and the fall in blood-pressure rather than from direct action on the kidney. It has also been shown (Alwens) that when the tricuspid valves of the heart have been injured in animals, they can be poisoned by smaller quantities of arsphenamine than usual, and this has been attributed to the drug acting more strongly on the congested abdominal organs, especially the liver.

Excretion.—When a single dose is injected intravenously, arsphenamine appears unchanged in the urine in five to ten minutes and persists in this form for five to six hours; thereafter arsenic is found in the urine for some days, apparently in the form of arsenites and arsenates. It is excreted in the stools in larger proportions than in the urine, and the bile contains large amounts. It disappears from the blood at about the same time as from the excretions, but may be found in the liver, spleen, bone-marrow and kidney rather later; an arsenic reaction may be obtained from the liver and marrow as late as ten days after the intravenous injection in animals, but no arsenic is to be found in any of the organs after fifteen days.

It would thus appear that after its intravenous injection most of the arsphenamine disappears from the blood in a few minutes, though small amounts remain there for several hours. Some arsphenamine may be excreted in the urine unchanged, but after some hours inorganic arsenic compounds take its place and are excreted in the urine and fæces. The total excretion is slow and some appears to be stored in the liver and other organs, from which it is gradually released into the blood. Arsenic is not found in the cerebrospinal fluid after the intravenous injection of arsphenamine.

The excretion of neoarsphenamine resembles that of arsphenamine, but is more rapid. Pentavalent compounds, like atoxyl or tryparsamide, are much more rapidly excreted, probably because they are not fixed to the same extent by the tissue cells.

Therapeutic Uses.—Arsphenamine was introduced by Ehrlich for the treatment of *syphilis* and has been succeeded by neoarsphenamine, which

has the advantage of being available with less manipulation, but is generally admitted not to be quite so efficient. At first it was hoped that a single injection of arsphenamine would suffice to destroy the spirochætes of syphilis and realize the ideal of complete sterilization of the tissues as far as the virus of this disease was concerned. Although this hope has not been entirely fulfilled, the introduction of these arsenical compounds in the treatment of syphilis is a very important advance in medicine. Very frequently a single injection of arsphenamine frees the blood and local lesions from parasites within a few hours, and the Wassermann reaction, which is specific for syphilis, disappears; in a certain number of early cases the disease is healed, but in others the reaction returns. Some weeks or months later the spirochætes can be found again and symptoms of secondary syphilis begin to appear. The first injection suffices to destroy the great mass of parasites, but a few survive and reinfect the tissues. In practice it is found that repeated injections are necessary. Voegtlin found that in rabbit syphilis, 4 doses of 6 mgs. per kilo at intervals of six days gave better results than 24 mgs. per kilo in a single dose and concluded that the effectiveness of repeated fractional doses is due to the prolonged contact of the drug with the tissues.

It is now advised therefore that arsphenamine or neoarsphenamine should be injected repeatedly at intervals of one or two weeks, and that vigorous mercurial treatment should be initiated simultaneously with, or immediately after, the first arsphenamine injection and carried out as was customary before these new arsenicals were introduced. The treatment with arsenic compounds and mercury should be instituted as soon as the diagnosis is made, as the action of these specifics is much more efficient when the invasion of the parasites is only beginning and before they have reached inaccessible positions in the tissues. In the later stages, arsphenamine is also very valuable, but when the parasites are distributed in the central nervous system it appears to be unable to reach them, and while those in the blood and organs may be destroyed, the symptoms of nervous sclerosis often show little improvement; even in these nervous (parasyphilitic) affections, however, the process seems to be arrested or retarded in some cases.

Arsphenamine differs from mercury in syphilis in its greater rapidity of action; the parasites disappear after mercury treatment just as after arsphenamine, but a sterilizing concentration of mercury can be reached only after several days, and frequently entails more or less pronounced symptoms of mercurialism. The intravenous injection of arsphenamine on the other hand acts within a few hours, but most of the drug is excreted within three days, and the surviving parasites multiply unrestrained. When arsphenamine and mercury are used together, the immediate action of the one is obtained and is reinforced by the slower and prolonged action of the other. In addition, it seems likely that some parasites escape owing to their being only slightly susceptible to arsphenamine (see p. 200), but the chances are small that the same individuals have a low susceptibility to arsphenamine and also to mercury. The combined treatment with arsenic and mercury may thus be justified

by theoretical considerations, and has been abundantly supported by clinical experience in the last few years. More recently bismuth has been used extensively in place of mercury to supplement the action of arsenicals, on the same principle as the combination of mercury and arsenic.

In the treatment of several other protozoal diseases, arsphenamine has proved as successful as in that of syphilis. Thus in *frambœsia* (yaws), *recurrent fever*, and *Vincent's angina*, it is remarkably efficient, and in *spirillosis* of the lower animals an equal success has followed its use. In malaria arsphenamine is inferior to quinine, and in sleeping sickness it is less useful than tryparsamide.

In a number of diseases in which inorganic arsenic had previously been used, arsphenamine has been given as a substitute; thus pernicious anæmia, rheumatism and various skin diseases have been treated with it, but the results do not seem better than those obtained from the older arsenical preparations.

In cases of emaciation and malnutrition, the organic arsenic preparations are to be used with special care and in low doses, and in disease of the heart, vessels, or brain, and in very old and feeble persons or those suffering from nephritis or diabetes, arsphenamine should not be employed except under special precautions. In such cases the patient should be prepared for the injection as if for an operation and should not be allowed to resume his ordinary occupation for several days; and the doses should be reduced in amount.

4. Neoarsphenamine and Other Derivatives of Arsphenamine.

The chief drawbacks with arsphenamine are its instability, the technical difficulties of its administration, and its toxicity. Many new compounds have been investigated pharmacologically, and tested clinically, with a view to obtaining an even more satisfactory substitute for it, and the more important of these will be mentioned.

Neoarsphenamine. Neosalvarsan (sodium arsphenamine-methanal-sulphoxalate) was introduced by Ehrlich himself. Unlike arsphenamine it is soluble in neutral solution and is soluble over a wider range of pH than arsphenamine. It is more easily prepared for injection, and can be given intramuscularly without causing severe pain or necrosis, but is generally given intravenously.

It acts generally in the same way, and is used in the same diseases, as arsphenamine. It is excreted more rapidly and some authorities believe that it is hardly as efficacious as arsphenamine in curing syphilis. It has, however, almost completely displaced arsphenamine as it is less toxic and more easily administered.

The toxicity of neoarsphenamine as prepared by different manufacturers varies considerably, so that it requires careful physiological standardization, and the same care is required in preparing it for administration as is needed with arsphenamine.

Sulpharsphenamine, a formaldehyde-bisulphite derivative of arsphenamine, contains about 20 per cent of arsenic. It is more resistant to oxidation than the previous compounds, and also less irritant to the

in tabes. Visual disturbances, such as have been described under atoxyl, are liable to occur, but usually these clear up when the drug is discontinued.

It is claimed that 20–40 per cent of cases of general paralysis are improved by treatment with tryparsamide. Lorenz considers that the *total* therapeutic dose may vary from 50–1500 G., and the duration of treatment from one-half to two years. A usual dosage recommended is 1–3 G. in 10 cc. of distilled water given once a week, preferably in courses of 20 injections with two months' intervals between. Dimness of vision with contraction of the field gives warning before irreparable damage is done to the eyes. Visual disturbances are alleged to occur more frequently in tabetics.

Hawking and his co-workers have used a new method for estimating the penetration of arsenical compounds into the cerebrospinal fluid. After a suitable interval following the administration of a compound to a patient, a sample of the cerebrospinal fluid is withdrawn and its trypanocidal power *in vitro* determined as an indication of probable therapeutic efficacy. After tryparsamide the cerebrospinal fluid has considerable trypanocidal activity and after sulpharsphenamine slight activity; but after other compounds, *e. g.*, neoarsphenamine or stovarsol, the trypanocidal activity was negligible. There was no relationship between the total arsenic content of the fluid and its trypanocidal activity, so that this activity must depend upon the condition in which arsenic exists in the fluid.

Another pentavalent arsenical compound, **Acetarsol** or **Acetarsone** (hydroxyacetylaminophenyl arsenic acid), was introduced by Fourneau under the name Stovarsol. It is the first of these compounds for which the claim is made that it will act when given by mouth. It is stated to be a reliable *prophylactic* against syphilis if taken early. Good results have been reported in yaws, Vincent's angina and relapsing fever.

It has been used with success in amœbic dysentery, especially in chronic cases which have become resistant to emetine or in which this alkaloid is contraindicated. Leake and his colleagues have investigated a group of arsenical compounds related to acetarsone with regard to their toxicity and amœbicidal activity and have recommended "carbarsone" ($AsO(OH)_2 \cdot C_6H_4 NHCONH_2$) as the least toxic and most effective compound. Anderson advises 0.25 G. carbarsone in capsules twice daily for ten days, and records that it rids 90 per cent of cases of their pathogenic amœbæ. (Page 751).

Germanin.—The Bayer firm has put on the market a substance of which the composition is not revealed, called *Germanin* or Bayer 205. Fourneau has prepared a substance, "*Fourneau 309*," of apparently identical composition. It belongs to the class of trypanocidal dyes and though not an arsenical compound, may be mentioned briefly here as it is mainly used in trypanosomiasis. It can be given by mouth, intravenously, or intramuscularly but is usually best given by vein. It has some remarkable properties. It has no obvious effect on trypanosomes *in vitro* but may render them non-infective. When injected its action is delayed but prolonged. A dose injected into a

mouse, for example, frees the blood from trypanosomes in a few days but also renders it resistant to infection for weeks or months. During that period its serum exhibits a curative action if injected into another animal infected with trypanosomes, and the serum does not lose this property when heated. Its trypanocidal action varies very much with different strains of trypanosomes and with the same strain in different hosts. Only conjectures have been made as to how it acts.

Therapeutically it has proved of very distinct value in some forms of trypanosomiasis in lower animals and in sleeping sickness in man. So far as man is concerned it has proved most effective in the early hæmic cases of infection with T. Rhodesiense. Tryparsamide seems to be more effective in infection with T. Gambiense. Some authorities combine the treatments, beginning with Bayer 205 and continuing with tryparsamide.

Bayer 205 has produced severe nephritis in some cases. It is a white flocculent powder, readily soluble in water, and a usual dose is 1 G. intravenously, for 10 weekly injections.

Mention may be made here of the treatment of general paralysis by artificial inoculation with the Plasmodium malariæ, either from infected blood or from the mosquito. This method of treatment was introduced by von Jauregg in 1917, since when it has been extensively tried in most countries. The attack of benign tertian malaria thus produced is allowed to run its course for about 6–10 rigors, when it is stopped with quinine. In some cases the patient has been allowed to have relapses of malaria according to the effect produced on the paretic symptoms. The malaria is then permanently stopped by quinine medication. In about 25 per cent of the cases marked amelioration of the original symptoms occurs. Malaria seems to act as a kind of "shock" therapy, which is partly due to the fever induced. Other forms of fever, artificially produced, have been tried in neurosyphilis with beneficial effects, not, however, superior to those produced by malaria. The introduction of malarial and tryparsamide therapies in neurosyphilis has made the outlook much more favorable, especially in early cases of the disease.

ATOXYL, sodium arsanilate ($C_6H_7NAsO_3Na$), is a white crystalline powder containing 27.2 per cent of arsenic metal, soluble in 6 parts of water or about 125 parts of alcohol. It has a faint saline taste. Dose hypodermically, 0.1 0.3 G. (1½–5 grs.) per day in 10 per cent solution.

ARSPHENAMINA (U. S. P.), ARSPHENAMINE, SALVARSAN, diamino-dihydroxy-arsenobenzene hydrochloride, $HClNH_2OHC_6H_3As=AsC_6H_3OHNH_2HCl + 2H_2O$, is a yellow, crystalline powder containing 31.5 per cent of arsenic metal and readily oxidizing in the air; it is accordingly kept in vacuum tubes. It is readily soluble in water with an acid reaction. Dose, 0.3–0.6 G. (5–10 grs.) by intravenous injection. The arsphenamine tube should not be opened until required. The contents are dissolved in sterilized saline (0.9 per cent) and neutralized to litmus with normal caustic soda solution (0.85 cc. of normal NaOH is required for each 0.1 G. of arsphenamine); a precipitate is formed which redissolves on shaking. The solution should be very dilute for intravenous injection, at least 25 cc. being used for each 0.1 G. arsphenamine. Great care must be taken that the solution is not injected into the tissues around the vein as it causes intense pain and induration.

NEOARSPHENAMINA (U. S. P., B. P.), NEOSALVARSAN, is a yellow crystalline powder, containing about 20 per cent of arsenic. Three parts of neoarsphenamine therefore equal in arsenic content about 2 parts of arsphenamine. Dose, intravenously, U. S. P., 0.6 G. (10 grs.); B. P., 0.15 0.9 G. ($2\frac{1}{2}$-14 grs.). The contents of a newly opened tube are dissolved in 10–15 cc. of sterile, recently distilled water. The solution is neutral in reaction and requires no addition of alkali as in the case of arsphenamine.

SULPHARSPHENAMINA (B. P.), an orange-yellow powder, readily soluble in water, yielding an acid solution. For intramuscular or subcutaneous use it is dissolved in freshly-prepared distilled water in the proportion of about 0.1 G. to 0.3 cc.; for intravenous use in the proportion of 0.1 G. to 3 cc. Dose by subcutaneous or intramuscular injection, 0.1–0.6 G. ($1\frac{1}{2}$-10 grs.).

TRYPARSAMIDUM (U. S. P., B. P.), a white crystalline powder containing about 25 per cent of arsenic. Dose, 2 G. (30 grs.) dissolved in 10 cc. distilled water, intravenously; also given intramuscularly.

ACETARSOL (B. P.) (stovarsol), a white crystalline powder, almost insoluble in cold water, soluble in dilute alkalies. Contains about 27 per cent of arsenic. Dose for adults, 0.06–0.25 G. (1–4 grs.).

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V. PHOSPHORUS.

In the early part of last century phosphorus played a very important rôle in therapeutics, and, in fact, was regarded almost as a panacea, but at present its use is much more restricted, and doubt is entertained as to its possessing any therapeutic value whatever. At the same time, it has been the subject of much and laborious investigation, partly because it has frequently given rise to poisoning, and partly because the study of its effects has thrown much light on some physiological and pathological processes. A more detailed account of these effects was given in previous editions of this book. Phosphorus seems to be of diminishing therapeutic and toxicological importance, so that only a brief survey of its actions is now necessary. It is no longer official.

Phosphorus is absorbed with difficulty, because it is very insoluble in water and the body fluids and is only slowly volatilized at ordinary body temperature.

Large masses of phosphorus may thus pass through the alimentary canal without serious effects, because they fail to be dissolved and absorbed. But when it is taken in a finely divided condition or in solution in oil, it gives rise to symptoms in very small quantity, and has been found to induce fatal poisoning in man in doses of 0.05–0.1 G. (1–2 grs.). In these conditions it is absorbed partly as vapor, partly in solution in water, which dissolves only traces, however, and probably chiefly in solution in the fats and oils, in which it is much more soluble. Phosphorus vapor is also absorbed by the lungs, and the symptoms of chronic poisoning in match factories are believed to arise in this way. The red amorphous phosphorus is much less poisonous than the ordinary yellow form, because it is less soluble and also less volatile, and consequently fails to be absorbed.

Phosphorus has often been used as a suicidal poison, generally in the form of rat poison or match heads. Formerly each match head was estimated to contain 3–5 mg. of phosphorus, so that 15–20 match heads might induce fatal poisoning. The use of poisonous yellow phosphorus in match manufacture is now generally prohibited by law. Phosphorus sesquisulphide (P_2S_3), now usually employed, seems to be even safer than red phosphorus. "Safety matches" have no phosphorus on the sticks, only red phosphorus on the striking surface.

Phosphorus exists in the blood as such, and the effects on the tissues are unquestionably due to the element itself, and not to the oxygen or hydrogen compounds, as has been supposed. Some phosphuretted hydrogen (PH_3) may be formed in the bowel, but is comparatively unimportant, the great mass of the phosphorus being absorbed unchanged. As soon as it is oxidized, phosphorus loses its specific action, all of the acids being comparatively harmless. Phosphorus has been detected in the blood, and, it is said, in some of the excretions.

It is devoid of action on albumins in solution and has no immediate irritant effects, such as are seen in poisoning with the heavy metals.

Symptoms.—When a poisonous dose of phosphorus is swallowed, no effects are elicited, as a general rule, for several hours. The first symptoms are pain and discomfort in the region of the stomach, nausea and eructation of the vapor with its characteristic garlic odor, and then vomiting, the contents of the stomach having the same odor, and being phosphorescent in the dark. Later, bile may be vomited, and some diarrhœa may set in, although this is not a common symptom. The nausea and vomiting often continue without further symptoms for several days, but frequently disappear, and the patient apparently recovers, particularly if the dose has been small, or if most of it has been removed by vomiting or by washing out the stomach. In the course of a few days, however, the symptoms recur, and are generally accompanied by some jaundice; the pain extends from the stomach to the liver, and soon to the whole of the abdomen. The vomited matter no longer contains phosphorus, but may be bloody. The patient complains of general weakness and faintness; the pulse is weak, the liver extends far below the ribs, and the urine shows characteristic changes (see page 213); hæmorrhages occur from the nose, bowel, uterus and under the skin, and eventually a condition of collapse and fatal coma or delirium and convulsions follow.

Exposure to the fumes of phosphorus has long been known to give rise to periostitis and necrosis of the lower jaw. The disease begins from a carious tooth or from some lesion of the gum, and may involve most of the jaw, which becomes swollen and painful and eventually evacuates large quantities of pus with pieces of dead bone. This necrosis was formerly frequent in match factories, but has become almost only of historical interest since amorphous phosphorus has been substituted for the yellow form, and since greater attention has been paid to the ventilation of the factories and to the condition of the teeth of the employees. Magitot has advanced the opinion that exposure to phosphorus fumes gives rise to a mild chronic form of poisoning, quite aside from the necrosis, which is comparatively rare. The symptoms are cachexia, slight jaundice, anæmia and albuminuria, and in more advanced cases, chronic enteritis and diarrhœa, bronchitis and a curious fragility of the bones.

Action: Fatty Infiltration.—A very striking feature in phosphorus poisoning is the appearance of numerous fat globules in the cells of many organs, notably

In the earlier phases the secretion of bile pigment is increased, denoting an unwonted activity of the liver, but later as the cells become infiltrated with fat, they press on the bile capillaries and occlude them, so that the bile is absorbed into the blood-vessels and gives rise to jaundice. During recovery the cells lessen in size and cease to press on the ducts, and the jaundice color disappears from the skin as the bile pigment is reabsorbed. The bile very often contains albumin in considerable amount while the bile salts are reduced; in the later stages red blood cells may occur in it.

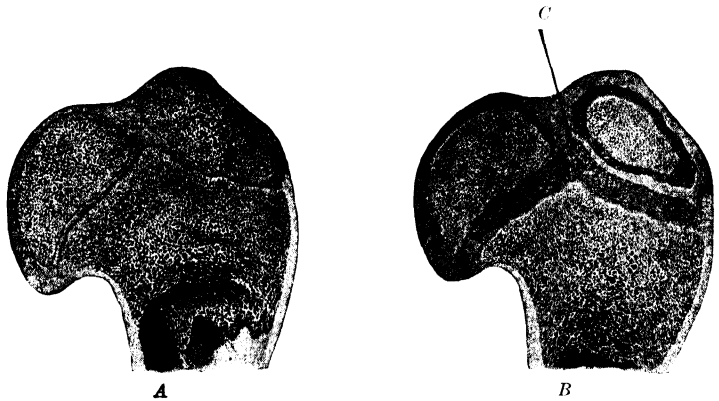

FIG. 5.—Section of the head of the femur in a calf. *A*, normal; *B*, after treatment with minute doses of phosphorus; *C*, the cap of dense bone at the growing point. (After Wegner.)

In the **Kidney**, the fatty degeneration of the epithelium may account for the albuminuria, which is not generally severe, and is not infrequently absent in cases of poisoning. Fatty casts and even globules of fat are often found in the urine in cases which run a chronic course. Blood and hæmoglobin may also appear in it from hæmorrhages into the kidney. The urine is normal in quantity in the early stages of the intoxication, but afterward becomes deficient, and towards death complete anuria may be observed. When icterus is present, the urine may be dark in color from the bile pigment excreted, and bile acids are also often contained in it.

Metabolism.—The great similarity between the results of normal autolysis and of phosphorus poisoning has led to the view that the essential effect of phosphorus is an acceleration of the autolytic process, which occurs in normal cells. This accelerated destructive metabolism is less completely carried out than normally, so that intermediate products, such as leucin, tyrosin and other amino-acids appear in large quantities in the organs and often in the excretions; lactic acid is similarly a product of autolysis, which fails to be oxidized to carbonic acid as in the normal body. This accelerated autolysis occurs not only in the liver but also in other organs, although in a less marked degree.

According to this view, the fatty infiltration is a secondary result of the accelerated autolysis; the cells are supposed to absorb fat from the blood more rapidly than normally and to store it in their interior in the form of globules, and as the fat of the blood is thus reduced, the normal fat deposits in the body are drawn upon to replace it and this results in the transference of fats from the subcutaneous tissues to such organs as the liver, kidney, and heart. But these have lost to a large extent their normal capacity of decomposing fats, which are therefore deposited in the cells.

Yeast, infusoria and bacteria are very little affected by the presence of this poison, and living microbes are found in large numbers on solid pieces of phosphorus.

The **Temperature** is often low in the later stages of phosphorus poisoning, but slight fever is also observed in some cases.

The **Fate** of phosphorus in the body is still obscure. It is possible that some of it is oxidized to phosphoric acid, and some phosphorus is said to be excreted by the lungs, although the statement that the breath becomes phosphorescent seems to be extremely improbable. It is also excreted in the urine in some organic combinations, of which nothing is known, though they are said to be volatile. In pregnant animals poisoned with phosphorus the fœtus is found to undergo fatty degeneration, so that the poison would seem to pass through the placenta. Phosphorus injected hypodermically acts much slower than when swallowed.

Phosphuretted hydrogen (PH_3) induces the same symptoms as phosphorus, when it is given in repeated small quantities. Large doses are very rapidly fatal, and the symptoms differ entirely from those of phosphorus poisoning, consisting of marked dyspnœa, purgation, weakness, tremor, and finally violent convulsions and respiratory failure. The oxygen compounds do not seem to have any such effects, and for the most part are harmless except in very large doses.

Phosphorus has been recommended for a variety of purposes in therapeutics, but has never acquired an assured footing. Its action on bone has suggested its use in rickets, osteomalacia, ununited fractures and caries, but the results have been unconvincing and phosphorus is now rarely used.

Treatment of Phosphorus Poisoning.—Phosphorus is comparatively slowly absorbed from the alimentary canal, so that in the early stages an attempt ought to be made to remove it by emetics or the stomach tube, and by purges. Fats and oils must be avoided, as they tend to dissolve the poison and promote its absorption. Phosphorus has been found in the stools three days after its ingestion, and a sharp purge may therefore be of use up to this time.

Sulphate of copper is recommended in phosphorus poisoning, a large dose being given first as an emetic, and afterward smaller doses to form an insoluble compound, copper phosphide. Permanganate of potassium solution, 1 in 1000, has been recently advised to oxidize the phosphorus, while peroxide of hydrogen solution is of less value. In the secondary stage alkalies are recommended in order to neutralize the excess of lactic acid formed in the tissues.

Phosphorus necrosis has to be treated surgically on the same principles as other necroses of bone.

Phosphorus was formerly prescribed in doses of 0.0006 G. ($\frac{1}{100}$ gr.), given in solution in oil or in pill form.

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PART II.

SUBSTANCES WHICH ARE CHARACTERIZED CHIEFLY BY THEIR LOCAL ACTION.

This class contains a very considerable part of the drugs included in the pharmacopœias, although it bears a smaller proportion than formerly to the other classes. There is still, however, in it a large number of drugs which have practically identical effects, and there is no question that it might be considerably curtailed without loss to therapeutic practice. Many of its members are irritants, and these have been subdivided for convenience into groups according to the organs on which they exert their chief action and the purposes for which they are used in therapeutics, as gastric, intestinal, cutaneous irritants. Others act as protectives, covering injured surfaces (demulcents, emollients), and still others precipitate the proteins on the surfaces to which they are applied (astringents).

I. SKIN AND MUCOUS MEMBRANOUS PROTECTIVES.

1. **Demulcents.**—A large number of colloid substances—chiefly gums, dextrins, certain sugars and starches—owe their use in medicine, not to any changes they produce in the cells with which they come in contact, but to the fact that they are cohesive and serve to protect surfaces mechanically. When they are applied to a sensitive surface, they retard the movement of fluid or air against it and thus preserve it from the effects of these agents. This may be illustrated by familiar examples in which the taste of food is altered by their presence, although they have often no taste or odor in themselves. Sugar dissolved in mucilage tastes less sweet than in water, and acids are also less appreciated, as may be observed in many fruits. For example, the raspberry contains more acid and less sugar than the currant, but in the former the acid taste is concealed by the presence of large quantities of colloids, so that the raspberry is regarded as a sweet fruit, the currant as an acid one. Even cold is felt less when a colloid substance is present in the fluid swallowed; thus, ice-cream or iced milk does not feel so cold on the tongue and throat as frozen water, because the colloid protein substances form a protecting layer over the surface, and prevent the cold mass from reaching the sensory terminations so freely as it otherwise would. A number of experiments carried out by Tappeiner show that other organs may be protected in the same way by colloid solutions. Strong salt solution applied to a motor nerve first stimulates and then slowly paralyzes it, but Tappeiner found that both of these effects are much less marked if the solution be made up with mucilage instead of with

water, because the salt does not reach the nerve so readily. In the same way, intense pain is caused in a wound by strong salt solution, but is much less severe if the solution contain colloid material.

When demulcents reach the stomach, they act as protectives in some measure so that the reflexes from the epithelium are less active; and irritants cause less inflammation if they are suspended in demulcents than if they are dissolved in water; at the same time the presence of colloidal unabsorbable bodies may increase the efficiency of purgatives by preventing their absorption in the upper part of the bowel. The digestion of proteins outside the body is retarded by the presence of the demulcents, and probably this is also true of the process in the stomach. Colloid bodies also retard the absorption of fluids from the stomach and bowel, and this leads to a feeling of distention, which is much less marked if the same amount of fluid be swallowed without colloid; for instance, water is absorbed more rapidly than milk.

Demulcents are used to cover inflamed surfaces; in tonsillitis, for example, they may be applied as gargles, or better by sucking lozenges containing them. They are not often applied externally for this purpose, as they are liable to serve as media for the growth of microörganisms. In gastric and intestinal catarrh their use is objectionable for the same reason, their slow absorption leading to decomposition with the formation of irritants, which may do more harm than is counterbalanced by their protective action. Instead of demulcents, some of the oils, such as olive oil (p. 219), have been recommended as protectives in disease of the stomach and intestine.

In acute irritant poisoning the demulcents are often of great value, as they protect the stomach wall from the effects of the poison. The best remedy in these cases, because the most readily obtainable, is milk or white of eggs.

Demulcents are often given instead of pure water in cases where it is desired to administer large quantities of fluid, as they have more "body" and are more agreeable to the taste. Thus, barley water or some other demulcent may be advised in order to assuage the thirst of fever, or to dilute the urine when it is too concentrated or too acid.

Demulcents are often used as the basis of enemata which are intended to be absorbed, because solutions containing colloids are less irritant and therefore less liable to set up peristalsis than pure water. For this purpose starch solution is generally used.

Some of the gums, notably acacia and tragacanth, are seldom advised as demulcents, but are often prescribed in order to hold in suspension in water such insoluble bodies as resins and oils, or to give cohesion to pills and lozenges.

Gelatine is largely used as a demulcent in the preparation of pastilles for the local application of medicaments to the throat. It is also used to solidify glycerin for use as a suppository, and in similar combination for bougies and pessaries. Pastes of gelatine are also prepared for external application. In the form of soups and jellies it is used as a nutrient, being easily digested and capable of replacing to a certain extent the ordinary proteins of the diet.

Preparations.

Acacia (U. S. P., B. P.) (gum arabic), a gummy exudation obtained from Acacia Senegal, consists of the potassium, magnesium and calcium salts of a weakly acid substance, arabin, or arabinic acid ($C_6H_{10}O_5$). It is soluble in equal parts of water, and is used as a demulcent, but more largely as a vehicle for other drugs.

Mucilago Acaciæ (U. S. P.), 35 per cent acacia in distilled water. Dose, 15 cc. (4 fl. drs.). (B. P.) Forty per cent acacia in chloroform water. Dose, 4–16 mils. (60 240 mins.).

Tragacantha (U. S. P., B. P.), a gummy exudation from various species of Astragalus, contains salts of arabin and tragacanthin. Tragacanthin differs from arabin in not dissolving, but merely swelling up into a jelly in water. Tragacanth is used chiefly to suspend heavy powders in water.

Mucilago Tragacanthæ (U. S. P.), 6 per cent Tragacanth with water and glycerin. Dose, 15 cc. (4 fl. drs.). B. P., 1.25 per cent in chloroform water. Dose, 4 16 mils. (60 240 mins.).

Amylum (U. S. P., B. P.), or starch, may be formed into a jelly by boiling in water, and may then be used for the same purpose as the demulcents.

Glyceritum Amyli (U. S. P.), Glycerinum Amyli (B. P.), is a jelly formed by heating starch with water and glycerin.

Glycyrrhiza (U. S. P., B. P.), or liquorice-root, the root of Glycyrrhiza glabra (var. glandulifera), is used as a demulcent, and more largely to flavor medicines. It has a pleasant, sweet taste, owing to the presence of Glycyrrhizin, an acid glucoside. Dose, 2 G. (30 grs.).

Extractum Glycyrrhizæ (U. S. P., B. P.). Dose 0.6–2 G. (10 30 grs.).

Fluidextractum Glycyrrhizæ (U. S. P.). Dose, 2 cc. (30 mins.). Extractum Glycyrrhizæ Liquidum (B. P.). Dose, 2–4 mils. (30–60 mins.).

Pulvis Glycyrrhizæ Compositus U. S. P., dose, 4 G. (60 grs.); B. P., dose, 0.6 4 G. (10–60 grs.), contains senna and sulfur.

Mistura Opii et Glycyrrhizæ Composita (U. S. P.), "Brown Mixture," contains opium, antimony and spirits of ethyl nitrite. Dose, 4 cc. (1 fl. dr.).

The extract is largely used in the form of lozenges for its demulcent action, and is frequently used to make up pills. It is slightly laxative, and may be used as a pleasant aperient for children; the compound powder is more reliable for this purpose, owing to its containing senna and sulfur. The brown mixture is used in cough and in bronchitis.

Numbers of other substances are used as demulcents in domestic medicine, and are found in different pharmacopœias. Examples of these are sassafras pith (*Sassafras Medulla*), slippery elm (*Ulmus*), marshmallow root (*Althæa*), linseed (*Linum*), barley (*Hordeum*), salep, verbascum and quince seeds. Iceland moss is a lichen (Cetraria islandica), and contains starch bodies together with acids, which can be removed by soaking in dilute alkaline solutions for some time. Irish moss or Carragheen (*Chondrus*), a seaweed gathered on the coasts of Ireland and Massachusetts, contains a carbohydrate, carrageenin. The decoction forms a jelly when cold, and was formerly supposed to form a valuable food in illness, but it is of little value for this purpose, for only about $\frac{1}{20}$–$\frac{1}{10}$ of the jelly is solid matter, the rest water.

2. **Emollients and Protectives.**—Emollients are bland, oily substances which are applied to the skin to protect it from irritation, and to render it softer and more elastic; they thus bear the same relation to the skin as the demulcents to the mucous membranes. Their effect in rendering the skin softer and more pliable may be due in part to their penetration into the surface layers, but may also be explained by the slight congestion induced by the rubbing and massage used in their application.

The older emollients were chiefly animal and vegetable fats and oils, but several newer drugs of this class are derived from petroleum. The

effects of these drugs when applied to the skin are purely local. The emollient preparations are supposed to promote the absorption by the skin of drugs dissolved in them, because they mix readily with the thin layer of oily sebaceous matter which covers it. The active substances dissolved in them therefore come into intimate contact with the absorbing cells lining the ducts of the glands, while watery solutions are separated from the living cells by a layer of sebum. Aqueous solutions come into more intimate contact with the cells of the mucous membranes and with the subcutaneous tissues, and are therefore more readily absorbed by these than oily solutions. It has generally been supposed that substances are more easily absorbed from the skin if the vehicle is an animal fat, *e. g.*, lard or lanolin, but Bliss found no difference in absorption of iodine, quinine, etc., whether the ointment base was soft paraffin, lard or lanolin. Macht similarly found that none of the common bases used in ointments (*e. g.*, fixed oils, fats, lanolin or petrolatum) facilitated the absorption through the normal skin of drugs incorporated in them. Volatile substances, especially if soluble in fats, are however readily absorbed through the skin. Solutions in oil of such antiseptics as carbolic acid are much less powerful than those in water, because carbolic acid being more soluble in oil fails to diffuse into the watery protoplasm of the microbe, for which it has less affinity. But antiseptics which are more soluble in water than in oils are said to be equally active in both solvents.

The emollients are applied as protectives in abrasions, cuts, bruises, chapped hands, burns; they are less often used alone in extensive skin diseases, but are usually prescribed in these as the basis of ointments in which other remedies are incorporated. There is no question that the protection afforded to the part and the exclusion of the air and of germs by the oily emollient plays an important part in the action of these remedies, and it seems probable that in many cases equally good results would follow the application of the emollient without any active ingredient.

The emollient ointments are also applied to wounds and mucous membranes as protectives and also as vehicles for other remedies. Here they have a more lasting effect than watery applications, which are more readily absorbed. Emollients are seldom applied to the mouth because of their unpleasant oily taste, but the eye, nose, urethra, vagina and rectum are often treated with them.

Preparations.

Adeps (U. S. P., B. P.), lard; the prepared internal fat of the abdomen of the pig, purified by washing in water, melting and straining.

Adeps Benzoinatus (U. S. P., B. P.), benzoinated lard, is prepared from lard by the addition of benzoin, which is believed to preserve it from becoming rancid, and certainly conceals the odor.

Unguentum (U. S. P.), ointment, is a mixture of lard and white wax, and is the basis of many other ointments.

Lard contains the ordinary constituents of animal fats, stearin, palmitin and olein, and is seldom used alone but forms the basis of numerous ointments and especially of benzoinated lard.

ADEPS LANÆ HYDROSUS (U. S. P., B. P.), hydrous wool-fat, lanolin, the purified fat of sheep-wool, mixed with not more than 30 per cent of water.

ADEPS LANÆ (U. S. P., B. P.), wool-fat without water.

UNGUENTUM SIMPLEX (B. P.), containing wool-fat and paraffins.

Wool-fat has been used extensively in medicine only in the last few years. It consists of cholesterin esters with some impurities, does not become rancid, and differs from the older fats also in being miscible in twice its weight of water without losing its ointment consistency. Lanolin is very often used as an emollient application, as well as to form a basis for more active drugs. The unhydrated wool-fat is too sticky to be satisfactory. The hydrated form is generally too hard to be used as an ointment and is therefore diluted with soft paraffin (3 parts) or olive oil (equal parts).

PETROLATES OR PARAFFINS. When the more volatile constituents of petroleum are distilled off, there remains a number of higher hydrocarbons, chiefly of the marsh gas series, which are used in medicine as emollients. The lower of these hydrocarbons are fluid at ordinary temperatures and are known as:

PETROLATUM LIQUIDUM LEVE (light liquid petrolatum) (U. S. P.), and

PETROLATUM LIQUIDUM (U. S. P.), PARAFFINUM LIQUIDUM (B. P.), a colorless, oily transparent liquid without odor or taste. When these are removed there remains:

PETROLATUM (U. S. P.), and PETROLATUM ALBUM (U. S. P.), PARAFFINUM MOLLE (B. P.), soft petrolate, vaselin, which has the consistency of an ointment, is yellow or white in color, and is liquefied a few degrees above the temperature of the blood. When the distillation is carried further, the residue is solid at ordinary temperatures, and is known as

PARAFFINUM (U. S. P.), PARAFFINUM DURUM (B. P.), or hard paraffin, which melts at a somewhat higher temperature than vaselin.

Soft petrolate is more extensively used than the others as an emollient and as a basis for ointments, and has the advantage over lard that it does not become rancid; as a general rule it is too soft but may be made of the proper consistency by the addition of wool-fat or of starch or zinc oxide (equal parts); or the UNGUENTUM PARAFFINI (B. P.), containing hard and soft paraffin and beeswax, may be employed.

Several OILS are also used as emollients.

OLEUM OLIVÆ (U. S. P., B. P.), olive oil, a fixed oil obtained from the ripe fruit of the olive, Olea europæa.

OLEUM AMYGDALÆ EXPRESSUM (U. S. P.), OLEUM AMYGDALÆ (B. P.), a fixed oil expressed from bitter or sweet almonds. It is to be distinguished from the volatile oil obtained from the bitter almonds. The fixed oil contains no prussic acid.

OLEUM MAYDIS, corn oil (U. S. P.), a clear light yellow oil expressed from the germ of Zea mays.

UNGUENTUM AQUÆ ROSÆ (U. S. P.), cold cream, is formed of white wax, oil of almonds, and some borax, scented with rose water.

UNGUENTUM AQUOSUM (B. P.) contains beeswax, soft paraffin, olive oil and water, with some borax.

OLEUM GOSSYPII SEMINIS (U. S. P., B. P.), cotton-seed oil.

These all resemble each other in their composition, and may be used as emollients. Olive oil is applied externally as an emollient and sedative to inflamed surfaces and is used extensively in the preparation of liniments, plasters, etc. Almond oil is usually preferred for cold creams and toilet preparations. Given internally, olive oil sometimes gives relief in biliary colic and dysentery and in some gastric disorders accompanied by pyloric spasm, probably from its acting as a protective to the mucous membrane of the stomach and duodenum and lessening the acid gastric secretion. A wineglassful is given two or three times a day before meals; in these large doses it possesses a high food value.

Wax (CERA), spermaceti (CETACEUM) and suet (SEVUM) are of harder consistency than lard, and are added to the other emollients to make them firmer, which is especially desirable in hot climates and in summer.

GLYCERINUM (U. S. P., B. P.), glycerin, a liquid obtained by the decom-

position of animal or vegetable fats or fixed oils, and containing not less than 95 per cent of absolute glycerin, $C_3H_5(OH)_3$; clear, colorless, of a syrupy consistence, oily to the touch, with a sweet taste and no odor, soluble in water and alcohol.

Glycerin is used as a solvent for a number of other drugs, the preparations being known as GLYCERITES (U. S. P.), GLYCERINES (B. P.).

Glycerin is somewhat irritant to the unbroken skin, when it is applied in the pure form, and even diluted glycerin causes pain and smarting when it is applied to unprotected surfaces such as cuts or burns, but the pain soon disappears, and glycerin then acts as a protective. The irritation is due to the glycerin abstracting the fluids of the tissues owing to its avidity for water. Diluted with one or two volumes of water or rose water, glycerin is useful as an emollient in conditions of irritation of the skin and the lips from exposure to cold, and in similar conditions. Glycerin is not a disinfectant except in strong solution, in which it probably acts by the withdrawal of water from the microbes.

OLEUM THEOBROMATIS (U. S. P., B. P.), cacao-butter, a fixed oil expressed from the seeds of Theobroma cacao, forms a yellowish-white solid having a faint, agreeable odor and a bland chocolate taste. It melts a little below the temperature of the body. Cacao-butter is used almost exclusively to form suppositories, in which astringents and other remedies are incorporated. When introduced into the rectum they melt and the active principle is liberated.

SAPO DURUS (U. S. P., B. P.), hard soap, white Castile soap, is prepared from soda and olive oil.

SAPO MOLLIS (U. S. P., B. P.), soft soap, sapo viridis, a soap made from potash and olive oil.

SAPO ANIMALIS (B. P.), curd soap, soap made with sodium hydroxide and purified animal fats consisting chiefly of stearin; it contains about 30 per cent of water.

These soaps are used in therapeutics as ingredients of liniments and plasters. Water containing soap is often thrown into the rectum as an enema, and in infants a soapstick inserted into the anus generally provokes evacuation of the bowels in a few minutes.

Soaps impregnated with antiseptics, such as perchloride of mercury, carbolic acid, tar, or iodine, are often used to disinfect the hands.

The chief preparations in which soap is used in the pharmacopœias are:

LINIMENTUM SAPONIS (B.P.), soap liniment, and

LINIMENTUM CAMPHORÆ ET SAPONIS (U. S. P.), both contain about 4 per cent of camphor and are used as mild counter-irritants in sprains, etc.

LINIMENTUM SAPONIS MOLLIS (U. S. P.).

The liniments consist of alcohol with soap in suspension, perfumed with volatile oils, and are mildly irritant to the skin. They are used largely as bases for other liniments.

PLASTERS are sticky, adhesive substances which are chiefly used to give mechanical support, but which are often impregnated with active remedies in order to elicit their local action on the skin. The basis of many of the plasters is lead plaster, which is obtained by the action of lead oxide on olive oil and consists for the most part of lead oleate.

EMPLASTRUM COLOPHONII (B. P.), adhesive plaster.

Court plaster is formed from isinglass, the dried swimming bladder of several species of sturgeon, which is dissolved in water, alcohol, and glycerin, and painted on taffeta. Isinglass differs from lead plaster and its derivatives in being transparent, so that if it is spread on a flesh-colored cloth, it disfigures the hands and face less than the others.

Lead plaster, adhesive plaster and isinglass plaster are used only to cover and protect cuts and abrasions, and to keep the edges of wounds in apposition. The adhesive plaster and isinglass plaster are superior to lead plaster, as they stick more firmly. It is perhaps unnecessary to add that plasters are always applied spread on cloth.

Another series resembling the plasters in their sphere of usefulness is formed

by the COLLODIA. Their basis is pyroxylin, or soluble gun-cotton, which is formed from cotton by the action of sulphuric and nitric acids, and which consists of a mixture of nitrates of cellulose. Collodion is formed by dissolving pyroxylin in a mixture of alcohol and ether. When these evaporate, there remains a fine layer of pyroxylin, which protects the surface to which it is applied and gums the edges of slight cuts together. This collodion is rendered less brittle by the addition of Canada turpentine and castor oil in small proportions, and is then known as flexible collodion. A blistering collodion is formed by the addition of cantharidin to the flexible preparation.

PYROXYLINUM (U. S. P., B. P.), soluble gun-cotton, colloxylin.

COLLODIUM (U. S. P.), collodion.

COLLODIUM FLEXILE (U. S. P., B. P.), flexible collodion.

KERATIN (not official) is a substance obtained from horns, hoofs, nails, etc., which is insoluble in the gastric juices, but is dissolved by the alkaline pancreatic secretion. It is used to coat pills which it is desired to protect from disintegration in the stomach.

Along with the emollients, or oily protectives, may be mentioned another class of mechanical agents, the **Dusting Powders.** Any dry, insoluble, fine powder applied to irritated surfaces of the skin, or slight abrasions, will protect these from the air, and from contact with the clothes and other sources of pressure. These powders, at the same time, soak up any secretions, and render the injured spot less liable to bacterial infection, as they form a more or less impermeable crust. Powders used for this purpose should not be absorbed, or, if absorbable, should not induce any toxic effects. Those most commonly employed are the phosphate and carbonate of lime, talc (*Talcum Purificatum*, U. S. P.) (magnesium silicate), *Terra Silicea Purificata*, U. S. P. (Kieselguhr), fullers' earth and kaolin (*Kaolinum*, B. P.), (aluminum silicates) and starch.

A large number of powders are used as surgical dressings, most of them being credited with more or less antiseptic power. In many instances, however, their antiseptic action is so slight that it would appear that most of their virtues are due to their mechanical properties, and not to their bactericidal action. Thus it has been shown that kaolin absorbs certain toxins, a property possessed also by other fine powders.

Kaolin is also used in the form of *Cataplasma Kaolini*, B. P., which has largely replaced the domestic linseed and bread poultices.

II. SKIN IRRITANTS AND COUNTER-IRRITATION.

The practice of applying irritants to the skin in internal diseases is one of great antiquity. The theories on which this therapeutic method is based have changed with the advance of medical knowledge, until, no explanation satisfactory to modern scepticism being forthcoming, the use of these remedies has fallen into a certain disrepute in recent years. The old theory of revulsion or derivation was at first based on the belief that disease was a malignant entity or humor, which might be drawn from the deeper organs to the surface by means of irritation of the skin. Later, it was supposed that the congestion of the diseased organs might be relieved by the withdrawal of fluid to the skin, and this belief has been held in more or less modified forms in

quite modern times. In addition, it was recognized very early that irritation of the skin relieved pain in many instances. The means by which the skin irritation was attained were extremely numerous and varied; large numbers of drugs have been used, and in addition mechanical devices of all kinds were employed, such as burning, electrical currents, or the introduction of setons. In many of these the idea of irritation was combined with that of leaving a way of escape for humors. This latter is only of historical interest, but the practice of relieving internal organs by external irritation or *counter-irritation* persists still, and perhaps merits more attention than it receives at the hands of many physicians.

The effects of an irritant applied to the skin are local and remote. The first symptoms of irritation are congestion and redness of the part, and many drugs which produce only this degree of irritation in ordinary circumstances, are known as *Rubefacients*. Stronger irritants cause blistering, and are called *Vesicants*, while some drugs which cause irritation and small discrete suppurations, receive the name of *Pustulants*.

Local Symptoms.—The application of an irritant to the skin causes a feeling of warmth, and often of itching, which may later become intensified into actual pain. The skin becomes red, congested, warm, and at first is more sensitive to touch and painful stimuli, though the sensitiveness is afterward lessened. This condition persists for a longer or shorter time according to the nature of the irritant, and then passes off slowly. Very often desquamation follows, if the rubefacient has acted for some length of time. Stronger irritation is followed at first by the same results, but soon small globules of fluid appear below the epidermis, and these coalesce so as to form a large accumulation of fluid, which raises the epidermis completely off the true skin, forming a blister. If the irritant be removed, the fluid of the blister undergoes a slow absorption, so that in the course of a few days the epidermis forms an empty sack, which, however, is not obliterated by the adhesion of the walls. If the blister be opened, the sensitive dermis is exposed, and the secretion of fluid continues for some time, until a new epidermis has been formed.

The distinct and separate points of inflammation caused by the pustulants are due to their affecting the orifices of the skin glands and not intervening tissue. They cause the same sense of warmth and prickling of the skin as the other irritants, but even in the earlier stages of their action small, dark-red, raised points are observed, exactly as in some of the exanthemata, and these afterwards form small abscesses. If the application be persisted in, these discrete abscesses may burst through the intervening tissues and become confluent, and large abscesses have thus been formed in the skin. When the irritant is removed before the formation of pus, the inflammation of the ducts slowly subsides and the epidermis peels off as after the milder irritants. Pustulants are seldom employed at the present time; croton oil applied vigorously may induce pustulation, and tartar emetic was formerly largely used for this purpose.

The local effects of the rubefacients and vesicants are identical with those of acute inflammation. The pain and discomfort are due to the action on the nerve terminations, while the redness and swelling betray the local dilatation of the vessels. This latter appears to be due to a reflex from the sensory terminations to the vasodilator nerve ends on the vessels; the central nervous system is not involved in this reflex, for it occurs after division of the nerves of the part, but not after the peripheral fibres have degenerated; it is thus of the nature of an axon reflex (Bruce). The dilatation of the vessels and the slowing of the blood current in them lead to the transudation of fluid and leucocytes into the tissues, especially at the points where the irritation is greatest, and the accumulation eventually pushes off the horny epidermal layer from the living layers and forms a blister. The fluid in the blister has been shown to contain some of the irritant, which diffuses into it through the epidermis. The œdema and swelling are not confined to the skin, but extends into the subcutaneous tissue and the more superficial layers of muscle.

If the irritation be continued long enough, suppuration may commence in the blister and lead to deep erosion of the tissues.

Remote Action.—Local irritation cannot exist without causing certain general changes which affect the whole organism, and which arise from the reflex stimulation of various centres in the medulla oblongata. Attempts to base the explanation of counter-irritation on these general effects have all failed, however, and many of them are elicited only by widespread irritation or by more intense localized irritation than is induced by ordinary therapeutic methods.

The centres involved are those regulating the heart, the tone of the vessels, and the respiration. Moderate irritation of the skin causes an acceleration of the heart-rhythm, while more powerful irritation slows the heart through the inhibitory centre. The blood-pressure measured in the arteries is considerably increased by ordinary irritation of the skin, but if it be very severe or widespread, the slowness of the pulse may cause a fall of tension. This increase in the blood-pressure is due to the reflex stimulation of the vasomotor centre, which causes a constriction of the arterioles of the abdominal organs chiefly, while the vessels of the limbs and probably those of the skin are not contracted. The result is that more blood is supplied to the muscles and skin and less to the internal organs than normally.

The effects of skin irritation on the respiration are less uniform. In the rabbit the breathing is sometimes accelerated, sometimes slowed by mild stimulation, while stronger stimuli seem to slow it always. The effect of the application of skin irritants on the respiration in man has not been observed accurately, but that sudden stimulation of the skin causes gasping and irregularity of the respiration, may be observed whenever cold water comes in contact with the more sensitive parts of the body.

Some change in the temperature of the body has been observed when the skin is irritated, but in man this is said to amount to less than 0.1° C. as a general rule. The internal heat tends to fall, while that of the skin rises, from the change in the distribution of the blood which has been described above.

The metabolism has been found to be altered by the application of irritants to the skin, and, although in the experiments on which the statement is based, the surface exposed to the irritant was larger than that affected in therapeutics, it seems probably that some change is produced by the ordinary agents also. Zuntz and Rohrig found that bathing animals in strong salt solution increased

the oxygen absorbed and the carbonic acid excreted much more than bathing in ordinary water, and Paalzow obtained the same result from the application of mustard plaster. The nitrogen of the urine is also said to be increased. This increase in the oxidation of the tissues is of the same nature as that produced by cold, and is due to an augmentation of the muscular activity, which, however, is too slight to cause any perceptible movement.

Irritation of the skin induces leucocytosis in the same way as irritation of the alimentary canal. This is especially evident after the application of a vesicant such as cantharides plaster, while rubefaction seems to have less effect.

Lastly, in considering the effects of skin irritation on the general vitality, it may be mentioned that a sudden application may awake the consciousness, as is seen in the effects of dashing cold water on the chest, or of striking the hands in narcotic poisoning. Another example is seen in the improved mental condition so often observed in fever patients treated with cold baths. This improvement is due to the local action on the skin, and not, as is often said, to the fall in temperature, for the latter is often insignificant.

All of these effects are produced by irritation at any point of the surface, and are quite insufficient to explain the practical use of counter-irritants to affect a particular organ. For example, in gastric disorders a counter-irritant is often applied just over the ensiform cartilage, while in facial neuralgia a blister behind the ear often gives relief. If the beneficial results were due to the general alteration of the circulation, respiration, or temperature, there would be no reason to vary the point of application, for the effect would not vary.

It has been shown by several observers (Zuelzer, Lazarus-Barlow) that when an irritant is applied to the skin, the muscles beneath are congested and rich in lymph, and Erlanger states that solutions are absorbed more quickly from the pleural cavity when mustard is applied to the skin of the chest and attributes this to an acceleration of the lymph stream. But these observations apply only when the organs to be affected are not only contiguous, but also continuous with those directly affected, and offer no explanation of the effects of irritation of the skin upon the stomach or lungs.

Much light has been thrown on the subject by the observations of Mackenzie and Head, who found that visceral disease is often accompanied by tenderness of the skin and underlying muscles, and that the pain arising in these cases is referred to this area of skin and not to the organ involved. Thus in painful diseases of the stomach, tenderness is often found in the skin and muscles of the epigastrium, while in œsophageal stricture, pain may be referred to a point near the angle of the scapula and to another in the neighborhood of the apex beat. Similarly in heart disease, pain is often felt in the left chest-wall and shoulder extending down the left arm. These points are, of course, only connected with the diseased organ by means of nerve-fibres, and it thus appears that impulses from such an organ arouse a condition of heightened sensibility in the region of the cord on which they impinge; this affects all the synapses in the neighborhood (Fig. 6), so that impulses from very different structures may be altered by the affection of one. The sensation of pain aroused by this exaggerated sensibility is of course referred to the periphery, not to the focus in the cord, and this gives the

impression of tenderness in the skin and muscles. It therefore seems probable enough that an affection of these superficial areas may affect the corresponding internal organ more than the rest of the body, and this is exactly what is required to explain the benefits derived from the use of counter-irritants. It is especially noticeable that several of the skin areas affected by internal disease are precisely those points at which experience has shown irritation to be most beneficial (Fig. 7). Thus the application of a blister over the epigastrium has long been recognized as a means of relieving gastric disorders. Similarly the old treatment of iritis by means of a blister on the temple may be justified by the fact that Head found areas of tenderness on the temple accompanying this disease.

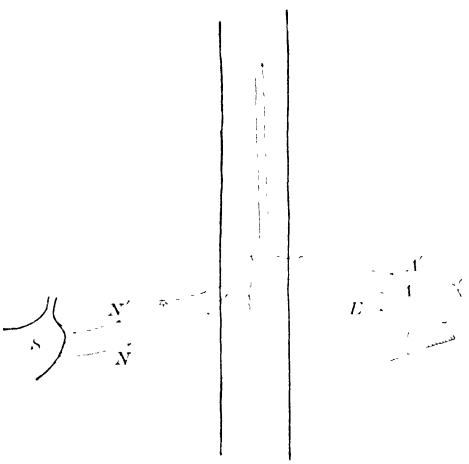

FIG. 6.—Diagram to illustrate the effects of visceral disease on sensation (after Mackenzie). *S*, diseased viscus, with afferent nerve fibre *N* and efferent fibre *N'* issuing from the same area of the spinal cord. The impulses from the diseased area induce a condition of heightened sensibility in the shaded area. *E*, a motor nerve fibre to muscle, which carries more impulses than usual from the area in the cord and thus leads to a tonic contraction of the muscle. *A*, the afferent nerve from the muscle and *A'* from the skin entering the cord in the sensitive area and thus giving rise to the sense of pain and tenderness, which is referred to the peripheral distribution in the skin and muscle.

The exact nature of the effects of counter-irritation on the internal organs has not been ascertained, but it would seem most probable that an alteration in the calibre of the vessels is induced. These alterations may be accompanied by changes in the activity of the organs; for example, there seems good reason to believe that in many cases irritants applied to the abdomen produce evacuation of the bowels. The most obvious effect of counter-irritation very often is the relief of pain, and this seems explicable in the light of the observations of Mackenzie and Head. For if the pain in visceral disease is due to the disorder of the synapses in the spinal cord at the level at which the fibres from the viscus and from the superficial tissues meet, it is possible that new impulses reaching this area from the skin may alter its condition or

may occupy a common path to the brain to the exclusion of impulses arising from the seat of disease. Or, if the pain arises from cramp in a superficial muscle innervated from the same level of the cord as the diseased viscus, an irritant applied over the muscle may increase its circulation and warmth and thus relieve the cramp and the pain.

Besides these physiological effects of counter-irritation, it must not be forgotten that a great impression is produced on the patients, and that some of the benefit may be due to suggestion.

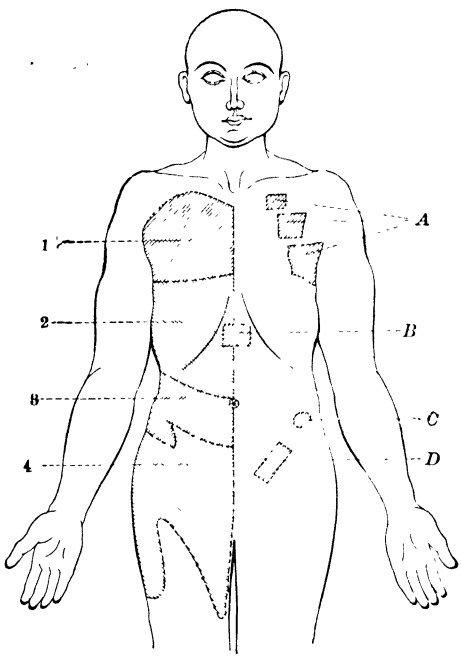

FIG. 7.—The right side is divided into segments which correspond to some of the skin areas in which Head found tenderness in internal diseases. 1. Area of tenderness in disease of the lungs. 2. In diseases of the stomach. 3. In ovarian disease. 4. In disease of the Fallopian tubes and other appendages. On the left side are represented the points of application of counter-irritants in disease of the lungs (*A*), of the stomach (*B*), of the ovary (*C*), and the uterine appendages (*D*).

Therapeutic Uses.—Local irritants are applied occasionally to produce an alteration in the nutrition and blood supply of the skin itself and of the subcutaneous tissues. Thus in some chronic inflammatory conditions, with effusions into, or indurations of the subcutaneous tissues, the improvement of the circulation produced by slight irritation may be of benefit. An example of this is the treatment of ulcers of old standing with irritants. Another case in which a slight inflammatory attack causes very obvious improvement is in corneal opacity, which may be removed entirely in some cases by the acute inflammatory reaction produced by such irritants as abrin. Probably a

similar effect is produced on subcutaneous effusions, as in bruises. It has been found experimentally that when abscesses in the subcutaneous tissues are treated with mild irritation of the skin over them, they improve more rapidly than controls left without treatment; the increased blood supply leads to a larger supply of leucocytes and protective substances around the inflammation than would otherwise be present. Similarly, the absorption of pigments injected into the rabbit's ear is much accelerated by the application of irritants to the skin over the part, which suggests that toxins are removed more rapidly under similar treatment (Wechsberg). Sollmann induced a series of nodules in the skin of his forearm by intracutaneous injections and found that their disappearance was hastened by the application of iodine over them. For these purposes only the milder irritants are required in fact, vesication may do more harm than good.

Mild irritation alters the sensitiveness of the sensory organs of the skin, and heat is often applied to alleviate pain and discomfort in the skin itself. In other instances pain is increased by heat, and, in fact, it is sometimes applied in the treatment of local anæsthesia, with the object of rendering the surface more sensitive. In many forms of skin disease, mild irritants are found to be of benefit; this is sometimes attributed to their antiseptic action, but the slight irritation is undoubtedly of some importance.

Counter-irritants are used in a large number of diseases, often without any definite idea of what precise effects they will elicit, but merely because they have been found to give relief in similar conditions. As a general rule they are placed over the affected organ, and this corresponds fairly in most cases of disease of the trunk with Head's area of skin tenderness. In the head, however, the segmental arrangement has been rendered very irregular by the compression in development, and counter-irritants are often found to be most effective when placed at some distance from the seat of pain, *e. g.*, behind the ear in some forms of facial neuralgia. They are used in acute inflammation of the lungs and pleura, in gastric disorders accompanied by much pain, in colic and in neuralgia and neuritis. Their action is very uncertain, but their application is often followed by great relief, more especially of pain. They are also used occasionally in shock or collapse, not for their effect on any individual organ, but to elicit the reflex alterations in the circulation which have been described already. A blister is often recommended in internal hæmorrhage, and may very possibly lessen the bleeding by altering the distribution of the blood in the organs, although it is difficult to estimate how far the improvement is due to the remedy and how far it is spontaneous. In order to produce any marked effect on internal organs, the more powerful irritants must be used, such as mustard or cantharides. It is not necessary, however, to produce actual vesication in the great majority of cases.

Counter-irritation must be applied only with the greatest caution in weak, badly nourished, or very old persons, as it may cause sloughing. In diabetes, the tendency to gangrene contra-indicates blistering, and in very young children only mild irritants are used.

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An enormous number of drugs produce irritation of the skin, and it would be idle to attempt to enumerate them here. In many instances, however, the irritant action is insignificant in comparison with the other effects produced, and these will, therefore, be discussed elsewhere; among these are found some of the alkaloids, the acids and alkalies, and many other inorganic preparations. Irritation of the skin may also be produced by heat and cold, and in fact burning in various forms was formerly used as a means of counter-irritation. Heat is still employed to cause irritation of the skin and subcutaneous tissues, and to promote their circulation. Thus, poultices and hot water compresses are beneficial in many local inflammations, though the same effects may generally be obtained by the use of the milder irritants. Somewhat similar results may be obtained in the trunk by dry cupping, in which the blood is drawn to the diseased superficial tissue by applying a glass tightly to the skin and exhausting the air in its interior.

Apart from those drugs in which the irritation of the skin is merely an incident in a wider general action, there are a number of preparations which are used almost exclusively for this purpose. They may be divided into three classes: the volatile irritants, such as turpentine oil; the mustard series, some of which are also volatile; and those which are either non-volatile or only boil at high temperatures, such as cantharidin.

1. The Turpentine Oil Group.

Under the volatile irritants may be included a large number of the ethereal oils and many members of the methane and of the aromatic series; but among the ethereal oils those which possess a low boiling point, that is, those which contain a large proportion of terpene, with comparatively little oxygen, are found to possess a more penetrating action than the others. At the same time, the taste and odor of these oils is often less pleasant than that of the others, so that they are less used as flavors and carminatives. The oils derived from the Coniferæ have, for this reason, been more largely used than the others for their effect on the skin, although several other volatile preparations are recognized by the pharmacopœia for this purpose. The action of

these oils is similar in other respects to that of the general group (see p. 234), so that it need not be discussed here.

Therapeutic Uses.—Turpentine oil is used externally as a rubefacient, and differs from mustard and cantharidin in its greater penetrating power. It is not so irritant; however, it blisters after long application, and the vesication produced is very painful and heals slowly, from the vapor penetrating into the deeper tissues. It is, therefore, employed to produce rubefaction only, and ought to be removed when this is attained. For this purpose any of the liniments of the group may be employed, or a more intense action may be got from the "turpentine stupe," which is made by dipping flannel in hot water, wringing it dry, and then dropping warm turpentine oil on it. Turpentine preparations are used especially in rheumatic affections of the joints or muscles, and in sciatica. Turpentine oil is a fairly strong antiseptic, and is less irritant than many of the more powerful ones. It is often inhaled in lung diseases such as tuberculosis or gangrene, and has the effect of lessening the odor in the latter; the oil may be simply allowed to evaporate, but is much more efficient when sprayed into the air. Many of the resorts for phthisical patients are stated to be rendered especially suitable for this disease by the neighborhood of coniferous forests, which are supposed to dissipate the oils into the atmosphere; but this is probably only an insignificant factor in the treatment. Turpentine oil is occasionally added to baths in order to cause a slight general irritation of the skin, which may be of benefit in some skin diseases and also in general debility under certain conditions; and pine-needle baths have some reputation in Germany for the same reason, the water being supposed to extract the oil.

Internally, turpentine oil is occasionally employed as a vermifuge, but is inferior to other preparations used for this purpose. A few drops are often added to purgative enemata to increase their efficiency. It has been given by the mouth in order to lessen flatulence and to disinfect the intestine in various diseases, among others, typhoid fever, although its value here is disputed. Preparations of turpentine oil and juniper are reliable and fairly powerful diuretics, but must not be prescribed in irritation of the kidney The turpentine preparations have a certain reputation as expectorants; they are also given internally as pulmonary disinfectants and in neuralgia and internal hæmorrhage, but are probably entirely valueless for these purposes.

Some remedies which produce irritation of the skin of approximately the same degree as turpentine oil, but which are discussed elsewhere are camphor, chloroform, dilute acetic acid, ammonia, alkalies, alcohol, iodine and some of the heavy metal preparations.

Preparations.

Oleum Terebinthinæ Rectificatum (U. S. P.), Oleum Terebinthinæ (B. P.), is formed from ordinary oil of turpentine by redistillation and consists of a mixture of terpenes ($C_{10}H_{16}$). Dose, 0.3 cc. (5 mins.); as an anthelmintic, 8–16 cc. (2–4 fl. drs.).

Emulsum Olei Terebinthinæ (U. S. P.), 2 cc. (½ fl. dr.).

Linimentum Terebinthinæ (B. P.).

LINIMENTUM TEREBINTHINÆ ACETICUM (B. P.) is formed by mixing turpentine, glacial acetic acid, and camphor liniment.

In addition to these preparations the following may be mentioned here as possessing similar action and uses.

LINIMENTUM SAPONIS (U. S. P., B. P.), very slightly irritant.

ARNICA and its preparations enjoy a popular reputation as skin applications but do not appear to have any action which entitles them to consideration.

2. Mustard.

Black Mustard contains a glucoside, *Potassium Myronate* or *Sinigrin*, and a ferment, *Myrosin*, which decomposes it in the presence of water into dextrose, potassium bisulphate and allyl-isosulphocyanate, or volatile oil of mustard.

$$\underset{\text{Sinigrin}}{C_{10}H_{18}KNS_2O_{10}} = \underset{\text{Volatile oil}}{C_3H_5NCS} + C_6H_{12}O_6 + KHSO_4$$

Volatile oil of mustard is formed in various other Cruciferæ when they are mixed with water. Thus horseradish root (Armoracia, B. P.) contains it, while the allied species Cochlearia officinalis apparently contains the corresponding isobutyl compound.

Action.—Volatile oil of mustard is intensely irritant when applied to the skin, and if left long enough produces blistering which is more painful than that caused by cantharides, and is said to heal less readily. This is probably due to the oil penetrating more deeply into the tissues, and thus setting up more extensive inflammation. Mustard is accordingly used only to induce rubefaction, and ought to be removed before actual vesication occurs. When the crude drug is moistened and applied to the skin, the oil is formed only slowly, so that the longer it remains applied, the more intense is the action. The glucoside in itself has little or no action, and the products of its decomposition are harmless, with the exception of the oil.

Uses.—Mustard is largely used as a condiment and to promote appetite, but is never prescribed for this purpose. In large quantities it causes violent irritation of the stomach and bowel, with vomiting, purging, acute pain and tenderness in the abdomen, and collapse. Mustard and warm water is a convenient emetic in emergencies, as in cases of poisoning.

The plaster or leaf (charta) is the form in which it is generally used in therapeutics. It contains the glucoside, which is slowly decomposed by the ferment when the plaster is dipped in warm water for a few minutes before application. Another popular application is the mustard poultice, in which powdered mustard is sprinkled on an ordinary poultice. Mustard is also added to baths occasionally when slight irritation and consequent congestion is desired over a large surface. For this purpose 2–4 teaspoonfuls of the dry powder are added for each gallon of water. In preparations of mustard it is important to avoid a temperature of over 60° C. (140° F.,) as the ferment is destroyed above this. The plaster is left on the skin only for fifteen to thirty minutes when it is used as a rubefacient.

PREPARATIONS.

SINAPIS NIGRA (U. S. P.), the dried ripe seeds of Brassica nigra.

EMPLASTRUM SINAPIS (U. S. P.), black mustard powder rendered adhesive by India-rubber, applied to sheets of paper and dried.

OLEUM SINAPIS VOLATILE (U. S. P.), derived from black mustard.

3. Cantharidin Series.

Another series of local irritants comprises non-volatile substances, of which cantharidin ($C_{10}H_{12}O_4$) is the best known. It is an anhydride and when acted on by bases forms cantharidates, which resemble it in action. It is found in Spanish fly (Cantharis vesicatoria, or Lytta vesicatoria) and in several allied species of Coleoptera (beetles).

Action.—Applied to the *skin*, cantharidin produces redness, smarting and pain, followed very soon by small vesicles, which later coalesce into one large blister. This is much less painful than the vesication produced by mustard, because less of the irritant penetrates into the deeper tissues than in the case of the volatile mustard oil. If the blister be broken, however, and the unprotected dermis be allowed to come in contact with the irritant, violent inflammation with much pain, suppuration and even sloughing may follow.

When large quantities of cantharidin are given *internally*, the same irritant action takes place along the alimentary tract. If taken in solution, blisters arise in the mouth and throat, and the pain and swelling in the œsophagus may be so acute as to prevent swallowing. The irritation of the stomach produces vomiting, followed by purging with excruciating pain in the abdomen, and all the symptoms of shock and collapse.

Cantharidin is absorbed from the alimentary canal, and also to a lesser extent from the skin, but has no important action on the internal organs, with the exception of those by which it is eliminated. Vomiting occurs on subcutaneous injection from some of the poison being excreted into the alimentary tract. Comparatively small quantities irritate the bladder, and cause a constant desire to micturate, with pain in doing so. In somewhat larger amount it sets up an acute nephritis with albuminuria, pain in the kidney region, and sometimes blood in the urine. The inflammation of the bladder and urethra produces intense pain and often priapism; in women abortion is said to occur occasionally, and in both sexes the irritation may lead to increased sexual desire.

The irritation of the kidneys by small doses increases their secretion, and cantharides was therefore considered a diuretic formerly. The tendency to produce nephritis renders it a dangerous internal remedy, however, and its diuretic power is quite insignificant in comparison with that of caffeine.

Animals vary very considerably in the degree in which they react to cantharidin, the most noted example being the hedgehog, which is capable of surviving a dose of the poison sufficient to poison an adult man. Fowls and rabbits also possess a high degree of congenital tolerance for this poison, although none of these is absolutely insusceptible to it.

Therapeutic Uses.—This drug is at present used almost exclusively as a skin irritant, and more particularly as a vesicant. The plaster is the form generally used. It is to be noted that in order to produce actual blistering, the plaster has to remain in contact with the skin some eight to ten hours, but an equal effect may be achieved by replacing the plaster by a hot poultice after four to six hours, when the skin irritation has reached the stage of redness. The ointment is said to induce blistering sooner than the plaster. Cantharis is also used to cause rubefaction and commencing vesication (flying blister); this may be done by the use of the plaster.

Cantharidin is liable to be absorbed from the skin, and its application is therefore avoided where there is any tendency to renal inflammation.

Cantharis has been not infrequently used as an aphrodisiac, and several cases of poisoning have occurred from its administration for this purpose. In cattle it is largely employed to this end in some countries, and in man it has undoubtedly similar effects in some cases through the irritation of the bladder and urethra, but its use for this purpose is always liable to produce nephritis. As an emmenagogue, cantharis has a certain popular reputation, which, however, has been shown to be unmerited, any influence which it may possess on the menstrual flow being quite insignificant, and probably due only to the irritation of the bladder and urethra.

Cantharis has been advised internally in some forms of renal and vesical disease, but it is an exceedingly dangerous remedy in these conditions. It is sometimes a constituent of hair washes, its irritant action on the skin being credited with causing a more rapid growth of the hair.

In cases of **Poisoning** with cantharides, the stomach ought to be emptied as rapidly as possible by the stomach tube, provided the œsophagus allows of its passage. Demulcents and albuminous substances are of use in slowing the absorption, but all oily or fatty bodies must be avoided, as they tend to dissolve the cantharidin and thus promote its absorption. Opium may be given for the pain, and if collapse sets in, the ordinary measures must be taken to combat it. Ellinger states that the action on the kidney in rabbits is more severe when the urine is acid than when it is alkaline, and this suggests the treatment of the renal symptoms with alkalies.

Preparations.

U. S. P.—Cantharis, Spanish Fly, the dried beetle, Cantharis vesicatoria.
Ceratum Cantharidis, containing 35 per cent of cantharides.
Emplastrum Cantharidis, the cerate spread on adhesive plaster.
Tinctura Cantharidis, 10 per cent, 0.1 cc. ($1\frac{1}{2}$ mins.).
B. P.—Cantharidinum, $C_{10}H_{12}O_4$, obtained from various species of Cantharis or of Mylabris.
Emplastrum Cantharidini, containing 0.2 per cent.
Liquor Epispasticus, blistering liquid, 0.4 per cent.

Poison Ivy and Poison Oak.—The commonest form of poisoning in the United States is the skin eruption produced by the leaves of poison ivy and poison oak (Rhus toxicodendron and venenata), which Pfaff showed to be due to the presence of a neutral body, *Toxicodendrol*. The

effects of poison ivy can arise only from touching the plant, the poisonous principle not being volatile. Very minute quantities of toxicodendrol are sufficient to produce skin eruptions, however, $\frac{1}{1000}$ mg. causing distinct symptoms in susceptible persons. The popular belief that skin affections can be induced by approaching the plant, without actually touching it, is probably accounted for by the facts that the eruption may not appear until several days after contact, and that poison ivy is very frequently mistaken for harmless climbing plants. The statement that the poison ivy does not affect some individuals is also probably erroneous, though persons of delicate skin are undoubtedly more susceptible. Immunity is not acquired for the poison by repeated attacks of dermatitis. Other species of Rhus, *e. g.*, R. vernicifera (the lacquer tree) also give rise to dermatitis.

In the dermatitis from poison ivy, Pfaff recommends the skin to be washed and scrubbed with soap and water, or with alcohol, or a solution of lead acetate in alcohol. Ointments and oily liniments are to be avoided, as they dissolve the toxicodendrol and tend to spread it over the skin and thus produce further inflammation. For the same reason, the alcohol used to wash the part must be removed entirely, as the poisonous principle is soluble in it, while insoluble in water. Potassium permanganate solution is said to be an efficacious application. For this purpose fairly strong solutions are recommended—a 1 per cent solution will sometimes prove effective where weaker concentrations have failed.

Eruptions similar to that from poison ivy arise from contact with a number of other plants of which the best known is the *Primula obconica;* this plant secretes some unknown substance which is intensely irritant to the skin of many people, and has frequently given rise to severe inflammation in gardeners and others. Cash found an alkaloid obtained from East India Satinwood (*Chloroxylon*) equally irritant when applied to the skin; the dermatitis from these bodies often appears only two to three weeks after contact with them, and even after application of the poison. Dermatitis from other woods has been described *e. g.*, S. African boxwood, W. African mahogany and teak.

A number of the Ranunculaceæ are irritant to the skin like cantharides, but the active constituent has not been definitely determined. *Mezereum*, which was formerly official, is similarly irritant, apparently from the presence of an irritant oil (Springenfeldt). *Cardol*, found in the fruits of Anacardium occidentale and in Semecarpus anacardium, is a very powerful irritant, and has been used to a limited extent as a vesicant. Cardol is probably a mixture of a number of substances, but it is unknown to which of these it owes its activity. *Euphorbin* is said by Buchheim to be the irritant principle in the Euphorbia resin (Euphorbia resinifera, etc.), and to resemble cantharidin in its anhydride form, but the salts and the euphorbic acid which is formed from them by acids are inactive. A very poisonous member of the Euphorbiaceæ is the Manicheel tree, growing in the West Indies, and it apparently belongs to this series.

Capsicum (p. 251) contains one or more non-volatile irritant substances and is used occasionally as a skin irritant. Pepper is also used as a rubefacient in domestic medicine.

Dichlorethylsulphide, or Thiodiglycolchloride $(CH_2ClCH_2)_2S$, the notorious "Mustard Gas" of the Great War, is a synthetic substance which

rivals or perhaps excels toxicodendrol in its irritant and destructive action on the skin, and which, being volatile, penetrates to the lungs and proves fatal through pulmonary irritation when inhaled in even minute quantities. It is a volatile oily fluid. Effects of contact with the fluid or vapor come on after a latent period of some hours. These consist of inflammation, leading sometimes to vesication or necrosis. Mucous membranes, *e. g.*, of the eye and of the alimentary and respiratory tracts are affected earlier than the skin.

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III. VOLATILE OIL SERIES.

The group of volatile, ethereal, or essential oils contains a large number of preparations in the pharmacopœias of all countries. These oils are obtained from plants by distillation, or more rarely by pressure, and must be distinguished by the student from the fatty or fixed oils, which are non-volatile. The volatile or ethereal oils are found chiefly in the fruits and flowering parts of plants, and are very widely diffused through the vegetable kingdom, though some orders, such as the Labiatæ, Umbelliferæ, Aurantiaceæ, Cruciferæ, and Coniferæ, are pre-eminent in their production. They are all strongly odorous, and are therefore used in perfumery, and to conceal nauseous odors and tastes in medicine.

Their composition is extremely variable. The commonest constituents are *Terpenes*, and some oils contain these only, while in a few oils no terpene has been found (Attar of Roses). Terpenes are hydrocarbons of the aromatic series, and possess the general formula $(C_5H_8)_n$. The great majority of them, or the terpenes proper $(C_{10}H_{16})$, are combinations of a dihydrobenzene with propyl and methyl $(C_6H_4(H_2)C_3H_7CH_3)$. Some twelve terpenes of this formula are known, varying in their chemical structure and in their stereometrical form. Another group of these hydrocarbons is formed by the *Sesquiterpenes* $(C_{15}H_{24})$, while a few *Diterpenes* $(C_{20}H_{32})$ are known. Some volatile oils consist of these hydrocarbons only, but most of them contain in addition some oxidized aromatic substances, such as phenols, ketones, aldehydes, acids, and their compounds; as instances of these may be cited camphor, thujon (from oil of absinthe), sabinol (oil of savine), safrol, thymol, eucalyptol, myristicin and vanillin. Many of these oxidized products crystallize out when the volatile oil is cooled sufficiently, and especially on long standing, and the resulting solid is known as a *Stearoptene*, while the fluid remaining is sometimes called *Elæoptene*. The oils containing oxygen are not so volatile as the pure hydrocarbons, but the odor is often due chiefly to the oxidized substances. A very few oils

contain nitrogenous bodies, generally in the form of cyanides, while, on the other hand, the majority of the volatile oils of the Cruciferæ contain sulphur bodies, which lend them a pungent disagreeable odor, quite different from that of the other oils.

The volatile oils are generally clear, colorless fluids, although some of them are green or blue in color. After long keeping they often acquire a yellowish color and an acid reaction, from the formation of resins. They are generally light, sparkling fluids, but the oils of copaiba and cubebs are more viscid. They are insoluble in water except in very small amount, which, however, is enough to lend their characteristic odor to the solution; in strong alcohol, ether, benzene, chloroform, and fixed oils, they are freely soluble.

Many of the plants from which the volatile oils are obtained possess other active constituents, such as bitters, and as many of the preparations used in therapeutics are formed, not from the distilled oils, but from the crude parts of plants, it must be noted that the oil is not the only active principle in them.

Action Externally.—The volatile oils all possess antiseptic properties, which are doubtless due in part to their volatility and their solubility in lipoids enabling them to penetrate readily into protoplasm. Many of them appear to be more germicidal than carbolic acid in favorable circumstances, but they are generally too insoluble in water to be employed easily in surgery.

Applied to the skin, they cause redness, itching and warmth, owing to a local dilatation of the vessels, which may be due to the penetration of the oil to the cutaneous arterioles or veins, or to a local reflex from the irritated terminations of the sensory nerves. When painted on the mucous membranes, such as those of the eye or nose, or on wounds, the volatile oils cause similar irritation, which is betrayed by redness and congestion, pain and smarting.

Action on the Alimentary Canal.—Strong solutions of the oils have generally a hot, burning taste, and if kept in the mouth, cause redness and irritation of the mucous membranes, although some of them induce a sense of coolness at first. At the same time the organs of smell are affected by these oils, which are almost all possessed of characteristic odors. The irritation of the mouth leads to a reflex secretion of saliva, which is often very profuse. The antiseptic action of the oils is exercised in the mouth as elsewhere, and may have a beneficial effect in some conditions.

On passing into the stomach, the oils cause the same sensation of warmth in the gullet, and this is accompanied by a sense of well-being and comfort, the appetite is often increased, and any feeling of distention after meals is relieved. This is often attended by the eructation of quantities of gas. Substances which produce these effects in the stomach are known as *carminatives*, and many explanations of their action have been offered. The antiseptic action may occasionally play a part in the carminative action, and possibly the secretion may be encouraged by the slight irritation and by the agreeable odor and taste; the activity of the ferments is retarded rather than augmented. The movements and

tone of the stomach are decreased by small quantities of the oils applied to the mucous membrane; this weakening action probably extends to the sphincters, and their relaxation may explain the relief of the feeling of distention and the eructation of gas from the stomach after the administration of these oils. In the intestine small quantities generally increase the movements, while larger ones decrease them; sometimes the bowel is relaxed owing to a reflex arising from the action on the stomach. In practice they often relieve intestinal flatulence and distention and lessen the spasms which cause colic. Small quantities are incorporated in the preparations of the more powerful purgatives to lessen the pain and griping which these are liable to induce.

An indirect effect of the local action on the gullet and stomach is slight flushing of the skin from dilation of its vessels, along with a feeling of warmth and relief of chill. This appears to arise from a reflex traveling from the sensory ends in the mucous membranes to the vasomotor centre in the medulla oblongata and is most frequently seen under camphor.

Excretion.—Many of the terpenes are oxidized to phenols in the body and are then excreted in the urine, for the most part in combination with glycuronic or sulphuric acid. Traces pass out in the expired air and impart an odor to the breath. The urine also contains some in a free form and may thus smell of the original oil or of some of its derivatives. Some of the constituents of the oils are oxidized to acids and excreted in the urine as salts.

In the course of excretion, some of the oils cause irritation of the lungs and kidneys, so that some of them are employed to increase the bronchial secretion, while others have a distinct diuretic action. This irritant action is of course not confined to the tissue, but extends to microbial guests, so that some of the volatile oils are given internally almost exclusively for their antiseptic action in the urine.

Poisoning.—The various oils differ a good deal in their activity while resembling each other closely in the general characters of their effects. All of them may produce marked irritation of the stomach and bowel when given in large quantities, but the oils of tansy, sage, and English pennyroyal are distinguished especially by the violent inflammation they cause, and by the frequency with which fatal poisoning occurs from their use. The symptoms are those of acute gastric, intestinal, and often renal irritation: vomiting, purging, acute pain in the abdomen, blood in the stools and in the vomited matter, collapse, weakness of the pulse and respiration, anuria, or albumin and blood in the urine, and convulsive attacks ending in coma and death. Great hyperæmia of the abdominal organs, often blood in the peritoneal cavity, and sometimes acute inflammation of the kidney are the chief post-mortem appearances. Though they do not increase the uterine movements directly, the congestion of the organs of the abdomen may cause abortion in pregnancy, or increase the menses, and in most cases of poisoning, these oils have been taken to induce abortion; too often they have proved fatal without this end being achieved. Oil of eucalyptus has frequently given rise to poisonous symptoms.

General Action.—The small quantities of volatile oils administered in ordinary medicinal use pass through the tissues without modifying them perceptibly, their only effects arising in the organs by which they are absorbed and excreted. In large quantities, however, some of them (the oils of wormwood, nutmeg, sage, savine among others) produce symptoms from a direct action on the central nervous system, which is first stimulated and then depressed.

The relative importance of these two stages differs in different oils, some, *e. g.*, turpentine oil, causing only a transient excitement, followed by marked weakness and depression, while others, such as the oil of absinth, cause very marked excitement and convulsions. The activity of the oils as nervous poisons also varies greatly, some producing only insignificant effects on the central nervous system compared with those from their local action, while in others such as the oil of absinth or wormwood, the symptoms from the nervous system predominate in cases of poisoning. As a general rule the higher divisions of the central axis are affected more than the lower, and epileptiform or clonic convulsions may be induced (camphor), or tremors similar to those described under carbolic acid and presumably of similar origin (safrol and nutmeg oil). In many cases a combination of excitement and ataxia is observed, the animal moving about restlessly, but being unable to balance itself. In the later stages of poisoning the spontaneous movements cease, while the excitation of the lower centres still persists, and convulsive movements may accompany the final arrest of the respiration. The respiratory centre is finally depressed, but this depression is often preceded by stimulation, the breathing increasing both in rapidity and in volume. The vasomotor centre undergoes similar changes, the blood-pressure falling from some oils immediately, from others only after a preliminary increase.

The *heart* does not seem to be affected by most of the volatile oils, except indirectly from the collapse and shock. The frog's heart perfused with Ringer's solution containing a volatile oil is often accelerated, but soon becomes slow and weak.

Involuntary *muscle* suspended in Ringer's solution containing small amounts of volatile oil ceases its rhythmical movements and relaxes, apparently from a direct action of those bodies on the muscle fibre; the same action is seen in the *uterus* suspended in this way.

Some of the constituents of the oils (pulegon, myristicin, safrol) cause fatty degeneration of various organs, especially of the liver and kidney, while others of very similar constitution have no such effect.

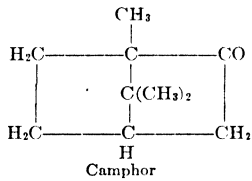
Most of the oils are poisonous to the *protozoa* in fairly dilute solutions; as a general rule the movements of these organisms are accelerated by very small quantities of the oils. The protozoa are much more susceptible to the oils than the *bacteria*, some of which continue to live in 5 per cent solutions.

Although these general effects of the volatile oils have no therapeutic importance, the frequent occurrence of epilepsy and insanity in habitual absinth drinkers and occasional poisoning from others of the series have given them some practical interest.

1. Camphor.

Some of the volatile oils deposit crystalline substances or stearoptenes after standing for some time, especially when they are exposed to cold. As a general rule these bodies are present in only small amounts, and have not been investigated apart from the volatile oils of which they form constituents; but a few of them have attracted attention in therapeutics, not only on account of their local effects, which resemble those elicited by the volatile oils in general, but also because of their action in the tissues after absorption. The chief of these is **Camphor,** which has been used in Chinese medicine for many centuries, and which has also played a considerable rôle in Western therapeutics. It is

derived from the Cinnamomum camphora of China and Japan, and possesses the formula $C_{10}H_{16}O$, differing from the terpenes in possessing a ketone (=CO) link.



Camphor

Another body closely resembling ordinary camphor is Borneol or Borneocamphor ($C_{10}H_{18}O$), which is derived from the Dryobalanops aromatica, and which apparently differs from ordinary camphor in containing the group (=CHOH) instead of (=CO). Ngai-camphor, which is obtained from Blumea balsamifera, is very closely related to borneol. Another stearoptene which has been used in medicine apart from the volatile oils, is **Menthol** ($C_{10}H_{20}O$), which is obtained from the oil of peppermint, and apparently contains a CHOH group like borneol, but is more completely hydrated. **Thujon**, an isomer of camphor occurring in the oil of wormwood or absinth and in many other plants, has not been used in medicine, but is of importance as the cause of epilepsy in chronic absinth drinkers.

Local Action.—Camphor is possessed of some antiseptic action, although it is much weaker than some of the bodies of the carbolic acid group, and also than many of the volatile oils. Leucocytes cease their movements at once when exposed to camphor solutions or vapor, and Darwin found that it acts as a stimulus to the tentacles of Drosera, an insectivorous plant, and apparently renders them more sensitive to mechanical irritation.

Camphor produces redness and a feeling of warmth when rubbed into the **Skin**. Sometimes, however, a distinct sensation of cold may be experienced, providing the rubbing is not too energetic. Menthol generally induces this feeling of cold, accompanied by more or less prickling, and afterward by heat and burning. The cold is not due to cooling of the skin, for the vessels of the part are dilated, and the thermometer indicates a higher skin temperature there than in other parts of the body. It has been ascribed to menthol being more irritant to the terminations of certain nerves which convey the sensation of cold than to those of the heart nerves and pain nerves, but this is denied by Rollett who states that menthol acts only on the terminations of the nerves of common sensation or pain. A feeling of numbness and partial anæsthesia follows its application after some time.

When taken internally, camphor acts as an irritant and carminative on the mucous membranes like the volatile oils; it has a hot, bitter taste, and in small quantities induces a feeling of warmth and comfort in the stomach, while after large doses nausea and vomiting may be caused by gastric irritation. Some dilatation of the skin vessels follows after it is swallowed, with a sense of warmth; this may probably arise reflexly from the action in the stomach, and is comparable to the dilatation under alcohol and other slight gastric irritants. No other effects follow the use of camphor in therapeutic doses.

When large quantities are taken, they are rapidly absorbed and induce headache, a feeling of warmth, confusion, and excitement in man, with slowing of the pulse and flushing of the skin. This excitement may be shown in hilarity and delirium with hallucinations, in restlessness, or in sudden violent movements, which pass into epileptiform convulsions. These alternate with periods of quiet and unconsciousness, which become longer until the patient sinks into complete stupor. In some cases of poisoning no excitement is observed, the patient falling into a condition of drowsiness, unconsciousness, and stupor immediately. In the lower mammals, camphor induces very similar symptoms, wild excitement and epileptiform convulsions, followed by depression, stupor, collapse, and death from failure of the respiration. Not infrequently, however, the respiration ceases during a convulsion and fails to return when it passes off.

In the frog no excitement is observed except from the local irritation; the animal falls into a condition of depression, in which no spontaneous movements are made, although the reflexes seem to be little affected at first. Later, the reflexes disappear and the animal lies completely paralyzed.

Action: Central Nervous System.—In the frog camphor depresses the brain and later the spinal cord, so that the action is a descending paralysis similar to that seen under chloroform and other anæsthetics; thujon often induces violent spasms, which appear to arise from stimulation of the spinal cord and medulla oblongata.

The convulsions in mammals are certainly not due to any action on the spinal cord, but to stimulation of the higher areas of the nervous axis. The cerebral cortex is involved in the action, for the convulsions are less marked on its removal; but in the lower mammals the chief action seems to be exerted on the nervous centres situated between the cerebral peduncles and the medulla oblongata. It is not improbable that in man the cerebral action may be more marked than that on the lower areas, for on descending lower in the scale it is found that the cerebral action becomes less evident; thus in birds the removal of the cerebrum seems to have no effect on the convulsions. The loss of consciousness and the stupor observed in man and the higher animals point to a final paralysis of the cerebral cortex. Later the spinal cord and the medulla are paralyzed and respiration ceases; some observers state that the reflexes of the spinal cord are first augmented by large doses of camphor but others describe depression as the first result.

The **Terminations of the Motor Nerves** are paralyzed in the frog by large doses of camphor, but not in mammals. The **Muscles** are weakened and paralyzed when they are directly exposed to its solutions or vapor.

The **Heart** is sometimes slowed by camphor and its allies in man and animals, but is generally little affected in either strength or rate. It has been stated that the heart has less tendency to pass into fibrillation under camphor, but this is not confirmed. Camphor dilates the coronary vessels but it is not certain that this occurs in man with therapeutic doses. In the frog camphor appears to have some stimulant action on the heart muscle when directly applied to it, but in mammals its effects on the heart in therapeutically possible amounts are trifling or entirely negative.

In mammals, camphor may reduce the **blood-pressure** though there is sometimes a transient rise at first. The slight fall in pressure appears to be due to dilatation of the peripheral vessels through direct action on their walls; the pulmonary vessels share in this dilator action. The vasomotor centre is not affected directly by small doses. When sufficient camphor is given to cause convulsions, great variations in the blood-pressure occur, a very marked rise

being observed during the convulsive attacks, while in the intervals it falls to below the normal height; these variations appear to arise from a direct action on the vasomotor centre, which partakes in the general stimulation. The slight dilation of the vessels is the only change in the circulation observed after camphor, unless when quantities sufficient to cause convulsions are injected.

The **Respiration** is scarcely altered by camphor given in ordinary quantities. During the convulsions it is arrested, while in the intervals it may be accelerated from the muscular exertion during the spasms.

The normal **Temperature** is not affected by camphor, but in fever it acts as an antipyretic, like many other aromatic bodies.

Camphor is partially oxidized in the tissues, forming camphorol ($C_{10}H_{16}O_2$), which is **Excreted** in the urine in combination with glycuronic acid, COH-$(CHOH)_4$COOH, and also in part in combination with a nitrogenous body, which is probably uramidoglycuronic acid. Camphorol acts like camphor, but its glycuronic acid combinations are inactive, so that the effects of camphor pass off quickly in such animals as the dog, in which these combinations are rapidly formed.

The action of borneol, menthol, bromated camphor, and camphorol is almost identical with that of camphor itself. Borneol is less irritant locally, and the convulsions are less severe than after camphor, so that animals seldom die during the convulsive stage, and may remain in a state of stupor and collapse for one or two days before the respiration finally ceases. After menthol, the convulsions are even less developed than after borneol. Both of these are excreted in combination with glycuronic acid. Bromated camphor seems to resemble borneol more closely than camphor or menthol, while amido-camphor produces symptoms similar to those of camphor, but is much less powerful. Natural camphor is dextrorotary; the lævorotary isomer has been formed recently, and is found to be identical with the natural form in its action.

Therapeutic Uses.—Camphor is used externally in the form of the liniment or spirit as a mild rubefacient in bruises and sprains, and also to destroy parasites. Internally the spirit is prescribed as a carminative and as an intestinal disinfectant. It is frequently given to prevent or relieve "chill," and acts here in the same way as alcohol (page 307).

There is no reason to believe that camphor in even the largest therapeutic doses has any effect after absorption except a slight dilatation of the skin vessels, and it is probable that this also may arise from its gastric effects. Its former uses in hysteria, epilepsy and other nervous disorders, as an aphrodisiac and as an anaphrodisiac were all equally irrational; if any improvement occurred, it was due to hypnotic suggestion and not to the action of the drug.

It has been used in unconsciousness and collapse arising from different causes, in the depression and weakness of acute fevers, and in the most varied forms of failure of the heart and circulation. In many of these cases, improvement in the pulse is said to have been observed; this, like the similar improvement seen after alcohol, may perhaps be explained by its action as a local stomachic irritant producing changes in the circulation reflexly; the value of camphor in heart diseases is still far from being established and most divergent results, both from the pharmacological and clinical sides, have been published as to the effects of camphor on the circulation. Solutions of camphor in oil have been injected subcutaneously in these cases. The local irritation produced by the injection may sometimes cause a reflex rise of blood-pressure, and stimulation of the respiration.

Camphor is often prescribed in expectorant mixtures, especially in combination with opium, as in paregoric.

Menthol is used almost exclusively for its effects on the sensory nerve terminations, and is applied by rubbing the crystals or sticks on the skin in case of headache and neuralgia.

Borneol and monobromated camphor are entirely superfluous. The latter was at one time used as a sedative in nervous excitement, but does not seem to have been at all beneficial and has fallen into disuse.

PREPARATIONS.

CAMPHORA (U. S. P., B. P.) ($C_{10}H_{16}O$), Laurel camphor, a stearoptene obtained from Cinnamomum Camphora, or prepared synthetically, forms white translucent, crystalline masses, which are almost insoluble in water but dissolve readily in alcohol, ether, chloroform, fixed and volatile oils. 0.2 G. (3 grs.), in emulsion or pill. As much as 1 G. has been injected subcutaneously in 10 per cent solution in oil.

AQUA CAMPHORÆ (U. S. P.) 10 cc. (2½ fl. drs.); (B. P.) 15–30 mils. (½–1 fl. oz.).

SPIRITUS CAMPHORÆ (U. S. P.), 1 cc. (15 mins.); (B. P.) 0.3–2 mils. (5–30 mins.).

LINIMENTUM CAMPHORÆ, camphorated oil (U. S. P., B. P.).

TINCTURA OPII CAMPHORATA (U. S. P., B. P.), paregoric, 2–4 cc. (½–1 fl. dr.).

MENTHOL (U. S. P., B. P.) ($C_{10}H_{20}O$), a stearoptene obtained from the oil of peppermint, consists of colorless crystals slightly soluble in water, freely soluble in alcohol or ether. 0.06 G. (1 gr.).

Metrazol (Cardiazol).—Attempts have been made to obtain synthetic compounds which would have a more certain stimulating effect than is possessed by camphor and which would also be soluble in water. One such compound, metrazol, pentamethylentetrazol, known by the trade name of "Cardiazol" has been extensively used. It was found by Hildebrandt (1926) to produce epileptiform convulsions in frogs and mammals with large doses, and with small doses stimulation of the respiration and augmentation and acceleration of the heart when that organ was previously weakened by chloroform or other depressants. It has been recommended as a remedy for circulatory failure as an improved substitute for camphor but other investigations have found no evidence, pharmacological or clinical, for this effect. The evidence that it stimulates the respiratory and vasomotor centres is more convincing and is in keeping with its undoubted effect in stimulating other areas of the central nervous system. It has an awakening effect in animals depressed by narcotics and is said to have some tendency to prevent the onset of respiratory arrest due to overdosage with ether.

It has been extensively used in the treatment of schizophrenia on the original recommendation of Meduna. Here it is administered intravenously in a dose sufficient to produce a brief epileptiform convulsion. This shock or stimulus to the brain seems to arouse its dormant activities in this condition. Details of procedure and dosage differ in individual cases but usually a series of 15 or more injections are given at intervals of three or more days, and especially in cases of schizophrenia characterized by confusion and stupor, the beneficial effects of cardiazol injections may be pronounced and lasting. Cardiazol (metrazol) is a white crystalline powder, freely soluble in water. It is absorbed quickly both from oral or subcutaneous injection.

Coramine.—Another synthetic compound for which similar therapeutic claims have been made bears the trade name of "Coramine." Chemically it is pyridine-β-carboxylic acid diethylamide, and is a yellowish liquid, freely miscible with water. Faust (1925) found that it produced an increase in the respiratory rate with rise of blood-pressure, due to stimulation of the medullary centres. Toxic doses produced excitement, tremors, and finally convulsions. It has been widely used as a stimulant for the respiration and circulation, and has been specially recommended for cases of overdosage with avertin, morphine or other narcotics. The evidence goes to show that it is a useful respiratory stimulant and that the beneficial effect on the circulation when it occurs is due partly to the stimulation of the vasomotor centre and possibly other reflex centres and is partly secondary to the improved respiration. Hicks found that cardiazol had a more rapid and prolonged effect than coramine on the human respiratory centre depressed by morphine, but the absolute and comparative value of these two stimulants and their spheres of utility have hardly yet been sufficiently established, in spite of the extensive literature on the subject. The value of different analeptics in narcotic poisoning evidently varies considerably with the particular narcotic.

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2. Malodorous Volatile Oils.

Some of the volatile oils differ from the others in possessing an odor which is disagreeable and nauseating to most people, although not to all. The best known of these are the *Oils of Asafœtida* and *Valerian*. The former occurs along with resins and gums exuding from some species of Ferula, and contains several organic sulfur compounds, to which it owes its odor. Oil of Valerian, from Valeriana officinalis, is almost without odor when freshly distilled, but when kept for some time and exposed to the air, it assumes a somewhat unpleasant penetrating odor. It contains two terpenes, borneo-camphor, and numerous esters of formic, acetic and valerianic acid. While both of these oils are generally regarded as possessing very unpleasant odors, asafœtida is used in India as a condiment, and valerian was formerly used in England as a perfume. Another drug of the same kind formerly in use is *Sumbul*, the root of Ferula Sumbul.

Asafœtida and valerian are used in hysterical affections, and the benefits accruing from their administration have generally been attributed to the mental impression produced by their unpleasant odor and taste, and not to any action they produce after absorption. Macht observed a sedative action in rats after the inhalation of traces of asafœtida and valerian preparations.

The ordinary valerianic salts have no further effects than other salts of the acetic acid series, so that it is quite irrational to use such bodies as valerianate of quinine for their action in hysteria.

Asafœtida is also used like the ordinary volatile oils as a carminative and as an expectorant, and the emulsion is given by the mouth or in an enema to relieve abdominal distention.

Preparations.

Asafœtida (U. S. P.), a mixture of volatile oil, gum, and resin from Ferula fœtida and other species. 0.25 G. (4 grs.).

Emulsum Asafœtidæ, 15 cc. (4 fl. drs.).

Asafœtida (B. P.), a gum-resin obtained from the root of Ferula fœtida and probably other species. 0.3–1 G. (5–15 grs.).

Tinctura Asafœtidæ, 2–4 mils. (30–60 mins.).

Pilula Aloes et Asafœtidæ, 0.2–0.5 G. (4–8 grs.).

Valeriana (U. S. P., B. P.), valerian, the rhizome and roots of Valeriana officinalis. Dose, 2 G. (30 grs.).

Tinctura Valerianæ (U. S. P.), 4 cc. (1 fl. dr.).

Tinctura Valerianæ Ammoniata (B. P.) 2–4 mils. (30–60 mins.).

IV. DRUGS AFFECTING TASTE.

1. Sugar.

Sugars are used in medicine chiefly to disguise preparations of unpleasant taste, and in the small quantities usually employed have little further effect. In large quantities sugars, like other diffusible bodies, act as irritants to the stomach and bowel, and comparatively small quantities of some sugar substances possess an aperient action; this seems to be due to their colloid form, as pure sugar has no such

effect, and it is possible that they merely delay the absorption of fluid, and thus cause softer evacuations than would otherwise occur.

Preparations.

Sucrosum (U. S. P., B. P.), $C_{12}H_{22}O_{11}$, refined cane sugar.

Syrupus (U. S. P., B. P.), a concentrated solution of sugar. Syrup is the basis of a large number of medicated syrups of the pharmacopœias. Sugar and syrup are used exclusively to sweeten mixtures and to aid in the suspension of insoluble bodies. In place of ordinary syrup many of the flavored preparations may be used, such as the syrups of citric acid, acacia, almonds, or of the volatile oil group. Intravenous injection of a hypertonic solution of sucrose has been used, merely for its osmotic properties, to relieve intracranial pressure in cases of brain tumor. For this purpose, 50 cc. or more of a 50 per cent solution is injected very slowly.

Lactosum (U. S. P., B. P.), $C_{12}H_{22}O_{11}.H_2O$; sugar of milk, lactose, is not so sweet as ordinary sugar, and is much less liable to deliquesce, so that it is used largely to give bulk to powders. It has been said to have diuretic properties when given with large quantities of water, and to cause purgation when given in a more concentrated solution. It is largely used in the humanization of cow's milk for infants.

Lævulosum (B. P.), fructose, consists chiefly of lævulose ($C_6H_{12}O_6$) with small quantities of dextrose. It has greater sweetening power than cane sugar. It is used in diabetes, in which it does not cause glycosuria to the same extent as ordinary sugar. It is also used as a test for disordered liver function.

Dextrosum (U. S. P., B. P.), $C_6H_{14}O_6$, dextrose, also known as glucose, is a sugar usually obtained by the hydrolysis of starch. Glucose is a food which is readily absorbed and is given in debilitating diseases, when the intake of food that can be digested is insufficient. A liver rich in glycogen resists the action of toxic agents better than one poor in glycogen, and hence glucose is given to prevent damage to the liver from chloroform, cinchophen or other liver poisons. Solutions of glucose are often given by intravenous injection in cases of acute circulatory failure, such as may occur in infectious diseases or in case of shock or hemorrhage, to supply fluid. It is usually given in a 5 or 10 per cent solution, the former concentration being approximately isotonic with blood. It may also be given in the form of an enema. Pure dextrose must always be used for such injections.

Dextrosum is a white crystalline powder and must not be confused with liquid glucose, Glucosum (U. S. P.), Glucosum Liquidum (B. P.). The latter is a viscid, syrupy liquid containing a mixture of dextrose, maltose, dextrin and water, and is chiefly used for its physical properties as a pill excipient. It cannot be used for intravenous injection, etc.

Extractum Malti (U. S. P., 15 G. [4 drs.]; B. P., 4–16 mils. [60–120 mins.]).

Extract of malt is a brownish viscous liquid with a sweetish taste. It contains nutritive carbohydrates and also usually diastatic ferments capable of converting starch into sugar. It is given both for nutritive and digestive properties. It forms a good vehicle for giving cod-liver oil, as in the B. P. Extractum Malti Cum Oleo Morrhuæ, 4–16 mils. (60–240 mins.).

Mel (U. S. P.), Mel Depuratum (B. P.), clarified honey, is used to give taste to mixtures, and has a very slight aperient action, so that it may be advised as an article of diet in habitual constipation. Some medicated honeys are used, of which Mel Boracis is included in the B. P.

A number of saccharine preparations with a slight aperient effect are ingredients of the preparations of the more powerful purgatives. Thus purging Cassia (Cassia, B. P.), tamarinds (Tamarindus, B. P.), figs and prunes form constituents of the Confection of Senna and other preparations. They are not prescribed alone, but the fruits may be advised as articles of diet where a mild laxative is required. The tamarind pulp may owe its aperient action in part to the presence of tartrates, citrates, malates, and other cathartic salts. (See Saline Cathartics.)

2. **Flavoring Substances.**

Frequently other flavors are preferred to sugar, which is especially disliked in fever cases, as sweet fluids do not quench the thirst so effectually as acids and bitters. Many of the preparations of the volatile oils and some of the demulcents are used almost exclusively as flavoring agents, and in some both sugar and volatile oil are combined, as in the syrups.

Instead of sugar some artificial compounds have been introduced of late years. **Saccharin** (U. S. P.), $C_6H_4\langle^{CO}_{SO_2}\rangle NH$, and its sodium salt (*Saccharinum Solubile*, U. S. P., B. P.), $C_6H_4\langle^{CO}_{SO_2}\rangle NNa$, or soluble saccharin, are the best known of these. Saccharin is a light, white, crystalline powder, soluble in 400 parts of water and in 25 parts of alcohol. It is about 500 times as sweet as sugar, and gives a distinct flavor to 70,000 times its weight of water. It does not taste exactly like sugar, however, there being a distinct flavor besides that of sweetness, and patients generally object to it after a short time. It has been used as a substitute for sugar in diabetes, but has, of course, no food value. Saccharin in ordinary amounts has no deleterious action on the digestion or after absorption.

Some pharmacopœial preparations are designed to give color to solutions, but are seldom or never prescribed, although they are sometimes added by the pharmacist.

Among these are cochineal (*Coccus*, U. S. P., B. P., *Tinctura Cocci*, B. P.) and saffron.

3. **Volatile Oils Used as Flavoring Agents and Carminatives.**

Many plants depend for their odor and taste upon the presence of volatile oils and these have been employed from earliest times to give flavor to medicinal preparations. One oil is used by one physician, another by another, and the selection is largely a matter of custom and taste. Some volatile oils are used as carminatives (p. 235) when no marked irritation of the stomach or intestine is present, but the gastric juice seems unable to cope with the food, especially in children and in persons of sedentary habits. In cases of colic, flatulence and abdominal distention they are often of use, provided that these are not due to peritonitis and other inflammatory diseases. Several of them have been employed as surgical antiseptics, but they are more widely used as parasiticides for scabies, pediculi, etc. Some of the oils, such as oil of cloves, are used in dentistry to relieve pain, and also for their antiseptic action; the relief of pain is due to their paralyzing the exposed nerve ends after a preliminary irritation. Eucalyptus has been advised in septic conditions and in malaria but is of no value in these conditions; its chief constituent, eucalyptol ($C_{10}H_{18}O$), is equally devoid of any special virtues to distinguish it from the other volatile oils. Volatile oil preparations are sometimes given internally in the hope that in their excretion

through the lungs they will exercise an antiseptic action in pulmonary disease, but the traces excreted in this way are quite incapable of any noticeable effect on microbial growth, and the tubercle bacillus, against which these measures are most frequently directed, appears to be peculiarly resistant to the action of this group of remedies. They are frequently inhaled with a similar object. Some of them have been used as anthelmintics to destroy tapeworms in the intestine, and thymol has recently proved very effective in destroying the intestinal parasites in uncinariasis (see Thymol). Externally some of them are used as mild skin-irritants, generally in the form of spirits. Arnica has a great popular reputation as a stimulating local remedy in bruises and sprains, although it has no specific action and is in no way preferable to the other members of the series.

The volatile oils are largely used as flavors in cookery and sweet-making, and are important constituents of many of the popular liqueurs, and therefore have a certain dietetic importance.

Preparations.

Crude Drugs.—Many of the pharmacopœial preparations are whole plants, seeds, leaves, or flowers, and are never prescribed, although some of them are used in popular medicine in the form of infusions or "teas." The virtues of these old-fashioned remedies lie perhaps more in the large draughts of warm water than in the traces of volatile oil which they contain, but the presence of the latter prevents, to some extent, the nausea produced by warm water alone. These infusions are used to induce perspiration in fevers or chills, as diuretics, or to relieve colic and griping, and generally contain about a tablespoonful of the herb to one or two cupfuls of water. The most frequently used for this purpose are peppermint and spearmint leaves and tops (Mentha Piperita and Mentha Viridis, U. S. P.); Coriander seeds (Coriandrum, B. P.); Chamomile flowers; Anise, the fruit of Pimpinella anisum; Elderflower and Horehound. In different countries, however, the constituents of the herbalist recipes vary according to the local flora. The U. S. and B. Pharmacopœias recognize a number of other crude drugs of this group which need only be enumerated here: Aurantii Amari Cortex (bitter orange peel), Caryophyllum (cloves), Cinnamomum (cinnamon), Cardamomum (cardamom), Carum (caraway), Myristica (nutmeg), and Zingiber (ginger).

Prunus Virginiana (U. S. P.), Prunus Serotina (B. P.), contains amygdalin or some nearly related substance, and emulsin, and forms benzaldehyde and prussic acid when rubbed up with water. The Syrupus (U. S. P., B. P.) is frequently used as a flavoring agent and in cough mixtures.

The Volatile Oils themselves are also represented in unnecessarily large numbers in the pharmacopœias.

U. S. P.—Oleum Menthæ Piperitæ (oil of peppermint), Ol. Menthæ Viridis (spearmint), Ol. Lavandulæ (lavender), Ol. Eucalypti (eucalyptus), Ol. Limonis (lemon), Ol. Aurantii (orange), Oleoresina Zingiberis (ginger), Ol. Amygdalæ Amaræ (bitter almonds), Ol. Caryophylli (cloves), Ol. Cinnamomi, Ol. Coriandri (coriander), Ol. Sassafras (sassafras), Ol. Anisi (anise), Ol. Fœniculi (fennel), Ol. Rosæ, Ol. Rosmarini (rosemary), Ol. Juniperi (juniper), Ol. Myristicæ (nutmeg). Dose, 0.2 cc. (3 mins.).

B. P.—Oleum Anethi (oil of dill), Ol. Anisi (anise), Ol. Cajuputi (cajuput), Ol. Cari (caraway), Ol. Caryophylli (cloves), Ol. Cinnamomi (cinnamon), Ol. Coriandri (coriander), Ol. Eucalypti (eucalyptus), Ol. Lavandulæ (lavender), Ol. Limonis (lemon), Ol. Menthæ Piperitæ (peppermint), Ol. Myristicæ (nutmeg), Ol. Rosmarini (rosemary). Dose, 0.2–3 mins.

The majority of these oils resemble each other very closely in their effects

and require no special comment. The oils of rosemary, juniper, and savine are more irritant than the others, and are seldom used. The oils of wintergreen and of birch consist mainly of methyl salicylate, and may be used instead of the other salicylates. Nutmeg and mace oils are more poisonous than the others, not from their local irritant action so much as from their effects after absorption.

The volatile oils themselves are comparatively little used. A single drop may be added to powders, pills or solutions to give a pleasant odor, and their presence in tooth powders renders these more or less strongly antiseptic. Occasionally they are given in cases of colic or in chill by pouring a few drops on a piece of sugar, which is sucked.

Spiritus are formed from many of the volatile oils by dissolving them in alcohol, sometimes with the addition of water and sometimes with some of the crude drugs, so that the preparation is really a mixture of tincture and spirit. The spirits or essences of the volatile oils are used very largely as flavoring agents in mixtures for internal use, and are often added to external applications to lend them odor. They may also be prescribed where alcohol is indicated but is distasteful to the patient; the spirits of the volatile oils contain 80 per cent or more of alcohol, and have to be diluted accordingly. Any of them may be used as carminatives, but the spirits of peppermint, cinnamon, anise and lavender are more frequently used for this purpose than the others. Another useful carminative preparation is camphorated tincture of opium, which contains camphor and several volatile oils along with a small amount of opium; the last aids the real carminative in relieving the discomfort by its action after absorption.

Spirit of juniper is often given as a diuretic, either alone or along with other drugs. Spirit of rosemary is generally used externally. Many of the common perfumes are spirits of different volatile oils; thus eau de Cologne contains the oils of bergamot, lemon, rosemary, lavender and orange-flower, along with acetic ether and alcohol.

U. S. P.—Spir. Anisi, Spir. Aurantii Compositus (containing the oils of orange peel, lemon, coriander, and anise), Spir. Cinnamomi, Spir. Lavandulæ, Spir. Menthæ Piperitæ, Spir. Menthæ Viridis, 1 cc. (15 mins.).

Elixir Aromaticum and Elixir Glycyrrhizæ are preparations of the Spir. Aurantii Compositus, which are used exclusively as flavors.

B. P.—Spiritus Cajuputi, Sp. Menthæ Piperitæ. 0.3–2 mils, (5–30 mins.).

Aquæ.—The volatile oils are very insoluble in water, but when they are shaken in it, enough remains in the water to give it the odor and taste of the oil. In the process of obtaining the oils from the crude drugs by distillation, some oil is held by the water, and a number of these waters (aquæ) are contained in the pharmacopœias. They are used as substitutes for distilled water in making up prescriptions, the small quantity of volatile oil serving merely to give a pleasant odor and taste.

The aromatic waters of the U. S. P. are made either by distillation of the appropriate part of the plant or by solution of the volatile oil in water. The B. P. contains some prepared by distillation (Aquæ Destillatæ) and others made by simple solution of the essential oil. It also contains a few Aquæ Concentratæ (*e. g.*, Aqua Cinnamomi Concentrata) which, on dilution with thirty-nine times their volume of distilled water, yield preparations approximately equivalent in strength to the distilled waters.

U. S. P.—Aqua Anisi, Aq. Aurantii Flor., Aq. Cinnamomi, Aq. Fœniculi, Aq. Menthæ Piperitæ, Aq. Menthæ Viridis, Aq. Rosæ, Aq. Rosæ Fortior (the latter twice as strong as the other).

B. P.—Aqua Anethi Destillata, Aq. Anisi Destillata, Aq. Cinnamomi Destillata, Aq. Menthæ Piperitæ Destillata. Each of these has a corresponding concentrated water.

Some of the preparations containing volatile oils are derived not from the oil itself, but from the crude drug, and therefore contain non-volatile substances which are generally absent from the preparations already mentioned. As a general rule these non-volatile bodies are inactive, but in some cases, bitters or resins are contained in the preparations, and may influence their action. Thus a bitter glucoside, hesperidin, is found in the orange peel, and is present in the preparations formed directly from it, while it is absent from those formed from the volatile oil. Ginger contains a resin of hot, burning taste, which increases the carminative action of the oil. Cinnamon contains some tannic acid, which passes over in the tincture, while a fixed oil is contained in cardamom.

Among the preparations formed from the crude drugs are the **Syrups,** which are used exclusively as flavoring agents.

U. S. P.—Syrupus Aurantii Florum, Syr. Aurantii, Syr. Pruni Virginianæ, Syr. Balsami Tolutani. Dose, 4–16 cc. (1–4 fl. drs.).

B. P.—Syrupus Aurantii, Syr. Limonis, Syr. Pruni Serotinæ, Syr. Zingiberis, Syr. Tolutanus. Dose, 2–4 cc. (½–1 fl. dr.).

The **Tinctures** are used for the same purposes as the spirits of the pure oils.

U. S. P.—Tinct. Aurantii Amari, Tinct. Aurantii Dulcis, Tinct. Limonis, Tinct. Cardamomi Composita (containing cardamom, cinnamon, caraway), Tinct. Lavandulæ Composita (oils of lavender, rosemary, cinnamon, cloves, nutmeg). Dose, 2 cc. (30 mins.).

B. P.—Tinct. Aurantii, Tinct. Cardamomi Composita (containing cardamom, caraway, cinnamon), Tinct. Cinnamomi, Tinct. Limonis, Tinct. Zingiberis Mitis, 2–4 mils. (30–60 mins.), and Tinctura Zingiberis Fortis (Essence of Ginger), 0.3–0.6 mils. (5–10 mins.).

Fluidextracts of the volatile oil series.

U. S. P.—Fluidextractum Zingiberis, 0.5 cc. (8 mins.).

Other Preparations.

Pulvis Aromaticus (U. S. P.) contains cinnamon, cardamom, ginger, and nutmeg in powder, and is a useful carminative in doses of 1 G. (15 grs.).

Pure Principles used as flavors:

Vanillinum (U. S. P.), vanillin ($C_6H_3 \cdot OH \cdot OCH_3 \cdot COH$), occurs in vanilla and is also made synthetically. It forms white needle crystals, slightly soluble in water, easily soluble in alcohol and ether, and possesses the odor and taste of vanilla. Dose, 0.03 G. (½ gr.).

Eugenol (U. S. P.), a phenol ($C_6H_3OH \cdot OCH_3 \cdot C_3H_5$) obtained from oil of cloves and other oils, and forming a colorless liquid with an odor like cloves and a hot, burning taste. Dose, 0.2 cc. (3 mins.).

These principles are used chiefly to give flavor and color.

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4. Simple Bitters.

This group includes a number of substances which have little in common except their bitter taste and their comparative inactivity in the body. Several alkaloids may be placed in it, *Berberine*, *Buxine*, *Menispermine* and *Canadine*, for, although these are poisonous in very large quantities, they are harmless in those in which they are contained in the preparations used in therapeutics. In addition to these there may be placed in it numerous neutral bodies, possessing an intensely bitter taste, but with little or no further action, such as the *Quassiins*, *Calumbin*, and a few weak acids and glucosides.

Pharmacological Action.—These substances, or rather the preparations containing them, are largely used in therapeutics in order to increase the appetite, and their administration is often followed by a distinct improvement in the digestion and an increase in weight.

Alimentary Tract.—These effects are explained by the action of bitter substances in increasing the secretion of gastric juice, which has been shown to occur in man and animals by a number of experiments. This is not, however, through the bitters acting on the gastric mucous membrane directly, for when they are applied through a gastric fistula, they have no specific action on the secretion. Pawlow has shown that the chief factor that determines the activity of the gastric secretion is the odor and taste of food; thus in dogs with œsophageal fistulæ, in which the food swallowed does not pass into the stomach but escapes through a wound in the œsophagus, the taste and odor of food cause a profuse secretion of gastric juice (psychical secretion). Bitters given shortly before a meal sometimes augment this reflex in normal animals but this is more distinct and occurs more often when cachexia is present (Moorhead); this is due to action in the mouth only, for it is seen when the bitter is not swallowed, and is absent when it is passed into the stomach through a fistula. This change in the secretion is accompanied by improved appetite in cachexia, while the hunger contractions of the stomach are arrested by bitter tastes; introduced directly into the stomach, the bitters have little or no effect in therapeutic doses. The action of the bitters is therefore to increase the psychical secretion of gastric juice, possibly because of the contrast offered by the bitter and the

pleasant tastes. The inference may be drawn that the therapeutic effects are best elicited when the bitters are given shortly before a meal, and this accords with universal experience. And the use of the bitters is attended with benefit only in cases in which the gastric juice is deficient. The increase of the gastric juice is followed as usual by a more active secretion by the pancreas. In addition, it is to be remembered that the improvement is largely subjective, and that the bitters are capable of producing a considerable impression upon patients, so that the effects may be due in part to suggestion and not to any real action of the drug.

In comparison with their effects on secretion, the other changes induced in the alimentary tract by the bitters are insignificant. They have little or no effect on the activity of the ferments in themselves, but the tannin and colloids of the usual preparations may retard their action. And they do not affect the growth of bacteria or yeasts. Absorption from the alimentary tract and the movements of the stomach and bowel are not altered by their presence. The salivary secretion is generally augmented by bitter tastes, and some increase in the leucocytes and red cells of the blood is said to occur after their use.

In very large quantities some of the bitters produce effects that are obviously due to their absorption, but these play no part in their therapeutic effects and have seldom or never been elicited in man.

Instead of the simple bitters, cinchona and nux vomica preparations are often used in small quantities. Many of the preparations which will be enumerated under the volatile oil series owe much of their effect to the bitter which accompanies the volatile oil, and in numerous other pharmacopœial preparations bitters are present, although their effect is hidden by the action of the drug in other directions.

Therapeutic Uses.—The bitters are used chiefly to increase the appetite and the digestion. In convalescents, in persons of sedentary habits, and occasionally in chronic dyspeptic conditions they are of value, while in cases of more acute gastric irritability and in hyperacidity they may do harm rather than good. Gentian, Quassia and Calumba are the only simple bitters that are largely used, and the first is much the most important. They are generally prescribed as tinctures, infusions or other fluid preparations. The last two may be prescribed with iron preparations, as they contain little or no tannic acid and thus cause no precipitate. Pills are sometimes prescribed with extract of gentian which has little, if any, effect when given in this form, as the bitter taste, on which its action depends, is largely concealed. Compound tincture of gentian is sometimes used to give flavor rather than for any effect on the digestion. Quassia infusion (10 per cent) is injected as an enema in the round worms of children.

Preparations.

Gentiana (U. S. P., B. P.), gentian, the root of Gentiana lutea, contains a glucoside, gentiopicrin, and a trace of tannic acid. 1 G. (15 grs.).

Extractum Gentianæ (B. P.), 2–8 grs.

Tinctura Gentianæ Composita (U. S. P., B. P.), containing gentian, bitter orange peel, and cardamom, 4 cc. (1 fl. dr.); 2–4 mils. (30–60 mins.).

Quassia (B. P.), the wood of Picrasma excelsa or of Quassia amara, contains several neutral bitter substances, resembling each other closely chemically and known as quassins.

TINCTURA QUASSIÆ (B. P.), 2–4 mils. (30–60 mins.).

INFUSUM QUASSIÆ RECENS (B. P.), 15–30 mils. (½–1 fl. oz.).

CALUMBA (B. P.), columbo, the root of Jateorrhiza palmata, or Columba, contains columbin, a neutral body, columbic acid, and three alkaloids, columbamine, jateorrhizine, and palmitine, closely resembling berberine.

TINCTURA CALUMBÆ (B. P.), 4 mils. (1 dr.).

INFUSUM CALUMBÆ CONCENTRATUM (B. P.), 2–4 mils. (30–60 mins.).

INFUSUM CALUMBÆ RECENS (B. P.), 15–30 mils. (½–1 fl. oz.).

Many other remedies have been used in medicine, which owe their reputations to their bitterness only. As a general rule they have been introduced as possessing specific properties in some such disease as gastric cancer, but have failed to maintain their promise and gradually are recognized to be in no way superior to gentian and other established bitters. Their use as bitters often forms a prelude to their complete abandonment. Among these unnecessary bitter drugs may be mentioned SERPENTARIA (U. S. P., B. P.), snakeroot, the rhizome and roots of two species of Aristolochia, containing an unknown bitter principle and an alkaloid, aristolochine. This is retained only as a constituent of TINCTURA CINCHONÆ COMPOSITA.

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5. Pepper Group.

The pepper group comprises a few drugs which are used for their effect on digestion but which have a much more pungent taste than the bitters, and cause marked irritation when they are applied in large doses. They thus stand midway between the simple bitters and the carminative volatile oils, and are sometimes known as aromatic stomachics.

Black Pepper contains a weakly basic substance, *Piperine* (which is broken up by caustic alkalies into *Piperidine* and *Piperinic acid*), in addition to a volatile oil and a bitter pungent resin. Piperine is insoluble in water, and has therefore no taste when absolutely pure, but is hot and pungent to the taste when it is taken in solution.

Pyrethrum, or pellitory, contains similar constituents but is scarcely used except as an ingredient of insect powders.

Capsicum, or Cayenne pepper, contains *Capsaicin,* a neutral body with a hot pungent taste.

Pepper and capsicum are largely used as condiments, and are comparatively seldom prescribed in therapeutics. *Unguentum Capsici* (B. P.) is used as a rubefacient. *Tinctura Capsici* (U. S. P.), 0.5 cc.–8 mins. (B. P.) 0.3–1 mil. (5–15 mins.), is sometimes used as a stomachic and has been employed in chronic alcoholism in order to provide a substitute for the local irritant effects of spirits in the stomach.

Piper Methisticum, or Kava Kava, is used in the South Sea Islands to prepare an intoxicating liquor which, according to Kesteven, differs from the

alcoholic preparations in producing marked muscular weakness without affecting the mental powers. Other observers state, however, that it causes confusion and sleep very much as alcohol does. Its local action resembles that of pepper, and like it, it has been advised in gonorrhea. Its virtues seem to reside in two resinous bodies.

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V. DIGESTIVE FERMENTS.

A number of digestive ferments have been introduced into therapeutics for the treatment of gastric and intestinal disorders. The earlier members of the series were proteolytic ferments, intended to reinforce the pepsin of the stomach, but of recent years the amylolytic ferments have also been strongly advocated.

1. Pepsin.

The pharmacopœial preparations of pepsin are generally obtained from the pig's stomach. It digests only in acid solution, the best results being obtained in a solution of 0.2 per cent of hydrochloric acid. In alkaline solution it is inert, and in fact is rapidly decomposed, so that when pepsin and alkaline carbonates or bicarbonates are prescribed together, the effects are due to the alkalies only.

Pepsin is used in therapeutics on the theory that the stomach does not secrete enough of the ferment in certain conditions. But it may be questioned whether this is true in even a small proportion of the cases treated with pepsin, for the gastric juice is almost always capable of digesting proteins if it is acid in reaction. In a number of forms of dyspepsia the acid secretion is insufficient, but the ferment is almost always present in quantity, for it digests proteins outside the body as soon as it is acidulated. On the other hand, the administration of hydrochloric acid tends to diminish gastric secretion; hence, in cases of defective gastric secretion, better results may be obtained if pepsin is added when acid is given by the mouth.

PREPARATIONS.

PEPSINUM (U. S. P.), a proteolytic ferment obtained from the glandular layer of fresh stomachs from healthy pigs, and capable of digesting not less than 3000 times its own weight of freshly coagulated egg albumin. The B. P. preparation may be obtained from the pig, sheep or calf and is required to digest 2500 times its weight of hard-boiled white of egg. It is a fine, white, amorphous powder or thin scales, free from offensive odor and having a mildly acid or saline taste, usually followed by a suggestion of bitterness. 0.5 G. (8 grs.), in powder, or in solution in 0.2 per cent hydrochloric acid.

Pepsin is generally given during or after meals. As has been stated, it is very rarely indicated, as the gastric juice almost always contains sufficient ferment.

2. **Pancreatic Ferments.**

The pancreatic ferments have also been introduced into therapeutics, generally in the form of an extract of the gland, *pancreatin*. These ferments differ from pepsin in acting only in alkaline or neutral solution, and besides digesting proteins, form sugar from starch and saponify and emulsify fats. The pancreatic ferments are rendered inert by a comparatively short exposure to the acid gastric juice.

The value of pancreatin is even more problematical than that of pepsin, for though it would no doubt be valuable where the digestive ferments, particularly those of the pancreas, were deficient, this has not been shown to occur. On the other hand, the pancreatic ferments are certainly destroyed in passing through the stomach. It has been suggested, however, that they may act in the stomach, if they are given before or with the food, as the acid gastric juice is only secreted slowly, and some time must elapse before the pancreatin is rendered inert. Attempts have been made to preserve the pancreatin from the deleterious effects of the gastric juice by administering it in capsules which are dissolved only in the intestine. It is certainly possible that the pancreatin may be useful in rare cases, where the ferments of the pancreas are absent and the acid of the stomach so deficient as not to be destructive. Pancreatin is now used chiefly to digest the food before it is taken, about 5 grs. sufficing for a pint of milk.

Preparations.

Pancreatinum (U. S., B. P.), a mixture of the enzymes naturally existing in the pancreas of warm-blooded animals, usually obtained from the fresh pancreas of the pig. It forms a yellowish, yellowish-white, or grayish, amorphous powder, having a faint, not disagreeable odor and a meat-like taste, and is slowly soluble in water. U. S. P., 0.5 G. (8 grs.), in powder or in capsules. B. P., 0.2–0.6 G. (3–10 grs.).

3. **Vegetable Ferments.**

Besides these animal digestive ferments, a number of vegetable proteolytic enzymes are known, and have enjoyed a more or less short-lived popularity. Probably many more plant juices are able to digest proteins than are at present generally recognized; thus many of the bacteria liquefy gelatin and albumin, and the insectivorous plants, such as Drosera (sundew) and Dionea, secrete a digestive fluid. Figs, pineapple (*bromelin*), the scarlet pimpernel (Anagallis arvensis), and many others of the higher plants have been shown to possess these ferments, but the best known of these is the carica papaya, or pawpaw, which contains a digestive ferment known as *papain*, *papayotin*, or *papoid*. This ferment acts in neutral, slightly acid, or alkaline solution at the temperature of the body and in the cold. It has been used instead of pancreatin and pepsin in disorders of the digestion, and also as an anthelmintic.

Several milk-curdling ferments have been found in plants, but none of them has been used in therapeutics.

4. **Diastase.**

Several amylolytic or sugar-forming ferments have been used more or less in therapeutics, the first of these being the *diastase* or *enzyme of malt*, which is known under the names of malt extract, or maltzyme.

When grain is allowed to germinate, its starch is formed into a soluble form (sugar) by means of a ferment known as diastase, and it was supposed that this diastase might aid the digestion of starchy foods in the body. When malt extract is formed at a low temperature, it unquestionably contains diastase and is capable of digesting starch, but many of the extracts on the market are quite inert, the ferment having been destroyed by heat. Those extracts are therefore devoid of digestive power, but form a pleasant, easily digested food. More recently some other sugar-forming ferments have been brought forward, notably *Taka-diastase* obtained from Eurotium oryzæ, a mould of the aspergillus family; it has been recommended in cases in which there is supposed to be a deficient digestion of starch. It ceases to act in the gastric juice as soon as the acidity exceeds 0.1 per cent, but may be able to digest a certain amount of starch in the mouth and stomach before it is destroyed. Until it is shown that in some cases the digestion of starch by the intestinal ferments is insufficiently performed, the diastase preparations would seem to be superfluous, though they are fairly frequently prescribed.

5. **Bile.**

The bile is very seldom used in therapeutics at the present day, although it was formerly credited with great healing virtues. It has a bitter taste, and may have some effect like the vegetable bitters, but has no advantage over these, and is not likely to be used to promote the appetite now, although it was formerly used as a stomachic. The bile is found to precipitate the peptones in test-tube experiments, but does not appear to retard digestion in the stomach materially, judging from experiments carried out in a case of gastric fistula. In the intestine it is generally believed to act as an antiseptic, chiefly because the stools have a strong putrefactive odor in cases of retention of bile. Limbourg has also shown that the addition of bile to protein solutions delays their decomposition, while there is some evidence that it promotes pancreatic digestion. It has some purgative action, as is shown by the obstinate constipation which often occurs when it is prevented from reaching the intestine; according to Stadelmann, the bile acids irritate the mucous membrane of the large bowel and thus induce purgation. Some of the drastic purgatives fail to act in the absence of bile, apparently because they are not dissolved by the other secretions (p. 264). Bile increases the activity of the fat-splitting ferment of the pancreas and thus augments the absorption of fats, but it is doubtful whether bile given by the mouth has this action. Most of the bile given by the mouth is absorbed in the intestine and carried to the liver, which excretes it again, while a small quantity of the bile acids escapes in the urine. In the liver it increases the secretion of both the fluid and the solids of the bile; in fact, the bile is the only reliable cholagogue known. The constituent which acts on the liver secretory cells seems to be the bile acids, and their increase is greater than can be accounted for merely by the excretion of that administered, so that it would seem that they exercise some specific stimulant action on the

secretory cells. The bile pigment is also augmented when bile acids are absorbed, owing to the destruction of the red cells of the blood, as the liberated hæmoglobin is carried to the liver and there formed into bile pigment.

Bile given by the mouth does not cause any symptoms except those from the intestine and liver. When it is injected into the blood, however, it depresses the central nervous system and the heart muscle from its direct action on these organs, and dissolves the red cells of the blood in the same way as do the saponins, which it resembles in reducing the surface tension. Muscles and nerves suspended in a solution of bile salts rapidly lose their irritability, and some unicellular organisms are killed and dissolved by them. The poisonous constituent of the bile seems to be the salts of the bile acids, but several authors have stated that the pigment is also active. However, Still, working with specially purified preparations, came to the conclusion that the pigment bilirubin was relatively non-toxic and that the acids were the most toxic elements in bile. Bile itself is not so toxic as an equivalent quantity of bile acids, due doubtless to the presence in the bile of protective substances (cholesterol). The injection of toxic amounts of bile acids into dogs produces an increased rate of the respiration and a profound fall in blood-pressure.

Fraser discovered that the bile acts to some extent as an antidote to the snake venoms through its containing cholesterol, which retards the absorption of the venom; it is much more efficient when it is mixed with the poison before its application than when it is injected after the bite. Others have found that the bile of animals dying of an infectious disease (rinderpest) possesses some curative properties in other animals suffering from the same malady, this being explained by the excretion of the antitoxin in the bile.

Therapeutic Uses.—Bile has been used as a purgative, and it has been particularly recommended in the form of an enema. It does not seem to be reliable, however, and presents no advantages over soaps and similar substances.

As a cholagogue it is without rival, but no condition is known in which an increase of the bile secretion is indicated, for though it has been proposed to expel gall-stones by raising the pressure in the gall-ducts by cholagogues, it is found that when the pressure is only slightly increased, the secretion is arrested. It is inconceivable that the small rise in pressure could force out an impacted gall-stone.

Bile might be used to aid the absorption of fats, particularly when it is deficient in the bowel; in a case of biliary fistula Joslin found that much less fat and nitrogenous food escaped in the stools when the patient was treated with bile pills, than when no treatment was adopted.

It has been found recently that the presence of bile in the intestine is very important for the absorption of vitamin K (page 622).

Preparations.

U. S. P.

Fel Bovis, ox gall, is the fresh bile of the ox.

Extractum Fellis Bovis. 1 G. of the powdered extract of ox gall represents 8 G. of fresh ox gall. 0.4 G. (6 grs.).

B. P.

Extractum Fellis Bovini, purified ox bile, is prepared from fresh ox bile and contains the bile salts and pigments. 0.3–1 G. (5–15 grs.).

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VI. VEGETABLE ASTRINGENTS—TANNIC ACID SERIES.

A large number of vegetable substances owe their action to their containing tannin substances, while in many other preparations the effect of more important constituents is modified by the presence of these widely distributed bodies. Tannic acid proper is a feebly acid substance derived from the oak gall, and is a compound of gallic acid, $C_7H_6O_5$, into which it is easily decomposed. Gallic acid is formed from a large number of other bodies which closely resemble tannic acid in their general features, but are by no means identical with it. Their constitution is altogether unknown,[1] but they possess a number of reactions in common and are generally classed together as the tannic acid substances. Some of them contain a sugar, and tannin or tannic acid is therefore sometimes said to be a glucoside. These bodies precipitate albumins, gelatin, alkaloids and some glucosides, and the salts of the heavy metals. The salts of iron form a bluish-black or greenish-black precipitate.

Action.—The pharmacological effects of these bodies are due to their precipitating albumins and other proteins, and this reaction may therefore be described before their action in the body. If tannic acid solution is added to a neutral or weakly acid solution of albumin, peptone, or gelatin, a white precipitate falls, which is entirely insoluble in water, but is soluble in excess of albumin or gelatin, in stronger acid, and in alkaline solutions. This protein tannate, exposed to the action of the gastric juice, undergoes digestion and is dissolved in the same way as an ordinary coagulated protein such as fibrin. During the process the tannic acid is set free from its combination and if it reaches a position in which the reaction is nearly neutral, it can again precipitate proteins. Strong alkali prevents the precipitation and the so-called tannates of the alkalies are thus devoid of this action.

Tannic acid applied to animal tissue, as in the tanning of leather, causes a precipitation of the proteins, and the tissue becomes harder and tougher and tends to shrink together; at the same time it has less tendency to undergo putrefactive changes and does not lose its flexibility, as it would in drying. Applied to a living mucous membrane, which is neither strongly acid nor alkaline, a dilute tannin solution precipitates a fine pellicle of mucus and protein, which protects the cells beneath and lessens their sensitiveness to external stimuli. A stronger solution

[1] See *McGookin and Heilbron:* Jour. Pharm. and Exp. Ther., **26**, 421, 1926, for discussion of chemistry of tannin in kino of eucalyptus calophylla with extensive bibliography.

may cause some precipitation in the cells themselves and thus injure them and cause irritation.

Tannic acid solutions have a harsh, bitter, "astringent" taste, and produce in the mouth a feeling of constriction, dryness and roughness, along with a sense of stiffness in the movements of the tongue, and some loss of taste. These effects are due to the coagulation of the superficial layers of protein, which substitutes for the ordinary smooth surface a firmer, less even one over which the tongue can no longer move easily. The feeling of constriction may, perhaps, be caused by an actual shrinking of the superficial layers of the epithelium, or may be due merely to the impaired movements and sensation.

The astringent feeling is continued in the throat as the solution is swallowed, and occasionally some irritation or even nausea and vomiting are provoked by it, but as a general rule, no such effects are observed. The stools are rendered harder and firmer by the administration of tannic acid, and constipation is often produced by it. In excess, tannic acid sometimes causes irritation of the intestine and diarrhœa, but beyond these symptoms of local irritation of the stomach and bowel, no effects arise even from enormous quantities of the drug.

In the resting stomach, tannic acid combines with any protein substance with which it may come in contact and precipitates it, but as digestion progresses and the reaction becomes more strongly acid, this combination is broken up. In the intestine, the reaction becoming again less acid, tannic acid causes the same superficial precipitation as in the mouth, and the pellicle of precipitated protein acts as a protective to the mucous membrane. The contents thus have less effect in starting the peristaltic reflex and the movements are retarded, so that there is longer time for the absorption of the fluid part of the contents, although this proceeds more slowly under tannic acid than normally (Gebhardt). The secretion of mucus by the intestinal epithelium is lessened (Frey), and this may also retard the passage of the contents, which therefore become drier and harder. Hesse states that the constipating action is exercised chiefly in the large bowel when tannalbin is given, but this may not hold for the ordinary forms of tannin. Yeasts and microbes are precipitated by tannin, and this may tend to lessen the fermentation in the bowel in some cases, although some preparations of tannic acid which have been examined in regard to this point have been found to have little or no effect on intestinal putrefaction.

The local application of tannic acid causes a diminution of the secretions of glands, as has been demonstrated by Schütz. This is due to its effects upon the protoplasm of the secreting cells, which probably undergoes the initial stages of coagulation.

It is often stated that tannic acid constricts the vessels of any part to which it is applied, but this is not supported by accurate observations. In acting as a protective to mucous surfaces, it may reduce congestion, but there is no reason to suppose that it acts more directly on the vessel walls, or, in fact, that it ever reaches them in an active form. In the same way it may indirectly lessen the inflammatory exudation from the vessels and the leucocytosis.

When tannic acid comes in contact with blood in a test-tube it precipitates the proteins, and when it is injected intravenously, the precipitate formed leads to the formation of emboli.

The fate of tannic acid in the body has given rise to some discussion. When it is taken internally, a small proportion is sometimes eliminated by the bowel unchanged, but very often none is to be found in the stools; traces are apparently absorbed and excreted in the urine in both man and animals, although some investigators have failed to detect these. But much the greater part of the tannic acid is decomposed in the intestine into gallic acid, some of which often passes out in the stools, some in the urine. Only about 1 per cent of the tannic acid swallowed reappears in the excretions, either as tannic or gallic acid; the rest apparently undergoes complete oxidation, for no further trace of it can be found. After tannic acid is administered, some tannic or gallic salt is present in the blood, for iron salts give a darker color to it, but it is impossible to state whether this is tannin or a gallate, although in all probability it is the latter. According to Harnack, the gallic acid in the urine sometimes forms pyrogallol on standing, but this poisonous substance is not formed from tannic acid in the intestine or tissues.

Tannic acid then does not exist in the tissues as such, but only in the form of traces of the gallate or tannate of sodium, which are so small as to be devoid of astringent properties. The effects of tannic acid are therefore limited to the point of application, and it exercises no action after absorption. The alkaline tannates are generally believed to be entirely devoid of astringent effects, but the tannic acid is freed to some extent by such feeble acids as carbonic acid, so that the astringent action is present in the intestine.

Gallic acid given by the mouth is absorbed and is excreted by the kidneys to some extent. Much of it disappears in the tissues, however, apparently by oxidation. Gallic acid has no astringent properties and is quite useless in therapeutics.

The numerous preparations of the pharmacopœias which owe their activity to their containing tannic acid, differ from the pure drug in that the acid is only slowly dissolved out from the colloid mass, and therefore acts less on the stomach and affects a greater length of intestine.

Therapeutic Uses.—The preparations of tannic acid ought to be used for their local effects exclusively. They are applied externally in cases of excessive secretion, as in local sweating or weeping ulcers, and occasionally to harden the skin. For this purpose tannic acid may be used in solution in water, or in the form of the glycerite or ointment, or some other fluid preparation may be preferred. A similar use is made of the metallic astringents, lead, zinc, and alum salts. Tannic acid is used as a mouth wash in cases of swollen gums, or relaxed throat, and may here be prescribed in a flavored solution or in the form of lozenges, of which the pharmacopœia offers a choice. In certain forms of diarrhœa the astringent action of tannic acid is of considerable value, and occasionally when such drugs as cod-liver oil cause diarrhœa, tannic acid prevents this action without hindering their general effects. The pure drug is seldom used in these cases, as it is liable to derange

the stomach and to form compounds with the albumins before it reaches the bowel, and catechu, krameria or kino may be prescribed, either in the form of pills or in fluid preparations. An old preparation was the compound kino powder, which combined the astringent action of tannin with the specific action of opium on the intestine. Recently the preparations mentioned above have been largely replaced by some of the newer synthetic compounds such as acetyltannic acid or the tannate of albumin. In these and similar compounds the tannic acid is in a relatively firm combination with the rest of the molecule. Accordingly it is not freed in the stomach, the compound having to pass into the intestine before it is broken up, releasing the tannic acid. Tannic acid stops hæmorrhage by precipitating the proteins when it comes into immediate contact with the bleeding point, but it is not of so much value for this purpose as epinephrine or some of the metallic astringents. When the bleeding point can be reached directly, the pure acid is used, but for hæmorrhage of the intestine or stomach one of the extracts is preferred. Large enemata containing tannic acid have been advised in cholera, dysentery, and similar conditions. During the past decade tannic acid has been extensively used in the treatment of burns, and has now been generally adopted as the treatment of choice. The details of the method differ in different hands, but the general procedure is as follows. It is usual to give a preliminary injection of morphine to lessen pain and shock due to the burn. If the burn is extensive, the patient is given an anæsthetic, preferably gas and oxygen and the burnt area is cleaned and loose epithelium removed. A solution of tannic acid is then applied. This may be done by means of a spray of a 2 to 5 per cent solution which may be sprayed on the burnt area every hour for twelve to twenty-four hours. Quick drying of the solution is ensured by the aid of an electric drier or lamps. If the surface is well coagulated and dry at the end of twenty-four hours, no further local treatment may be necessary for several days, during which time the surface is, if possible, exposed to the air. The surface remains hard and dry and in uncomplicated cases the coagulum is allowed to separate itself when the new epithelium will have grown beneath it. Instead of as a spray, tannic acid may be applied in gauze soaked in the solution, or a solution may be painted on by a camel-hair brush.

The advantages of this method are that it is rapidly analgesic; pain, discomfort and frequent dressings are avoided and, in superficial burns, sepsis is usually absent and healing is rapid. In addition to these local effects, the acute toxæmia accompanying burns is lessened. Probably there are several reasons for this. It has been supposed that the coagulation of the surface proteins lessens the absorption of toxic substances, including histamine which may be partly responsible for the general symptoms. Others believe that the primary shock is largely due to the escape of fluid from the burnt area. The blood becomes concentrated and there is loss of fluid and of chlorides. The coagulation of the surface by tannic acid lessens the loss of fluid. To replace this loss an important part of the constitutional treatment is the administration of fluids, *e. g.*, a 5 per cent solution of glucose in normal saline intravenously.

Tannic acid is not itself a direct antiseptic unless perhaps the strength is at least 10 per cent, and in deep burns, sepsis may occur under or at the edge of the coagulum. To lessen or prevent this various additional antiseptics have been recommended, *e. g.*, 1 in 10,000 bichloride of mercury or 1 in 1000 acriflavine, or 1 in 100 gentian violet.

It seems undoubted that this routine treatment has resulted in a great diminution of mortality from burns. Picric acid (p. 786) has also been used but seems less satisfactory, apart from the risk of poisoning from its application to extensive raw surfaces.

In cases of poisoning with metals and alkaloids, tannic acid is often used to cause their precipitation in the stomach, but the tannate formed must be removed at once, as it is gradually dissolved in the digestive fluids. The administration of tannic acid is therefore only a temporary expedient to allow of active measures being taken to empty the stomach.

Some individuals are peculiarly susceptible to the action of tannic acid, which induces local irritation and inflammation wherever it is applied in these cases.

PREPARATIONS.

U. S. P.

ACIDIUM TANNICUM, 0.5 G. (8 grs.).
GLYCERITUM ACIDI TANNICI, 20 per cent tannic acid; 2.5 cc. (40 mins.).
UNGUENTUM ACIDI TANNICI contains 20 per cent tannic acid.
KINO, 0.5 G. (8 grs.).
TINCTURA KINO, 4 cc. (1 fl. dr.).
ACIDUM ACETYLTANNICUM, 0.6 G. (10 grs.).
ALBUMINI TANNAS, 2 G. (30 grs.).

B. P.

ACIDUM TANNICUM, 0.3–0.6 G. (5–10 grs.).
GLYCERINUM ACIDI TANNICI, glycerite of Boroglycerin, 30 per cent boric acid in glycerin. 0.6–2 mils. (10–30 mins.).
SUPPOSITORIUM ACIDI TANNICI, each suppository contains 3 grs. of boric acid.
TROCHISCUS ACIDI TANNICI, each lozenge contains $\frac{1}{2}$ gr. tannic acid.
UNGUENTUM ACIDI TANNICI, 20 per cent tannic acid.
CATECHU, Gambir, 0.3–1 G. (5–15 grs.).
TINCTURA CATECHU, 2–4 mils. (30–60 mins.).
KRAMERIA, 0.6–2 G. (10–30 grs.).
EXTRACTUM KRAMERIÆ SICCUM, 0.3–1 G. (5–15 grs.).
TROCHISCUS KRAMERIÆ, each lozenge contains 1 gr. of Krameria extract.
TROCHISCUS KRAMERIÆ ET COCAINÆ, each lozenge contains 1 gr. of extract of Krameria and $\frac{1}{20}$ gr. of cocaine hydrochloride.
TINCTURA KRAMERIÆ, 2–4 mils. (30–60 mins.).

Other astringent drugs of this series, which offer no advantages over those already given are: Witchhazel (HAMAMELIS), the leaves and bark of Hamamelis Virginiana; Logwood (HÆMATOXYLON), the wood of Hæmatoxylon campechianum; Eucalyptus gum (KINO EUCALYPTI), obtained from several species of Eucalyptus; Nut-gall (GALLA) an excrescence on one of the oaks caused by the punctures and ova of an insect, Cynips Gallæ tinctoria. These are still contained in some pharmacopœias, but promise to follow a large number of similar bodies which have been discarded.

Several preparations of tannic acid have been introduced into therapeutics of late years, chiefly for use as intestinal astringents. Tannic acid itself is liable to produce irritation of the stomach, and to be decomposed or ab-

sorbed to a large extent before it reaches the large intestine, and although the cruder preparations are less liable to these changes, even they are by no means devoid of disagreeable features. Meyer therefore, introduced TANNIGEN, ACIDUM ACETYLTANNICUM (U. S. P.), or diacetyltannin, which is relatively insoluble in water but appears to be dissolved in the intestine and there to act like tannic acid. TANNOFORM and TANNOPIN are similar compounds. TANNALBIN, ALBUMINI TANNAS (U. S. P.) 2 G. (30 grs.) is a combination of tannic acid and albumin, dried at such a temperature as largely to prevent the action of the gastric juice upon it, but being capable of being broken up by the more powerful pancreatic fluid. It is almost entirely insoluble and is not astringent until digested in the bowel, so that it has no irritant action on the stomach and is tasteless. TANNOCOL is a combination of tannic acid and gelatin, resembling tannalbin in most respects. The dose of these artificial compounds is 0.5–2 G. (10–30 grs.) in powder.

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1. Charcoal.

Charcoal, like spongy platinum and other porous bodies, possesses the property of adsorbing gases in its interstices and thus ordinarily contains considerable quantities of oxygen. When brought into contact with decomposing matter, the oxygen is released and hastens the oxidation of the putrefying mass, while the gases arising from the bacterial action are adsorbed by the charcoal, which thus acts as a deodorant. It has no direct action on the microbes of putrefaction, but may by introducing oxygen favor the development of the aerobic organisms at the expense of the anaerobic. Besides gases, charcoal also adsorbs many organic bodies, such as the coloring matter of plants, proteins and alkaloids.

Different samples of wood charcoal vary in their power of adsorption, those prepared from hard woods being generally more efficient.

Charcoal has no appreciable effect on the economy, apart from its lessening the eructations of gas and the flatulence in some cases. It passes through the stomach and intestine unabsorbed, and may in rare cases cause some mechanical irritation and increased movement.

Carbo Activatus (U. S. P.), the residue from the destructive distillation of various organic materials, treated to increase its adsorptive power. Dose, 1 G. (15 grs.).

Charcoal is used internally to remove the gases in flatulence and dyspepsia, and is prescribed in powder or in the form of charcoal lozenges. It may be given in any quantity, but is most commonly prescribed in 4–8 G. (60–120 grs.) doses. It has been advocated in poisoning with alkaloids and other vegetable poisons to take these up in the stomach and delay their absorption into the blood. It is employed externally as a deodorant in cases of foul ulcers, cancerous sores, or malodorous secretions from any source; for this purpose it is added to poultices or used dry in bags of fine cloth.

VII. PURGATIVES.

Purgatives are drugs which are employed in medicine to evacuate the bowel of its contents. Many drugs produce evacuation in the course of their action, but have other effects of importance and are not included in this class; for example the skin irritants if taken by the mouth may cause diarrhœa, but this is accompanied by irritation of the mouth, throat and stomach, and these preclude their use as purgatives. The ideal purgative is devoid of any effects whatsoever, save in the intestine; it passes through the stomach without materially deranging its function, and is not absorbed, or at any rate has no significant action after absorption. The vegetable purgatives act through their irritant properties, which in some instances are elicited only by the action of the secretion of the intestines and of the neighboring glands. Thus some of the purgatives pass through the stomach in the form of bland, non-irritant compounds (castor oil), which are broken up by the digestive processes in the intestine, while others perhaps owe their activity in the intestine to their solution or suspension in the juices.

Many classifications of the purgatives have been based on their effects, and some of the terms are still retained, such as *aperient, eccoprotic, laxative, purgative, cholagogue, hydragogue, cathartic, or drastic.* But the effect of the purgatives is determined largely by the dose and by the condition of the intestine, so that a small dose may act as an aperient, laxative or eccoprotic, while a larger quantity of the same drug, or even the same dose in a more susceptible individual, may act as a drastic or hydrogogue cathartic. They are therefore classified in three groups: (1) the mild aperients, castor oil group; (2) the purgatives of the anthracene series; (3) the jalap and colocynth group.

Symptoms.—In moderate doses the purgatives simply hasten the normal movements of the intestines, and the stool is of the ordinary appearance and consistency (laxative, aperient, or eccoprotic action). In larger quantities they cause a more profuse evacuation than normally, and the stools, which are repeated at short intervals, are of a looser, more fluid consistency. Their action may be accompanied by considerable pain and colic, and the hurried movements of the intestine are shown by the characteristic gurgling sounds. Large quantities of the more powerful purgatives may cause all the symptoms of acute enteritis, the stools at first contain the ordinary fæcal substances accompanied by more fluid than usual, but later consist largely of blood-stained mucous fluid with little or no resemblance to ordinary fæces. This violent purgation, which is not induced in therapeutics, is accompanied by pain and tenderness in the abdomen, and may induce shock, collapse, and eventually death.

Action.—The peristaltic movements of the intestine which move the contents along the canal, arise from a complicated local reflex, which is aroused by the pressure of the contents on the sensory apparatus of the mucous membrane. This reflex may be increased (1) by anything that induces irritation of the mucous surface and thus renders it more sensitive to the pressure of the contents, and (2) by increasing the bulk of

the contents until they exert more pressure on the mucous surface. The accelerated peristalsis after the vegetable and mercurial purgatives is due to their irritating the mucous membrane, while the purgation of the saline cathartics arises from their increasing the bulk and dilution of the contents. In neither case is there any reason to suppose that the neuro-muscular apparatus of the bowel is directly affected by the drugs; nor is the central nervous system implicated in the reflex whether normal or exaggerated by the purgatives.

In small quantities, such as are used in the vast majority of cases in therapeutics, the irritation produced by the vegetable purgatives is apparently only enough to accelerate peristalsis, and the fluid of the stools is drawn partly from the food and partly from the ordinary secretions of the digestive organs. In these cases the intestine is not actually inflamed, although some congestion may occur in it, as in all organs in a state of abnormal activity. On the other hand, when large quantities are ingested a true inflammation of the intestine occurs, manifested by increased movement, congestion, exudation of fluid into the lumen of the bowel, and pain. In these cases the intestine presents the usual signs of inflammation; it is red and congested, and contains a muco-purulent fluid and often blood. The origin of the fluid of the stools thus varies with the dose of purgative used; if it be small, the fluid is not an exudate, if it be large the fluid is partly an inflammatory product. The stools following the administration of purgatives differ from the normal fæces in containing a larger proportion of water and also of soluble substances. In fact, they resemble rather the contents of the small intestine than the normal excreta, and contain bodies which would normally have been absorbed and utilized, but which have been hurried through the bowel too rapidly to permit of their being taken up by the epithelium.

The colic produced by purgatives is not due to the inflammation of the intestinal wall, but is explained by the more vigorous contractions of the walls of the bowel and the compression of the mucous membrane between the muscle and hard fæcal masses in the large intestine. The tenderness produced by large quantities of the purgatives, on the other hand, would seem to indicate inflammation.

The different purgatives seem to act on different parts of the bowel (Magnus). Thus senna, and in all probability the other anthracene purgatives, appear to have no effect on the movements of the stomach and small intestine, but act only in the large intestine; the contents reach the colon at the normal rate, but as soon as they have left the small bowel, rapid movement begins and they are evacuated almost immediately. Castor oil on the other hand accelerates the peristalsis of the small intestine, through which the food passes very rapidly, while the large gut is much less irritated. Colocynth quickens the movement of both small and large intestine and considerable quantities of fluid are effused into the lumen. All three arrest the antiperistaltic movements in the large intestine.

Some of the purgatives cause evacuation of the bowel when they are injected subcutaneously or intravenously (senna, aloes, cascara, colcynth, podophyllum),

and croton oil has long been rubbed on the skin in order to relieve constipation, and is found to cause intestinal inflammation and purging when injected intravenously. It has accordingly been suggested that these have a specific action on the bowel quite apart from their irritant effects; but it is probable that their intestinal effects are here due to their excretion into the bowel, which has been shown to occur in several instances. Other irritants applied subcutaneously or intravenously often produce similar effects on the alimentary canal.

The interval which elapses between the administration of a purgative and its effects varies with the dose, and also with the individual drug. In ordinary therapeutic doses, evacuation of the bowels occurs in most cases in five to ten hours, but if large quantities of the more powerful purges, such as jalap or croton oil, be given, the effects may be elicited in two hours. Aloes, cascara and podophyllum differ from the others in the length of the interval, catharsis rarely or never occurring earlier than ten to twelve hours after their administration, and often only after twenty to twenty-four hours.

The movement of the intestine induced by purgatives is accompanied by an increase in the leucocytes of the blood similar to that observed in other forms of intestinal activity, *e. g.*, during digestion.

The effects of the purgatives vary greatly in different animals. Thus, the rabbit is very refractory to most of the series, and often is killed by intestinal irritation without any evacuation being produced. The, frog is unaffected by quantities which would produce poisoning in man, while the dog and cat respond much more readily.

It was formerly supposed that purgatives increased the secretion of bile, and certain of them, which were believed to have a special activity in this direction, were known as *Cholagogues*. It has been shown of recent years that none of them possesses any action on the secretion of bile, although they may increase its excretion by hurrying it through the intestine and preventing its reabsorption. On the other hand, the presence of bile in the intestine is a condition necessary to the activity of many of the purgatives. Thus Buchheim and Stadelmann found that in the absence of bile podophyllum, jalap, scammony, rhubarb, and gamboge are either quite inactive or very much less powerful than usual. This is probably due to some solvent action of the bile, for Stadelmann found that when soaps were given with some of these drugs their activity returned, and in other cases a comparatively slight modification of their chemical form was sufficient to restore their activity, even in the absence of either bile or soap. Analogous results have been observed from causes other than the absence of bile; thus some of the pure principles of the purgatives are much less active than the crude drugs because the impurities of the latter alter their solubility. This alteration of the solubility may act in two ways: if the principle is rendered too soluble, it may be absorbed in the stomach and upper part of the bowel, and therefore fail to produce purgation; on the other hand, it may be rendered so insoluble that it fails to come into intimate contact with the bowel wall, and therefore does not irritate it. The effect of such colloid substances as the bile and gums is to delay the absorption of soluble substances in the upper part of the bowel and at the same time to keep the insoluble resins in suspension.

Few of the purgatives have any appreciable action after absorption, but general effects may be produced indirectly from their intestinal action. It is probable that reflexes are elicited by irritation of the bowel analogous to those discussed under skin irritants, but in addition, the congestion of the bowel produced by its activity must alter considerably the distribution of the blood in the body. The belief in the efficacy of a purge in congestion of the brain may thus be based on a true "revulsive" action; for the dilatation of the intestinal vessels must necessarily lower the blood-pressure and thereby lessen the blood supply to the brain. The congestion of the lower intestine is accompanied by a similar condition in the other pelvic organs, and those purgatives that act strongly on the large bowel, therefore often cause congestion of the uterus, with excessive menstrual flow, or, more rarely, in the case of pregnant women, abortion. Lastly, a certain amount of fluid is withdrawn which would otherwise be excreted by the urine, which is found to be proportionately diminished in amount.

1. Mild Aperients, the Castor Oil Group.

Castor Oil (Oleum Ricini) resembles olive oil in most respects, but on saponification forms ricinoleic acid instead of oleic acid. This acid ($C_{17}H_{32}(OH)COOH$) differs from the fatty acids obtained from ordinary oils in being unsaturated and in containing a hydroxyl group. Castor oil is itself a bland, non-irritating fluid, but on passing into the intestine is saponified by the pancreatic juice, and the ricinoleates thus formed are irritant and cause purgation. When the oil is saponified and the free acid given by the mouth, the effects are quite different from those of the oil, for the taste is acrid and unpleasant, and discomfort, nausea and vomiting may follow its ingestion from its irritant action on the stomach. The oil, on the other hand, has a bland, if unpleasant, taste, and produces no effects on the stomach. Several other esters of ricinoleic acid have been shown by Meyer to resemble the glycerin ester (castor oil) in their purgative effects.

Castor oil is absorbed from the small intestine and thus does not act on the large intestine directly. In the tissues it disappears in the same way as an ordinary oil. It may be given in very large quantities without producing any symptoms, save those of a mild laxative, which induces evacuation in about six to ten hours. It is occasionally used as an emollient to the skin, and has been employed as a protective or emollient for application to the eye. The harmless nature of castor oil is shown by its use in China as an article of diet.

In the beans from which castor oil is derived, a toxalbumin is found, which was at one time supposed to be the active principle of the oil. (See Ricin.) It has been shown, however, that the oil is entirely free from this poison, and that its action is due solely to the ricinoleate.

OLEUM RICINI, a fixed oil expressed from the seed or bean of Ricinus communis. Dose, U. S. P., 15 cc. (4 fl. drs.); B. P., 4–16 mils. (1–4 fl. drs.).

Castor oil is difficult to take owing to its unpleasant taste. It may be given alone, in an emulsion flavored with sugar and some volatile oil, in orange juice, spirits, or glycerin, or in flexible capsules.

Liquid Paraffin, a mixture of liquid hydrocarbons obtained from petroleum, is often used as a laxative, and, though its method of action is quite different from that of castor oil, it may conveniently be mentioned here. It has an oily consistency and is insoluble in water. It has practically no odor or taste. It is non-irritant, not acted on by the digestive ferments and is not absorbed. It acts mechanically partly by increasing the bulk of the intestinal contents and partly by softening the contents and acting as a lubricant. It has been widely used in intestinal stasis, often with success.

It may pass through the intestinal canal without carrying with it the ordinary contents and in some patients it tends to escape from the anus in small quantities without causing an evacuation of the bowel. Occasionally it seems to retard digestion, probably from its coating food particles and preventing access of digestive ferments.

Petrolatum Liquidum (U. S. P.), dose 15 cc. (4 fl. drs.).

Emulsum Petrolati Liquidi (U. S. P.) contains liquid petrolatum (50 per cent) emulsified with acacia with some syrup and alcohol. 30 cc. (1 fl. oz.).

Paraffinum Liquidum (B. P.), 7.5–30 mils. ($\frac{1}{4}$–1 fl. oz.).

Sulphur (Sulfur, U. S. P.) is in itself an inert body but, while much the greater portion escapes in the stools unchanged when it is swallowed, some of it forms sulphides in the intestine, and these cause irritation, especially in the large bowel, increased peristalsis, and a soft, formed stool; in large quantities it has caused, in some instances, more severe symptoms with bloody evacuations. The sulphides form some hydrogen sulphide, which gives rise to eructation. Some 10 to 40 per cent of the sulphur taken by the mouth is absorbed as sulphide, which is excreted to a small extent by the lungs, giving the characteristic disagreeable odor to the breath, and to a much larger extent by the urine as sulphates and in organic combination. Sulphur may produce a slight diuretic and diaphoretic action which may explain the beneficial effects it sometimes produces in chronic rheumatism.

Applied to the skin in ointment, sulphur appears to be changed in part to sulphide, particularly if some alkali be added; the sulphide is destructive to animal parasites and sulphur ointment has therefore been extensively used in the treatment of scabies. The ointment is rubbed into the skin after a hot bath and scrubbing with soap to open up the burrows of the insect. If applied too frequently it may produce irritation of the skin and a rash, but as a rule a few applications suffice to cure the disease. It may also be of value in skin disease through the sulphides tending to soften and dissolve the horny epidermis. For this purpose it may be associated with salicylic acid.

Preparations.

Sulfur Sublimatum (U. S. P.), Sulphur Sublimatum (B. P.), Flowers of Sulphur, sublimed sulphur, and Sulfur Lotum (U. S. P.), washed Flowers of Sulphur, form fine yellow powders insoluble in water and very slightly soluble in alcohol.

Sulfur Præcipitatum (U. S. P.), Sulphur Præcipitatum (B. P.), Milk of Sulphur, is prepared from sulphide of calcium by precipitation and forms a fine, almost white powder.

Dose of all three preparations, U. S. P., 4 G. (60 grs.); B. P., 20–60 grs.

Unguentum Sulfuris (U. S. P., 15 per cent), Unguentum Sulphuris (B. P., 10 per cent), formed from sublimed sulphur, which is also contained in the Compound Liquorice Powder.

CONFECTIO SULPHURIS (B. P.), 4–8 G. (60–120 grs.).

Crude sublimed sulphur often contains arsenic, but the B. P. preparation is practically free from it. The milk of sulphur is in a finer state of division than the flowers, and is said to be a somewhat more active aperient.

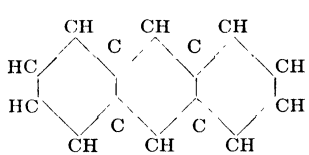
Glycerin.—When glycerin is injected into the rectum, it withdraws fluid from the mucous membrane and thus causes irritation, peristalsis, and evacuation of the bowels; the stool is of almost ordinary consistency, and no pain or colic is felt subsequently, nor does the remedy cause more than one evacuation. Glycerin may be injected into the rectum for this purpose (dose 2–5 cc., ½–1 teaspoonful), but a more convenient form is the glycerin suppositories, **Suppositoria Glycerini**, which are made up with stearic acid and sodium carbonate, U. S. P., with gelatin, B. P. Glycerin suppositories are used in constipation instead of the ordinary aperients. Large doses of glycerin taken internally sometimes cause purgation, but it is not a reliable remedy when administered in this way. Instead of glycerin suppositories, small pieces of soap may be inserted in the rectum, and the same purpose may be served by the injection of a little strong soap solution in water.

Glycerin in large quantities is poisonous, whether it is taken by the mouth or injected hypodermically or intravenously. It is true that no case of glycerin poisoning in man is known, but large doses are fatal to animals in the course of a few hours. The chief symptoms are restlessness, agitation, acceleration of the heart and respiration, general weakness, tremor and convulsions, which finally end in somnolence, coma, and death from failure of the respiration. Glomerulonephritis has also been observed in animals. Glycerin is absorbed rapidly from the intestine, and undergoes combustion in the tissues, only a very small fraction of it reappearing in the urine.

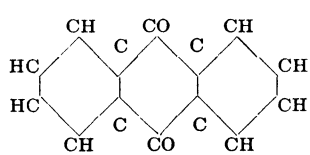
2. The Anthracene Purgatives and Phenolphthalein.

A number of purgatives, *Rhubarb*, *Senna*, *Aloes*, *Cascara* and *Frangula*, owe their activity to the presence of irritant *anthracene* ($C_{14}H_{10}$) compounds. The chemical examination of these drugs is a matter of difficulty, as they often contain several active principles which are very nearly related to each other, and some of which are undoubtedly the products of the decomposition of more complex bodies.

All those which have been completely isolated hitherto have proved to be derivatives of anthraquinone,



Anthracene.



Anthraquinone.

and some of the oxyanthraquinones seem to be widely distributed. Thus all the members of the group contain *Emodins* or trioxymethylanthraquinone, ($C_{14}H_4(CH_3)(OH)_3O_2$), and several of them contain *Chrysophanol* or dioxymethylanthraquinone, ($C_{14}H_5(CH_3)(OH)_2O_2$). In addition, a number of other anthracene bodies occur in these purgatives, some of them combined with sugars to form glucosides, but little is known regarding them and hardly any

of them are definitely established as pure substances. Among the names applied to these bodies are *cathartin* or *cathartic acid*, *frangulin*, *aloin*, but it is to be noted that the bodies designated by these names vary in character and are alternately asserted to be pure principles and composite mixtures by different investigators.

None of the pure principles are as satisfactory in their action as the crude drugs, perhaps because they are less soluble in the intestine. For example, *aloin* is less certain in its effects than aloes, and it seems to be indisputable that the crystalline aloin itself is inactive in the bowel, but is there changed under certain conditions to an amorphous compound which has irritant effects. The presence of bile in the intestine is not necessary to elicit the action of this group, except perhaps in the case of rhubarb.

The absorption of these bodies has not been satisfactorily determined in most cases. The urine is rendered yellow after rhubarb and senna, owing to the absorption and excretion of chrysophanol, but it is questionable whether the more active principles pass into the urine in appreciable amounts. When aloin is injected subcutaneously or intravenously, it is excreted for the main part into the bowel, and there produces irritation and catharsis. The yellow pigment of the urine after rhubarb and senna becomes a purple red on the addition of alkalies; the milk and skin also are said to assume a yellowish tinge from the presence of chrysophanol.

In the rabbit aloin seldom causes purgation, and is excreted by the kidney in considerable quantity, especially when injected hypodermically. In passing through this organ it causes marked irritation and epithelial necrosis, which often proves fatal in a few days. No irritation of the kidney occurs in man, the dog, or the cat after aloin. The anthracene purgatives have little action until they reach the large intestine, presumably because they do not find suitable conditions for solution in the small bowel. The interval between their administration and the evacuation of the bowel therefore tends to be longer than under most other purgatives; and for the same reason they tend to cause greater pelvic congestion. Among them aloes is especially slow in action and tends to cause congestion of the uterus.

Straub and Friendl found that the active principles of senna are absorbed when given orally and are also active by parenteral administration. Between administration and action there is a variable latent period during which there is a ferment-splitting of anthranol and an oxidation to anthraquinone which is apparently the active principle. The peristalsis of the large intestine is increased without influence on the pendulum movements.

Rhubarb contains a considerable amount of tannic acid, which acts as an astringent and therefore tends to cause constipation after the evacuation of the bowels. It is not well tolerated in some cases, its administration being followed by nausea, headache and giddiness, more rarely by skin eruptions of different kinds. Senna preparations are generally found to have a greater tendency to produce griping than the other members of this series.

PREPARATIONS.

U. S. P.

RHEUM, rhubarb, the rhizome of Rheum officinale and other species. 1 G. (15 grs.).

EXTRACTUM RHEI, 0.25 G. (4 grs.).

TINCTURA RHEI AROMATICA (contains several volatile oils), 4 cc. (60 mins.).

SYRUPUS RHEI AROMATICUS. Dose, 10 cc. (2½ fl. drs.).

B. P.

RHEUM, rhubarb, the rhizome of Rheum palmatum; 0.2–1 G. (3–15 grs.).

PILULA RHEI COMPOSITA (contains rhubarb, aloes, myrrh, and oil of peppermint), 4–8 grs. (0.2–0.5 G.).

PULVIS RHEI COMPOSITUS (Gregory's Powder) contains rhubarb, light and heavy magnesia and ginger, 10–60 grs. (0.6 G.).

TINCTURA RHEI COMPOSITA, formed from rhubarb, cardamom and coriander, ¼–1 fl. dr. (2–4 mils.).

U. S. P.

SENNA, the leaflets of Cassia acutifolia (Alexandrian senna), and of Cassia angustifolia (Indian senna). 4 G. (1 dr.).

FLUIDEXTRACTUM SENNÆ, 2 cc. (30 mins.).

SYRUPUS SENNÆ, 8 cc. (2 fl. drs.).

Senna is often administered as a simple infusion, senna tea, a teaspoonful of the leaves being used in a cupful of water.

B. P.

SENNÆ FOLIUM, the dried leaflets of Cassia acutifolia (Alexandrian senna), and of Cassia angustifolia (Tinnevelly senna).

CONFECTIO SENNÆ, 4–8 G. (60–120 grs.).

SENNÆ FRUCTUS (Senna Pod), the dried ripe fruit of Cassia acutifolia or angustifolia.

EXTRACTUM SENNÆ LIQUIDUM, 0.6–2 mils. (10–30 mins.).

SYRUPUS SENNÆ, 2–8 mils. (30–120 mins.).

INFUSUM SENNÆ CONCENTRATUM, 2–4 mils (30–60 mins.).

INFUSUM SENNÆ RECENS, 15–60 mils. (½–2 fl. oz.).

MISTURA SENNÆ COMPOSITA (Black Draught), formed from magnesium sulphate, liquorice, compound tincture of cardamom, aromatic spirit of ammonia, and infusion of senna, 1-2 fl. oz. (30–60 mils.).

U. S. P.

ALOE, the inspissated juice of the leaves of several species of aloe.

ALOINUM, a pentoside or pentosides obtained from aloes, 0.015 G. (¼ gr.).

PILULÆ ALOES, 2 pills.

Aloes is also contained in compound rhubarb pill, compound extract of colocynth, and compound tincture of benzoin.

B. P.

ALOE, the dried juice of Aloe chinensis and other species, 2–5 grs. (0.1–0.3 G.).

PILULA ALOES, 4–8 grs. (0.2–0.4 G.).

PILULA ALOES ET FERRI, 4–8 grs. (0.2–0.4 G.).

PILULA ALOES ET ASAFŒTIDÆ, 4–8 grs. (0.2–0.4 G.).

Aloes is also contained in the compound extract of colocynth, pill of colocynth and hyoscyamus, compound tincture of benzoin and compound rhubarb pill.

U. S. P.

CASCARA SAGRADA, the bark of Rhamnus Purshiana.

EXTRACTUM CASCARÆ SAGRADÆ, 0.25 G. (4 grs.).

FLUIDEXTRACTUM CASCARÆ SAGRADÆ AROMATICUM, 2 cc. (30 mins.).

FLUIDEXTRACTUM CASCARÆ SAGRADÆ, 1 cc. (15 mins.).

B. P.

CASCARA SAGRADA, the dried bark of Rhamnus Purshiana.
EXTRACTUM CASCARÆ SAGRADÆ SICCUM, 2–8 grs. (0.1–0.5 G.).
EXTRACTUM CASCARÆ SAGRADÆ LIQUIDUM, ½–1 fl. dr. (2–4 mils.).
ELIXIR CASCARÆ SAGRADÆ, 2–4 mils. (30–60 mins.).

Two synthetic compounds of oxyanthraquinone have been introduced under the name of *purgatin* and *exodin*, but have no advantages over the natural purgatives and the possibility of their inducing nephritis renders their use inadvisable.

Of these numerous preparations, the most extensively prescribed are the pills. The fluid preparations have an unpleasant, bitter taste, and are therefore less used, unless when disguised by the addition of sugar or volatile oils. The syrups of rhubarb and senna are often administered to children, and the confection of senna and the compound liquorice powder are also pleasant, easily taken preparations. The compound infusion or mixture of senna and the compound rhubarb powder are old and tried preparations, in which the virtues of the vegetable purgative are combined with those of a saline cathartic and antacid respectively; they are both possessed of a harsh, unpleasant taste. Cascara sagrada is a very popular remedy in habitual constipation, for which it is best given in small repeated doses, which can be gradually reduced as the condition of the bowel improves.

Phenolphthalein, $C_6H_4<\begin{matrix}C(C_6H_4OH)_2\\CO\end{matrix}>O$, a synthetic substance, has been used of late years as a mild aperient. It is very insoluble in water and is not irritant when applied to the ordinary mucous membranes. In the bowel it is dissolved by the bile and alkali and develops a mild irritant action in the small intestine and still more in the large intestine. Most of the phenolphthalein administered by the mouth is not absorbed but appears in the stools. A small amount undergoes absorption and is excreted by the kidney; if the urine is alkaline it is colored a brilliant pink. Phenolphthalein is practically not poisonous when injected intravenously in animals. It has a mild laxative effect when injected subcutaneously, and this arises from its being excreted into the bile and thus carried to the gut. In the large intestine it is reabsorbed into the blood and again carried to the liver and returned to the gut. It therefore acts for several days as a mild aperient, but as it is gradually eliminated in the urine and stools, the action passes off. The administration of phenolphthalein has led in many instances to the appearance of a peculiar eruption of the skin which in most cases consists of numerous polychromatic macular plaques of various sizes from a pin-head to several inches in diameter. The plaques may vary in color from a pink to a dark purple. The lesion is chronic and may last for months or even years, and when fading occurs a protracted pigmentation of the areas usually results. After the acute eruption has disappeared, relapses are common, especially if phenolphthalein be taken again, and the new lesions usually reappear on the site of the original eruption. The mucous membranes are also not infrequently involved. Tetrachlorphenol-

phthalein acts in the same way as phenolphthalein but is excreted only by the bile when injected subcutaneously and thus acts for a longer time.

PHENOLPHTHALEINUM (U. S. P., B. P.), a crystalline powder, white or grayish-white, soluble in 600 parts of water or in 10 parts alcohol. The solution turns red when alkali is added. Dose (U. S. P.), 0.15 G. ($2\frac{1}{2}$ grs.); (B. P.) 0.06–0.3 G. (1–5 grs.) in powder, pills, or capsules. It has been injected hypodermically in solution in olive oil.

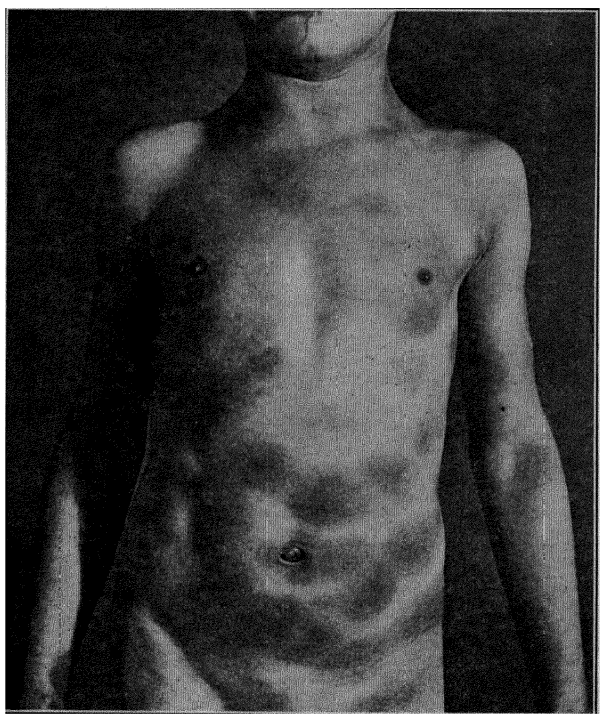


FIG. 8.—Typical phenolphthalein eruption.

3. The Jalap and Colocynth Group.

The third group of the vegetable purgatives comprises a number of resinous glucosides and acids, whose more intimate chemical structure is unknown, though a number of them appear to be nearly related chemically, so that it is possible that they all contain a common radicle like the members of the anthracene group.

Jalap resin contains two anhydride glucosides, *Convolvulin* and *Jalapin*, the latter only in very small quantity. Scammony consists very largely of *Jalapin*. Podophyllum contains two isomeric principles, *Podophyllotoxin* and *Picropodophyllin*. *Colocynthin* is a glucoside occurring in the colocynth fruit, and forms *Colocynthein* and sugar when treated with acids; colocynthein is said to be even more irritant than colocynthin.

Action.— These substances are in general much more powerful than any of the other purgatives, and are therefore classed together as the drastic purgatives or hydragogue cathartics. In small quantities they cause evacuation more rapidly than the anthracene purgatives, and in somewhat larger doses produce profuse watery stools with much pain and often tenesmus. In cases of poisoning, the bowel undergoes acute inflammation, and blood is passed in the stools, which often contain shreds of epithelium from the walls. The irritant action apparently is not confined to the bowel, for their administration is sometimes followed by uneasiness in the stomach, and occasionally by nausea and vomiting. On the other hand, moderate quantities are said not to induce colic so frequently as some of the anthracene purges. This is probably due to the fact that they accelerate the movement of both the small and large bowel; a quantity of unabsorbed fluid is thus poured into the cæcum and the contents are rendered softer and more easily moved than if these drugs, like the anthracene group, acted only on the large intestine. In the cat, jalap resin quickens the peristaltic movements of the small intestine, while on the colon it has rather a constipating effect, possibly due to an increase of the antiperistaltic movements of the proximal colon (Bloch).

Several of these resinous purges are irritant to the skin and especially to the mucous membranes of the eye, nose, and throat. The presence of bile in the intestine increases the purgative action of almost all these bodies, and in fact, seems essential for the action of most of them.

Podophyllotoxin and colocynthin cause purgation when injected subcutaneously; this is probably owing to their excretion into the bowel, as the former has been detected in the fæces after this method of administration. Podophyllotoxin causes glomerular nephritis and hæmorrhages into various organs when administered hypodermically or intravenously in large quantities, and when added to blood in a test-tube, it causes the formation of methæmoglobin in the corpuscles. It has been said to have a depressant action on the central nervous system, but this is probably a result of the shock and hæmorrhage produced by its intestinal action. Colocynthin is said to cause renal inflammation when applied subcutaneously or taken internally, and even when the powder is inhaled during its manufacture. Jalapin and convolvulin given by the mouth are found in the fæces in a partially decomposed state; none appears in the urine.

Preparations.

Colocynthis (B. P.), colocynth, the pulp of the fruit of Citrullus colocynthis deprived of its rind.

Extractum Colocynthidis Compositum (B. P.) (containing colocynth, aloes, scammony and cardamom), 0.25 G. (4 grs.).

Pilula Colocynthidis et Hyoscyami (B. P.) (colocynth, aloes, scammony, resin, oil of cloves, and extract of hyoscyamus), 0.25–0.5 G. (4–8 grs.).

Podophyllum (U. S. P.), the rhizome and roots of Podophyllum peltatum, May apple. 0.12–0.6 G. (2–10 grs.).

Resina Podophylli (U. S. P., B. P.), 0.01 G. ($\frac{1}{6}$ gr.); B. P., $\frac{1}{4}$–1 gr.

Podophyllin varies considerably in composition, and ought to be avoided.

Jalapa (B. P.), the tuberous root of Ipomœa Purga. 0.3–1 G. (5–15 grs.).

Pulvis Jalapæ Compositus (B. P.), contains jalap and bitartrate of potassium. 2 G. (30 grs.); 10–60 grs.

Ipomœa (B. P.), the dried root of Ipomœa orizabenzis, Mexican scammony root, Orizaba jalap root. 0.3–1.2 G. (5–20 grs.).

Scammoniæ Resina (B. P.), a mixture of resins obtained from Ipomœa. 0.03–0.2 G. ($\frac{1}{2}$–3 grs.).

Scammony resin is contained in the compound colocynth preparations.

The resinous purgatives are generally administered in pill form; very frequently two or more are combined in one pill, or they may be prescribed along with extract of belladonna or hyoscyamus, or with a drop of some carminative oil to prevent the pain and griping which often accompanies their action. The importance of these purgatives is much less than it was formerly, and several of them are very seldom used; the most important are colocynth, podophyllum, and jalap. In large doses they act rapidly, with the exception of podophyllum, which induces purgation very slowly (ten to twenty hours).

Therapeutic Uses of the Purgatives.—The purgatives are employed to cause evacuation of the bowel when for any reason its peristalsis is slow. In the choice of a purgative, the advantages of the vegetable purgatives must be weighed against those of the saline cathartics and of the mercurial preparations. In ordinary *constipation of short standing*, in which the peristalsis may merely seem somewhat more sluggish than usual, the milder laxatives are prescribed—castor oil, sulphur, senna, rhubarb, aloes, frangula, or cascara sagrada. The first two cause least disturbance of the bowel, but are disagreeable to take, and are less commonly prescribed for adults than rhubarb or cascara, or small doses of colocynth or podophyllum. In children or in debility in adults, senna and castor oil are frequently used; sulphur is often given along with magnesia in constipation in children, and in hæmorrhoids, in which it is often beneficial, not owing to any specific action on the hæmorrhoids but because it renders the stools softer and less liable to cause irritation mechanically.

In *chronic constipation* which cannot be controlled by hygienic measures, or by the use of a special dietary such as fruits or coarse foods, and where the intestine has apparently taken on a sluggish habit cascara, rhubarb, aloes, phenolphthalein, or colocynth may be ordered, but the saline cathartics often prove more satisfactory. Rhubarb tends to cause some constipation after its laxative effects, but is often used in these cases, as it possesses some bitter stomachic action, which compensates for its astringent after-effects. In obstinate constipation, in which the bowel contains hard fæcal masses, the milder purgatives often provoke griping without relieving the condition, and in these cases larger doses of colocynth, jalap, podophyllum, or croton oil are sometimes used, along with some of the extracts of the atropine group or with a carminative oil. They may be prescribed along with some of the saline cathartics, as in the compound infusion of senna or the compound powder of jalap. An enema may with advantage be given previously.

In some forms of *diarrhœa* constant irritation seems to be kept up by the presence of irritants in the bowel, and the indications are the removal of these by a purge rather than the administration of astringents. Castor oil is especially adapted for this purpose.

A purgative is often administered as a preliminary in the treatment of malaria, syphilis and other conditions, and seems to have beneficial effects, although these are difficult to explain. In the beginning of *acute fevers* also, a purge is often useful, perhaps through the conges-

tion of the bowel withdrawing the blood from the rest of the body, or through the removal of poisonous substances formed by the decomposition of the intestinal contents. In *congestion of the brain* and in high blood-pressure a purgative is often administered with good effects, which may also be attributed to the accumulation of blood in the mesenteric circulation, to the actually lessened bulk of the blood, and perhaps to some action analogous to counter-irritation of the skin. For these purposes a sharp purge is generally used, such as one of the jalap and colocynth series.

The more powerful purgatives were formerly largely used to remove fluid from the body in cases of *dropsy* or œdema, and they were generally prescribed along with the saline cathartics for this purpose. Other means, such as diuretics, are generally preferred now from a fear that the violent purging may weaken the patient, but good results are often obtained by means of this treatment, especially as a preliminary to the use of digitalis.

The congestion of the pelvic organs attending the purgative action of aloes has led to its use in amenorrhœa; it is generally administered along with iron which improves the condition of the blood.

The purges act as *intestinal disinfectants* by removing the microorganisms mechanically, though the vegetable purges are less used for this purpose than calomel or salines. A purgative is administered to remove poisons in the intestine when they have passed beyond the stomach or when they are excreted into the bowel.

Special mention must be made of *postoperative atony* of the intestine. In this condition the most effective remedies are physostigmine, pituitary, or one of the choline esters.

Purgatives are *contra-indicated* in conditions of acute intestinal irritation and intestinal obstruction. These should be given with care during menstruation and pregnancy, owing to the congestion of the pelvic organs, which may lead to an excessive flow in the one case and to abortion in the other; aloes is especially dangerous in these conditions. In collapse, asthenia and anæmia, powerful purgatives are contra-indicated, owing to the irritation they produce. In hæmorrhoids, aloes is often said to do harm by increasing the congestion of the rectum, and powerful purges are injurious from the straining they cause, but if constipation is present, a mild purgative is beneficial.

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4. Saline Cathartics.

Dilute solutions of such salts as the chlorides, iodides, and bromides of the alkalies are absorbed rapidly from the alimentary canal, but some of the other salts of these metals apparently permeate the epithelium with greater difficulty, and their solutions therefore remain unabsorbed for a longer time in the intestine. The contents of the intestine and the stools thus contain more fluid than usual and these salts are known as the saline cathartics. The chief salts of sodium and potassium which have this intestinal action are the sulfates, phosphates, tartrates and citrates; less known ones are the malates and ferrocyanides.

In these effects the acid constituent, or anion, is obviously the chief factor, for the same base, or cation, is present in readily absorbed salts such as the chlorides. And no pronounced differences between the action of chlorides and sulfates are observed, unless the salt can be given in large quantities, as is possible in the case of the salts of the alkalies. The effects of the sulfate and hydrochloride of morphine, for example, may be taken as identical, because the anion is present in so small amount as to be practically inert.

The cation of a salt may also fail to be taken up readily by the bowel; for example, magnesium chloride is absorbed slowly although other chlorides permeate rapidly, and magnesium salts thus act as purgatives in the same way as sulfates. When both ions are slowly absorbed,

as in the case of magnesium sulfate, the cathartic action is naturally more powerful than when only one has this character.

The chief saline cathartics used in therapeutics are the *sulfate of sodium* (Glauber's salt), the *sulfate of magnesium* (Epsom salt), the *double tartrate of sodium and potassium* (Rochelle salt) and the *phosphate of sodium.* In addition the *oxide* and *carbonate of magnesium* have some purgative action from being formed into soluble salts in the stomach and intestine.

Symptoms.—Most of the cathartics have a harsh, bitter, unpleasant taste, and when taken in concentrated solution, may induce some nausea, partly from the taste, and partly from the "salt-action" on the stomach, which they possess like other soluble bodies. Dilute solutions, however, provoke no such symptoms, but after one or two hours induce a profuse watery evacuation of the bowels. This is sometimes preceded by some pain and griping, but these are not nearly so frequent or so severe as after the vegetable purgatives. Not infrequently the urine is increased in amount afterward, or it may be found to have an unusually high percentage of salts. If a moderate quantity of a dilute solution be given, only one evacuation follows, but large doses of concentrated solutions induce repeated stools, which at first contain some fæcal matter, but later consist mainly of bile-stained mucous fluid.

Action: Intestine.—The saline cathartics differ from the vegetable purgatives in not inducing irritation of the intestine, unless when they are given in very large quantities. The characteristic effect is not irritation, but retarded absorption. The slow absorption of the salt entails the slow absorption of the fluid in which it is dissolved, for the salt holds on to the water and only permits of its being taken up by the bowel if an equivalent amount of salt is also absorbed. If a solution of sodium chloride isotonic with the blood serum be administered by the mouth to a dog with a cæcal fistula, little or none of it reaches the wound, as it is all absorbed in the stomach and small intestine. If, on the other hand, an equal amount of an isotonic solution of sodium sulfate be administered in the same way, most of the solution escapes by the fistula, only some 10–20 per cent having been absorbed by the stomach and small intestine. In a normal dog or in the human subject, a much larger amount of fluid therefore reaches the large intestine if sodium sulfate be dissolved in it than if sodium chloride be used instead. The contents of the large intestine are consequently more fluid than usual, and are passed down more easily toward the rectum. At the same time the weight and distention of the bowel induces increased peristalsis and the whole is evacuated. This increased peristalsis is due, however, not to any irritant action such as has been found to be induced by rhubarb or croton oil, but to the large amount of fluid contents, which arouses the usual peristaltic reflex.

This accelerated passage along the bowel has been observed in man by means of the rœntgen-rays, and appears to resemble that previously described in animals. When the distended small intestine empties its contents into the colon, the large bowel adopts a more rapid but otherwise normal movement and this leads to the evacuation of the rectum;

the first stool may thus be of almost normal consistency, but this is generally followed by a profuse watery movement which may contain the greater part of the salt administered.

If a weaker solution of sodium sulfate is administered, the only difference is that more of the fluid is absorbed and less reaches the large intestine; but however weak the solution, more of it reaches the large intestine than if a correspondingly weak solution of common salt had been given. An isotonic or hypotonic solution of a saline cathartic may produce purgation more rapidly than a more concentrated solution for the latter may cause contraction of the pyloric sphincter, so delaying the escape of the salt into the intestine.

If a hypertonic solution be administered, the effect is somewhat different. The salt is still unabsorbed, but it draws fluid from the blood into the bowel from its having higher osmotic pressure than the blood. A similar draining of the body fluids occurs when concentrated solutions of common salt reach the bowel, but the cathartic salts are much more powerful, because they do not pass out of the bowel into the blood so easily. Instead of an exchange of salt and fluid being carried on between the blood and intestinal contents, the blood gives up its fluid without any sufficient compensation in salt. Eventually the intestinal fluid becomes isotonic, and then some absorption of both salt and fluid occurs; in fact, some salt has been absorbed all along, as the epithelium is not absolutely impermeable to the cathartics. But much less of the sulfate is absorbed than of the chloride given in equal concentration, and as a general rule a strong solution causes such an accumulation of fluid that the bowel becomes distended and evacuates its contents. If, however, from any cause this fails to occur, a gradual absorption follows and the whole salt and fluid in the bowel is absorbed. These salts may fail to purge, for example, when the blood and tissues contain very little fluid, as in animals which have been deprived of water for several days previously. In this case the osmotic pressure in the bowel is unable to draw fluid from the concentrated blood, which on the other hand has a higher attraction for the fluid in the bowel than usual. But where large quantities of fluid are present in the tissues, as in œdema and dropsy, the saline cathartics drain them through the blood into the bowel, and very profuse evacuation occurs, with the disappearance of the exudate.

The saline cathartics fail to penetrate the intestinal epithelium, just as sodium chloride fails to penetrate the blood corpuscles (p. 42), through some peculiar physical character, which prevents them following the ordinary process of diffusion and which is at present unknown. In this relation it has been found by Hofmeister and Pauli that the purgative salts have a greater tendency to precipitate proteins and have less tendency to permeate into unorganized colloids than most of the non-purgative salts. In numerous other instances the sulfates, tartrates, and other cathartic anions have proved slower in permeating into living cells than the chlorides and bromides, and their effects on the blood cells, muscle, nerve, and some other tissues show marked deviations from those of the halogen salts. Another curious relation

between the purgative anions is that their calcium salts are all much less soluble than those of the salts which penetrate the epithelium, and it seems possible that they precipitate the calcium in the bowel wall. Most of the cathartic anions are bivalent and trivalent, but this is not true for all of them, for the higher members of the acetate series are absorbed with the greatest difficulty by the intestine.

The saline cathartics induce certain changes in the **Blood** indirectly through their action on the intestine. They prevent the absorption of the fluid of the food, or, if in sufficient concentration, actually draw fluid from the blood and tissues into the bowel, and under both conditions the blood becomes more concentrated than usual; in the first case because it is not reinforced by the usual amount of fluid from the food, in the second because it actually loses fluid into the intestine. This concentration of the blood leads to a sensation of thirst, and to a lessened excretion of fluid by the kidneys and other glands.

A certain amount of salt and of fluid is absorbed from the intestine, unless purgation follows very rapidly, and this salt acts in the blood and tissues in the same way as the salts which do not act as cathartics. When very dilute solutions of these salts are given, therefore, the blood becomes less concentrated and diuresis follows, but this does not occur so soon as after a similar solution of common salt, because the absorption is somewhat slower. Stronger cathartic solutions at first cause a concentration of the blood and lessened urine, but afterward the excess of salt in the blood may cause diuresis. The greater the purgative action, the less the diuretic, because more fluid and more of the cathartics are thrown out in the stools. If no purgation follows for any reason, as when the blood has been concentrated by long abstinence from water, the whole of the salt eventually passes into the blood and is excreted by the kidney, and may cause very considerable diuresis and a still further concentration of the blood. The sulfates are absorbed by the epithelium of the renal tubules with much greater difficulty than chloride, and thus offer osmotic resistance to the absorption of the fluid in the tubules; sulfates absorbed into the blood therefore induce a more profuse diuresis than an equal amount of chloride, but less of the former reaches the blood generally, so that the chlorides are better practical diuretics.

From the above it can be inferred at once that a saline cathartic injected intravenously causes no purgation, for instead of preventing the passage of fluid from the bowel into the blood, it rather encourages its absorption by increasing the osmotic pressure of the blood. And similarly the hypodermic injection of these salts is not followed by purging.

The statement is sometimes made that the saline cathartics act as cholagogues, *i. e.*, increase the secretion of bile, but this has not been confirmed by more careful observations.

The **Temperature** is often somewhat reduced by the action of the saline cathartics, but seldom more than one-half degree.

The habitual use of saline cathartics is often efficient in **Reducing the Weight** in obesity, and many of the natural mineral waters have a

considerable reputation in the treatment of such cases. This appears to be due in part to less proteins and fats being absorbed from the intestine, in part to the fluids of the body being decreased. There seems no reason to suppose that any marked change in the nitrogenous metabolism is induced by the cathartics, for the nitrogen in the urine is often practically unaltered in amount.

When purgation follows the administration of a saline cathartic, the most of the salt escapes in the fæces, never having been absorbed at all. When the salt fails to purge, however, and is absorbed, it undergoes the usual exchanges in the tissues and is excreted by the urine. there is no reason to suppose that any of it appears again in the stomach or intestine.

The **Sulfates** seem to pass through the tissues without injuring them, and but little effect is observed from injecting considerable quantities into the blood. When the sulphate ion is combined with a poisonous base, such as potassium or magnesium, the injection is of course followed by characteristic symptoms; but the anion seems to be comparatively harmless, and when the potassium or magnesium salt is taken by the mouth it also is quite devoid of general action. A trace of sulphide is sometimes formed in the bowel from sulphate given by the mouth.

The **Phosphates** are also very inactive after absorption. When they are injected subcutaneously or intravenously, the metaphosphates and pyrophosphates are poisonous, but this appears to be due to their alkalinity (Starkenstein). Phosphates absorbed in man and in the carnivora are excreted by the kidney and increase the acidity of the urine; in the herbivora they are excreted exclusively by the bowel wall.

The **Tartrates** are slowly oxidized in the tissues to carbonates but a considerable quantity is excreted in the urine unchanged. Injected into the blood directly, the tartrates seem to act as heart poisons, and in the rabbit nephritis is induced by their hypodermic application, but no such effects are observed in man from their administration by the mouth even in enormous quantities.

The oxide and carbonate of magnesium differ from the other saline cathartics in being very insoluble and in possessing an alkaline reaction. Part of that ingested is formed into magnesium chloride in the stomach, however, and the carbonic acid present in the intestine may dissolve part by forming the bicarbonate. Their alkalinity serves to remedy any excessive acidity of the stomach or intestine, while at the same time they are mildly cathartic. The prolonged use of large quantities of magnesia has in some cases led to the formation of large concretions in the bowel, resulting in obstruction.

Therapeutic Uses. The saline cathartics are very largely used to relieve constipation. Habitual constipation seems to be caused by insufficient peristalsis, and the slow passage of the contents through the intestines allows of a more complete absorption than usual, this in turn rendering the fæces hard and dry and difficult to move onward. The saline cathartics increase the fluidity of the intestinal contents, and thus facilitate their expulsion, and this is probably the only effect they have when taken in small quantities, and especially in dilute solution as in the natural mineral waters. In larger quantities, however, more water is retained in the bowel, and the weight and distention cause peristalsis, while in sufficient quantity they draw fluid

from the blood and cause profuse watery discharges. When a very complete evacuation is desired, the saline cathartics may be given along with some of the vegetable purgatives. Such mixtures are the official Black Draught (see Senna) and the compound powder of Jalap. The saline cathartics act much more rapidly than the vegetable purgatives, and a common method of combining their effects is to give the latter in the evening and the saline the following morning; in the same way a mercurial purge, such as calomel, given in the evening, may be followed by a Seidlitz powder in the morning.

The chronic constipation due to sedentary habits is much benefited by the saline cathartics, more especially by dilute solutions taken before breakfast. The sulfates and tartrates are harsh and unpleasant to the taste, and the natural waters are often preferred, or one of the effervescent preparations may be used in those cases.

The sulfates and tartrates are more frequently used where a single large dose has to be prescribed in order to empty the bowel, but here also the Seidlitz powder may be advised instead, as being more agreeable to the taste. These cathartics were at one time used in fever, partly from a theory that they reduced the temperature; they are certainly less liable to cause pain and griping than the vegetable purgatives, and thus tend to disturb the patient less.

Sodium phosphate is often prescribed for children, either as a powder to be given in jelly, or in solution in milk or other food which completely hides its taste.

The saline cathartics are used to lessen intestinal putrefaction, and are sometimes very efficient, though they do not act through any antiseptic power, but simply by removing the putrefying mass. The phosphate of sodium has been especially recommended in some forms of diarrhœa in children.

The saline cathartics are administered to remove accumulations of fluid in the body arising from cardiac or renal insufficiency, or from an old effusion. For this purpose the sulfate of magnesium is used in a large dose, dissolved in about its own weight of water; if purgation does not follow in one to three hours, an enema may be necessary, or the saline may be given along with a vegetable purgative. This form of treatment was very popular at one time, but is liable to weaken and depress the patient, and is specially contra-indicated, therefore, in asthenic conditions. Other methods of removing accumulations of fluid are by the use of diuretics (see Caffeine), diaphoretics (see Pilocarpine), or cardiac remedies (see Digitalis).

An analogous effect may play a rôle in reducing intracerebral pressure. Cushing found that hypertonic sodium chloride solution given by the mouth relieved high pressure of the cerebrospinal fluid, presumably by withdrawing the fluid of the blood by diuresis; the injection into the rectum of 6 to 8 oz. of a 25 per cent solution of magnesium sulfate is used for the same purpose, acting by withdrawing fluid from the blood into the intestine.

As diuretics the saline cathartics are inferior to other salts, such as the acetates or nitrates. Large quantities of dilute solutions of the

purgative salts are of value in the treatment of some forms of obesity, the mineral waters being generally prescribed for this purpose.

Magnesia and magnesium carbonate are less liable to purge than the soluble salts, and are specially indicated in hyperacidity of the stomach or in acid putrefaction in the bowel. They cause less disturbance of the digestion than the carbonates of the alkalies because of their insolubility, and at the same time have the advantage of acting as mild purgatives, while the insoluble alkaline lime preparations, tend to induce constipation. The magnesia preparations may be used also in diarrhœa as antacids, as they have no irritant action on the bowel. A combination of antacid, carminative, saline and vegetable aperient is found in Gregory's powder, which contains magnesia, rhubarb, and ginger (p. 269). Freshly prepared magnesia is recommended in arsenic poisoning to form an insoluble precipitate in the stomach, and in poisoning with acids it is also of value when it can be obtained readily. In both cases it is to be given in large quantities.

The phosphate of sodium has been given in various bone diseases, as in osteomalacia and rickets, this treatment being founded on the belief that the softening of the bones is due to the lack of phosphates in the food, but there is no reason to suppose that this idea is correct, and the treatment is not attended with success. It has also been recommended in the uric acid diathesis. The phosphates have been supposed to be of benefit in nervous diseases, on the theory that these were due to the insufficiency of phosphorus in the brain, and glycero-phosphates have been introduced for the same reason, but there is never any deficiency in the supply of phosphates in the food, and in practice no benefit is seen from the use of these salts.

The *hypophosphites* have been used in therapeutics in the belief that they had some special influence on nutrition. They were formerly supposed to be oxidized in the tissues to the phosphates, but this has been shown to be incorrect, as practically the whole of the hypophosphite administered can be recovered unchanged from the urine. No entirely satisfactory work on the effects of these salts on the nutrition has been done, but there is no ground to suppose that they have any further action than the other indifferent salts, such as the chlorides. The hypophosphites of sodium, potassium, and calcium along with hypophosphorous acid are contained in the *Syrupus Hypophosphitum* which has been used in doses of 2 fl. drs. in various conditions of malnutrition and cachexia in the popular belief that it improves digestion and assimilation. This is quite without foundation.

The *glycerophosphates* have been employed in therapeutics in the same way as the hypophosphites, there being some vague idea that they improve nutrition and supply organic phosphorus compounds to the nervous system. As a matter of fact they are rapidly decomposed and the phosphate is excreted in the urine and stools as inorganic salts, while the glycerin undergoes combustion; the administration of glycerophosphates has thus no more effect than that of glycerin and inorganic phosphates.

Preparations.

Sodii Sulfas (U. S. P.), Sodii Sulphas (B. P.), Glauber's salt (Na_2SO_4, $10H_2O$), soluble in about 3 parts of cold water, 15 G. (4 drs.). B. P., 2–16 G. (30–240 grs.).

Magnesii Sulfas (U. S. P.), Magnesii Sulphas (B. P.), Epsom salts ($MgSO_4$, $7H_2O$), soluble in $1\frac{1}{2}$ parts of cold water, 15 G. (4 drs.). B. P., 2–16 G. (30–240 grs.).

These are crystalline salts with a harsh, bitter taste.

Sodii Phosphas (U. S. P., B. P.) ($Na_2HPO_4 + 12H_2O$), a crystalline salt with a cool, saline taste, soluble in about 6 parts of cold water, 4 G. (1 dr.).

Potassii Bitartras (U. S. P.), Potassii Tartras Acidus (B. P.), cream of tartar ($KHC_4H_4O_6$), a crystalline powder with a pleasant acidulous taste, soluble in 200 parts of water, 2 G. (30 grs.). B. P., 1-4 G. (15–60 grs.).

Potassii et Sodii Tartras (U. S. P.), Sodii et Potassii Tartras (B. P.), Rochelle salt ($KNaC_4H_4O_6 + 4H_2O$), crystals or powder with a cool saline taste, soluble in 1.2 parts of cold water, 10 G. ($2\frac{1}{2}$ drs.). B. P., 8–16 G. (120–240 grs.).

Magnesii Oxidum, magnesia (MgO). U. S. P., antacid, 0.2 G. (4 grs.), laxative 3 G. (45 grs.); B. P., 0.6–4 G. (10–60 grs.).

Magnesii Carbonas, a mixture of carbonate and hydrate of magnesium. U. S. P., antacid, 0.6 G. (10 grs.), laxative 8 G. (2 drs.); B. P., 0.6–4 G. (10–60 grs.).

These form white amorphous powders with an earthy, not saline, taste. They are insoluble in water, but the carbonate is dissolved by excess of carbonic acid. The B. P. has a light (Leve) and heavy (Ponderosum) oxide and carbonate.

Magma Magnesiæ (U. S. P.), contains about 7 per cent of Magnesium Hydroxide. Dose, antacid, 4 cc. (1 fl. dr.); laxative, 15 cc. (4 fl. drs.).

Mistura Magnesii Hydroxidi (B. P.), contains about 8 per cent of hydroxide. 4–16 mils. (60–240 mins.).

Effervescing Preparations.

Pulvis Effervescens Compositus (U. S. P., B. P.), Seidlitz powder.

This powder is made up in two papers, of which the blue one contains a mixture of 3 parts of Rochelle salts and one part of sodium bicarbonate, in all 10 G. (160 grs.), while the white paper contains 2.2 G. (2.5 G., B. P.) of tartaric acid. When the powders are dissolved separately in water and the solutions mixed, the tartaric acid acting on the bicarbonate releases carbonic acid with effervescence.

Liquor Magnesii Citratis (U. S. P.) is a solution of magnesium citrate with excess of citric acid to which potassium bicarbonate is added. The whole is bottled tightly and effervesces when the cork is removed. 200 cc. (7 fl. oz.).

Sodii Sulphas Effervescens (B. P.), a similar mixture containing the sulphate of soda instead of citrate of magnesia. 4–16 G. (60–240 grs.).

Sodii Phosphas Effervescens (B. P., U. S. P.), similar to the above, but containing the phosphate in place of the sulphate.

Many other effervescent mixtures are used instead of the official ones—among them the tartrates and citrates of the alkalies, the acetate of magnesium, etc.

The sulphates of sodium and of magnesium, the tartrates of sodium and potassium and the phosphate of sodium are given in solution, the last often in milk. Unless under special conditions the salts ought not to be in greater concentration than 5–10 per cent. Magnesia and magnesium carbonate are administered in powder, sweetened if necessary. The effervescent preparations are always to be taken in solution in about a tumbler of water; in some instances in which this was not understood, severe distention of the stomach with alarming symptoms have arisen from the carbonic acid being freed in the stomach. The effervescent preparation ought to be kept dry, and the solution of magnesium citrate has to be kept tightly corked.

Very often the natural mineral waters are used instead of the pharmacopœial preparations, the best known purgatives among these being the Hunyadi-Janos water and Carlsbad water, which contain the sulphates of sodium and magnesium. "Carlsbad salts" are obtained by the evaporation of the waters, but are very often artificial imitations. Many other springs have the same effects, and a widespread belief exists that the natural waters are "more efficient" or "less depressant" or have some mystical virtues that are not shared in by the artificial salts, but this belief does not seem to have any real basis, and is probably a survival of the old religious belief in the healing properties of springs.

In the natural waters the purgative salts are always accompanied by other less active ones, such as the chlorides of sodium, calcium, etc.

Agar may be mentioned here as, although it has no chemical relation to the saline cathartics, its action presents certain analogies and it has been used for similar purposes. It is obtained from various East Indian sea-weeds, and consists mainly of gelose, a carbohydrate which is indigestible and unabsorbable and retains water in the alimentary canal in the same way as the saline cathartics. It thus increases the bulk of the contents of the bowel and causes their evacuation in constipation. AGAR (U. S. P., B. P.) forms slender translucent strips or a grayish-white powder. It is almost tasteless and is given suspended in water or in food in chronic constipation. Dose, U. S. P., 10 G. ($2\frac{1}{2}$ drs.); B. P., 4–16 G. (60–240 grs.).

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PART III.

SUBSTANCES CHARACTERIZED CHIEFLY BY THEIR ACTION AFTER ABSORPTION.

A. DEPRESSANTS OF THE CENTRAL NERVOUS SYSTEM.

I. NARCOTICS OF THE METHANE SERIES.

1. Alcohol-Chloroform Group.

A LARGE number of the simpler methane compounds of the open-chain series cause depression of the central nervous system, more especially of the cerebrum, and some of them are perhaps the most extensively used of all drugs, for among them are the universally used surgical anæsthetics, the soporifics, and alcohol. The general action of all of these is similar in character and consists of a first stage of imperfect consciousness and confused ideas, followed by one of wild excitement, and eventually by complete unconsciousness, which may terminate in death. The second stage is much more marked after some of the series than after others, and is often entirely absent. It has given rise to the theory that these drugs stimulate the nerve cells before paralyzing them, but an alternative explanation is that the functions of control and inhibition are lessened, and the centres of motion are thus left free and act more strongly than normally. This question has been most discussed in regard to alcohol, and will receive greater attention under that heading.

The action on the central nervous system is elicited by comparatively small quantities of these drugs, but other forms of living matter are also affected by them in somewhat greater concentration, and their action may in short be considered as coextensive with life, though in man and the higher animals the symptoms from the brain predominate.

The different members of the group vary greatly in their chemical affinities and in their tendency to enter into chemical combinations, and no relation can be found between their narcotic action and the presence of any one radical. This suggests that their effects depend on the properties of the molecule as a whole, and not on a chemical combination being formed with any constituent of the tissues. A very interesting view has been suggested by Meyer and Overton, who attribute the common action of these narcotics to a common physical character. They point out that practically all of them are more soluble in oils and lipids than in water and that when one of these drugs in watery solution meets an oil or lipid it passes from the water to the oil and remains dissolved in it. The same process occurs when these drugs are carried

in the blood; they tend to leave the watery plasma and to accumulate in the lipids of the body, and as the nerve cells are richest in lipids, the narcotics accumulate in the brain. This is a purely physical process and the amount of the drug taken up from the blood is determined by its relative solubility in the lipids and in the blood (*coefficient of partition* between oils and water). According to Meyer's view, the presence of the drugs in the lipids renders these more fluid and thus changes their relations to the other constituents of the cells; this derangement of their normal condition impairs the function of these cells and lessens their activity, that is, causes narcosis. This very attractive theory has been supported by a number of experiments and serves to explain a large number of observations; the accordance of the coefficient of partition and the narcotic power is seen to be very close, especially when members of an homologous series are compared; for example, the narcotic action of the simple alcohols rises from methyl and ethyl alcohol through propyl and butyl alcohol to amyl alcohol, which is the most powerful of the series, and the tendency of the alcohols to pass from water into oil rises similarly. On the other hand when the hydroxyl groups of the alcohols are increased, as in the series ethyl alcohol, glycol and glycerine, the partition coefficient between oil and water falls, and the narcotic action declines.

The experiments of Meyer, Overton and their followers suffice to show that these physical properties are factors in the narcotic action. But these are not the only determining influences. For when the relative narcotic action of less nearly related bodies is compared, the dependence on the partition coefficient is less exact; for example, the relative coefficients of partition of alcohol, chloral and acetone are approximately 1:2:6, but their narcotic action is 1:16:1. There is evidently some unknown factor which plays an important rôle in determining the action, besides the solubility coefficient. Other facts indicate that differential solubility in lipids is not an entirely satisfactory explanation of the action of narcotics. Many enzymes are poisoned by narcotics and there is here also a progressive increase in activity with increase in the number of carbon atoms in a homologous series of alcohols. Since enzymes are lipid-free the law of a homologous series cannot in this case depend on lipid solubility. Clark points out that the action of narcotics on ferments, cells and living tissues usually shows an approximately linear relation between concentrations and action and that there are striking resemblances between their actions on inorganic catalysts, on purified enzymes and on living cells. Any theory of narcotic action ought to account for all these phenomena and differential solubility cannot explain them. He inclines to the opinion, therefore, that narcotics act by covering enzymes or cell surfaces. The effect of such adsorption would be to interpose a layer of CH_3—CH_2 groups between the active surface and the watery solution, which might effect a barrier to the exchange of molecules between the surface and the solution. This would explain the obvious relations between the biological action of narcotics and their power of lowering surface tension.

Most authors have found that the permeability of plant cells, eggs, etc., is diminished by narcotics. Spiegel and Spiegel found that ether, chloroform or chloral produces an increase in the polarization index, indicating an increase in the density of cellular surface films, and that lipids play an important part in the mechanism of polarizability since differences in conductivity could be produced in artificial biocolloid membranes only if they contained lipids in fine dispersion. They suggest that narcotics diminish the surface tension of the lipid particles and their water-binding capacity, thus increasing their permeability for electrolytes.

Konsett has shown that in rats lipid-soluble dyes, *e. g.*, methylene blue, markedly increase the action of hypnotics though these dyes have, *per se*, no hypnotic effect even in much higher doses. Lipid-insoluble dyes like Congo red are inactive in this respect.

From all the work that has been done on this subject, certain factors emerge. Nearly all workers agree in supposing that the biological effect of narcotics is due to some action on cell surfaces. Some direct evidence for this is seen in the fact that narcotics injected into amœbæ do not produce the narcotic effect that they have when applied to the surface. Many of the biological phenomena can be correlated with physical properties of narcotics, but no single or simple property is still adequate to explain all the phenomena, or indeed is likely to be adequate in view of the extreme complexity of the living cell. The action of narcotics is related to their adsorption on the cell surfaces and solubility in lipids is an important factor which however may be an incidental one.

Various suggestions have been made of late years as to the nature of narcosis. The old view that it was due to changes in the blood supply and to anæmia of the brain has long been abandoned, since it was shown that the brain of a frog in which the blood was replaced by saline solution, could still be anæsthetized. There is no question that the action of the narcotics is a direct one on the nervous structures, and that the changes in the brain circulation, which are similar to those in normal sleep, are the result and not the cause of the narcotic action.

There is an increasing tendency to attribute narcosis to changes in the synapses between neurons; the passage of impulses from one cell to another is believed to be impeded and each neuron remains isolated from the influences to which it is normally subject and which have been developed and strengthened in the course of evolution and education.

Verworn believes that narcosis arises from the arrest of the oxidations in the cells, and in many instances a lessened oxidation has been shown to be present during narcosis. But on the other hand narcosis may be induced in cells which live in the absence of oxygen (intestinal parasites and anaerobic microbes), and cases are known in which narcosis is not accompanied by lessened oxidation. The decrease in oxidation which is seen in narcosis may thus be the result and not the cause of the action.

Lillie holds that the essential feature of narcosis is the diminished permeability of the cell membranes to ions, which can no longer penetrate as is necessary for activity. This diminished permeability may be the result of changes in the lipids such as are demanded in the Meyer-Overton theory.

Certain features of the chemical constitution of the members of this group have already been mentioned. Thus it is found that, as a general rule, the higher members of a series are more strongly depressant than the lower, provided they

are sufficiently soluble in water to be taken up by the blood, and a corresponding increase in the partition coefficient is presented. The increase in hydroxyl groups which augments the solubility in water has the opposite effect, lowering the narcotic action; but if the hydroxyl is substituted by chlorine the narcotic action returns; for example, propyl alcohol (C_3H_7OH) is narcotic but glycerin ($C_3H_5(OH)_3$) is indifferent, while trichlorhydrin ($C_3H_5Cl_3$) is less soluble in water and again acts as a narcotic.

The presence of the carboxyl group (COOH) generally prevents any narcotic action, probably because the acids formed circulate as salts and these cannot penetrate the cells in sufficient concentration. Butyric acid is said to have some narcotic effect, but this may arise from the presence of esters. When hydrogen atoms of these acids are replaced by chlorine or bromine, they acquire a much stronger action; thus acetic acid is practically devoid of narcotic action, while some of the chloracetic and bromacetic acids are narcotic. But their effects on the other organs of the body preclude their use in therapeutics.

This augmented action through the substitution of halogens for hydrogen is seen in many other instances; for example, methane (CH_4) is practically not depressant, but if one, two, or three of the hydrogen atoms in the molecule be substituted by chlorine, forming CH_3Cl, CH_2Cl_2, and $CHCl_3$, the narcotic power increases with each Cl added.

This increased activity of the halogen compounds is not due to any action of chlorine or bromine on the nerve cells, for these elements are not freed from their compounds, which act as unchanged molecules; for example, chlorine is not liberated from chloroform in the tissues, but the whole molecule $CHCl_3$ acts as an anæsthetic, while methane has little action.

The chlorine and bromine derivatives of methane are not only more powerful drugs, but also more powerful poisons than the ordinary compounds; much less chloroform is required to anæsthetize than methane, but much less is required to kill. In addition, these compounds, especially those containing chlorine, seem to have a more powerful action on the heart and circulation and on the metabolism than the others. In other words, the chlorine bodies have a less specific action on the nerve cells and thus involve a larger number of tissues in their effects. (See Chloroform.)

Many methane compounds are not narcotic because they contain more active radicles. Thus ethane (C_2H_6) is a member of the narcotic series, but ethyl nitrite ($C_2H_5O—NO$) cannot be classed with it, because the —O—NO group has a very powerful and entirely different effect; very small quantities of ethyl nitrite are required to produce the nitrite effect, so that the depressant action is pushed into the background. Members of the methane series often lose their depressant action when combined with nitrogen so as to form substituted ammonias. Thus trimethylamine ($N(CH_3)_3$) has no depressant action, although each of the methyl radicles alone would possess it. Again, the substitution of a member of the aromatic series for one of the fatty substances sometimes changes the action from that characteristic of the alcohol-chloroform group to that of the benzene series. For example, ether ($C_2H_5—O—C_2H_5$) is one of the most valuable anæsthetics, but if one ethyl radical be substituted by phenyl ($C_6H_5—O—C_2H_5$), it loses this property entirely. Others, however, retain their depressant action, as, for example, acetophenone ($C_6H_5—CO—CH_3$).

While the members of this group resemble each other closely in their effects on the central nervous system, they are used for very different purposes in therapeutics and may therefore be discussed in three subgroups: 1, alcohol; 2, general anæsthetics, and 3, soporifics or hypnotics. It must be recognized, however, that there is no hard and fast line dividing these subgroups; for the anæsthetics chloroform and ether, might be used in small quantities to produce rest and sleep, and would then, strictly speaking, be soporifics; while, on the other hand,

chloral and other hypnotics can give rise to complete anæsthesia when administered in large quantities.

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Alcohol.

Ethyl alcohol (CH_3CH_2OH) has been known in an impure form since the earliest times and, as far back as the history of medicine extends, has been used as a drug. Its medicinal reputation has undergone many fluctuations, by many held to be a panacea, by others it has been considered of importance only as a poison.

Alcoholic liquors are generally prepared by the fermentation of sugars, which either exist preformed in the fruits, or are derived from starch by a preliminary ferment action. The simple liquors (wines and beers) generally contain only a low percentage of alcohol (2–20 per cent), and the stronger preparations (spirits) are prepared from them by distillation, which raises the percentage to 30–60 per cent and at the same time removes the non-volatile constituents. Spirits and liquors are not, however, simple mixtures of alcohol and water but contain many other volatile substances, the character of which is little known, and which are called œnanthic ethers. Some of them have been shown to be higher members of the alcoholic series, while others would seem to be of entirely different constitution.

Action.—The value of alcohol in medicine depends upon three chief points: 1, its irritant local action; 2, its action on the central nervous system, and 3, its value as a food.

The **irritant action** is not so marked as that of many other substances, but is of much greater importance, owing to the habitual use of this drug. It is probably due to the partial precipitation of the proteins of the cells, and is shown by the results of its application to the skin, to wounds, and to the mucous membranes. Applied to the skin in sufficient concentration (*e. g.*, 60–90 per cent), it produces redness, itching and a feeling of heat like other volatile and irritant substances, such as the volatile oils. Alcohol is, however, much less irritant and at the same time more volatile than these, so that unless its evaporation is prevented, it may produce a sensation of cold and have little or no

irritant action; this is especially the case when dilute alcohol is used, no very distinct appearances of irritation of the skin being produced by solutions under 40–50 per cent. In ulcers and other unprotected surfaces, the irritant action is much greater and its application is attended by pain and smarting; the precipitation of the proteins lends alcohol an astringent action in certain concentrations, but if it penetrates deeper it may destroy the cells and it then becomes a corrosive until it is diluted by the fluids.

Its effects on mucous membranes are similar to those on wounds. In the mouth strong alcohol produces a burning, unpleasant sensation which passes to the throat and stomach when it is swallowed, and if the concentrated vapor be inhaled, it causes irritation and reflex closure of the glottis. The effects of alcohol on the digestive functions are so important that they will receive further attention (p. 296).

The action of alcohol on the **Nervous Centres** differs a good deal in individuals. In small quantities it generally produces a feeling of well-being and good-fellowship, along with increased confidence in the powers, mental and physical, of the subject of the experiment. Larger quantities are followed by a certain amount of excitement, marked by laughter, loquacity, and gesticulation. The face becomes flushed and hot, the eyes brighter and livelier, the pulse is accelerated. Even at this stage self-control is partially lost and the will power is weakened. The speech may be brilliant, but it often betrays the speaker; the movements are more lively, but they are often undignified. The loss of self-control is often indicated further by furious outbursts of anger and unreasonableness, or by the indulgence in maudlin sentimentality and sensual fancies. The sense of responsibility and the power of discrimination between the trivial and the important are lost, and the individual has no regard for the feelings of others, or the ordinary conventions of life. If the bout be further continued, the movements become uncertain, the speech becomes difficult and stammering, the walk becomes a stagger, and a torpid slumber follows. Often nausea and vomiting set in, although these are entirely absent in some cases. On awakening from slumber, very great depression is generally suffered from, together with nausea and vomiting, and want of appetite, which may last for several days and is associated with all the symptoms of acute gastric catarrh.

Very large quantities of alcohol lead to a deep, torpid sleep, which eventually passes into total unconsciousness, resembling the condition in chloroform anæsthesia; the respiration becomes stertorous and slow, and the face, which has hitherto been flushed, becomes pale or cyanotic. This condition may last for several hours and end in death from failure of the respiration, but in other cases the anæsthesia becomes less deep and after a very prolonged sleep the patient recovers. When the stage of anæsthesia is reached, it lasts much longer than that produced by chloroform and ether. It is said that persons rarely or never recover if unconsciousness lasts longer than ten to twelve hours after the drinking bout.

The effects of alcohol vary greatly, however, in different individuals

and in the same individual at different times. One person is rendered sentimental, another bellicose, while in a third there may be no appearance of excitement, the first distinct symptom being profound slumber. When drinking is indulged in in company, the excitement stage is a very common phenomenon, but if alcohol is taken without the exhilarating accompaniments of bright lights and exciting companionship, it is much less frequently seen, and the question has therefore arisen how far the environment produces the excitement in alcoholic intoxication.

It may be stated at once that there exist two distinct views as to the action of alcohol on the central nervous system: the one stoutly upheld by Binz and his pupils, that alcohol first stimulates and then depresses the nerve cells; the other championed by Schmiedeberg, Bunge and their followers, that it depresses the central nervous system from the beginning. The symptoms of excitement require no explanation on the first theory, which is rather to be looked on as the natural expression of the facts observed. On the other hand, Schmiedeberg explains them as not due to true stimulation of the motor areas, but as the result of these areas being freed from control by the weakening of the highest functions of the brain – the will and self-restraint. Even the smallest quantities of alcohol tend to lessen the activity of the brain, the drug appearing to act most strongly, and therefore in the smallest quantities, on the most recently acquired faculties, to annihilate those qualities that have been built up through education and experience, the power of self-control and the sense of responsibility.

The question is a most difficult one to decide, for on the one hand it has been shown that the simplest movement is the result of a combination of motor and inhibitory impulses from the brain, while on the other hand the measurement of the relative strength of these impulses is one of the most difficult problems of biology. The advocates of the stimulant action point to the confidence in their own powers exhibited by intoxicated persons, to the brilliancy of the after-dinner speech, and to the excitement stage as evidences of the increased activity of the brain. But there are obvious possibilities of fallacy here, for fluency in speech or conversation may be due to the speaker having lost his habitual shyness and nervousness. Moreover under conditions where the speaker has indulged in alcohol, his audience may also be less critical from the same influence. Certainly many experienced speakers, who are not averse to alcohol, indulge very sparingly, if at all, when they have to make a speech which must carry conviction.

The question has been the subject of many investigations, and as the methods have been developed and the difficulties and complexities have been appreciated, the evidence that alcohol is almost wholly depressant has become more definite, while the supposed stimulant action on the nervous system becomes less probable.

The effect on the simple reflexes have been examined carefully by Dodge and Benedict, who find that 30 cc. of alcohol in man lessens the speed and strength of the knee-jerk and of reflex closure of the eyelids; the reflex arc is therefore depressed by alcohol, and there is no question that this action is central in location.

The amount of work and endurance under alcohol has long been a subject of study from the early experiments of Parkes, who found that those regiments which were not supplied with alcohol marched farther and were in better condition at the end of the day than others to which it had been given. The experiments of Durig in climbing lead to the same result, the total work done being smaller under alcohol and the expenditure of energy greater. Forms of work requiring larger drafts upon the intelligence than the marching of soldiers are also performed less correctly with alcohol than without it; thus typesetters can do more work and make fewer errors when they abstain from its use.

The capacity for work depends not so much upon the actual strength of the muscles as upon the condition of the brain, and these experiments are therefore generally quoted as evidence of the depressant action of alcohol. Their results are not incompatible with the view that alcohol primarily stimulates the nerve cells, however, for Binz and his followers allow that the stimulation is transient and is followed by depression, and if a sufficient time elapse after the alcohol is taken, the stage of depression is elicited and the total work may thus be reduced.

Attempts have been made to measure the work done under alcohol, by recording with ergograph the work of which a muscle is capable before it is completely fatigued. The best investigations are those of Rivers, who took the precaution of disguising the alcohol with flavors so that the subject of the experiment was unaware when alcohol was given. His results indicate that small quantities of alcohol (5–20 cc.), have very little effect on muscular work measured in this way. When larger amounts of alcohol were taken, Rivers found that an exceptional amount of work could be performed before fatigue appeared, but he considers this due to the fact that the alcohol could not longer be concealed and the subject was now influenced by suggestion.

In measurements of intellectual work, the factor of suggestion is of still greater moment and the observations of Kraepelin lose much of their importance from the fact that the subjects knew when alcohol had been given them. He states that a person under even a small dose of alcohol makes more errors than usual in adding a row of figures and in reading a series of unconnected syllables, and apparently recognizes letters and words somewhat more slowly. It is interesting to find that the subject of the experiment is quite unaware of the inferiority of his work and is often persuaded that it is unusually good. Kraepelin's later investigations tend to show that this effect of alcohol lasts much longer than is generally recognized, the mental equilibrium being reinstated only twelve to twenty-four hours after even moderate indulgence in alcohol. He leans to the view that alcohol weakens and paralyzes some parts of the brain, while primarily stimulating others, but brings forward no new evidence that this stimulation is not fictitious and really due to the removal of the barriers of self-restraint by the paralysis of higher areas; and Dodge and Benedict in their careful studies on willed movements of the eyes and fingers were unable to find any stage of accelerated nervous activity, and conclude that alcohol only depresses the brain.

Most other psychological experiments give similar results, and no unequivocal evidence of the initial stimulant action on the brain has yet been adduced, for each new feature may be interpreted as really due to the depression of controlling or inhibitory functions. Of course, there is no absolutely convincing proof that no stimulation of the motor areas occurs, and no physiological measurement of the activity of controlling areas can be adduced, much less of their depression by alcohol. On the other hand, the effects of alcohol on cerebral activity are very different from those of caffeine, which definitely increases both muscular and mental efficiency, and thus is the typical brain stimulant. Exaggerated importance has been attached to this question from the idea that it is more justifiable to employ a "stimulant" than a "depressant," but in therapeutics this is not a valid argument for or against the use of alcohol.

In the lower parts of the central nervous system the evidences of primary depression are less open to question. For example, the coördination of the finer movements suffers at an early stage in alcohol drinking, long before the generally recognized forms of lack of coördination, such as indistinct speech and staggering, appear. Skilled work is performed more slowly, and far more errors occur in it than in normal conditions, and these errors may lead to serious accidents in industry.

The question of the action of small amounts of alcohol upon the central nervous system has assumed great importance in the past few years due to the constantly increasing use of automobiles and especially to the higher speeds at which they are driven. Statistics as to the number of accidents directly or indirectly due to alcohol are notoriously unreliable. Obvious drunkenness as manifested by staggering gait and impaired speech is easily recognizable and would rarely cause any great difficulty in ascribing the rôle played by alcohol in a catastrophe. The difficulty is much greater, however, when only small amounts of alcohol have been imbibed - amounts which produce no signs of gross intoxication but which are yet sufficient to render a driver highly dangerous upon the public highway. An impaired judgment and slowed reflexes may make all the difference between safety and death. The danger is especially great as alcohol disappears from the blood relatively slowly, and its action, therefore, persists much longer than is generally recognized. It should be understood that for such use of alcohol the term "drunkenness" is not applicable but rather "intoxication" or still better the statement that the individual was "under the influence of alcohol."

Courts of law have had considerable difficulty in deciding cases of accidents in which alcohol has been claimed as a contributory factor, and the rulings have by no means been uniform. Efforts have been made to develop a chemical test for alcohol in the blood or urine which could be employed in such cases, but naturally in many accidents such tests would not be available. An arbitrary amount of 0.02 per cent of alcohol in the blood has been frequently quoted as being capable of interfering with the proper handling of an automobile. The British Committee studying this question concluded that 2 to 3 ounces of

whisky usually affects adversely rapid and accurate coördination and must affect driving capacity.

There is no doubt but that the question is one of the most important connected with alcohol which is before the public today.

Alcohol has been found to cause a prolonged secretion of the cerebrospinal fluid and to raise the pressure in the subarachnoid space, and it has been suggested that this may account in part for its after effects which have generally been attributed to gastric disturbance.

Acute alcoholic intoxication leads to very distinct alterations in the histological appearance of the cells of the central nervous system, which have been described by Dehio, Stewart, and others. The chief change noted by them consists in replacement of the chromatin network by fine granules, which in turn seem to become dissolved in the general cytoplasm. Staining reagents therefore, give rise to a diffused coloration of the cell rather than to localized masses of color, such as are seen in the normal cells.

The medulla oblongata is the last part of the central nervous system to be acted on by alcohol, or at any rate to undergo complete paralysis.

The **Respiratory and Circulatory Centres** preserve their functions long after the occurrence of complete unconsciousness and the disappearance of the ordinary reflexes. The same question has been raised in regard to the respiratory centre, as has been already discussed in the consideration of the brain, and the same two opposing views have been upheld. These are of greater importance as regards the respiratory centre, because the advocates of the stimulation theory advise the use of alcohol in conditions of the respiration in which it is directly contraindicated if the other view be the correct one. The question here is apparently much more simple, because the activity of the respiratory centre can be estimated directly by measuring the number of the respirations and the amount of air inhaled during each; but a large number of such experiments have been performed with very varying results. If the number of the respirations be counted in a person in the excitement stage of alcoholic intoxication, it is often found to be much greater than normal, but this may be due to the muscular movements and need not indicate any direct action of the drug on the medullary centre. And, of course, this excitement stage is not elicited in therapeutics, and the value of alcohol as a respiratory stimulant must therefore be estimated in cases in which no such excitement is caused. A number of such estimations have been made in man and animals, and in many of these no excitement was produced and in some sleep followed, yet the amount of air inhaled was larger than before the drug was administered; the increase was generally more evident when alcohol was taken during fatigue and exhaustion than in ordinary conditions. This may not indicate a direct stimulation of the respiratory centre, however, for the increase is often not greater than that following an ordinarily meal, and may therefore be attributed to the respiratory centre being indirectly affected by the activity of the stomach and intestine. The actual excitability of the respiratory centre may be measured by its response to the inhalation of carbon dioxide, and Loewy's observations by this method do not lend support to the view that the excitabil-

ity is augmented. A careful analysis of the action on the centre in man made by Higgins by modern methods shows that the alveolar carbon dioxide tension falls in some cases under alcohol, which indicates that the centre is more sensitive to the presence of this gas in the blood; in other individuals no such change occurs, and in any case the effect of alcohol is small. In most of his experiments the rate of the breathing was not altered and the volume of air breathed per minute was actually lessened.

In the dog, no acceleration of the respiration occurs after alcohol, while in the rabbit, on the other hand, the respiration is much accelerated, and the amount of air inhaled shows a corresponding increase. It is still a matter of dispute, however, whether this arises from direct action on the centre or from the irritation of the stomach, the dilatation of the vessels, and other peripheral effects (Jacquet, Wilmanns, Singer).

In short, there is no unequivocal evidence that the respiratory centre is stimulated to any material extent by small doses, while on the other hand, no depression of the activity of this centre occurs except at a late stage of alcohol poisoning. Alcohol is often said to slow the respiration in fever patients and to stimulate it in cases of shock. In the first case the improvement (when present at all) is probably due to the alcohol lessening the excitement through its narcotic action, while its value in shock is disputed by most careful observers.

From a practical point of view the question is of little importance, for the changes in the respiration induced by alcohol are too small and too inconstant to play any part in the treatment of respiratory disorders.

Circulation.—The pulse is accelerated during the excitement of alcoholic intoxication, but this is due to the increased muscular effort and not to any direct action on the heart, for Jacquet has shown that the pulse rate is unaltered by alcohol in normal cases, provided that no excitement be produced by the environment. In animals also, the pulse rate is very little altered by alcohol, except in very large quantities, when it is slowed. The blood-pressure is said to be slightly increased in man in some cases after moderate quantities of alcohol (15–30 cc.), but in at least an equal number of observations it was found to be slightly reduced, and in many no definite change could be made out (Lieb). Brooks, who has succeeded in registering the blood-pressure painlessly in unanæsthetized animals, found that alcohol given by the mouth increased the arterial tension for about five minutes and then reduced it. When it was injected intravenously or by a gastric fistula, the tension was reduced. Alcohol is believed by some to augment the strength of the heart, but the change is small in extent and inconstant in its appearance. Larger quantities affect the heart in the same way as ether and chloroform, weakening the auricular and later the ventricular systole, and inducing dilatation and slowing of both chambers. The action of alcohol on the heart is much less than that of chloroform, however, about 200 times as much being required to arrest the frog's heart; and Loeb found that the mammalian heart continues to beat when perfused with 2 per cent alcohol.

The flushing of the skin which occurs in alcoholic intoxication indi-

cates dilation of the skin vessels, and this is sometimes accompanied by a very slight constriction of the vessels of the internal organs. These seem to arise from central vasomotor action, but whether it is due to direct stimulation of the centres or arises from a reflex from the stomach, is not yet determined. Very large quantities of alcohol cause a marked fall in the arterial tension, through weakening the vaso-constrictor centres and the heart muscle, but the quantities of alcohol required to cause any great fall in blood-pressure are far in excess of those used in therapeutics.

The recent work of Grollman showed that when moderate amounts (30 cc.) of alcohol in a diluted form are given occasional drinkers, there is a slight rise in pulse rate coming on in from fifteen to thirty minutes and not dependent upon psychic factors which might produce such changes in non-drinkers immediately after the drug has been taken. In moderate drinkers slightly larger amounts (35 cc. or more) caused appreciable increases in both blood-pressure and in cardiac output.

McDowall has shown that in cats the intravenous administration of small doses of alcohol is followed by a fall in the venous pressure while the arterial pressure is maintained by an increase in the rate of the heart which is produced reflexly. He believes that the same change is produced in man when alcohol is administered and that the lowering of the venous pressure acts to protect an overburdened heart such as is seen in pneumonia.

On the whole, the action on the circulation of small quantities of alcohol ($\frac{1}{2}$–1 oz.) may be favorable in some conditions, but is so slight and inconstant that it is impossible to regard it as a basis on which serious therapeutics can be founded. The slowing of the heart which often follows the administration of alcohol in fever, would seem due rather to its diminishing the cerebral excitement than to its direct action on the heart.

Alcohol has little effect on **Muscle** or on peripheral **Nerves** when it is carried to them by the blood, but Lee states that frog's muscle is strengthened by small quantities and weakened by larger amounts. This has been interpreted as indicating that small quantities of alcohol are utilized by the muscle as a source of energy, while this effect disappears under larger quantities which unfold the toxic action of the drug. And Durig's experiments show that in man alcohol may be utilized for work in the same way as the ordinary sources of energy, such as sugar. When the frog's nerve is exposed to alcoholic vapor its irritability is first increased and later diminished if the quantity applied be large enough. The sensory fibres are said to be depressed before the motor.

The effect of alcohol on the **Digestion** has been the subject of many investigations, both from the clinical and the experimental point of view. There exists a widespread belief in both lay and medical circles that small quantities of alcohol taken before a meal increase the appetite, while after food they accelerate the digestion. It is obvious that alcohol may affect digestion either by altering the activity of the ferments in the digestive canal, or by altering the secretion, movement, or absorption of the stomach and intestine. The digestive power of the ferments outside the body has been found to be practically unaltered when pure alcohol is present in small quantity. But when

somewhat larger amounts are added the gastric and pancreatic juices are retarded, and even small quantities of the ordinary wines and beers have this detrimental effect.

The presence of alcohol in the mouth causes (according to Chittenden, Mendel and Jackson) a very appreciable increase in the secretion of the saliva, presumably by reflex action, and a similar increase in the gastric juice may perhaps follow from its local irritant action on the stomach. But, apart from this, it appears to exert a specific action on the secretion after its absorption into the circulation. For when it is injected into the rectum, a profuse secretion from the gastric mucous membrane follows, and when part of the stomach is isolated from the rest of the organ, so that alcohol given by the mouth fails to enter it, this part still shares in the secretion; the pepsin secretion is not correspondingly augmented. It has been further demonstrated that the absorption of fluids from the stomach and bowel is accelerated by the addition of alcohol, while the movements of the stomach are unchanged or diminished by moderate quantities. Alcohol arrests the contractions of the stomach which are characteristic of hunger (Carlson) as distinguished from appetite, but it may not have this effect during digestion.

Digestion in the stomach may thus be influenced in two opposite directions when alcohol is administered in the usual form of wine, spirits, or beer. The action on the ferments is deleterious, while the changes in the stomach wall, the increased secretion and the accelerated absorption may possibly be beneficial in many cases. These two opposing factors may neutralize each other, as in the dog, in which the rate of digestion is scarcely altered, the retarding effects of alcohol on the proteolysis being compensated for by the more abundant secretion of the juice, which continues after the alcohol is absorbed, and therefore after its deleterious effects on the fermentation have disappeared (Chittenden, Mendel and Jackson). In man the result varies, the one factor predominating in some cases, the other in others. Thus, while Kretschy and Buchner found that the digestion of proteins in the human stomach was distinctly retarded by alcohol and beer, Eichenberg, Wolffhardt and others state that small quantities of alcohol or wine accelerate the digestion, and Gluzinsky came to the conclusion that as long as alcohol remains in the stomach the digestion is retarded, but that after its absorption the digestion progresses more rapidly than if no alcohol had been given. Zuntz and Magnus-Levy have shown that the addition of beer to the dietary does not affect the absorption and utilization of the food by the tissues. It is not unlikely that the taste has some influence on the result and that an alcoholic beverage induces a more rapid secretion and an improved digestion in those who enjoy it, while in those to whom it is disagreeable, the secretion is less altered. The narcotic effect on the brain in allaying anxiety and worry may also predispose to the enjoyment of food and improved appetite.

The divergence of opinion exists only in regard to the effects of small quantities, for all are agreed as to the deleterious action of any

but moderate doses of alcohol on the digestion. After large quantities (50 cc.) the irritation of the stomach wall leads to a profuse secretion of mucous, and to gastric catarrh. The nausea and vomiting may arise in part from the local irritation, but it is probable that the nervous centres are also involved directly, for these symptoms occur also under the anæsthetics in which there is no local irritation of the stomach. A large dose of concentrated alcohol sometimes leaves evidence of its irritant action in redness and injection of the mucous membrane, and, it is said, in ecchymoses, but in most cases of fatal poisoning no such appearances are to be observed after death.

Absorption and Excretion.—Alcohol is absorbed rapidly, about 20 per cent of that ingested being taken up in the stomach and 80 per cent in the small intestine. The rate of absorption varies with the concentration, strong alcohol appearing more quickly in the blood than the same amount in greater dilution; food delays the absorption when taken at the same time, especially if it contains much fat (Mellanby). The concentration of alcohol in the blood reaches its maximum about two hours after it is swallowed and then the level falls slowly, the amount in the blood being determined by the balance between that which is being absorbed and the amount undergoing oxidation and excretion. Harger and Halpieu found that 25 per cent alcohol given by mouth to dogs is absorbed very quickly. They say 89 per cent was absorbed in the first hour and that absorption was practically complete in two hours. The course of intoxication follows the curve of the concentration in the blood fairly closely.

It is found in largest proportions in the blood plasma, which contains about twice as much as the corpuscles; Grehant found as much as 6 parts per thousand in the blood of animals, but more than this was inevitably fatal; in a case of deep alcoholic coma in man the blood contained 2.25 parts per thousand (Sweisheimer). Traces remain in the blood for about twenty-four hours, but over 90 per cent of that ingested is oxidized in that time. The rate of oxidation of the alcohol in the body is proportional to the amount which is present in the body.

The oxidation may be hastened by the administration of dinitrophenol, under the influence of which the rate of consumption was practically doubled. The doses of dinitrophenol necessary to produce this effect were large, and the drug, therefore, would not be of practical value in the treatment of intoxication. Diathermy will also lessen the concentration of alcohol in the blood if the body temperature is maintained above normal for some hours.

The alcohol which escapes combustion in the tissues is excreted by the kidneys unchanged,[1] and by the lungs.[2] Haggard and Greenberg found in dogs that following the administration by stomach of 4 G. of alcohol per kilogram of body weight about 4 per cent of the amount taken was eliminated by the lungs during the first eight hours and that probably a total of 7 per cent of the alcohol taken is eliminated in the

[1] Some of the alcohol in the urine is combined with glycuronic acid in the rabbit, but not in man.

[2] The odor of the breath after spirit drinking arises from the higher alcohols and other by-products present in these and not from the ethyl alcohol.

expired air. The excretion of alcohol by the lungs is increased by muscular exertion and the consequent hyperpnœa. The amount excreted in this way can be raised, it is claimed, by increasing the volume of breathing by carbon dioxide and this method has occasionally been tried in the treatment of drunkenness, but exact studies have failed to indicate any decrease in alcohol concentration due to the carbon dioxide inhalation. The amount of alcohol excreted by the kidneys varies with the amount of urine, and the percentage of alcohol taken which is lost through the kidneys depends upon the amount of urine passed. During sixteen hours following the administration of alcohol to dogs approximately 2 to 4 per cent of the total amount taken is eliminated in the urine, the variation being due to the rate of urinary secretion. Haggard and Greenberg found that the concentration of alcohol in the urine in relation to that in the arterial blood corresponded closely to the relative solubility of alcohol in blood and in urine, and they conclude, therefore, that alcohol passes through the kidney by simple diffusion. More alcohol is excreted when it is taken on an empty stomach than when it is taken with food; but even in these conditions over 90 per cent undergoes complete combustion in the tissues. Traces are sometimes found in the sweat and milk, but there is no foundation for the legend that children may be intoxicated, or acquire a taste for strong drink from the alcohol absorbed in the milk of a drunken mother or wet-nurse. The amount and quality of the milk are unaffected by the administration of alcohol (Rosemann). Brauer states that alcohol is eliminated in some quantity in the bile and is then reabsorbed in the intestine; this is more marked in the case of amyl alcohol than in that of ethyl alcohol, and the alcohol in the bile is accompanied by albumin, epithelial cells, and casts of the finer bile ducts.

Is Alcohol a Food?—It has been shown that in man only 5 per cent or less of the ingested alcohol is excreted, while the rest of that absorbed from the stomach and bowel, amounting to over 95 per cent, undergoes combustion in the tissues. In undergoing combustion alcohol gives up energy to the body, and therefore is technically a food, but this does not imply that it is an advisable food in all conditions. Experiments in which the carbon dioxide excretion was measured under alcohol show that no more energy is required for its absorption than for that of other foods, and that alcohol taken in addition to the ordinary food undergoes oxidation instead of carbohydrate and fat, which in turn are used to build up reserves of energy in the body. Alcohol itself cannot be stored in the tissues and is therefore utilized in place of the carbohydrate, which is deposited as glycogen; an increase in the fat of the tissues has been shown to occur in animals treated with alcohol and is a common observation in man (Tögel, Brezina and Durig). Alcohol, therefore, acts as a substitute for carbohydrates and fat in the food and is utilized like them for the production of heat and work. Higgins has shown that its oxidation begins about five to ten minutes after it is swallowed; the body begins to utilize it as quickly as it does ordinary sugar.

It has long been recognized that when insufficient fat and carbohydrate is supplied to the body, the proteins are drawn upon to make

good the deficiency and the nitrogen eliminated rises accordingly. On the other hand, when the fats and carbohydrates of the food are increased, the organism economizes its protein and the nitrogen tends to fall. This is the most accurate method of testing the food value of non-nitrogenous substances, and alcohol has been the subject of a number of such investigations, which have finally decided this much disputed question (Neumann, Atwater and Benedict, and Rosemann and his pupils). The results may be best illustrated by an account of Neumann's first experiment.

This lasted thirty-five days, divided into six periods. The proteins of the food and the carbohydrates remained constant throughout, while alcohol was substituted for part of the fat for some time (see Fig. 9).

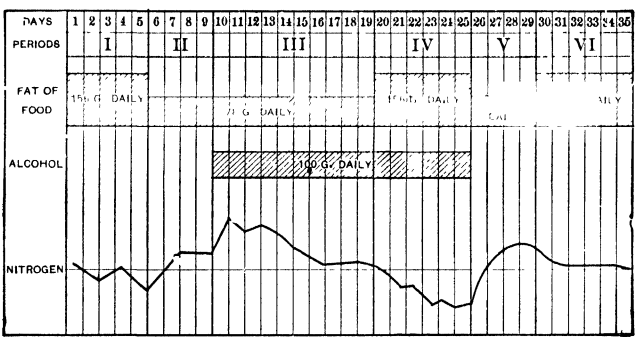

FIG. 9.—The effect of alcohol on nitrogen elimination. The wave-line represents the nitrogen excreted. It rises rapidly in the second period when the fat of the food was reduced to one-half, but soon falls in the third period where alcohol was substituted. 100 G. of alcohol is chemically equivalent to 78 G. of fat. (After Neumann.)

During the first five days the nitrogen excreted was practically equal to that of the food (nitrogenous equilibrium), while during the next four days one-half of the fat of the food was omitted and the immediate result was an increase in the nitrogen excreted, indicating that the proteins of the body were being drawn upon to make good the deficit in the fat of the food. The next ten days a quantity of alcohol chemically equivalent to the fat deficit was taken and the nitrogen elimination slowly fell to the normal (equilibrium). In the first five days of this period, however, the nitrogen remained high, showing that alcohol did not at first replace the fats completely. In the fourth period of six days, the same amount of fat was given as at first, while the alcohol was continued, and the nitrogen fell much below the amount ingested; *i. e.*, the alcohol again led to a saving of the proteins. Next, both alcohol and fat were omitted for four days and the protein tissues were again drawn upon. Finally the original diet was resumed and the nitrogenous equilibrium was at once restored. From this experiment Neumann drew the conclusion that alcohol can replace a chemically equivalent amount of fat in the dietary, for otherwise the nitrogen would not have returned to the normal toward the end of the third

period; and alcohol given along with a sufficient dietary leads to a further economy of the proteins just as additional fat would do; otherwise the nitrogen would not have fallen below the point of equilibrium in the fourth period.

The final result of all these investigations is that alcohol can take the place of some of the fat in the food, and leads to the same economy of protein as the ordinary non-nitrogenous constituents of the dietary. The first three or four days during which alcohol is substituted for fat it has little or no tendency to economize the proteins, but this is true of other forms of food also, any sudden change in the non-nitrogenous food leading to a temporary increase in the nitrogen excreted, which persists until the tissues have become accustomed to the new dietary.

Richter has shown that white rats can utilize an 8 to 16 per cent solution of alcohol as their steady fluid supply without intoxication or habituation. This high power of utilization is due to the high rate of metabolism in these animals and the amount taken is more than can be tolerated by man without signs of intoxication. These rats eat considerably less than controls receiving water alone but they grow just as fast and reach the same weight at maturity showing that in these animals alcohol not only replaced isodynamic quantities of food but also is used for growth and development.

Metabolism.—It was formerly supposed that alcohol economized the body tissues in some ill-defined way, by means of a direct action on the protoplasm of the cells; as it was expressed, alcohol lessened the combustion of the tissues. But moderate quantities of alcohol appear to have no action on the general metabolism except that which it shares with other nitrogen-free foods. When very large quantities of alcohol are taken, and depression and sleep follow, the combustion of the body is reduced, not through any action on the protoplasm generally, but through the muscular movements being lessened. In the same way, during the excitement stage, the carbon dioxide exhaled is doubtless much increased, because more energy and more of the body tissues are used up in the violent movements. The uric acid of the urine is considerably increased by moderate quantities in man, and this increase is shared by both the endogenous uric acid and that of the food. This specific action on the uric acid excretion has not been satisfactorily explained. The purin bases are increased to a smaller extent, while the creatinin excretion remains unchanged.

Effects on Growth and Progeny.—Large quantities of alcohol consumed continuously by growing rats were found by Sollmann to interfere with their growth and to lessen the consumption of food, but were not fatal even after several months; but these results have little bearing on the question of human consumption as the alcohol amounted to 2.5–9.5 cc. per kg., corresponding to about a quart of spirits per day in a man of average weight. Methyl alcohol was more than three times as deleterious.

Stockard found that when male guinea-pigs are intoxicated daily with alcohol for a week, and then crossed with normal females, the litters are often small and present numerous abnormalities, and this tendency may be transmitted through several generations; this indicates severe injury to the germ plasm of the original males, which is inherited by the

descendants. Others have made analogous observations, such as that the testes degenerate in both animals and man under the prolonged and excessive ingestion of alcohol; similarly the litters born of animals treated with alcohol are often small and are prone to die early.

Influence on Infection.—Persons addicted to the use of alcohol are known to show less resistance in acute disease and in operations accompanied by shock than more temperate individuals, and in very intemperate cases the prognosis must be guarded in an attack which would ordinarily be accompanied with little danger. This has been confirmed by a number of experiments on animals which were subjected to large doses of alcohol and then inoculated with pathogenic germs (Laitinen). The results have invariably shown a greater susceptibility to infection and a greater mortality than in control animals which had received no alcohol. A similar effect was observed when toxins were injected instead of bacteria, and great difficulty was encountered in rendering animals immune to the diphtheria toxin if they had previously been treated with alcohol. Various explanations of this reduced resistance have been given, Rubin ascribing it to paucity or inactivity of the leucocytes, while Abbot and Bergey found a reduction in the hemolytic complement, which suggests that the susceptibility to infection may be due to the failure to form the specific complement to the bacterial toxin. Reich, on comparing the reactions of the blood of abstainers and non-abstainers, found no difference in the phagocytosis of tubercle bacilli, while that of typhoid bacilli was greater in the abstainers and the serum also possessed greater bactericidal powers in these. The resistance of the red blood cells to the action of hypotonic saline solutions was also lower in the non-abstainers. But the differences in all respects were slight. It is often stated that alcohol given in the treatment of infectious diseases must have a similar deleterious effect on the resistance of the tissues, but this has not been shown to be the case.

These clinical and experimental results have raised the question whether the ordinary dietetic use of alcohol even in small quantities (15–30 cc.) may not lead to impairment of the resistance to infectious disease, and much interest attaches to Laitinen's later work, in which animals were treated with quantities of alcohol corresponding to those habitually used by temperate persons. The general result appears to be that the prolonged use of small quantities in animals (0.1 cc. per kilo) may affect their susceptibility to disease, but the average mortality is not greater than that of the controls to which no alcohol has been given.

A much more distinct effect from small doses of alcohol, such as correspond to temperate use in man, has been observed by Hunt, who finds that animals thus treated become more susceptible to the action of methyl cyanide. This poison acts in the tissues through being oxidized to hydrocyanic acid, and Hunt believes that the effect of the prolonged treatment with alcohol is to facilitate this oxidation, and that the reaction is evidence of an alteration of the metabolism of the body in this direction. The great importance of this observation lies in the fact that the modification of the metabolism which it demon-

strates, arises from the prolonged use of quantities of alcohol which are too small to give rise to definite symptoms of intoxication. Apparently the alteration is associated with the development of tolerance for alcohol.

Alcohol administered by mouth to normal dogs in doses of 2 cc. per kilo of body weight was found by Rosenthal to cause no increase in urobilin in the urine or bilirubin in the blood. The bromsulphthalein liver test showed slight impairment of liver function from which recovery was apparently complete within twenty-four hours. However, even this slight action on the organ seemed to render it more susceptible to the action of chloroform, as many dogs given a two-hour chloroform anæsthesia following recovery from the alcohol died within a few days with livers which showed the picture of acute atrophy. These findings are in harmony with those described by MacNider who found that in dogs which had been intoxicated with alcohol for twelve hours that the livers showed an injury which began in the periphery of the lobules and consisted of an œdema of the cells together with an increase in stainable lipid material. Associated with these changes there was an increased concentration of phenoltetrachlorphthalein in the blood. Recovery is largely complete in from two to three days.

The **Temperature** of the body falls somewhat after the administration of alcohol, but this is not due to any diminution in the oxidation and in the heat formed, but to the greater output of heat from the dilation of the skin vessels. The fall in temperature is comparatively slight, seldom being more than ¼–1° C., but it would seem that exposure to cold causes a greater fall in the temperature after alcohol than in normal conditions; this is perhaps due to the temperature-regulating mechanism being rendered less sensitive by alcohol.

The fall in temperature produced by alcohol is generally accompanied by a feeling of heat, and a thermometer applied to the skin may actually show a rise of several degrees, because more blood flows through the dilated vessels. If much excitement and movement follow the ingestion of alcohol, no fall in the temperature may result, the increased heat formed during the movement compensating for the increased output, and in some cases a rise of temperature occurs from the same cause. Very large quantities of alcohol may lead to a fall in temperature of 3–5° C., owing in part to the lessened movements during unconsciousness.

Repeated doses of alcohol produce **Tolerance**, which, although not so great as that acquired for morphine and nicotine, involves the prescription of double or triple doses in persons addicted to drinking. This tolerance has been shown by Pringsheim to arise in part from the tissues acquiring an increased capacity to oxidize alcohol; and as oxidation begins almost as soon as absorption, a large quantity of alcohol taken by an habitual drinker may not lead to the accumulation in the blood of a sufficient quantity to induce symptoms of intoxication (Fig. 10). But in addition to this factor, the brain reacts less than normally, for Sweisheimer finds that a given concentration of alcohol in the blood induces greater intoxication in an abstinent than in a toler-

ant person. In tolerance the amount of alcohol excreted in the breath and urine may sink to less than 1 per cent, all the rest undergoing combustion in the tissues. The close relationship between the narcotics of the fatty series is indicated by the fact that much more chloroform or ether than usual is required to anæsthetize persons in whom a tolerance for alcohol has been established.

Although alcohol seems to increase the **Urine** to some extent, it cannot be said to be a powerful diuretic in itself, and the diuresis may be explained in large part by the quantities of fluid taken with the alcohol and by the accelerated absorption from the alimentary tract. Some of the spirituous liquors, such as gin, produce a larger secretion of the urine, but this is due to their other constituents, and not to the alcohol.

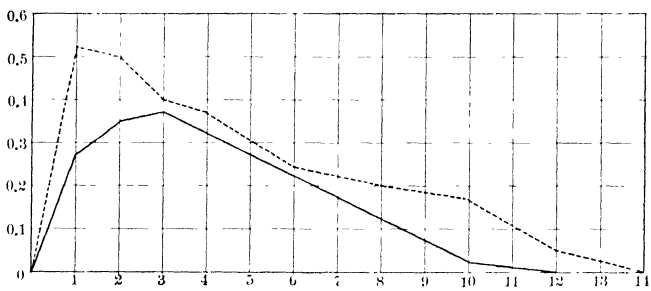

FIG 10.—The percentage of alcohol in the blood after giving 5 cc per kg. to rabbits. The percentage is indicated on the perpendicular line, the hours after administration along the horizontal. The broken line represents the changes in percentage in a normal animal, the unbroken that in an animal which had acquired tolerance through prolonged treatment with alcohol previously. (Pringsheim.)

MacNider has compared the effects of ethyl alcohol and of an alcoholic distillate made from meal and sugar or molasses upon the kidneys of normal and nephropathic dogs. He found that alcohol has little effect upon the kidneys of normal dogs but that nephropathic animals were more susceptible, the alcohol causing an increased urine formation and a slight increase in the albumin present in the urine. The fresh distillates were much more toxic, producing in normal animals an increase in urine with large amounts of albumin, the glomeruli showing evidence of fatty changes. In nephropathic animals the increase in urine was only slight and was followed soon by reduction in the quantity and finally by anuria. In the early stages the albumin in the urine was much increased and there were numerous casts. The greater toxicity of the fermented mixtures was evidently not due to the ethyl alcohol contained but to some other unknown substance.

Alcohol is generally credited with **Aphrodisiac powers**, that is, with increasing sexual desire, although no less an authority than Shakespeare states that it prevents the consummation of sexual intercourse. The unquestionable tendency toward sexual excess observed in intoxication is due, not to any effects on the generative organs, but to the loss of self-control, from the cerebral action of the poison.

Alcohol possesses only a weak **Antiseptic** action, for while the growth of some bacteria is delayed somewhat in a 1:1000 solution, many grow abundantly in 4 per cent alcohol, and some in even stronger solutions. Its disinfectant action has been the subject of a number

of researches recently and has been found to vary with the conditions. Dry bacteria may be exposed to absolute alcohol for twenty-four hours without losing their vitality, while 60-70 per cent alcohol is fatal to them, and also to moist organisms. The explanation of this curious observation seems to be that alcohol fails to penetrate microbes except in the presence of water. In less than 60 per cent the action is very slow, so that the optimum strength of alcohol as a disinfectant may be placed at 70 per cent. Below this concentration its disinfectant properties decrease rapidly so that when it is to be used to disinfect the skin, as in the case of the hands, they should be dried with a sterile towel after being scrubbed so as not to dilute the alcohol. (See Alcohol, as disinfectant, p. 787.) Many bodies which are antiseptic when dissolved in water have comparatively little effect when dissolved in alcohol.

Other simple life forms are more susceptible to the action of alcohol than the bacteria, though it does not act on these in such dilution as it does on the mammalian nerve cell. Even the plants can be subjected to its influence, showing that in sufficient quantity it is a general protoplasm poison. In most cases a stage of increased activity precedes that of depression and this has been used as an argument in favor of the primary stimulant action of alcohol in the brain.

Methyl alcohol, or wood alcohol, has assumed importance from a large number of cases of poisoning having occurred from its being substituted for ethyl alcohol as an intoxicant, from its presence in proprietary remedies, or from its use in the industries. In animal experiments it is found that, given in single doses, it is slightly less poisonous than ethyl alcohol, the action coming on somewhat more slowly, but lasting a longer time; the symptoms of gastric irritation are generally more marked than those induced by ethyl alcohol, and very often some convulsive movements are observed (Hunt). When the administration is repeated, methyl alcohol is found much more poisonous than ethyl, and this arises from its slower oxidation and consequent prolonged action. Thus it has been shown that when equal amounts of methyl and ethyl alcohol are administered to animals over one-third of the methyl alcohol can be found in the tissues for forty-eight hours, while of the ethyl alcohol only about one-tenth remains after fifteen hours. About 40 per cent of the methyl alcohol is oxidized in forty-eight hours, while 20 per cent escapes in the breath and 3 per cent in the urine. Pohl has pointed out that while ethyl alcohol undergoes complete combustion in the tissues, methyl alcohol is slowly oxidized to formic acid, most of which is excreted in the urine. According to Haggard and Greenberg, methyl alcohol is chiefly eliminated by the lungs (over 70 per cent) and only to a small extent oxidized.

In man the symptoms of wood alcohol poisoning differ from those of ordinary spirits in the more marked abdominal pain together with nausea and vomiting, muscular weakness and defective cardiac action with coma. Delirium may be much more intense and persistent than that seen in intoxication with ethyl alcohol. In a considerable number of cases death has followed from a single dose smaller than would have been fatal had ethyl alcohol been swallowed, and in some cases total and permanent blindness has followed or accompanied recovery. This condition is more often the result of repeated ingestion of the alcohol, however, and is due to optic neuritis and subsequent complete optic atrophy. The large number of cases of blindness or fatal intoxication collected by Buller and Wood demonstrate clearly the danger incurred in the use of this poison internally or even externally, or by inhalation of its vapor. Optic atrophy has been induced in animals repeatedly by the administration of wood alcohol while it is hardly liable to occur from ethyl alcohol.

The **other alcohols** are mainly of interest as impurities of the preparations of ethyl alcohol. They all resemble it in their general effects, but differ from it in toxicity; propyl alcohol is more powerful than ethyl, butyl than propyl, and amyl than any of them. Amyl alcohol, or fusel oil, is present in small quantity in most forms of spirits. It resembles ethyl alcohol in general, but is more irritant locally, and is believed by some authorities to have more deleterious effects in chronic poisoning than pure ethyl alcohol. This is not based on any very satisfactory evidence, however, and all the characteristic symptoms of chronic alcoholism have been produced in animals by pure ethyl alcohol. Furfurol is also present in many forms of spirits, but in such small quantities that it does not play any rôle in the symptoms induced by them.

Therapeutic Uses.—Alcohol is used *externally* in dilute solution as a cooling application to the skin, and in preventing bedsores, in which it is often applied in order to harden the epidermis. It has been employed as an antiseptic and mild irritant to broken surfaces, and if applied to the skin in concentrated form, and especially if kept from evaporation, acts as a rubefacient and irritant. Its use to wash the skin and hands before operations arises from its power of cleansing the skin and removing the oils and fats as well as from its disinfectant action. In the form of diluted claret it has been used as an astringent gargle. Strong alcohol (80 per cent or more) is often injected into nerves or ganglia for the relief of neuralgia, sciatica, and similar disorders and leads to degeneration of the nerve fibres and paralysis of sensation and motion, which lasts until the nerve fibres are regenerated after several months. The pain disappears until this restoration is complete, and sometimes permanently. The local nerve destruction arises from the precipitation of proteins and the solution of lipids.

The indications for the *internal* use of alcohol are ill defined, and cases which one physician would treat with alcohol often seem to progress as favorably without it in the hands of another. It has been prescribed very largely in the past as a "stimulant" under the impression that it increases the activity of the circulation, respiration, and other functions of the body. The basis for this belief has been discussed already, and the results may be stated shortly: alcohol may promote the vital functions to a slight extent, but this action is very transient and inconstant in its occurrence and is quite insufficient basis for any therapeutic application. The action which lends alcohol its value in therapeutics is not its stimulant but its narcotic action, which allays the anxiety and distress of the patient, promotes rest and sleep, and thus aids toward healing, or at the worst renders illness more tolerable. Small quantities of other narcotics might be substituted for alcohol, but perhaps none of them excel it in producing that spirit of hopefulness and restful confidence which contributes so much to recovery.

One series of symptoms which is often treated with wines is of gastric origin, and is manifested in want of appetite and enfeeblement of the digestion; in some of these cases the alcoholic preparations seem to be beneficial, while in others they appear to be positively harmful. This may be explained by the effect of alcohol on secretion and absorption, only those cases in which secretion is deficient being benefited,

but the tastes and mental condition of the patient are a more important factor; if he enjoys the taste and odor of wine, its administration may promote his appetite, and if he is anxious and worried the relief of this condition through the narcotic action of alcohol may restore confidence and improve appetite. In these cases "dry" wines are to be preferred, as the sugar of the sweet wines may irritate the stomach; champagne may be used, and the wine ought to be given immediately before or during a meal. In gastric disorders associated with hyperacidity the use of alcoholics is contra-indicated.

Cases of hemorrhage, shock and other forms of severe and sudden depression of the heart and central nervous system are very frequently treated by the administration of strong alcoholic preparations, such as brandy and whisky, this treatment being based upon the belief that alcohol is a cardiac and respiratory stimulant. It is extremely difficult to estimate the value of a remedy in these conditions, and it is possible that it may be of benefit in some cases by lessening the anxiety and pain of the patient if he is conscious.[1] But the beneficial effects of alcohol in these cases have been much questioned in recent years, and the belief that it is of little value is certainly more widely held at present than at any previous time; in experimental shock in animals, Crile found that alcohol generally increased the danger when given in average doses, and that smaller doses had no beneficial effects, but it is quite possible that in man different results may be obtained, from alcohol acting as a narcotic and removing nervous symptoms which would not arise in the lower animals. In unconsciousness it is probably of no value.

"Chill" appears to be a sudden constriction of the vessels of the mucous membranes in the nose and throat which arises reflexly from cooling of a more or less extensive surface of the skin of the trunk or head (Mudd and Grant); the diminished supply of blood lessens the resistance to the invasion of bacteria which may be present in the throat, and chill is therefore often followed by infection and fever. Anything which dilates the skin vessels, at once restores the circulation in the mucous membranes and at the same time relieves the sensation of cold arising from the ischæmia of the skin. Alcohol is often of benefit in chill especially when taken in the form of brandy or whisky diluted with hot water, and this is obviously due to the dilation of the skin vessels.

[1] Medical and lay tradition is in favor of giving alcohol in a concentrated form, *e. g.*, neat brandy or whisky, in cases of fainting or acute circulatory failure. Here possibly the irritant action of strong alcohol on the mouth and stomach may act as a reflex stimulant both to the vasomotor centre and cerebrum. On the other hand, when alcohol is taken for its exhilarating effect, preference is given to it in the form of wine. On this interpretation no better description of its therapeutic values has been given than that in the Book of Proverbs, which incidentally affords a fine example of biblical prose rhythm:

> "Give strong drink unto him that is ready to perish,
> And wine unto those that be of heavy hearts,
> Let him drink and forget his poverty,
> And remember his misery no more."

Nor were the dangers of alcohol in upsetting the higher faculties forgotten, for it is also admonished, "It is not for kings to drink wine, nor for princes strong drink, lest they drink and forget the law."

Other drugs with the same effect are the volatile oils, camphor and opium, especially when given with a diaphoretic as in Dover's powder.

In many cases of acute inflammatory disease, the prescription of alcohol seems to be attended with benefit, while in others it seems rather to increase the severity of the symptoms. No special indications can be given for alcohol in these cases, and the physician must be guided by its effects. It may tend to allay the irritability of the nervous centres, and thus reduce the delirium and slow the heart and respiration by lessening the muscular movement; Cabot and Dening and his pupils state that the administration of alcohol to patients is not followed by any significant rise of blood-pressure, but by a slight fall in most cases. Moreover, the tissue waste is much increased in fever, and at the same time the food absorption is less than normal, so that many of the symptoms may be due to starvation of the tissues. The food-value of alcohol is unchanged by the presence of fever (Ott); it demands less energy from the digestive organs than fats and starchy foods, and has a higher value as a producer of energy than sugar. It cannot supply the place of the nitrogenous foods, but given along with them, may lead to a greater economy of the tissues. Strong wines or diluted spirits are generally employed here and ought to be given in small quantities frequently.

Alcohol was formerly advocated especially in septic conditions, and here it may be of value on the same grounds as in acute fevers, although it does not seem to have any specific action in septic disease, as was once believed. A protest has recently been raised against the use of alcohol in these cases, on the ground that animals subjected to alcohol succumb more readily to infection than controls which have received no treatment, but this increased susceptibility does not seem to be induced by doses proportioned to those in use in modern practice. In addition, this deleterious action may be more than compensated for by its value as a food and by its narcotic effects allaying the nervous irritability and promoting sleep; this narcotic action may very well be conceived to be of benefit to man, while actually prejudicial to animals.

In some chronic forms of nervous disease alcohol may also be of value, although its administration must always be guarded, owing to the tendency to the formation of the habit. Thus, in some forms of melancholia and of neuralgia it gives relief; and in cases of distress of mind from any cause, such as grief, business anxiety or depression, alcohol acts by its narcotic action on the brain, but the danger of the alcohol habit is so great that most physicians refuse to take the responsibility of prescribing the drug in such cases.

In certain forms of brain defect, notably in epilepsy, alcohol often acts with unusual power and sometimes appears to cause a prolonged nervous disturbance which is very deleterious in these subjects.

In chronic conditions of cachexia and loss of flesh in general, and during convalescence, alcoholic preparations are often advised simply as foods, or as stomachics and in these cases the ales, beers and porters are generally to be preferred to the others, provided always that the

stomach is not irritated by them, as they contain other foodstuffs of value in addition to the alcohol.

In the treatment of diabetes by the withdrawal of carbohydrates, alcohol has been advised to maintain the supply of energy, which it does without increasing the sugar of the blood and urine. Here wines or beers are not available, and pure alcohol diluted to about 5 per cent is the best form; it may be given in quantities corresponding to 5–10 cc. of absolute alcohol every hour, and causes no symptoms, as it is completely oxidized in this time, and supplied 600 or more calories per day.

In poisonous snake bite, alcohol is generally administered in enormous quantities, either as whisky or brandy, but it is really of no value in these cases except as a narcotic.

Alcohol is of value as a mild hypnotic, a comparatively small quantity taken before retiring being often sufficient to secure quiet and refreshing sleep. Beer, or spirits and water, is generally used for this purpose.

Brandy has a certain reputation in the treatment of the milder forms of diarrhœa, while the other spirits have no effect in this condition. The way in which it acts here is unknown.

In the prescription of alcohol, the ordinary spirits, brandy or whisky, are much more frequently advised than the pure preparations, as the latter are more apt to pall upon the taste of the patient. Both of these spirits ought to be diluted with at least an equal quantity of water. The wines are more used in chronic conditions, although diluted spirits may be advised here also. Beers are employed only in debility unaccompanied by gastric symptoms.

Alcohol can be given to children in relatively larger quantities than to adults, and again in old age no such reduction in the dose is required as in the case of many other drugs. Where a tolerance for alcohol has been established, the dose has often to be more than doubled in order to have any effect, and in acute febrile conditions very large quantities of alcohol are often given without intoxication, though it seems questionable whether an equally beneficial result could not be attained with smaller doses. In gastric irritation, most preparations of alcohol are contra-indicated, but champagne is often of benefit in checking vomiting, especially that of pregnancy and of seasickness, this effect being due to the carbonic acid and not to the alcohol. In nephritis and other inflammatory conditions of the genito-urinary tract, alcohol is generally avoided on account of its supposed effect on the epithelium.

Preparations.

U. S. P.

Alcohol. Contains about 94 per cent of alcohol.

Alcohol Dehydratum. Absolute alcohol contains not less than 99 per cent of alcohol.

Alcohol Dilutum. Diluted alcohol contains about 50 per cent by volume of alcohol.

Spiritus Frumenti. Whisky.

Spiritus Vini Vitis. Brandy.

Whisky is an alcoholic liquid obtained by distillation of the fermented mash of wholly or of partly malted cereal grains and contains about 50 per cent by volume of alcohol.

Brandy is obtained by the distillation of the fermented juice of grapes and contains between 50 and 54 per cent of alcohol.

B. P.

Alcohol, 95 per cent. In addition to 95 per cent alcohol there are also included in the British Pharmacopœia eight dilute alcohols ranging in strength from 90 per cent alcohol to 20 per cent.

Alcohol Dehydratum. Dehydrated or absolute alcohol. Contains not less than 99.4 per cent of alcohol.

Spiritus Methylatus Industrialis. Industrial methylated spirit is a mixture of 19 volumes of 95 per cent alcohol and 1 volume of wood naphtha.

The **Spirits** are more frequently ordered than these preparations of pure alcohol. Whisky is made by distillation from an extract of fermented grain, brandy from wine, rum from fermented sugar refuse and gin from an alcoholic extract of various herbs.

These spirits all contain, roughly speaking, about 40-50 per cent of alcohol along with other volatile substances, some of which are alcohols of the same series as ordinary alcohol (butyl, amyl, etc.), while others are of entirely unknown constitution—the œnanthic ethers. Brandy and whisky act very much in the same way as pure alcohol. When freshly distilled they are more irritant and less pleasantly flavored than when kept for some years but they do not seem more deleterious, although the experiments of MacNider raise some doubt as to the latter statement in so far as the effect upon the kidney is concerned. (See page 304.) Numerous other preparations containing large quantities of alcohol, such as the spirits of the volatile oils, might also be included in this group, but they are not used, as a general rule, for the same purposes as the alcoholic preparations proper, and their effects are in part due to the volatile oils contained. Some of them have, however, been employed as intoxicants instead of brandy or whisky, and Eau de Cologne and other essences have gained a certain notoriety as a means of secret drinking among women. The liqueurs are too numerous to mention, and their composition is extremely diverse. Many of them contain considerable quantities of sugar, and the combination of alcohol and sugar would seem peculiarly deleterious to the gastric mucous membrane. Others, such as cherry water (Kirschwasser), contain hydrocyanic acid, and the others various bodies of the volatile oil series. None of them seems to have any properties which would recommend their use in therapeutics.

The **Wines** and **Beers** are much weaker preparations of alcohol, the light wines (hock and claret) containing about 6-8 per cent ethyl alcohol, while in sherry and port it may amount to 15-20 per cent. In addition, the wines contain the same volatile constituents as brandy, although in smaller amounts. The red wines contain a form of tannic acid derived from the skin of the grapes, and both red and white often contain considerable quantities of acids, chiefly tartaric acid. The amount of sugar varies with the different wines, and in fact in wine from the same locality but of different seasons. These constituents may lend to the wines a deleterious local action on the stomach, more especially when they are taken habitually. Champagne and the other sparkling wines contain large quantities of carbonic acid, which acts as a stimulant to the gastric mucous membrane. Champagne is considered one of the most "stimulant" of alcoholic preparations, although it contains a very low percentage of alcohol compared with spirits, a fact which is of some significance in the explanation of the "stimulant" effects of alcohol.

The beers are not pharmacopœial, and are less frequently advised than the other preparations. They generally contain a comparatively small percentage of alcohol (3-5 per cent), along with a large amount of solids. These solids

consist mainly of dextrin, sugar, and other starch products, which retard the absorption of the fluid, but are of some value as foods. The hops added in the preparation have probably no action save as bitter stomachics. The alcohol of beer is comparatively slowly absorbed, owing to the colloid constituents, and this allows time for fermentation changes in the sugars and dextrins, which may perhaps account for the discomfort produced by malt liquors in persons of feeble digestion. When beers and porter do not derange the digestion, they are the most nutritive of all the alcoholic preparations, owing to the large amount of carbohydrates they contain.

In regard to the **Habitual Use of Alcohol** by healthy persons, all authorities agree that it is a luxury, that it is entirely unnecessary for the growth and maintenance of the body, and that it neither promotes greater healthfulness nor in any way retards the onset of disease. It is true that it is utilized by the body as a food, but its value as such is limited because only small quantities can be taken without disturbance of the nervous system. At the same time it is difficult to prove that the moderate use of alcohol is injurious, for when taken after work it seems to cause no impairment of the capacity for work next day and often seems to remove the sense of fatigue. And in many it undoubtedly promotes happiness and allays the worries and anxieties of life. Attempts have been made to show that even the moderate use of alcohol lessens the resistance to the onset of disease, but these have not been successful. There are, however, two considerations which may be brought against the use of alcohol even in the most strictly limited quantities. The first of these is drawn from the statistics of life insurance, in which it is found that the prospects of longevity are better for total abstainers than for even moderate users of alcohol.[1] The second is that the moderate use of alcohol leads to chronic alcoholism in a certain percentage of persons.

The habitual indulgence in alcohol to excess is more easily intelligible than some other chronic intoxications, for, unlike nicotine, alcohol is taken not only for its local effects on the organs of taste and on the mucous membranes of the mouth and stomach, but also for its action on the brain in numbing the consciousness of unhappiness, and this weakening of the higher sensibilities by drink is generally the object sought by the drunkard. He finds that under alcohol his habitual depression disappears, and he loses the sense of degradation and remorse which possesses him when sober. The depression returns in exaggerated form after the effects of the drug have passed off, but it can be removed again by the same means, and in this way the habit is formed, each successive dose being rendered necessary by the depression produced by its predecessor. This descent into chronic drunkenness is facilitated by the lessening of the self-control, owing to the action of alcohol on the brain. The victim may form the best of resolutions, but his impaired will power and self-control are unable to carry them out.

The symptoms of **Chronic Alcoholism** are unfortunately common, but

[1] There seems no question that there is some advantage in favor of the abstainer, though it is smaller than is generally stated; no explanation has been offered, but it may be that the abstainer is less liable to accidents of all kinds including those of syphilitic infection.

may be treated better in detail in connection with various forms of disease, with which they are associated more closely than with the effects produced by the medicinal use of the drug. The earliest symptoms are generally observed in the stomach, throat and larynx, and consist of a chronic catarrh, which is often accompanied by skin affections, such as injection of the cutaneous vessels (especially those of the face), acne, or pustular eruptions. Fatty degeneration occurs in the liver especially, and is said to be accompanied by a marked decrease in the lecithin and other lipids of the cells. Cirrhosis of the liver is not now believed to be the direct result of alcoholism. Fatty degeneration is also found in the arterial walls throughout the body, and favors the development of atheroma and arteriosclerosis, which may lead to small aneurysmal dilatations, ecchymoses, or apoplexy. The heart undergoes more or less fatty change, which is accompanied by dilatation and weakness. In the central nervous system, the nutrition is imperfect owing to the vascular changes, but in addition to this, alcohol has a special action on the neurons, which is betrayed by the disappearance of the chromatin granules, and eventually by shrinkage of the whole cell. These alterations in the central nervous system lead to impairment of memory, self-control, and the other higher mental processes. Tremor, convulsive attacks, hallucinations and mania are eventually followed by idiocy and paralysis in the worst forms of the disease. The peripheral nerves seem to be acted on directly as well as through the changes in the centres, for neuritis has been frequently observed, ending in local paralysis. A form of amblyopia commencing with atrophy of the retinal ganglion cells and later extending to the fibres of the optic nerve has recently received some attention; it is much more readily elicited by methyl than by ethyl alcohol. Due to the similarity of the neuritic symptoms occurring in chronic alcoholism and in beri-beri it has been suggested that the neuritis ascribed to alcohol may, in reality, like that of beri-beri, be due to vitamin B_1 deficiency. This view has received considerable support since it has been shown that alcoholics suffering from neuritis are frequently not taking an adequate vitamin B-containing diet. Further it has been found that such patients may rapidly improve when this deficiency is supplied even though their alcohol intake may still be continued.

A characteristic result of chronic alcoholism is *delirium tremens*, an acute attack of insanity which is liable to occur after any shock, such as hæmorrhage or acute disease, but which is said to be also produced by the sudden withdrawal of alcohol, and sometimes occurs without any apparent immediate cause. It is characterized by tremor, perspiration, sleeplessness, fear, excitement, and hallucinations of the various senses, which differ from many other hallucinations of insanity in consisting of the multiple appearance of the same object. These objects are often animals, such as snakes, rats, dogs, but the hallucinations are not confined to those of sight, for whispering voices are complained of not infrequently.

The more severe forms of chronic alcoholism are confined almost entirely to the drinkers of undiluted spirits. Beers and wines seldom

cause any distinct lesions in the brain in themselves, unless spirits are also indulged in. The abuse of the weaker preparations of alcohol is always liable to lead to that of the stronger, however, as tolerance is established and the former lose their effect. The combination of spirits and malt liquors is said to be more liable to produce delirium tremens than the abuse of either alone.

The disastrous effects of the abuse of alcohol are seen in the statistics of the hospitals, prisons, and asylums in nearly all countries, but more especially in those in which the population is addicted to spirits. A large percentage of crime is admittedly done under the influence of alcohol or as a direct result of alcoholic excess, which is also responsible for a large part of the poverty and misery of the lowest classes of the population. A considerable proportion of the admissions to lunatic asylums is also often ascribed to alcoholism, although Mott has pointed out that this factor is not infrequently exaggerated. And it must be taken into account that only the more extreme cases come under the categories of criminals or lunatics, and the enormous number of cases of disease directly caused or aggravated by the lesions due to alcohol escapes recognition. At the same time, it is beginning to be appreciated that chronic alcoholism itself is probably due to a mental defect, so that in a certain number of these cases of insanity and crime, the over-indulgence in alcohol should probably be considered a symptom and not a cause. On the other hand, alcoholic excess aggravates the mental defect in these cases, both by its direct action and through the social and economic disabilities which arise from it; and this aggravation of a congenital weakness can be avoided only by abstention from alcoholic beverages. Attempts have been made of late years to demonstrate that the effects of alcohol are hereditary, that the children of alcoholics supply a larger proportion of cases of insanity and crime than those of the rest of the population. It would seem more probable, however, that the alcoholic excesses of the parent have no direct effect on the offspring, except in their nutrition at birth, but that the mental defect which leads to alcoholic excess in the one generation is inherited and leads to crime or insanity in the next. The deleterious effect of the alcoholic habit in the parent on the nutrition of the offspring is a well-established fact. (See p. 301.)

The treatment of acute alcoholic intoxication is to evacuate the stomach by means of the stomach tube or by the injection of apomorphine. The patient ought to be put in bed and kept warm, as there is a tendency to a marked fall in the body temperature. In case of great congestion of the brain, cold may be applied to the head in the form of ice-bags, and some authorities recommend bleeding. In cases of extremely deep unconsciousness, stimulants, such as caffeine or strychnine, may be employed, and, as a last resort, artificial respiration. In extreme cases the inhalation of a mixture of carbon dioxide, 10 per cent, and oxygen 90 per cent has been recommended. It is claimed for this method of treatment that patients receiving it breathe more deeply and regularly and that cyanosis disappears, being replaced by a more normal hue.

Chronic alcoholism is to be treated by the withdrawal of the poison, and this is best done gradually, as the immediate stoppage may lead to delirium tremens. It is usually necessary to incarcerate the patient in some retreat. A large number of drugs has been advocated in these cases, some of them, such as opium, acting as substitutes for alcohol, others (capsicum) replacing the local action on the stomach. The use of opium and other narcotics may, however, lead to a craving for these which would be even more serious than the original condition. Another method of treatment, which appears to be successful in some cases, is the addition of nauseating drugs such as ipecacuanha or apomorphine to the alcohol which is supplied to the patient. The association of nausea with liquor eventually becomes so strong that alcohol in any form becomes distasteful. The organic lesions must be treated individually.

The **treatment of delirium tremens** generally consists in the use of barbital, chloral or scopolamine to lessen the excitement. It may be advisable to allow small quantities of alcohol, as the sudden withdrawal may aggravate the condition.

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II. GENERAL ANÆSTHETICS.

1. Ether and Chloroform.

The term general anæsthetics is employed to indicate substances used to produce unconsciousness sufficiently complete to allow of surgical operations being performed. In the history of medicine there are repeated obscure allusions to substances used for this purpose, but it was not until the end of the first half of the nineteenth century that the era of surgical anæsthesia really opened. In 1798 Davy advised the use of nitrous oxide as an anæsthetic, but no practical use was made of his suggestion, and Wells may be said to have rediscovered this property of the gas in 1844, though his efforts to introduce it into general use met with no greater success than Davy's. Long used ether in 1842-1843 in surgical operations, but did not give any publicity to his discovery, and the honor of demonstrating publicly the practical use of ether in surgery must be awarded to Jackson and Morton in 1846. In 1847 Simpson introduced chloroform to the medical profession as a substitute for ether, over which he supposed it to possess several advantages. Its pharmacological action had been examined some months earlier by Flourens, but Simpson appears to have made his investigations quite independently. Chloroform soon ousted ether in popular favor in Europe, and, although in America a considerable number of surgeons continued to use it, ether was for many years little used throughout Europe, save in Lyons. The increasing number of accidents in chloroform anæsthesia caused a reaction to set in in favor of ether which is now far more extensively used than chloroform throughout the world.

Many attempts have been made to introduce other substances of the methane series as substitutes for the two generally recognized anæsthetics, and ethyl chloride is used for short operations. Soon after the introduction of ether and chloroform, nitrous oxide gained a permanent footing as an anæsthetic and more recently several new anæsthetics have been introduced.

These anæsthetics are invariably given by inhalation and not by the stomach, as it is found that the exact depth of the narcosis can be much more easily controlled by the former method. Both the absorp-

tion and excretion of these drugs occur almost entirely by the lungs, according to the ordinary physical laws of the absorption of gases by fluids. The more concentrated the vapor of chloroform in the lungs, the greater is the quantity absorbed into the blood and the deeper the narcosis. By regulating the proportion of the vapors in the air inhaled, therefore, an anæsthesia of any desired depth may be induced. The degree of narcosis and of danger is not indicated so much by the actual amount of the anæsthetic which has been used as by the concentration of the vapors which have been inhaled and the consequent concentration in the blood.

Symptoms.[1]—The action of chloroform and ether may be divided into three stages: (1) that of imperfect consciousness; (2) that of excitement; (3) that of anæsthesia.

The *first effect* of their application is a feeling of asphyxia, which is especially marked in the case of ether, and of warmth of the face and head and eventually of the whole body. The senses become less acute, the patient seeming to see only through a veil of mist, and the voices of those in the immediate neighborhood appearing to come from a distance. Ringing, hissing and roaring in the ears and a feeling of stiffness and of inability to move the limbs herald the approach of unconsciousness. With the exception of the first feeling of suffocation, the sensations are generally pleasant. During this stage the face is generally flushed, the pupils enlarged, the pulse is somewhat accelerated, and the respiration may be rendered irregular by the sense of suffocation, or may be slightly quickened. Even at this early stage sensation is blunted.

The *second stage* of excitement varies extremely in different individuals. In some cases, especially in children, it is entirely absent, and in others its presence may be indicated merely by tremor, by the stretching of the limbs, or by irregularities in the respiration, but in the majority of cases of anæsthesia it is much more marked. It often begins by movements of the arms, designed either to push away the inhalation mask or to enable the patient to rise; soon his other muscles are involved in the movement; he struggles, shouts, sings, groans, or bursts into laughter. The movements are generally not uncoördinated, but are evidently the result of some dream-like condition of

[1] The poet, Henley, has given the following description of his sensations under chloroform in Lister's wards in the Royal Infirmary, Edinburgh.

Then they bid you close your eyelids,
And they mask you with a napkin,
And the anæsthetic reaches
Hot and subtle through your being

And you gasp and reel and shudder
In a rushing, swaying rapture,
While the voices at your elbow
Fade—receding—fainter—farther.

Lights about you shower and tumble,
And your blood seems crystallizing—
Edged and vibrant, yet within you
Racked and hurried back and forward.

Then the lights grow fast and furious,
And you hear a noise of waters,
And you wrestle, blind and dizzy,
In an agony of effort.

Till a sudden lull accepts you,
And you sound an utter darkness—
And awaken . . . with a struggle . . .
On a hushed, attentive audience.

the consciousness, and these dreams are often connected with the operation or with the surroundings of the patient before the inhalation began. They are, of course, determined largely by his natural mode of thought—one person prays aloud and sings hymns; another abuses the surgeon, the hospital and all his recent surroundings, while yet another is overcome with the fear of impending death and laments his unfortunate position. In this stage the pulse is generally quickened, the skin is flushed and often cyanotic, the respiration is extremely irregular from the struggling, and the pupil continues somewhat dilated. If the anæsthetic be pushed, however, the movements soon become less powerful, the muscles relax and the stage of anæsthesia sets in.

In the *third stage* the face assumes a calm, death-like appearance from the relaxation of the muscles, the pupils contract somewhat and may not react to light. The reflexes disappear, one of the last to go being the closure of the eyelids on touching the cornea. The pulse is generally somewhat slow and weak; the face is pale in chloroform anæsthesia, but may be suffused and cyanotic after ether. The respiration is slow and shallow, but regular. This stage of anæsthesia may be kept up for hours without much change by the repeated inhalation of small quantities, although the pulse tends to become weaker and the respiration shallower unless the greatest care be exercised, and the body temperature invariably sinks. When the administration ceases, the patient passes again through the excitement stage, which, however, is not generally as violent, although it may be more prolonged, and then often sinks into sleep, which lasts several hours. Not infrequently, however, instead of sleep, nausea, giddiness and vomiting continue for some time after the return of consciousness.

In surgical anæsthesia, the third stage is often interrupted by short intervals of semi-consciousness and slight excitement if the administration of the drug be interrupted occasionally.

The use of these drugs is so widespread, and the indications of danger in anæsthesia are so important that a more detailed account of the alterations observed during their use in the human subject may be inserted here.

The *pulse* is often somewhat accelerated before anæsthesia, owing to the anxiety and nervousness of the patient, and in the first, and still more the second stage, a further acceleration may occur from the same cause, although in other instances marked slowing of the pulse may set in here from reflex stimulation. When the stage of anæsthesia is reached, the pulse becomes slower and weaker than normally, and this change increases with the depth of the anæsthesia produced. It remains perfectly regular, however, in ordinary cases, and, in fact, unless the anæsthesia has reached an extremely dangerous stage. In very prolonged, deep anæsthesia the weakness of the pulse may give rise to anxiety, especially if the temperature of the body is very low.

The *respiration* is generally fairly regular until the second stage, save that the breath may be held for some time owing to the choking sensation, and a deep gasp may follow; coughing is occasionally met with, especially in the first stage of ether anæsthesia. In the second

stage, the respiration is extremely irregular when the excitement is violent. The respiratory muscles are involved in the general convulsive movements, so that no air whatever can enter the lungs for several moments, and then several deep gasps may follow and load the blood with concentrated vapor. During the third stage the respiration becomes regular but shallower and slower than before the anæsthetic was applied, and if the operation be prolonged, the weakness of the respiration may give rise to alarm. Large quantities of saliva and mucus may hinder the respiration and require removal, and a common occurrence is the production of snoring from the falling back of the tongue, and this may also require attention.

The behavior of the *pupil* is of some importance in anæsthesia. During the first and second stages it is generally somewhat dilated, but as soon as complete unconsciousness is attained, it becomes rather narrower than it is normally. As the patient recovers, the slight dilatation slowly recurs; if the respiration and circulation be dangerously weak, rapid dilatation occurs in most cases. Dilatation of the pupil in the stage of anæsthesia, therefore, indicates danger, unless it is accompanied by symptoms of returning consciousness, such as reflex movements and vomiting.

The *hypersecretion* of saliva and of bronchial mucus is much more marked in ether than in chloroform anæsthesia. *Vomiting* occurs so frequently during anæsthesia that it may be looked upon rather as one of the attendant phenomena than as an accident. It may set in practically at any time, but is more often seen in the late than the early stages, and more frequently when the anæsthetic is applied soon after a meal than when the stomach is empty.

Action.—The action of ether and chloroform on the **Central Nervous System** is evidently similar to that of alcohol, although the phenomena habitually elicited in the use of the former are very rarely produced by the latter. In all three intoxications, however, there may be observed the stages of lessened consciousness, of excitement, and of total unconsciousness. Alcohol was formerly administered in very large quantities to allow of surgical procedure, and ether has not infrequently been used as an habitual intoxicant.

These anæsthetics produce the same progressive paralysis of the central nervous system as alcohol, commencing with the highest cerebral functions, those of self-control, and passing downward through the lower intracranial divisions. The spinal cord is affected before the medullary centres, which are the last part of the central nervous system to become paralyzed. As in the case of alcohol, it is at first difficult to believe that the excitement of anæsthesia is due to the suppression of the self-control only, but the wild movements are often aroused by the sense of restraint and opposition when the mind is unable to appreciate the necessity for these measures. The depression of the motor areas has been shown experimentally in the case of chloroform and ether, a much stronger electric stimulus being necessary to produce movement of a limb after these drugs than before them; their excitability by the electric current has not been tested, however, during the excitement stage. The

electrical current of action disappears in surgical anæsthesia and with it the conduction of nerve impulses from nerve cell to nerve cell (Forbes).

The anæsthesia is not produced equally rapidly throughout the body, the back and the extremities first becoming insensible, then the genital organs and rectum and last of all, the parts supplied by the trigeminus. The reflexes of the spinal cord are depressed by small quantities of ether or chloroform and are finally paralyzed completely; sometimes ether increases the reflexes for a short period (Leeuwen). The character of the reflex is changed, for Sherrington finds that stimulation of an afferent nerve which normally causes a reflex contraction, may under chloroform be followed by inhibition. A similar reversal has been described in the medulla oblongata by Bayliss.

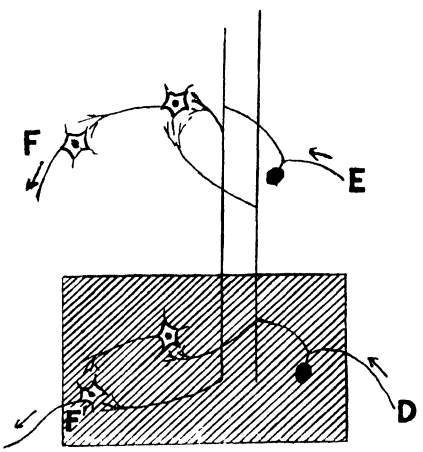

FIG. 11.—Diagram of Bernstein's experiment on the spinal cord; the part exposed to chloroform is represented by the shaded, while the rest is protected and normal. A sensory impression traveling by the posterior root fibre *D* does not elicit a reflex movement, but one reaching the cord through the unaffected root *E* causes reflex impulses, which may be sent out by the motor cell *F* in the unaffected area, or by *F'* in the poisoned area. The cells of the anterior horns, *F'* and the dendrites surrounding them are, therefore, intact after the reflex arc is interrupted at some other point.

Both of the anæsthetics affect the sensory functions before the motor, as is shown by movements occurring long after all sensation has disappeared. And Bernstein found in some cases that if chloroform was excluded from an area of the spinal cord by destruction of part of the pia mater, reflexes could be elicited in other parts of the cord by the irritation of sensory nerves whose cells lay in the protected area, while irritation of nerves, the cells of which were exposed to the chloroform, had no effect (Fig. 11). In the protected area there were, of course, both motor and sensory cells, and an impulse reaching the protected sensory cell was transmitted to the neighboring and also to more distant motor cells. An impulse reaching the exposed sensory cell, on the other hand, was not transmitted to the motor cells, although these were shown by the first part of the experiment to be capable of

stimulation. This experiment is best interpreted by supposing that the anæsthetics act first on the first synapse in the cord that is met by an afferent impulse. Later, however, the motor cells or their synapses are also paralyzed, as is shown by stimulation of the cord having no effect, even when the respiration is still active.

Electrical stimulation of the cerebral motor areas produces movement for some time after sensation has been lost, but as the anæsthesia becomes deeper, their irritability disappears. Finally the medullary centres are also paralyzed by the anæsthetic. There is some evidence that they are first stimulated directly by chloroform and ether (page 318). The medullary centres are liable to be affected by reflex stimulation up

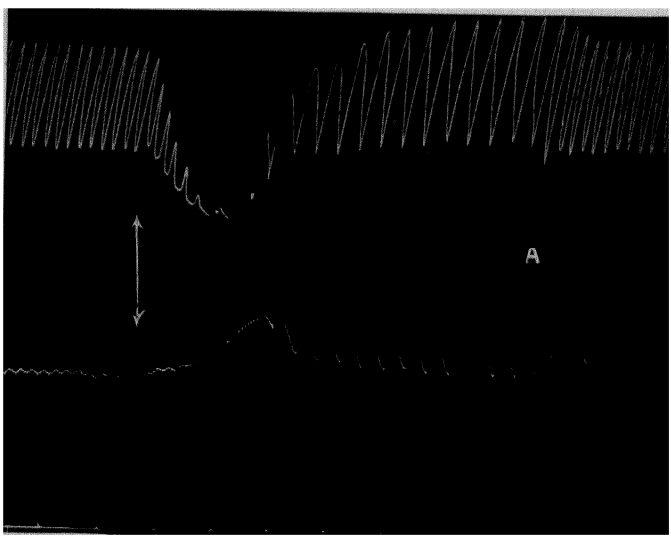

FIG. 12.—Tracings of the respiration (upper) and blood-pressure (lower) of a rabbit at the beginning of ether inhalation, which is indicated by the arrow. The respiration immediately becomes very shallow, and then after a pause becomes slow and deep (reflex inhibition). The blood-pressure rises and the pulse is slowed by reflexes acting on the vasomotor and vagus centers. The normal condition is restored at once when the ether is removed from the nose at *A*.

to the moment at which they cease to send out impulses, for the respiratory centre responds to stimulation of the superior laryngeal nerve as long as the respiration continues. It is possible that the motor cells are not directly paralyzed by the drug, but can only send out impulses received from the sensory cells, and that the paralysis of these is the cause of the asphyxia.

Shortly stated, the direct action of chloroform and ether on the central nervous system is a descending depression and paralysis which affects the medullary centres last of all, and which involves the synapses on the sensory and receptive tracts sooner than the motor neurons.

The action of chloroform and ether on the **Respiratory Centre** is

partly direct and partly indirect. In the first stage, the respiratory movements may be slowed or stopped temporarily by a reflex action set up by the irritation of the terminations of the trigeminus in the nose and throat and of the pneumogastric in the larynx and bronchi, but this interruption is only of short duration and may be induced by any irritant applied to the respiratory passages (Fig. 12).

Aside from the reflex stoppage of the respiration mentioned above two types of ether apnœa have been described, one coming early in anæsthesia and the other quite late. The former may be seen during rapid induction of anæsthesia when high concentrations of ether are used. The immediate effect is that the brain, which is richly supplied with blood, receives an undue concentration of ether which may cause cessation of breathing. The rest of the body including the great bulk of the blood has received no such concentration and, the cessation of the respiration having stopped further absorption for the time being, the ether in the arterial blood falls rapidly, relieving the brain of its excess and breathing soon reëstablishes itself spontaneously. The second type of apnœa is more serious as it occurs later in anæsthesia when the body as a whole has absorbed a considerable amount of ether. An undue increase in ether concentration in the brain cannot be remedied so easily by the blood as in the first instance because the blood itself has a fairly high level of ether and it may be necessary to carry out artificial respiration for a time to furnish oxygen to the blood and to aid in the elimination of the ether. (Haggard.)

During the second stage the respiration is often rendered irregular by the convulsive struggling, which produces alternately periods of asphyxia and deep gasping movements. There is further some evidence that the respiratory centre is rendered more irritable by low concentrations of the anæsthetics, more especially by ether. During the third stage, the respiration is regular and no reflex disturbance occurs, because the sensibility is so dulled that the continued irritation of the nerve ends causes no reflex response. In this stage the breathing is slow and shallow, mainly because the ordinary movements of the body are suppressed and thus less carbonic acid is carried to the centre, that is, the normal stimulus to the respiratory centre is diminished; partly, because the centre is reduced in excitability by the direct action of the anæsthetic. If the drug be pushed, the weakness and slowness of the movements increase until the respiration ceases entirely from paralysis of the centre. In addition to its direct action on the centre, chloroform affects the respiration in deep anæsthesia by inducing anæmia of the medulla through its effects on the circulation.

The effects of the anæsthetics on the **Circulation** are extremely complicated, because the heart varies in its reaction in different cases and under different anæsthetics, and in addition the changes in the respiration and the stage of excitement add to the difficulty of the subject. The changes observed in the pulse in man have already been described (p. 317). The blood-pressure in man has been found to be reduced by chloroform even in the earlier stages, and in deep anæsthesia the fall may be very marked. Under ether the pressure rises slightly in the first and second stages, partly from the reflexes arising from the local irritation, partly from the muscular movements, and partly perhaps from stimulation of the vasomotor centre. During complete anæsthesia from

ether it falls again to slightly above the normal or a few millimeters below it, but never reaches a point indicating grave circulatory disturbance.

In animals, the first change in the blood-pressure is often a result of the slowing or even standstill of the heart from the irritation of the air passages stimulating the inhibitory centre reflexly. The blood-pressure may thus fall abruptly, but in other instances the inhibition of the heart may be compensated by vasoconstriction from reflex stimulation of the vasomotor centre, so that the blood-pressure may rise while the heart is slowed (Fig. 12). Later, the blood-pressure falls slightly in chloroform anæsthesia, but strong vapor causes a marked and dangerous fall. The heart survives after the respiration fails in most experiments but the blood-pressure is very distinctly lower at this time (Fig. 13). Under ether the blood-pressure often is slightly lower, but it remains much

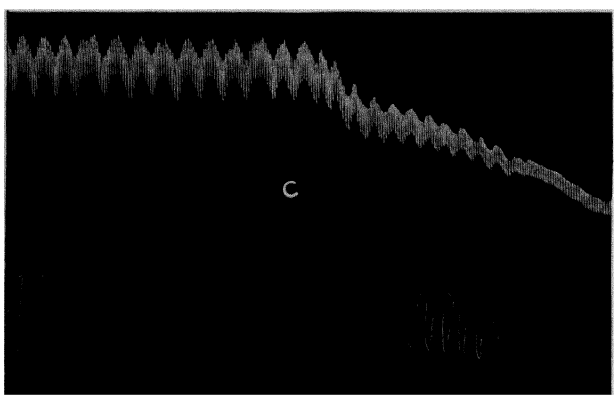

FIG. 13.—The respiration (lower tracing) and blood-pressure (upper tracing) in chloroform anæsthesia in a cat. At *C* strong vapor was inhaled and a rapid fall in the blood-pressure began. The respiration ceased, the heart continuing to beat for some time. (Contrast with Fig. 14.)

higher than under chloroform when the respiration fails (Fig. 14). The cause of the fall in blood-pressure under chloroform has been much disputed, but is now generally ascribed to the action on the heart. Ether being less poisonous to the heart has a correspondingly slight action on the blood-pressure.

Heart.—The frog's heart under chloroform or ether beats more slowly and more weakly, and at the same time undergoes a certain amount of dilatation, all owing to the paralyzing effects of these drugs on the cardiac muscle.

The effects on the mammalian heart under chloroform are very similar. The slowing is not so marked, however, as the weakness and the dilatation, so that the rhythm of the pulse does not indicate the extent to which the heart is affected. The auricles are weakened by smaller quantities than the ventricles, which relax more completely in diastole, however (Fig. 15). The diminution in the strength of the auricles progresses rapidly, while the ventricular dilatation soon reaches

a maximum and is accompanied by lessened force of contraction. The auricular weakness soon becomes so great that practically no blood is expelled by its systole, and the slowing of the heart, which has not been very marked up to this point, becomes distinct. The ventricular contractions next become extremely weak and occasionally fail entirely, and soon afterward the heart comes to a standstill in diastole. In its weakened state, the heart can be inhibited more easily than usual, and vagus stimulation may arrest it finally, the contractions not returning after the stimulation ceases (Embley).

When ether is inhaled in high concentrations the changes in the heart resemble those under chloroform, but it is difficult to elicit the extreme weakness and the standstill unless asphyxia is present also.

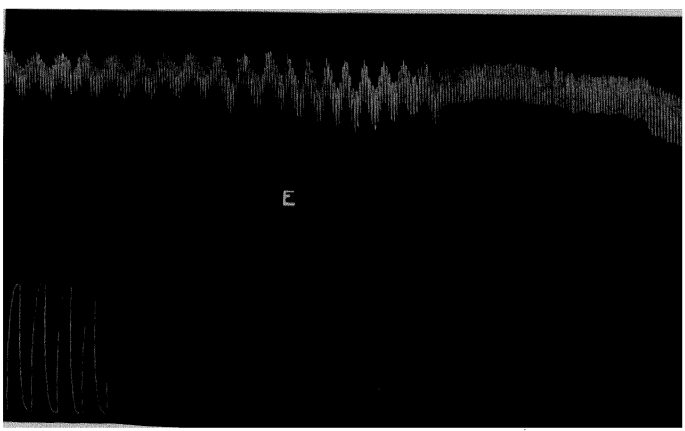

FIG. 14.—Respiration (lower tracing) and blood-pressure (upper tracing) of a cat under ether. At *E* strong vapor was inhaled and soon afterward the respiration ceased, while the blood-pressure remained high for some time afterwards. (Contrast blood-pressure in Fig. 13.)

The relative toxicity of chloroform and ether on the heart has been examined by perfusing their solutions in Ringer's solution through the coronary vessels; 0.001 per cent of chloroform had a distinctly deleterious action and 0.015 was sufficient to arrest it, while 0.4 per cent of ether was required to stop the heart perfused in the same way. This indicates that chloroform is 25–30 times as poisonous to the mammalian heart as ether; the same proportion has been found in cold-blooded animals and in mammalian hearts perfused with blood. The chloroform contained in the blood during anæsthesia is sufficient to injure the heart while when ether is inhaled in a concentration leading to arrest of the respiration, it does not damage the heart muscle.

Vessels.—It has been shown experimentally that the vasomotor centre is depressed by chloroform, though this is sometimes masked by its responding by increased activity to the weakness of the heart or to partial asphyxia (Pilcher and Sollmann); the direct action on the centre is of little importance. In the later stages the vasoconstrictor centre undergoes some obscure change, so that sensory impulses which normally excite it and cause constriction of the vessels, now inhibit it and

'cause dilatation of the vessels (Bayliss). The vasodilator centre continues to respond in its normal way to sensory impulses. Ether seems to have little or no direct action on the vasoconstrictor centre, but the dilatation of the skin vessels indicates that it excites the vasodilator function directly or indirectly.

The direct action on the vessel walls seems to be of greater importance than that on the innervating centres. When chloroform circulates in the vessels in the concentrations used in anæsthesia it tends to relax them from a depressing effect on the muscle fibres; all the vessels are not equally affected, however, those of the splanchnic area dilating more readily than those of the limbs, which may even be constricted. Chloroform in higher concentration may tend to constrict

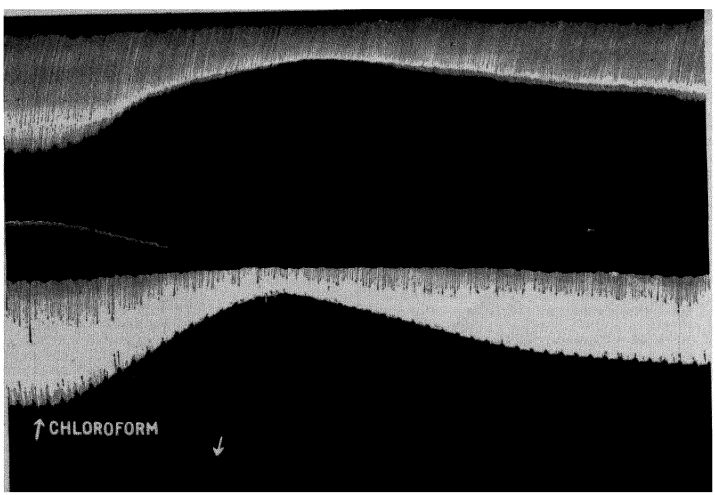

FIG. 15.—Effect of chloroform on circulation of a dog. Upper tracing, auricle. Middle tracing, blood-pressure. Lower tracing, ventricle. Levers move down in systole. Note increased dilatation and weakened systole in both cardiac chambers with fall in blood-pressure. Slow recovery after removal of chloroform. Artificial respiration

also the mesenteric vessels, but this does not occur in the intact animal, in which such concentrations would prove immediately fatal to the heart.

In practice, the low blood-pressure under chloroform is mainly due to the action on the heart; in less degree to the dilatation of the vessels in the abdomen.

Ether dilates the peripheral vessels like chloroform when it is perfused through them, and if it is inhaled in abundance of air this dilatation occurs in the living animal and may cause a fall in blood-pressure. This is often absent however, because the direct vascular action is opposed by the vasomotor centre which is excited by an insufficient air supply; for in ether anæsthesia there is very often present a partial asphyxia induced by the close approximation of the inhaler to the mouth and nose.

Syncope in Anæsthesia.—In a certain number of experiments the reaction of the circulation to chloroform is very different from the gradual depression described above. In these, the heart suddenly becomes irregular or ceases to beat abruptly, the blood-pressure falls to zero, and after a few gasping respirations all movements cease (Fig. 16). This sudden heart failure often occurs in the early stages of anæsthesia, or when the inhalation is irregular or has been suspended. Embley has explained it by inhibitory stimulation from which the weakened heart cannot recover. But Lævy attributes it to the onset of ventricular fibrillation and has brought a large amount of evidence for his view. This fibrillation is often the culmination of a series of irregularities, such as extrasystoles and tachycardia, but may not be preceded by these in all cases. It indicates a condition of abnormal irritability of the heart under chloroform, and other experiments have given some evidence for a phase of increased excitability preceding the depression ordinarily observed. This form of cardiac failure is very often final, but in a small proportion of cases the heart resumes its normal contractions and the animal recovers. Fibrillation is especially liable to occur from sensory nerve stimulation during light anæsthesia, and it is possible that here the excitatory effect on the heart is reinforced by reflexes through the accelerator apparatus or by an increased secretion of the suprarenal glands. It is not proved that the inhibitory nerves are involved in this form of heart failure, though there is some evidence in favor of this view.

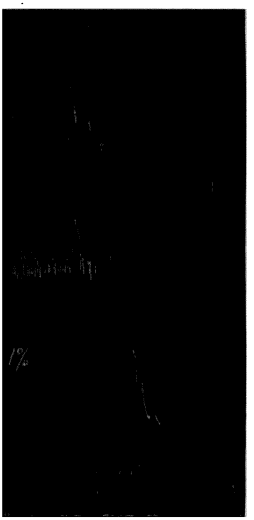

FIG. 16.—Tracing of the blood-pressure (lower) and of the respiration (upper) of a cat under chloroform; failure of the heart (ventricular fibrillation) immediately after violent struggling. The blood-pressure falls rapidly, while deep, gasping respiration continues for a short time and then ceases. (Levy.)

Ether does not seem to have any such action on the heart, and fibrillation of the ventricle has not been observed under it. In fact, sudden circulatory failure under ether is a very rare occurrence, compared with chloroform. Henderson suggests that these rare fatalities under ether may be the result of a great reduction of the carbonic acid of the blood (acapnia), from excessive breathing during the excitement stage or during imperfect anæsthesia. Acapnia is known to act deleteriously on the heart, but further work is required before this view of the fatalities under ether can be regarded as established.

The **Muscles** and **Nerves** are not affected by chloroform when inhaled, much higher concentrations being required to act on the nerve fibre than on the nerve cell. When a frog's muscle is exposed to an atmosphere of either of them, it is weakened, loses its irritability and eventually passes into rigor mortis; the limb muscles in mammals are weakened when strong solution (0.1–0.2 per cent) are perfused through them, but are unaffected by concentrations which

arrest the heart in a few minutes. Waller has shown that when a frog's nerve is exposed to chloroform or ether vapor in weak dilution, its irritability is at first increased; strong vapor, on the other hand, abolishes the excitability temporarily in the case of ether, generally permanently in that of chloroform, which is much the more powerful nerve poison of the two. The sensory fibres are said to be paralyzed sooner than the motor when chloroform or ether is applied to a mixed nerve (Pereles and Sachs), and some motor fibres of a trunk may remain unaffected, while others are paralyzed. The local paralyzing effects of ether have been elicited repeatedly in the human subject by its subcutaneous injection, and have occasionally been followed by neuritis and permanent weakness. Kobacker and Rigler have shown that ether paralyzes the vagi of cats, probably by acting on the ganglia.

Chloroform and ether hemolyze the **Red Corpuscles** and free the hæmoglobin when they are shaken with defibrinated blood outside the body, and chloroform is said to retard the reduction of oxyhæmoglobin by forming a loose combination with it; Da Costa holds that ether tends to destroy the red cells during anæsthesia, and advises caution in its administration in cases in which a diminution in their numbers may be of serious import. In the blood, chloroform is carried by the red cells for the most part, less than 10 per cent, being free in the plasma. It appears to form a loose combination or solution in the cholesterol and lecithin of the corpuscles. Ether is said to be more equally distributed between the corpuscles and plasma.

According to McCollum the corpuscles contain about 65 per cent of the chloroform in the blood—at the end of a two-hour period of anæsthesia the cells containing 37 mgs. and the plasma 24 mgs. chloroform per 100 G. He showed also that the brain and the other tissues store up the narcotic as the anæsthesia continues so that in an hour of surgical anæsthesia the chloroform content of both brain and blood is almost doubled.

The amount of chloroform in the blood during the stage of anæsthesia is about 25–35 mgs. in 100 cc. When the respiration fails the blood is found to contain 40–70 mgs. per 100 cc. (Buckmaster and Gardner). During the induction of anæsthesia the arterial blood contains more than the venous, part of the chloroform being taken up by the tissues as it passes through the capillaries. On the other hand, as the anæsthesia passes off, the venous blood contains more than the arterial, the anæsthetic taken up from the tissues in the capillaries being eliminated by the lungs. Rise found that in the rabbit a vapor of about 0.95 per cent of chloroform produced complete narcosis for several hours, 1.15 per cent arrested respiration in two hours, and 1.65 per cent in forty minutes. From the point of view of the concentration inhaled, there is therefore not a wide margin of safety. Nicloux states that in light anæsthesia from ether the blood contains about 100–110 mgs. per 100 cc., in deep anæsthesia 130–140 mgs., while 160–170 mgs. per 100 cc. proves fatal from failure of the respiration. The margin of safety in anæsthesia is thus narrower than is generally recognized, for the concentration in the blood necessary for anæsthesia is about half that which is fatal.[1]

[1] Haggard found the ether concentration of the blood in a dog with moderate anæsthesia with the corneal reflex to be 114 mgs. per 100 cc.; moderate anæsthesia with loss of corneal reflex 122 mgs. per 100 cc.; very deep anæsthesia 151 mgs. per 100 cc. In prolonged anæsthesia it was necessary to lessen the ether concentration from time to time to avoid respiratory failure. These figures agree quite closely with those published by Ronzoni and by Robbins.

The effects of chloroform and ether on the **Pupil** present some variation in different animals, and, indeed, are not very constant in man. No entirely satisfactory explanation of their mechanism has been offered as yet. The dilatation of the pupils in the first and second stages is merely the accompaniment of the general excitement and anxiety, and is not specific. The contraction in the stage of unconsciousness is similar to that seen in natural sleep, and is evidently of central origin. The dilatation occurring during wakening or vomiting is evidently caused by the same process as that of the preliminary stages. Just before death the pupil dilates, and this may perhaps be attributed to the effects of asphyxia on the muscle of the iris, and is so frequently observed in death from other causes that it cannot be regarded as a specific action of the anæsthetic.

The local effects of the anæsthetics on the **Alimentary Canal** and **Respiratory Passages** are confined to irritation with resultant reflexes. Thus the profuse secretion of saliva and mucus is due to the irritation causing increased activity of the glands reflexly, and can be arrested by atropine. It has been stated that the bronchial rhonchi are due entirely to aspirated saliva, but this is incorrect, as they occur in animals to which the anæsthetic has been given through a tracheal cannula The irritation is much greater with ether than with chloroform anæsthesia, largely because the former has to be given in higher concentration. The activity of the cilia in the trachea and bronchi is diminished (Ernst).

The *vomiting* which is so often a feature of anæsthesia may arise in part from the irritating action on the stomach of the chloroform or ether swallowed in the mucus, but is mainly of central origin, for vomiting also occurs when ether is injected intravenously in man and also under nitrous oxide anæsthesia in some cases; here the local irritation can only play a small part, and the medullary centre is probably involved directly, perhaps in the same way as occurs in shock and collapse. In the early stage vomiting sometimes occurs from the odor and taste of the anæsthetic, more especially in people who have been anæsthetized previously and have unpleasant associations with the odor.

The ordinary movements of the stomach and intestine have generally been supposed not to be influenced by the anæsthetics but Miller has recently shown that in dogs both ether and chloroform administrations are followed by marked relaxation of stomach, small intestine and colon. Sleeth and von Liere found that chloroform delays the emptying time of the stomach by 60 per cent, ether by 40 per cent, nitrous oxide and ethylene by 15 per cent, cyclopropane and vinyl ether by 7 per cent. The diminution in the movements of the various parts of the alimentary canal makes its appearance immediately following the irregularities occurring in the excitement stage and may be produced, in part at least, by temporary asphyxia due to the struggling. During the stage of surgical anæsthesia there is complete inhibition of the smaller contractions of the muscular structures, of peristalsis, and also loss of muscular tone. As recovery from anæsthesia follows there is a gradual return to the normal conditions, although complete recovery may not

take place for some hours. The stomach frequently remains somewhat depressed for hours while the small intestine may be abnormally active and the colon shows a high degree of tonicity.

These alterations in the activity of the alimentary canal are produced by the action of the anæsthetics upon the canal itself, the central nervous system apparently not being involved. It is quite probable that the changes described are responsible for some of the unpleasant postoperative symptoms sometimes encountered. The relaxation of the stomach will favor gastric dilatation and vomiting, the exaggerated intestinal peristalsis may be responsible for the "gas pains" and the spastic condition of the colon will favor accumulation of gas and fluid above.

The **Kidney** appears to be affected in a certain proportion of cases of anæsthesia in man, as is shown by the appearance of albumin in the urine. Chloroform induces typical fatty degeneration occasionally, while albuminuria has been observed in a certain proportion of cases after ether. The proportion of cases in which this organ is affected seems to vary extraordinarily, some authorities finding albuminuria in 30 per cent of the cases where chloroform was used; while others could detect it in less than 5 per cent. Kemp ascribes the renal effects of ether to vasoconstriction which arises from partial asphyxia from the inhaler being applied too closely; when asphyxiation is avoided, albuminuria is hardly met with under ether, and most surgeons consider chloroform far more deleterious to the kidney. The secretion of urine is generally diminished during anæsthesia with chloroform or ether, from the reduced blood-pressure and imperfect aëration of the blood; McNider finds that in the dog the damage to the kidney from the anæsthetics is much greater in old animals than in young ones and brings this into relation with the amount of stainable lipid in the renal cells. After recovery from ether anæsthesia some diuresis may occur, or the urine may remain scanty for some hours.

The **Uterine Contractions** during parturition seem little influenced by moderate anæsthesia, but are somewhat slowed in the deeper stages. Chloroform and ether pass into the fœtal blood, and some experiments are recorded in which the fœtus was killed by the inhalation, while the mother recovered. This may be caused either by the direct action of the drug on the young animal, or by the low maternal blood-pressure leading to its asphyxia. It does not seem dangerous to induce a moderate degree of anæsthesia during labor in human beings, although here, too, the effects on the child are shown by an increase in the nitrogen excretion in the urine for some days; some authorities attribute many of the diseases of the first days of life to the use of chloroform during labor, but the evidence is not convincing.

The **Temperature** falls during anæsthesia of even short duration. Thus Kappeler found it reduced 0.2–1.1° C. when chloroform was inhaled fifteen to forty minutes, and a fall of 3–5° C. has been observed during very long anæsthesia. This action is due partly to the greater output of heat through the dilated skin vessels, but mainly to lessened heat production from the diminished muscular movement; the production of CO_2 falls for the same reason, and doubtless the oxygen absorp-

tion. This is not evidence of direct action on the tissues, but is one of the consequences of the central nervous depression.

Of late years a good deal of interest has been manifested in the effects of the anæsthetics on the **Metabolism of the tissues**, and it is now generally recognized that chloroform, in addition to its action on the central nervous system, produces marked changes in the nutritive processes of protoplasm. The simpler organisms, which are devoid of nervous structure, are killed in comparatively dilute solutions, and chloroform water therefore retards putrefaction, the fermentation of yeasts, and the movements of cilia. It seems to hinder the action of some ferments, such as pepsin and rennet ferment, when added in comparatively large quantities, but increases their activity in greater dilution. Plants cease to assimilate carbonic acid, but are not killed by chloroform except in very large quantities. In the higher animals and in man, the processes of life and nutrition of the different organs also undergo alteration, quite apart from the effects on the nervous system. Thus fatty infiltration of various organs is produced by chloroform administered repeatedly and even by a single inhalation in some cases. The organs especially implicated in this change are the liver, heart and kidneys, but degeneration of ordinary muscle has also been observed occasionally. If this process attains a certain degree of development, it may lead to failure of the heart, but otherwise the tissues recover in the course of a few days. Traces of fatty infiltration have been observed after prolonged ether narcosis also, but they are so slight that no significance attaches to them from a practical point of view (Selbach). Given in small quantities for several months, chloroform leads to atrophic cirrhosis of the liver, and, to a less extent, of the kidneys, spleen and lungs, this cirrhotic change forming a sequel to preliminary fatty changes of the parenchymatous cells. In young adults chloroform has occasionally given rise to a form of liver affection which closely resembles acute yellow atrophy. In these cases after recovery from the anæsthetic, the patient becomes restless and uneasy and in a few hours delirium and coma may appear. Jaundice, cutaneous hæmorrhages (from a diminished amount of fibrinogen in the blood), tenderness over the liver suggest an affection of this organ, and in fatal cases it is found to present the same appearance as in acute yellow atrophy, the cells in the centre of the lobules having undergone necrosis; chemical examination proves that an acute autolytic destruction of the organ has occurred (Wells). In animals this necrosis is less liable to occur if the diet previously has been rich in carbohydrates, while fats seem to predispose to it (p. 335).

As further evidence that, even in ordinary anæsthesia, the damage to the liver from chloroform used as an anæsthetic is by no means negligible is shown by the experiments of Rosenthal and Bourne. These workers found that normal dogs excrete in the bile within fifteen minutes at least 85 per cent of one of the phthalein dyes, bromsulphthalein, which has been given intravenously. On the other hand, if the liver has been damaged the removal of the dye is greatly delayed. When the animal was subjected to chloroform for even half an hour, dye retention lasted for eight days, and when chloroform was given for

two hours, dye retention lasted for six weeks. With ether, however, while there is some evidence of damage, as shown by a slight delay in the excretion of the dye, the damage is evidently quickly repaired, as excretion is normal on the second day. Ravdin and his co-workers have found that 35 per cent of the glycogen is lost from the liver during two hours' anæsthesia with chloroform and 94 per cent during the twenty-four hours following anæsthesia. As the liver glycogen decreases, the fatty acid concentration in the liver increases, effects due to an action on the liver parenchyma. Forbes, Neale and Scherer found that an extract of hog's liver prevented the necrosis of the liver of rats poisoned by carbon tetrachloride and the active principle of this extract was later found to be sodium xanthine. Other workers have also found that sodium xanthine and certain other purine substances protect against liver damage by chloroform or carbon tetrachloride. It is not yet known whether sodium xanthine will be of value in man in preventing liver damage due to chloroform anæsthesia.

The effects of chloroform on the nutrition of the tissues are shown in the urine secreted during and after anæsthesia, though they are more marked when the drug is swallowed, from its being more slowly absorbed and thus acting for a longer time. The nitrogen eliminated is considerably increased, and the unoxidized sulfur shows a similar augmentation, and these would seem to indicate an increased protein destruction and a disturbance of the oxidation in the tissues; another observation pointing in the same direction is the appearance of creatin in the urine and the reduced excretion of creatinin.

The carbohydrate metabolism is also impaired, for acetone and sugar are often present in the urine after chloroform, and it has long been known that diabetes is liable to be aggravated by this anæsthetic and may prove fatal. The sugar of the blood is increased and the glycogen of the liver diminished or absent, from a specific action on the liver cells (Paton).

Bile pigment is said to occur in the urine in a considerable number of cases of anæsthesia with chloroform, especially one or two days after the administration. The chlorides and the acidity of the urine are augmented and this has sometimes been regarded as evidence that chloroform is decomposed in the tissues, but the chlorides are also increased by ether though not in the same degree.

These effects of chloroform on the metabolism resemble very closely those of phosphorus poisoning, and have, like them, been ascribed to autolysis and the formation of acid in excess in the tissues; this acid may be furnished in part by the decomposition of chloroform, with the formation of hydrochloric acid. They seem to occur only after those substances of the aliphatic series in which chlorine is substituted, ether having little or no effect in producing fatty degeneration or in changing the proportion of the sulfur compounds in the urine. An excess of sugar is found in the blood after ether anæsthesia in dogs and leads to glycosuria. It was suggested that this might arise from excessive activity of the suprarenal bodies during the excitement or during partial asphyxia, and not from any direct action of the ether on the metabolism,

but this is not correct as the condition is also found in animals from which the suprarenal glands have been removed. In light anæsthesia from ether, the available alkali of the blood is slightly reduced and the hydrogen-ion concentration rises, and this becomes more marked as the anæsthesia becomes deeper. This condition of acidosis is probably largely due to the production of lactic acid which seems to come from the muscles.

Distribution in the Body.—When chloroform or ether vapor is inhaled, it passes rapidly into the blood by diffusion and is distributed throughout the body, mainly by the blood cells in the case of chloroform, while the plasma carries a considerable amount of ether. The anæsthetic immediately begins to leave the blood for the tissues and appears to be taken up especially quickly by the central nervous system on account of the large blood supply to the brain so that with rapid induction this organ will approach saturation at a much more rapid rate than will the rest of the body. If induction is slower the saturation of the brain is also slower, as the rest of the body will tend to act as a buffer by taking up a part of the ether circulating in the blood. The amount of ether in the blood in the internal jugular vein is an index to the amount in the brain while the amount in the blood in the right heart reflects the condition in the body as a whole. In the early stages of anæsthesia the concentration of ether in the jugular blood is greater than in the mixed venous blood in the right ventricle, but during recovery from anæsthesia the concentration of ether in the ventricular blood is the greater. This latter relationship is due to the fact that the brain eliminates the ether more rapidly than the remainder of the body due to its abundant blood supply (Haggard). An unequal distribution of anæsthetic between the different organs of the body probably arises from the greater amount of lipid substances in the central nervous system, which dissolve the chloroform and ether and retain them. This flow from the pulmonary alveoli to the blood and thence to the tissues lasts until the vapor tension is the same in each, and the amount in the brain is thus determined by that in the blood, which again depends on that in the alveoli. If the inhalation ceases, the tension in the lungs falls and a backward flow follows from the blood into the air and from the brain into the blood.

The **Excretion** of both ether and chloroform takes place mainly by the lungs. Most of the anæsthetic is eliminated very rapidly, but traces of chloroform are said to be found in the breath for twenty-four hours after the inhalation and even longer in cases in which there is a tenacious mucus secretion in the bronchi. Small quantities of chloroform escape by other channels, for it has been found in the urine, and is said to occur in the perspiration and the milk. Ether is eliminated almost exclusively by the lungs as approximately 90 per cent of the amount absorbed has been recovered from the expired air after cessation of the administration. Small amounts are excreted in the urine where the ether concentration approximates that in the arterial blood. This is due to the fact that, like the brain, the kidney blood supply is abundant and there is little difference in the ether concentration between the arterial and venous blood in this organ. Nevertheless the amount

of ether so eliminated in the urine is small due to the small amount of urine excreted during anæsthesia. Small amounts of ether are also eliminated in the sweat and also by the serous surfaces as is shown by the fact that air enclosed in the abdomen during anæsthesia rapidly assumes an ether partial pressure equal to that of the alveolar air (Haggard).

Differences Between Chloroform and Ether.—Ether and chloroform resemble each other closely in their general effects, but differ in power and in other points of importance. Their relative strength as anæsthetics is shown by a comparison of the vapor concentration of each in a hundred volumes of air required to induce anæsthesia.[1]

Chloroform	Ether	
0 5–0 7	1 5–2 5	Insufficient to cause anæsthesia.
1 0	3–3 5	Causes anæsthesia on prolonged inhalation.
2 0	6 0	Arrests respiration after ten to fifteen minutes.

The amount of anæsthetic in 100 cc. of the blood shows the same proportion.

Chloroform.	Ether	
25–35 mgs.	100–140 mgs.	Anæsthesia
40–70 mgs.	160–170 mgs.	Respiratory arrest.

The depressant effect of chloroform on the brain is thus 3 $3\frac{1}{2}$ times as great as that of ether, and its power to arrest respiration is about 3 times as great. The depressant action on the heart of chloroform is about 25–30 times that of ether, and the extremely dangerous cardiac syncope which is seen under chloroform is unknown under ether. Ether has to be given in more concentrated form to produce anæsthesia, and, therefore, produces more irritation of the air passages, as shown by the greater secretion of saliva and mucus, by coughing, and by the sensation of asphyxia. Anæsthesia is produced with greater difficulty, more slowly and often less perfectly than with chloroform, and the stage of excitement is generally more violent and prolonged. But the pulse is not nearly so much affected as by chloroform; it may be somewhat slower than usual, but is full and strong. The concentration of chloroform which is necessary to produce anæsthesia is very close to the concentration which causes serious impairment of the heart's action, while, on the other hand, $3\frac{1}{2}$ per cent ether vapor is sufficient to maintain narcosis, but a very much stronger concentration is required to cause a dangerous condition of the heart. In the same way, the difference in the concentration required to produce anæsthesia and that which will stop the respiration is smaller in chloroform than in ether, and the anæsthetist has thus more leeway when the latter is used. The changes in the metabolism following the use of chloroform are not produced to the same extent, if at all, by ether.

Regarding the **Choice of an Anæsthetic**, it must be said that each has its advantages, but that ether is less liable to cause dangerous symp-

[1] Boothby finds a much higher percentage of ether necessary than any other author, thus he recommends a vapor of about 13 per cent of ether by volume to induce anæsthesia and one of 6 per cent to maintain it. Others have found this percentage fatal within a short time.

toms than chloroform, and ought, therefore, to be used wherever special circumstances do not indicate the latter. Chloroform is always preferred by the patient, for it causes less irritation and less feeling of suffocation, and it is often preferred by the surgeon because it induces anæsthesia sooner and less of it is required. In cases where excitement is to be avoided as much as possible, or in which very deep anæsthesia with complete muscular relaxation is required, and in irritated conditions of the air passages, chloroform ought to be used rather than ether. In drunkards, ether sometimes fails to induce deep anæsthesia, and in very hot climates anæsthesia with ether may be difficult and unpleasant to induce owing to its rapid evaporation, so that in these cases chloroform may be necessary. Lastly, where artificial lights are necessary (except the electric), or where the actual cautery is to be used, ether is dangerous on account of its inflammability, and chloroform is indicated. On the other hand, chloroform is specially contraindicated in cases of fatty change of the heart and in renal disease.

The **Dangers of Anæsthesia** are caused only in part by the direct action of the ether or chloroform, for fatal accidents have occurred from objects such as false teeth or tobacco plugs falling into the air passages and causing asphyxia, while vomited matter has been drawn into the larynx in some cases. Very often the relaxation of its muscles permits the tongue to fall back into the throat, rendering the breathing labored and stertorous; this is at once relieved when the tongue is drawn forward. The accumulation of saliva and mucus or blood in the throat may lead to similar symptoms. In these accidents the chloroform or ether is only indirectly the cause, but in a large and ever-increasing number of cases, the fatal effects must be ascribed to the direct action of the anæsthetics. The proportion of accidents during anæsthesia is very difficult to estimate, and great discrepancies occur in the statistics of different surgeons. Thus, in one of the London hospitals, 1 death occurred from chloroform in 1236 cases of anæsthesia; Juillard gives 1 in 3258, McGuire 1 in 15,000, as the proportion of fatalities, while Lawrie gives a series of over 40,000 cases without a single death. A fair average would seem to be 1 death in 3000 chloroform inhalations. The statistics of ether fatalities also vary from 1 death in 3000 to 1 in 16,000 cases, but probably 1 in 10,000–12,000 cases would represent the average mortality.[1]

The **Cause of Death** in anæsthesia has been a subject of discussion for over fifty years, and it is only now being recognized that there are at least two different forms of fatality which may occur. The first of these may be termed *Cardiac Syncope*, and occurs chiefly in chloroform anæsthesia, to which it contributes the great part of the fatalities. In these cases it is generally stated that the pulse suddenly disappears, the patient's face assumes a death-like pallor, the reflexes fail, and the pupils dilate. The breathing suddenly becomes deep and labored (this often being the first symptom observed) and ceases after a short time. This accident is generally stated to occur in the early

[1] Gurlt's careful statistics of 330,000 cases of anæsthesia gave a mortality of 1 in 2000 for chloroform and 1 in 5000 for ether, but these both seem unusually high.

stages of anæsthesia, often before the operation has begun, but it is also met with after vomiting and other interruptions to a smooth course of anæsthesia. No explanation of the fatality was given until Embley's and Levy's researches on animals showed that a similar sudden heart failure may be observed experimentally. Embley regards these accidents as the result of excessive and abnormal inhibitory activity, and it is not impossible that the inhibitory apparatus may be involved in some of them. But Levy's explanation (p. 325) that the ventricle passes into fibrillation is more satisfactory and more in accordance with the clinical observations. The conditions which favor the onset of this condition are still obscure. Imperfect anæsthesia is obviously one of them, but this may conduce to the fibrillation either through permitting reflexes to act on the heart, or by subjecting it to the influence of a concentration of epinephrine sufficient to induce it. Fibrillation has not been shown to occur under ether, and sudden cardiac syncope is a very rare occurrence under it and has not been investigated except by Henderson, whose views have been given already (p. 325).

A second form of accident in anæsthesia may be termed that from *Overdosage* and is less likely to be fatal. In this form the respiration becomes shallower and finally ceases while the pulse can still be felt, or the heart beat can still be felt or heard. The interval between the failure of the breathing and that of the pulse varies in different accounts and in some both are said to have disappeared simultaneously. But in these cases the gasping respiration, which is characteristic of the cardiac syncope, is not seen. This accident occurs especially when the anæsthetic has been pushed, or after prolonged inhalation. It may occur under chloroform or ether, and the majority of fatalities under the latter appear to be of this character, while the great bulk of chloroform deaths are due to cardiac syncope. This death from overdosage is easily elicited in animals (Figs. 13 and 14), and has been the subject of a large amount of experimental investigation, which has been directed chiefly to the question whether the respiration or the heart is the first to fail. This appears to depend on the concentration of the anæsthetic. If dilute chloroform or ether be inhaled, the respiration always ceases several minutes before the heart, which continues to beat fairly strongly at first but rapidly becomes weaker. If more concentrated vapor be used, the respiration again ceases before the heart, which is, however, much weakened and comes to a standstill after a short interval; and as the concentration is increased, the weakness of the heart, at the moment when the respiration fails, also increases, and the interval between the arrest of the respiration and that of the heart-beat becomes shorter. Finally, when air saturated with vapor is inhaled, the interval between the two is so short as to be inappreciable. When concentrated vapor of either chloroform or ether is inhaled, the pulse may be so weak as to be no longer perceptible before the respiration ceases, and the anæsthetist, therefore, believes that heart failure has been the cause of death, but if the movements of the heart be registered directly, it is found beating as long as the respiratory movements are carried on. The importance of the condition of the

heart is further shown by the results of attempts to resuscitate the animal after the respiration has ceased; for if artificial respiration be commenced at once, the animal can almost invariably be restored to life, provided the heart has not been weakened too much; but if concentrated vapors have been inhaled, the heart is unable to carry on the circulation, and the animal can be resuscitated only with difficulty, if at all.

Hill has pointed out that the failure of the respiration may be caused in part by the anæmia of the central nervous system from the fall in blood-pressure. The weakness of the heart induced by chloroform is therefore fraught with double danger, for not only is the circulation imperilled by it but the respiration is indirectly weakened.

From a practical point of view, it is of comparatively little importance whether there are a few fluttering beats of the heart after the last inspiration or not. The all-important question is whether the heart has been so injured as to be unable to carry on the circulation.

The autopsy in cases of death by chloroform or ether shows no specific lesions. The blood is often dark colored from the asphyxia, and the heart is found dilated. Irritation of the respiratory passages may be present in ether poisoning, and the odor of the anæsthetic may be recognized in the different organs. Microscopic examination may show some alterations in the cells of the respiratory centre and cardiac ganglia, fragmentation of the heart muscle, and some degeneration of the liver, kidneys, spleen and heart after chloroform (Toroschin).

Late Deaths.—A good deal of interest has been excited by the discovery that the perils of anæsthesia are not over when consciousness returns, but that fatal consequences may follow several days later. These late fatalities are due to fatty changes of the heart, liver and kidneys or to diabetic coma in the case of chloroform, to bronchitis, pulmonary œdema, and pneumonia after ether. No reliable data are as yet available as to the frequency of these sequelæ, as it is very difficult to distinguish between the results of the anæsthetic and the ordinary forms of disease. Even the proportion of cases in which albuminuria occurs after chloroform seems to vary remarkably in different hospitals, for it is given as low as 5 per cent by some authors and as high as 30 per cent by others; this may perhaps be explained by differences in the duration of the anæsthesia. "Delayed chloroform poisoning," as it is sometimes called, occurs more rarely nowadays, at any rate in an extreme degree, since drastic purgation and starvation are not enforced before operation and since chloroform is avoided in cases where any existant toxic condition of the liver is suspected. The chief symptoms (see also p. 329) are protracted vomiting, headache, ketosis and jaundice. The condition may become steadily worse until the patient becomes comatose and dies. When the condition is established, no treatment is very satisfactory but the administration of glucose and insulin has been advocated. The irritant effects of ether and the liability to pulmonary affections afterward have been so evident that some surgeons have returned to the use of chloroform, believing that the late effects in ether claim as high a proportion of victims as the more immediate effects of

chloroform. This irritant action of ether may be avoided to some extent by allowing the vapor to be inhaled in a more dilute form than is often used in inducing anæsthesia. And there is reason to believe that the pulmonary effects are often intensified by the air inhaled being chilled by the evaporation of the ether, and that they may be lessened if this is avoided by suitable inhalers.

Ether Convulsions.—Clonic movements of the limbs may, as has already been described, occur early in ether anæsthesia and usually pass off when anæsthesia is deeper. Apart from the inconvenience they cause, these convulsive movements are of little importance. Occasionally convulsions occur later in the anæsthesia which are of much more serious import. They are often preceded by irregular and rapid respiration followed by twitching in the muscles of the face. The convulsions may spread quickly to other muscles, rendering it difficult to keep the patient on the operating table. It is a grave condition as the convulsions may persist until the patient dies. The cause is not known but the condition, which fortunately is rare, is apparently not due, as was at one time supposed, to impurities in the ether. Payne, in a recent critical study of the literature, concludes that the late ether convulsions are due to a combination of factors, extreme youth of the patient, toxæmia, deep anæsthesia and high external temperature.

Apparatus and Principles.—The principles on which the safe production of anæsthesia is based, then, are comparatively simple, but their translation into practice has given rise to various methods. Several apparatus have recently been constructed which allow of an exact gradation in the strength of the vapor inhaled, but they are rather cumbrous, and while they are used in hospitals, they are certainly not convenient for ordinary practice.

The advantage of this principle of measuring the concentration of the vapors is further only relative, for it has been shown that vapors so dilute as to be absolutely safe do not induce anæsthesia within a reasonable time. To induce anæsthesia, therefore, vapors have to be used which would in time be fatal, and only after the reflexes disappear is it possible to reduce the concentration to the point of absolute safety. In the vast majority of cases, however, much simpler apparatus is used, and the ordinary mask on which the anæsthetic is poured is not responsible for a larger proportion of accidents than the more complicated forms of apparatus. When no inhaler is used, the anæsthetist attempts to regulate the concentration of the vapor according to the symptoms, and this can be usually done with success by watching the respiration closely. If the breathing be shallow, much less concentrated vapor is inhaled into the alveoli than if it be deep and gasping, for in ordinary respiration the air in the smaller bronchioles and alveoli is not exchanged directly with every respiration, but only by a process of diffusion from the larger air passages. The deeper the respiration, however, the further does the vapor penetrate and the lower the concentration needed to change the quantity in the blood. An experienced anæsthetist, by watching the respiration, raising the mask during deep breathing and replacing it when it becomes steady, can regulate with sufficient

nicety the concentration of the anæsthetic in the alveoli and thereby the quantity in the blood. When anæsthesia has been attained, he of course reduces the concentration until the return of the reflexes indicates awakening consciousness, and even then applies much smaller quantities than were necessary at first.

This method of inducing anæsthesia requires the anæsthetist to watch only the respiration and the reflexes, and is that advised by Simpson and his followers (see Hyderabad Commission Report). A further safeguard has been sought for in the condition of the pulse, and this would seem the natural consequence of what has been stated above as to the importance of the condition of the heart. The pulse, however, is not very reliable as a guide in anæsthesia, for in the second stage, in which a certain number of fatalities occur, it is quickened by the excitement and may be irregular, and only gives indications of danger when it is too late to take measures to prevent it. In the third stage it may become gradually weaker, and thus indicate approaching danger, but if the respiration be watched the warning is given earlier. A large number of anæsthetists advise that the pulse and respiration both be watched, and this would seem to be the safest method, provided always that the anæsthetist does not depend on the pulse too much for indications of danger, and does not allow it to distract his attention from the more important indications given by the respiration.

Preliminary Examination.—Before anæsthesia, a careful examination should be made of the condition of the patient, and if there is great anxiety and excitement, a hypodermic injection of morphine or one of the barbituric acid group of drugs may be given. Valvular disease of the heart does not contra-indicate an anæsthetic unless there are marked symptoms of inefficiency, such as dropsy or œdema. In fatty disease of the heart, on the other hand, chloroform is to be avoided, and if it seems extensive, ether is also dangerous from the strain put on the circulation during the excitement. Atheromatous arteries are dangerous from the tendency to apoplexy during the second stage also, and if anæsthesia is absolutely necessary, an opiate ought to be given previously. In cases of bronchitis and catarrh of the air passages, chloroform or the gas anæsthetics are to be preferred to ether as they are less irritating, while in Bright's disease chloroform is generally more injurious than ether from the resultant albuminuria and tendency to fatty degeneration, although ether is also believed by many to disturb the renal functions. Here again the gas anæsthetics are to be preferred. Advanced diabetes contra-indicates chloroform or ether anæsthesia, the sugar increasing in the urine afterwards and coma and death sometimes supervening in the course of a few days. Da Costa recommends that where there are symptoms of anæmia, an examination of the blood should be made before anæsthesia, and states that where the hæmoglobin is found to be deficient, great care is necessary.

Practical Anæsthesia—The patient preferably should not have anything to eat for several hours before the anæsthetic is to be given, so that the stomach may be empty and vomiting avoided as far as possible. He should then be laid on a table of suitable height with a low pillow

and should remove false teeth and any other foreign objects from the mouth. The clothing about the neck, chest and abdomen is to be loosened or removed to allow of perfectly free respiration, but warm blankets or warm bottles should be applied as far as possible to prevent the fall of temperature if the operation is likely to be a long one. The eyes are closed in order to protect the conjunctiva from the irritating vapor. The anæsthetic is then dropped on a mask, which ought to be freely permeable by the air, and ought not to fit closely to the face. Masks were formerly employed to administer ether (closed method) in which the respiration was seriously impeded, so that the patient was partially asphyxiated besides receiving a highly concentrated ether vapor. It must be remembered that the air passes through cloth with much greater difficulty when it is wet by the saliva and mucus, and that a mask which is freely permeable at the commencement of an operation may lead to asphyxia after it has been soaked during the first and second stages. The patient is instructed to breathe as regularly as possible, or to count from one upwards, and some of the anæsthetic is dropped on the mask. If the breath be held, the mask should be raised a little from the face, as the next inspiration will be a very deep one. During the excitement stage the respiration is irregular, and great care must be taken to avoid the inhalation of too concentrated vapor. As soon as the conjunctival reflex disappears, the mask is raised, and is replaced only when it reappears or when the patient evinces signs of pain. The object of the anæsthetist should be to maintain an even anæsthesia and to avoid sudden changes; this is best attained by raising and lowering the mask slightly, or by varying the number of drops of anæsthetic falling on it; the inhalation should not be completely interrupted except in danger. Throughout the anæsthesia care must be taken to prevent any interference with the respiration by the operator leaning on the thorax or abdomen. Very often stertorous respiration sets in from the tongue falling back into the throat, and this has to be remedied by pressing forward the angle of the jaw, or if this is not sufficient, by pulling out the tongue with a blunt-pointed forceps. Vomiting is a very common occurrence in anæsthesia, and when it sets in, the head is turned to one side and the vomited matter removed with a sponge.

A more serious accident is the failure of the respiration. A reflex arrest often occurs in the first stage, but is not of importance in itself, but only from the deep gasping inspiration which follows it. If the anæsthetic be given too long in concentrated form, however, the respiration fails from direct action on the centre, and this demands immediate attention. The head ought to be lowered at once, and the lower limbs elevated, in order to drive the blood to the head as far as possible and thus remedy the anæmia of the brain from the weakness of the heart that accompanies the cessation of the respiration. The epiglottis must be raised by pressing forward the angle of the jaw or by pulling forward the base of the tongue. Artificial respiration in one or other form ought to be commenced at once, and carried on as long as is necessary; a large number of methods of performing artificial

respiration have been proposed, but they can only be taught in a practical class and need not be entered upon here.[1] If the pulse is weak, intermittent pressure over the heart may aid it in carrying on the circulation, and in some cases the abdominal cavity has been rapidly opened and the heart compressed between one hand below the diaphragm and the other on the chest wall. This heroic measure has in some cases restored the heart beat and the respiration. Various drugs have been recommended in these cases, but it is exceedingly questionable whether they are really of service; ether has been injected subcutaneously, and may conceivably cause such local irritation as to reinstate the respiration reflexly, although this is improbable. Strychnine, caffeine and cardiazol (metrazol) are most commonly tried as respiratory stimulants. In animal experiments, the best results in circulatory failure are obtained by the intravenous or intracardiac injection of epinephrine in saline solution and this method has often proved successful in man.

Cardiac syncope and fibrillation is the most dangerous accident of anæsthesia, and probably is irremediable when fully developed. The treatment consists of inversion, artificial respiration, and massage of the heart. Embley recommends the injection of atropine, on the view that the condition is due to inhibition, and it might be thrown into the heart directly by means of a long hypodermic needle. The experiments of Levy show that epinephrine favors ventricular fibrillation under chloroform, and this powerful stimulant is therefore inadmissible in syncope due to fibrillation.

In long operations, the attention of the anæsthetist should be directed to maintaining an even level of unconsciousness. When anæsthesia is reached it may be maintained by comparatively small quantities, and on the other hand, owing to the fall of temperature and the prolonged action of the drug, the amount necessary to produce cessation of the respiration and the heart is much smaller than during shorter operations. In order to induce anæsthesia within a reasonable time, comparatively strong vapor may be used, but as soon as unconsciousness is reached, the vapor ought to be diluted as far as is compatible with the continuation of the narcosis.

On the completion of the operation, the patient should be watched until there is complete recovery of consciousness. After prolonged anæsthesia heat may be applied by warm bottles, etc., as the temperature often continues to fall for some time after the administration of the drug has ceased. If vomiting persists after the recovery of consciousness, cracked ice may be given, and relief is sometimes obtained by lavage of the stomach.

The patient should always be placed in the recumbent position when possible, as otherwise the weakened heart tends to drive the blood in the direction of least resistance, that is, downward, and in the depressed condition of the vasomotor centre, this is not counteracted by the contraction of the arterioles of the abdomen, and anæmia of the brain and fainting are liable to result. The operation ought not

[1] For a comparison of the efficacy of different forms see *Schafer*, Medico-Chirurgical Transactions, vol. **86**, supplement, 1904.

to be commenced until anæsthesia is complete; otherwise reflex inhibition of the heart or syncope may result and lead to fatal consequences.

Various drugs have been advised as preliminaries to anæsthesia, generally with the object of lessening the anxieties of the patient, and for this purpose small doses of morphine are probably most satisfactory. In addition atropine is often given, partly to stimulate the respiratory centre but still more to arrest the mucus secretion and to lessen the likelihood of vomiting. The injection of 0.01 G. ($\frac{1}{6}$ gr.) of morphine along with 0.5 mg. ($\frac{1}{120}$ gr.) of atropine (or scopolamine) has become a routine procedure in some clinics, from which satisfactory results are recorded. In place of morphine as a preanæsthetic agent many surgeons are now employing certain members of the barbituric acid series of hypnotics to quiet the patient and to lessen anxiety before the administration of the volatile anæsthetic is begun. (See Barbiturates, p. 371.)

Intravenous Infusion Anæsthesia.—The intravenous injection of ether has been advocated (Burkhardt), especially in operations on the mouth and throat. A solution of 5–8 per cent of ether in sterilized Ringer's solution is slowly infused through a cannula introduced into a vein, and as anæsthesia is induced the rate of flow is lessened until the point is reached which is just sufficient to maintain unconsciousness. The method is liable to cause hæmoglobinuria and is now rarely used. Soporifics, especially certain barbiturates, have been used as anæsthetics by intravenous injection (see p. 371).

Various **Mixtures of the Anæsthetics** have been advised at different times. Of these the ACE mixture (alcohol 1, ether 2, and chloroform 3 parts by volume) is the best known. Its use has, however, been attended with numerous fatalities, as was only to be expected from a consideration of the volatility of the different ingredients. Ether is most volatile, then chloroform, and then alcohol. The mixed vapor inhaled therefore will not correspond with the proportions of the three substances in the mixture and will tend to contain more ether at first and then more chloroform. The action of such mixtures is a simple sum of the actions of the constituents; there is no synergism between chloroform and ether.

Ethyl Chloride (C_2H_5Cl) has been advocated of recent years as an anæsthetic for minor operations and examinations, and possesses the advantages of acting very quickly and of leaving no after effects except occasionally some nausea, the patient generally feeling perfectly well in a few minutes. It is kept in sealed tubes and inhaled through a mask as it is extremely volatile, boiling at about 12° C. Anæsthesia is obtained in about two to five minutes, but complete muscular relaxation is often absent. Recovery follows a few minutes after the removal of the mask. It is not unpleasant to inhale and generally induces no excitement or other unfavorable symptoms, though occasionally muscular spasms may occur causing asphyxia from spasm of the larynx or respiratory muscles. The pulse is generally slowed, while the respiration is deep. Embley states that in animals the effects are similar to those of chloroform, but that it is less poisonous to the heart, about nineteen times as concentrated vapor being necessary to weaken it. The concentration of ethyl chloride vapor necessary to induce cardiac inhibition is four times that of chloroform, and this inhibition is not fatal as the heart muscle is less affected. The vapor may be inhaled in 5–7 per cent concentration without inducing inhibition in the dog. Nicloux found about 20 mgs. of ethyl chloride per 100 cc. in the blood in light anæsthesia, from 30–150 mgs. in deep anæsthesia and 40–180 at death. A number of fatalities have occurred under its use. Some major operations have been performed under ethyl chloride, but it is found difficult to maintain a uniform anæsthesia, owing to the rapidity with which consciousness returns. It is now chiefly employed for short operations in children for whom nitrous oxide is in some ways less suitable, or to induce anæsthesia, which is then main-

tained with ether. Ethyl chloride should not be administered in larger quantities than 4–5 cc.

Vinyl Ether.—Vinyl ether (divinyl ether or divinyl oxide, $CH_2{\cdot}CH\ O\ CH{:}CH_2$) is a clear colorless liquid which boils at 28.3° C. and is highly inflammable. It has recently been introduced as a volatile anæsthetic, and at the present time it is being used to a limited extent, especially for short operations or in obstetrics, but its use is distinctly in the experimental stage. It may be given by the closed or by the open method. In order to reduce the rate of evaporation when it is used by the cone method a small percentage of absolute alcohol is added to the ether, and an antioxidant is also added in order to prevent oxidation and polymerization.

Anæsthesia comes on quite rapidly under its influence, usually in from one-half to one and one-half minutes, and recovery is in like manner rapid, occurring in about two and one-half minutes. In addition to the rapidity of its action it is claimed that it is less irritant to the respiratory tract than ether and that it produces little or no postoperative nausea. It produces excellent muscular relaxation and is superior to ethyl chloride in not producing spasm of the respiratory muscles.

The relative safety of vinyl ether as compared to ether and nitrous oxide is still under investigation. The concentration of vinyl ether in the blood is considerably below that of ethyl ether when equal degrees of narcosis are compared. For instance, in the third stage of anæsthesia a concentration of 18 mgs. per 100 cc. has been found as compared with 132 mgs. per 100 cc. in the case of ethyl ether. This figure would not necessarily indicate a greater degree of safety but might merely indicate a more potent agent.

The question of toxicity is also an unsettled point. A few deaths have already been reported following its use, and the effect of the substance upon the liver seems to be of especial importance, which would indicate that caution should be used in employing it in long operations or in those in which there is any suggestion of previous hepatic impairment. The duration of its use appears to be especially important as regards possible liver damage, and it has been recommended that it should not be employed for longer than one-half hour when it is given by the open method although it can be given for a longer time when used with oxygen in a closed system. Even under these conditions some advise that it should not be given longer than one and one-half hours.

It is now chiefly used for brief anæsthesia required for short surgical procedures or for induction anæsthesia. Bourne has recommended it as suitable for anæsthesia in obstetrical practice on account of its safety for mother and child. It is also used as an adjuvant to nitrous oxide and oxygen when increased muscular relaxation is required. The absence of coughing makes it suitable for nose and throat surgery (Cartwright).

Methane, CH_4, a colorless gas, was studied by Brown who found that it was necessary to use a concentration of about 87 per cent in order to produce anæsthesia and about the same percentage to maintain the condition when it had once been induced.

Various other members of the fatty series have been introduced as general anæsthetics at different times, but few of them have proved to have any advantage over chloroform and ether, and fatalities have occurred after all of those that have received a wide trial. **Pental,** trimethylethylene ($(CH_3)_2C = CHCH_3$) was introduced for short operations but a number of accidents occurring under it led to its being abandoned. It produces anæsthesia before the reflexes disappear or the muscles relax, and not infrequently the jaws are tightly closed after consciousness is lost. In some cases tremor and convulsive attacks have occurred during its administration, but it seems to have very little action on the heart or circulation. **Ethyl Bromide** (C_2H_5Br) has also been used for short operations instead of chloroform, and produces anæsthesia with great rapidity. Consciousness returns quickly after the removal of the mask, but the inhalation is not so pleasant as that of ethyl chloride and patients complain of greater depression and discomfort afterward; several deaths have occurred from its use in dentistry, and this together with its tendency to decom-

pose on keeping has led to its disuse. Ethylene dibromide ($C_2H_4Br_2$) is a still more dangerous anæsthetic.

The other members of this series possess no practical importance. It may be mentioned that carbon tetrachloride (CCl_4) differs from the others in causing convulsions, while perchlorethane (C_2Cl_6) is a crystalline solid and possesses too high a boiling point to be available for inhalation.

Therapeutic Uses.—Anæsthesia is generally induced for the purpose of surgical operations and examinations, and in labor. Until recent years, when it was necessary to perform an operation or manipulation involving much pain, the surgeon had to consider only which of the two general anæsthetics was the better adapted to the case. But the improvements introduced in the methods of inducing local anæsthesia and the reintroduction of nitrous oxide as a surgical anæsthetic have now enlarged his field of choice, and the further question has to be met whether unconsciousness is desirable, or whether the necessities of the case may not be met by paralyzing sensation at the seat of operation only. The advantages claimed for local anæsthesia will be discussed under cocaine, but the general conditions in which chloroform and ether are to be preferred may be stated shortly (see also nitrous oxide). General anæsthesia is absolutely essential where complete relaxation of the muscles is desired, and where the movements of the patient may imperil the success of the operation. Operations on the abdominal organs and around joints and such others as involve wide and deep incisions will almost certainly continue to be performed under chloroform or ether, although a few such operations have been performed under cocaine. In many less serious operations it is necessary also to have recourse to the older methods, which allow greater freedom to the surgeon, who is under no apprehension that he may reach a sensitive area and has thus one less source of anxiety than if the anæsthesia were localized. Another argument for the use of general anæsthetics is the effect which the anxiety and the sights and sounds of the operating room may have on a nervous patient even when no actual pain is felt. And a considerable amount of practice is required before complete local anæsthesia can be induced over an extensive field of operation, while the surgeon has often to interrupt his manipulation in order to admit of a fresh area being rendered analgesic. But there is no question that many operations in which ether or chloroform has hitherto been employed, will in the future be performed more often under local anæsthesia, nitrous oxide, or ethylene. In this class may be included most minor operations in which only very short or partial anæsthesia is necessary and in which no complications are to be anticipated. Nitrous oxide and ethylene also have the great advantage that the patient can be dismissed within a few minutes after the operation is completed, while if ether or chloroform is employed complete recovery is only reached after several hours; when the latter are used in minor operations, the discomfort resulting from the anæsthetic may be altogether out of proportion to the actual surgical manipulation.

During labor only the lighter degrees of anæsthesia are necessary, the object being to dull the pain without lessening to any marked extent the reflex irritability of the spinal cord, and accidents are ex-

tremely rare in this use of anæsthetics, although the common statement that they are unknown is incorrect. Some cases have been recorded in which it is believed that chloroform was fatal to the child and not to the mother, but it is, of course, impossible to state with certainty that the anæsthetic was the cause of death. If too deep anæsthesia is produced, however, it is quite conceivable that the labor may be prolonged, or the blood-pressure so reduced as to lead to an imperfect exchange of gases in the placenta and this to the death of the infant; or, as another explanation, it might be suggested that the irritability of the respiratory centre of the child may be so reduced that it fails to react when the placental circulation is interrupted.

Anæsthetics are also employed in cases of extreme excitability of the central nervous system, as in strychnine poisoning, tetanus and other convulsive affections. In order to reduce these, it is unnecessary to produce deep anæsthesia, a few whiffs of chloroform being generally sufficient to produce quiet, often without affecting the consciousness to any marked extent. In cases of very acute pain, chloroform or ether may be used, but as a general rule morphine or opium is preferable, as the action lasts longer and the administration is more convenient, but in certain cases of colic, such as gall-stone colic, the use of the volatile anæsthetics may be of great value during the paroxysms of pain. Immediate relief is given by the inhalation of a few drops of chloroform in some forms of asthma.

The local action of chloroform and ether on the stomach and skin is entirely independent of their action as anæsthetics, and is discussed separately below.

Preparations.

U. S. P.

Chloroformum. Oral dose, 0.3 cc. (5 mins.).
Æther. Oral dose, 1 cc. (15 mins.).
Æthylis Chloridum. Ethyl chloride.
Æthylis Oxidum. Ethyl oxide or Solvent Ether.

B. P.

Chloroformum. Oral dose, 0.06–0.3 mil. (1–5 mins.).
Æther. Oral dose, 1–4 mils. (15–60 mins.).
Æther Anæstheticus. Anæsthetic or purified ether.
Æthylis Chloridum. Ethyl chloride.

Chloroform and ether are also included in both Pharmacopœias in various preparations designed for internal and external use. Among the preparations for internal administration are the Aqua and the Spirits of Chloroform and the Spirits of Ether, while the Liniment of Chloroform is employed externally.

Chloroform of the U. S. P. contains 99–99.4 per cent by weight of absolute chloroform ($CHCl_3$) and 0.6–1 per cent of alcohol.

Chloroform of the B. P. contains 98 per cent of chloroform ($CHCl_3$) and 2 per cent of absolute alcohol. Its specific gravity is 1.485–1.490.

Æther, ether, a liquid composed of about 96 to 98 per cent by weight of absolute ether or ethyl oxide ($(C_2H_5)_2O$) and about 2–4 per cent of alcohol and water. The U. S. P. provides that ether which is to be used for anæsthetic purposes must be preserved in small well closed containers. It also directs that

the contents of these containers which have been opened for more than twenty-four hours shall not be used for anæsthetic purposes. The U. S. P. also provides an ether which can be used for solvent or for purposes other than for anæsthesia under the name of ÆTHYLIS OXIDUM. This ether which is to be used for technical purposes need not be kept in small containers.

ÆTHER ANÆSTHETICUS, ether, contains about 95 per cent of absolute ether ($(C_2H_5)_2O$) along with some alcohol and water and has a specific gravity of 0.720.

ÆTHYLIS CHLORIDUM, C_2H_5Cl, a very volatile liquid of specific gravity 0.92–0.96, and containing not less than 99.5 per cent of ethyl chloride.

CHLOROFORM is ordinarily formed by the action of chlorine on alcohol, the chlorine being added in the form of chlorinated lime. The crude drug is purified by repeated washing with water and sulphuric acid, and dried over calcium chloride. The fatalities following its use have frequently been ascribed to impurities, and a certain demand has arisen for a purer article than that required by the pharmacopœias. Another method of preparation has therefore been introduced, the decomposition of chloral by soda (CHLOROFORMUM E CHLORAL PRÆPARATUM). Other pure forms are prepared from ordinary chloroform by crystallizing it by cold (Pictet), or by forming a compound with salicylid and decomposing it again by slight heat, CHLOROFORM (ANSCHUTZ) or CHLOROFORM (SALICYLID).

The impurities of chloroform are due partly to imperfect manufacture and partly to decomposition. Along with the chloroform there distils over a small quantity of heavy, oily fluid, which may be isolated by Pictet's method, but whose composition is entirely unknown. DuBois-Reymond found that this fluid acted more strongly on the heart than pure chloroform, but it is very questionable whether the minute quantities inhaled in ordinary anæsthesia produce effects of any importance, and, on the other hand, it is quite certain that the use of absolutely pure chloroform does not prevent accidents.

2. Ether and Chloroform (Local Action).

In addition to their use as anæsthetics, chloroform and ether are sometimes prescribed for the same purposes as the volatile oils. Chloroform has a hot, sweetish taste, while ether is bitter and suffocating in the mouth; a sensation of heat and often of pain in the stomach follows when they are swallowed, and chloroform may cause gastric irritation and catarrh when given undiluted. When ether has been exposed to air and sunlight and to a varying temperature, it may contain acetaldehyde and peroxide bodies, which render it more irritant to the mucous membranes. The whole effect is similar to that produced by the volatile oils, but absorption probably takes place more rapidly. On the skin, ether evaporates too rapidly to cause much irritation, but chloroform is occasionally used as a rubefacient in the form of a liniment.

PREPARATIONS.

The pure substances may be administered by the mouth, but more frequently other preparations are prescribed.

CHLOROFORMUM, 0.3 cc. (5 mins.).

ÆTHER, 1 cc. (15 mins.).

SPIRITUS ÆTHERIS (B. P.), Hoffmann's drops, 20–40 mins.

SPIRITUS CHLOROFORMI (U. S. P., B. P.), 2 cc. (30 mins.) (5–20 mins. for repeated doses, B. P.).

AQUA CHLOROFORMI (U. S. P., B. P.).

LINIMENTUM CHLOROFORMI (U. S. P., B. P.).

Therapeutic Uses.—These preparations are used for the same purposes as the corresponding preparations of the volatile oils. Thus the spirits may be prescribed as carminatives or in colic, while the liniment is used as a counter-irritant. Chloroform water is an antiseptic of considerable power, but is too volatile for surgical use.

Spirits of ether and ether itself are often given internally or subcutaneously in cases of shock or sudden collapse in the same way as brandy or whisky, though Elfstrand states that ether injected hypodermically has no effect on the heart or blood-pressure; spirits of ether contains a much larger percentage of alcohol than ordinary whisky. Both ether and chloroform, but more especially the latter, have been used internally for tapeworm with success. There is always some danger, however, that, besides destroying the parasite, they may cause irritation and lasting injury to the intestinal wall.

Hoffmann's drops is a favorite carminative, and is often added to other drugs to lend them an agreeable odor and taste. It is also used in dilution as a stimulant in the same indefinite way as wine and spirits, and its large percentage of alcohol entitles it to be ranked among the alcoholic preparations.

Spirits of ether is used occasionally in expectorant mixtures and is believed to increase the bronchial secretion.

Ether evaporates very rapidly and leaves a sensation of cold, and when thrown on the skin in a fine spray it produces sufficient cold to numb sensation in the part and allow of minor surgical operations (see uses of cocaine). Instead of ether, still more volatile substances, such as ethyl chloride (boiling point 12.5° C.), methyl chloride (boiling point −23° C.) and liquefied carbon dioxide have been introduced. These are supplied in pressure cylinders, and are allowed to escape against the skin.

The local anæsthesia produced bears no relation to their action when inhaled, but is due simply to the cold produced by their evaporation. The vessels of the part contract, and the absence of blood and hardness of the tissues facilitate some operations, but the subsequent reaction is liable to produce considerable soakage of blood from the wound. The cold elicited ought not to be great enough to actually freeze the tissues, otherwise the healing may be slow. The intense cold is often quite as painful as the operation itself would be without any anæsthetic.

Chloroform undergoes decomposition when exposed to light and air, hydrochloric acid and chlorine being set free in small quantity. These can affect the course of anæsthesia only through their local irritant action, but if present in sufficient quantity may cause the respiration to be more irregular than usual in the earlier stages; the chloroform used for anæsthetic purposes ought, therefore, to be kept in a dark place or in colored bottles. Another decomposition occurs when chloroform is evaporated in the neighborhood of a large flame, such as that from gas or lamps, and hydrochloric acid and carbonylchloride or phosgene ($COCl_2$) are formed; phosgene is one of the most dangerous gases known, for even 1 volume in 40,000 of air is sufficient to induce pulmonary œdema if inhaled for thirty minutes; the œdema comes on very slowly and proves fatal only after eight to twelve hours. Several accidents have occurred from this gas being formed in small operating rooms, both patient and attendants suffering from severe poisoning afterwards.

Chloroform is a heavy volatile fluid, of characteristic pleasant odor and hot, sweetish taste. Its specific gravity is 1.476 (U. S. P.) and 1.485–1.490 (B. P.), and it boils at 60–61° C. A number of tests are given for impurities, but those of importance can generally be detected by the odor, especially if some chloroform is allowed to evaporate in a watch-glass, when the last drop ought to have no irritant effect when inhaled. Chlorine and hydrochloric acid may be tested for by shaking the chloroform with distilled water, and testing the latter with potassium iodide and starch and with silver nitrate. The water ought to give no acid reaction to litmus. If left in contact with concentrated sulphuric acid, chloroform should not become darker within one hour, as this indicates the presence of some unstable foreign body. The other impurities require complicated chemical processes for their detection.

Ether is prepared by the action of sulphuric acid on alcohol, and is subsequently purified by washing with water and alkalies. It seldom contains impurities of importance. Æther anæstheticus (B. P.) or Æther (U. S. P.) is a very volatile fluid, of a suffocating, irritant odor and bitter taste. Its specific gravity is 0.716–0.717 (U. S. P.), and 0.720 (B. P.), and its boiling point is 35° C. It evaporates very rapidly in the air and should leave no foreign odor and no residue. When ether has been exposed for a considerable time to air and sunlight and to a varying temperature, it may contain acetaldehyde and peroxide bodies, which have been said to render it more irritant to the mucous membranes but Bourne states that acetaldehyde up to 0.5 per cent, in ether produced no significant effects while 1 per cent produced respiratory embarrassment. Recent studies tend to show that ether which has been exposed to air through having the container opened from time to time does not undergo deterioration within a reasonable period of a few weeks. They have also shown that untoward effects during or after an anæsthesia are as likely to occur when ether from small containers is used as when "drum" ether is employed. Ether peroxide, 0.5 per cent, caused a lowering of blood-pressure and respiratory disturbance. Ether should not color litmus paper, nor be colored within an hour when shaken with potassium hydrate solution. Ether vapor is exceedingly inflammable when mixed with air, and it should therefore be kept in a cool place, away from gas flames or lamps.

Ethyl Chloride is obtained by the action of hydrochloric acid on alcohol, and is a gas at ordinary temperatures, but is supplied condensed into a colorless fluid with a pleasant odor. It is very volatile, inflammable and mobile, and is liable to contain traces of the same impurities as have been mentioned under chloroform. It should be kept in a cool place, away from lights or fire.

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3. Nitrous Oxide.

The oldest of the anæsthetics, nitrous oxide, N_2O, does not belong to the methane series, but may be discussed at this point.

Symptoms.—When a mixture of nitrous oxide and air is inhaled for a few seconds, a condition resembling alcoholic intoxication is produced, with much hilarity and laughter, so that the oxide is known popularly as "laughing gas."[1] Even at this point a certain amount of anæsthesia is obtained, and it was the observation that persons falling during this stage did not complain of pain that first suggested to Wells the anæsthetic properties of the gas. Davy had noted these forty years previously, but his suggestion that nitrous oxide might be used in surgical operations passed unnoticed.

The inhalation of a mixture of nitrous oxide, 4 parts, and oxygen, 1 part, causes after a few seconds a rushing, drumming, hammering in the ears, indistinct sight, and a feeling of warmth and comfort. The movements become exaggerated and uncertain, the gait is staggering, and the body sways from side to side. The patient seems brighter and more lively, and often bursts into laughter. Somewhat later a feeling of drowsiness may come on, but this is not constant;

[1] "A young man, a Mr. Davy . . . has made some discoveries of importance, and enthusiastically expects wonders will be performed by the use of certain gases, which inebriate in the most delightful manner, having the oblivious effects of Lethe, and at the same time giving the rapturous sensation of the Nectar of the Gods. Pleasure even to madness is the consequence of this draught." Maria Edgeworth, 1800.

the sensibility to pain is much less acute than normally, but no complete anæsthesia is produced by this mixture of gases; the sense of touch is comparatively little altered, and total unconsciousness never results. The pupil is generally slightly dilated, the face flushed, and the pulse somewhat accelerated.

When pure nitrous oxide is inhaled without the admixture of oxygen, the patient passes almost instantaneously through the symptoms already described, but then loses consciousness completely; the face is cyanotic, the respiration becomes stertorous and dyspnœic and ceases after a weak convulsion, while the heart continues to beat for some time afterwards. If the mask through which the patient has been inhaling the gas is removed when the cyanosis becomes marked, very complete anæsthesia lasts for thirty to sixty seconds, and the patient then recovers within a few minutes and suffers from no after-effects whatever. No prolonged anæsthesia can be produced, however, as the respiration becomes endangered if the mask be kept on longer than the beginning of the cyanotic stage.

Action.—Nitrous oxide supports combustion outside the body, for if a glowing splinter of wood be held in it, it bursts into flame exactly as if it were immersed in oxygen. In the tissues of the body, however, nitrous oxide behaves in the same way as any other indifferent gas, such as hydrogen or nitrogen; that is, the tissues exposed to it suffer from asphyxia owing to the oxygen of the air being excluded. Thus, plants do not grow in an atmosphere of nitrous oxide and seeds do not germinate. Animals die after inhaling nitrous oxide in almost the same time as after hydrogen or nitrogen, and at death the spectrum of the blood shows no oxyhæmoglobin to be present, the tissues having used up all the available oxygen. Nitrous oxide, therefore, does not support combustion in the animal body, the nitrogen is not split off from the oxygen at body temperature as it is when the oxide is exposed to high temperatures outside the body.

But nitrous oxide has a special effect on the central nervous system, although in the rest of the tissues it acts only by excluding the oxygen; it depresses the brain by virtue of its molecular form just as chloroform or ether does. This has been shown in a variety of ways; thus, if it were a perfectly indifferent body no more effect would be produced by it when mixed with one-fourth of its volume of oxygen than by air, which consists of 1 part of oxygen and 4 parts of an indifferent gas, nitrogen. But 80 per cent nitrous oxide has definite effects on the behavior of animals, as has been mentioned, and even 73 per cent produces some slowing of the respiration.

The narcotic action was studied by Paul Bert in a series of experiments on man and animals. He noted that only imperfect anæsthesia was produced by 80 per cent nitrous oxide, while the pure gas produced asphyxia. The problem was to introduce as much gas into the blood as would pass in under pure nitrous oxide, and at the same time to supply sufficient oxygen to prevent asphyxia. The absorption of nitrous oxide depends upon its partial pressure in the lungs, as it is simply dissolved in the blood without forming any real combination with it, and the quantity absorbed by the blood may be augmented by increasing the barometric pressure. Bert, therefore, administered a mixture

of 80 parts nitrous oxide and 20 parts oxygen to animals in a glass case in which the pressure was raised one-fourth above the ordinary atmospheric pressure. The absorption of the nitrous oxide was the same as if the animal had breathed the pure gas at the ordinary air pressure, and at the same time as much oxygen was absorbed as in ordinary air. The result was apparently a complete anæsthesia without asphyxia, which could be maintained for three days without injury to the animal. Kemp has shown that mixtures of oxygen and nitrous oxide can be inhaled for some time and produce anæsthesia, which passes off at once when nitrogen is substituted for nitrous oxide. He has further investigated the blood gases during nitrous oxide anæsthesia, and finds that the oxygen contained in the blood at the deepest stage of anæsthesia is quite sufficient to maintain life and consciousness were no nitrous oxide present. Again Goltstein found that frogs were narcotized in five and one-half minutes in an atmosphere of nitrous oxide, in one and one-quarter hours in hydrogen, and showed that the narcosis and death in mammals from nitrous oxide differed in several details from that under indifferent gases. There can, therefore, be no doubt that nitrous oxide has distinct effects on the central nervous system, although it is indifferent to the other tissues. The anæsthesia is due to a specific action on the nervous tissues although this may be reinforced by the asphyxia present.

Several workers have recently reëxamined the relationship of nitrous oxide to oxygen in surgical anæsthesia and their results in general point to the importance of the oxygen content of the blood as determining the degree of anæsthesia taking for granted that there is an adequate concentration of nitrous oxide present. Greene and his co-workers have shown that for light anæsthesia in dogs the inhalant mixture must contain not more than 7.6 per cent by volume of oxygen and for deep anæsthesia even as little as 3.49 per cent by volume may suffice. For satisfactory surgical anæsthesia 94 to 96 per cent of nitrous oxide is needed, thus a certain degree of anoxæmia is always present.

The experiments of Bert described above have also been critically reëxamined by Brown, Lucas and Henderson and they are led to question the possibility of securing anæsthesia under conditions of increased pressure unless the amount of oxygen is restricted. They have raised doubt as to whether the animals employed in the Bert experiments were really in a condition of surgical anæsthesia or whether they were not rather in a state of analgesia. They failed to secure anæsthesia under pressures up to 2 atmospheres if the partial pressure of the oxygen was equal to that of the atmosphere, namely 156 mm. If the oxygen percentage was decreased to about one-half, the animals became anæsthetized and they therefore conclude that surgical anæsthesia with this gas depends not only upon the depressing action of the gas but also upon a certain degree of anoxemia.

The same question arises regarding the action on the nerve cells as has been met with in the members of the methane series, and here again the preliminary excitement may indicate not stimulation of the brain areas, but lessened activity of the functions of control and restraint.

Death during nitrous oxide anæsthesia probably occurs, not from the direct action of the nitrous oxide on the respiratory centre, but from the lack of oxygen, although the depression of the centre is undoubtedly a contributing factor.

The respiratory centre is depressed when the gas is inhaled in comparatively dilute form, for Zuntz and Goltstein found the breathing

slower and deeper after 73 per cent. The respiration ceases somewhat earlier under nitrous oxide than under indifferent gases, which would indicate that the cessation of the breathing is due at any rate in part to the specific depressant action. In asphyxia from nitrous oxide there is less convulsive movement than under hydrogen, owing to the general depression of the nerve cells.

The circulation is little affected by the nitrous oxide directly, the rise in the blood-pressure and slowness of the pulse being due to the asphyxial condition of the blood; the pulse is not so slow as in ordinary asphyxia or in asphyxia from nitrogen or hydrogen, because the inhibitory centre is less capable of activity. The heart is not affected directly, but only by the lack of oxygen.

The blood dissolves more nitrous oxide than water, apparently because it is taken up by the lipids of the corpuscles in the same way as chloroform. Nicloux found about 40 mgs. in 100 cc. blood at the beginning of anæsthesia, 50 mgs. in complete anæsthesia, and 60 mgs. when the respiration ceased.

Nitrous oxide is a gas at ordinary temperature and pressure, and is invariably administered by inhalation from a cylinder into which it has been forced under high pressure. The mask generally covers both nose and mouth, and the inhalation is carried on until distinct cyanosis appears, when the anæsthesia is sufficient to allow of short operations, such as those of dentistry. It is without doubt the safest of the anæsthetics, for millions of persons have been subjected to its influence, and only a comparatively few cases of death are reported from its use, but several of these do not seem to have been due to the direct action of the gas.

The question of the toxicity of nitrous oxide has recently been raised once more by a study made by Lowenberg, Waggoner and Zbinden. These workers report upon histological studies carried out upon the brains of three individuals who died in from two to three days following nitrous oxide-oxygen anæsthesia. In these cases the respiration usually stopped more or less abruptly, and there was muscular rigidity with tremor. The breathing was reinstated after a time but was not normal. The patients remained in a comatose condition until death with periods of marked rigidity, muscular twitching and hypertonicity of the extremities. The temperature rose toward the end to a high point, 105°–106°.

Postmortem examinations in each case showed marked destruction of the brain parenchyma, which is ascribed to a toxic action of nitrous oxide on the parenchyma. The cortex and basal ganglia were much more severely damaged than were the brain stem and cerebellum, resulting in the clinical picture of decortification. In experiments on animals Bock found that when oxygen was supplied to avoid asphyxia, a pressure of three atmospheres of nitrous oxide was the lowest fatal concentration; that is the fatal concentration is three times as great as that necessary for anæsthesia, a much greater difference between the efficient and the fatal dose than holds for any other anæsthetic.

Different types of apparatus have been devised to allow of prolonged operations under nitrous oxide employing oxygen at the same time in order to prevent too high a degree of cyanosis. These various forms of apparatus differ from each other in the details of construction but they consist essentially of tanks for the two gases and rubber bags into which the gases are led. A valve permits certain percentages of the two

gases to be delivered to the cone which is placed over the patient's mouth and nose. The inhalation is commenced with pure nitrous oxide but after ten or fifteen seconds oxygen is admitted and administered in a concentration of 4 or 5 per cent. This amount is gradually increased a little later as signs of deficient oxygenation become more apparent until in two or three minutes a percentage mixture of the gases is found which will produce a satisfactory anæsthesia without marked cyanosis. For this purpose about 92 or 93 per cent of nitrous oxide is necessary with 7 or 8 per cent of oxygen. When a satisfactory percentage mixture is found the narcosis may be continued indefinitely making only such changes in the mixture as may be indicated by the signs shown by the patient. Returning consciousness necessitates a diminution in the oxygen, stertor and cyanosis an increase.

This form of anæsthesia is admirably adapted for many operations and may be maintained for hours if necessary. The circulation and respiration are less seriously altered than by either chloroform or ether, and the return of consciousness is almost immediate. A great drawback to its use in prolonged operations is that for a safe and satisfactory anæsthesia considerable skill is necessary in its administration and in addition a somewhat cumbrous apparatus is required. Complete muscular relaxation is sometimes hard to attain and this precludes its use in some operations, in which, however, it may be employed at first and then be replaced by chloroform or ether, whose preliminary disagreeable effects are thus avoided. In some operations 80 per cent nitrous oxide has been used after partial anæsthesia had been attained by the hypodermic injection of morphine and scopolamine and the results have been favorable. Klikowitsch proposed the use of 80 per cent nitrous oxide, not for complete anæsthesia, but to relieve pain and spasm in cases of asthma, in labor and similar conditions. The patient could inhale it if necessary without the presence of a medical attendant, and it has the advantage over the other depressants that it need only be inhaled when an attack of pain is approaching and that it leaves no depression afterward. But 80 per cent is apt to induce symptoms closely resembling those of alcoholic intoxication.

The high blood-pressure induced by nitrous oxide asphyxia is sometimes said to be dangerous in elderly persons from their liability to apoplexy, and of the few fatalities under the gas several would seem due rather to this than to the drug directly, but the danger is often overstated, and, in fact, it is a question whether the shock caused by the operation without gas would not be more dangerous than the effects of the gas itself. No such symptoms arise when the nitrous oxide is administered diluted with oxygen.

Occasionally some glycosuria occurs after the inhalation, not owing to the gas itself, but to the accompanying asphyxia. It is merely temporary and has no practical importance.

The treatment of accidents in anæsthesia under nitrous oxide consists of artificial respiration alone.

PREPARATION.

U. S. P. and B. P.

NITROGENII MONOXIDUM, Nitrous Oxide, when drawn from a cylinder contains not less than 93 per cent of nitrous oxide.

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4. Ethylene.

One of the substances recently introduced as a surgical anæsthetic is ethylene. Brown, and Luckhardt and Carter, practically simultaneously published reports of the anæsthetic effect of this substance on animals, and the latter authors also included preliminary reports of its effects on man, given under laboratory conditions. Very shortly afterward Luckhardt and Carter reported a series of 108 cases in which the gas had been used clinically, and since that time it has been employed quite widely for the production of surgical anæsthesia.

Ethylene, $CH_2{:}CH_2$, is a gas at ordinary conditions of temperature and pressure. When a proper mixture with oxygen is inhaled a state of surgical anæsthesia is promptly induced, The action seems to be intermediate between ether and nitrous oxide, resembling ether as to depth but nitrous oxide as to rapidity of induction and recovery. The induction period is short, usually with little or no evidence of excitement. After a very few inhalations the patient loses consciousness and in from two to five minutes as a rule is completely anæsthetized. Occasionally individuals are found who are refractory to this anæsthetic just as they may be to others. With cessation of administration recovery is also prompt and relatively free from the unpleasant after-effects of ether anæsthesia. In order to obtain and maintain full surgical anæsthesia 90 per cent ethylene and 10 per cent oxygen is usually required. With this concentration the relaxation is sufficient for most major operations, but occasionally it may be necessary to supplement the ethylene-oxygen with small amounts of ether vapor. It is said that this addition becomes less frequently required with the development of skill on the part of the anesthetist. Premedication with morphine also makes possible the attainment of a greater degree of relaxation. Often in prolonged operations the concentration of ethylene may be decreased even to 80 per cent without disturbing the even sequence of anæsthesia.

The patient under ethylene presents rather a striking contrast to one under ether. The concentration of oxygen permitted makes it possible to keep a good color, usually with no trace of cyanosis. More-

over an occasional increase in oxygen to much higher concentrations than 10 per cent can be permitted for one or two breaths with no resulting irregularity in the depth of the anæsthesia. The skin remains dry there being little or no increase in perspiration and therefore little or no fall in body temperature. The respiration is slow and regular and somewhat shallow, and the pulse, which in most patients is accelerated before induction, gradually falls to normal and remains there. When the anæsthetic is removed, recovery is very prompt, the patient frequently regaining consciousness while on the table. Some retching movements or actual vomiting may occur on awakening and about one-third of all patients vomit sometime during the first three or four hours. Luckhardt found that about 30 per cent showed nausea and vomiting during this period as compared with about 75 per cent in a similar series using ether. Vomiting when it does occur is rarely severe or prolonged, and post-anæsthetic gas pains are very much less frequent and less severe than with ether. It is believed by some that the presence of impurities in the ethylene may have something to do with the incidence of emesis.

From the pharmacological standpoint, ethylene-oxygen anæsthesia is interesting in that a satisfactory degree of suppression of consciousness and of the reflexes can be produced with scarcely any effect upon other functions. The vasomotor centre seems scarcely to be affected, although with prolonged anæsthesia there may be a slight fall in blood-pressure (10-15 mm. Hg., Luckhardt). If the concentration is increased to a toxic point the respirations are increased for a time due to the asphyxia and then fail, but at this time the circulatory mechanism is in good condition so that prompt recovery results from the administration of artificial respiration. According to Miller and Plant there is an increase in amplitude of contractions of the stomach, small intestines, and colon during light anæsthesia from ethylene which lessens or returns to the normal with full surgical anæsthesia. There is no irritation of the mucous membranes of the nasopharynx, and therefore no excessive secretion of saliva or mucus. Nor is there any evidence of any kidney injury even after repeated and prolonged administration. The elimination of the gas seems to be entirely through the lungs, although this point has not as yet been completely investigated. The blood changes under ethylene-oxygen anæsthesia have been studied by Leake and Hertzman, who have shown that they are less than follow the other anæsthetics. In observations up to fifty minutes there was only a slight fall in blood alkalinity, remaining within normal limits provided sufficient oxygen was supplied to avoid the development of anoxæmia.

The advantages of ethylene largely will appear from the above discussion. It acts promptly, gives a greater degree of relaxation than nitrous oxide but less than ether, is not irritant, permits of sufficient oxygen being given to avoid asphyxia, and is relatively free from unpleasant after-effects. In the relatively short time since its introduction it has been used not only in all types of general surgery, but in the specialized fields of genito-urinary surgery, obstetrics and dentistry.

It has the practical disadvantage of forming explosive mixtures with air, which precludes its use in the presence of the open flame, cautery,

or electric spark. A few cases of explosions brought about by the development of static charges and subsequent sparking have occurred. This danger from the use of ethylene and oxygen mixtures has been fully discussed by a committee under Henderson. They point out that while the risk of an explosion is very slight and most of the causes are easily avoidable by ordinary care, there still remains a certain element of danger due to the fact that ethylene and oxygen yield explosive mixtures throughout a very considerable series of dilution percentages. For instance, for full anæsthesia the concentration of ethylene is above the explosive limits, and the chief risk is when the ethylene is shut off and the patient's lungs are washed out with oxygen. During this time the gas mixture passes through the entire explosive range, the most explosive mixture seeming to be a combination of ethylene 25 per cent and oxygen 75 per cent. The immediate cause of the explosion is the discharge of static electricity developed within the anæsthetic apparatus itself. The conditions producing such discharges not being fully understood at the present time, they are not preventable by care. Two measures which have been adopted to minimize the dangers are humification of the atmosphere of the room and electrical grounding of the anæsthesia apparatus and operating table.

In spite, however, of the defects of the anæsthetic apparatus, the risk of an explosion when using this anæsthetic is statistically very small indeed, especially when it is compared with such hazards as the pulmonary complications which only too often follow the use of some of the older anæsthetic agents, such as ether. The unpleasant odor which is present in varying degree in the gas, as thus far produced, may be a disadvantage to the surgeon, but is practically never complained of by the patient. It may be due to impurities in the gas.

Preparation.

U. S. P. and B. P.

Æthylenum, Ethylene, $CH_2=CH_2$ contains not less than 99 per cent (U. S. P.) or 98 per cent (B. P.) by volume of ethylene.

Ethylene, like nitrous oxide, is marketed in steel tanks under pressure. It must be free from carbon monoxide, the presence of which has caused several serious or fatal cases of poisoning.

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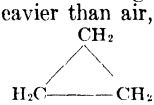
5. Cyclopropane and Propylene.

Cyclopropane (Cyclopropanum, U. S. P.—$CH_2.CH_2.CH_2$). In the search for new inhalation anæsthetics which might offer advantages over those in general use an examination of the action of propylene was made. It was found, how-

ever, that certain cardiac disturbances followed its use which apparently made it undesirable as an anæsthetic. In an effort to locate the agent responsible for the cardiac damage a study of cyclopropane, an isomer of propylene, was carried out, and in this study it was discovered that this gas itself possessed powerful anæsthetic properties.

This substance was first prepared by Freund in 1882, but no particular use was found for it until 1929 when Lucas and Henderson published their findings of its anæsthetic properties. Cyclopropane is a gas which is heavier than air, having a specific gravity of 1.46 and a structural formula,



It is almost insoluble in water but is very soluble in lipids. It is inflammable and is capable of exploding when mixed with oxygen in concentrations as low as 3.8 per cent. This property makes it important to take precautions against using it in the neighborhood of a flame.

Cyclopropane will produce narcosis when inhaled in concentrations as low as 4 per cent, but much higher concentrations are used depending upon the depth and duration of anæsthesia required. The gas may be given by the closed carbon dioxide absorption technique, in which the mask is supplied with oxygen and cyclopropane, the latter being shut off after one to three minutes. Narcosis takes place in a few minutes as the gas becomes distributed in the tissue. Oxygen is then supplied according to the needs of the patient, and if necessary further cyclopropane may be added if the anæsthesia is insufficient. In the administration of the gas care must be taken not to increase its concentration too rapidly as time is needed for adequate distribution in the tissues. The gas is quite potent and high concentrations can be inhaled without irritation and without much change in respiration until a stage of very distinct depression is reached. Muscular relaxation is less complete than with ether.

In the early stage of anæsthesia the eyelid reflex is gradually lost followed by extra-ocular paralysis with fixation of the eyeball in the "looking forward" position. As the anæsthesia deepens the intercostal respiratory movements lessen, breathing finally being entirely diaphragmatic until it too ceases and respiratory paralysis follows. A dangerous stage in the anæsthesia is also indicated by arrhythmia and slowing of the heart. The appearance of the patient may be misleading as he will have a good pink color due to the oxygen content being adequate. In case of doubt as to the condition it is recommended that oxygen should be given rather than the anæsthetic gas as a concentration of 21 per cent of the gas may cause severe respiratory depression and 43 per cent complete respiratory paralysis.

In experiments on dogs high concentrations of cyclopropane produced arrhythmia with ventricular extrasystoles followed later by tachycardia and fibrillation. According to Robbins and Baxter these cardiac irregularities are due to anoxæmia and are prevented by premedication by morphine and amytal. Amytal especially reduces the amount of cyclopropane necessary for anæsthesia without an appreciable reduction in the concentration which will produce respiratory arrest (Robbins, Baxter and Fitzhugh). Cyclopropane favors the occurrence of ventricular rhythms and tachycardia and therefore the association of adrenaline is contra-indicated as in chloroform anæsthesia (Meek, Hathaway and Orth).

Ordinarily induction of anæsthesia with cyclopropane is less rapid than with nitrous oxide, but it lacks usually the feeling of fullness in the head commonly experienced with the latter agent. In the recovery stage nausea and vomiting are usually slight. Those experienced in its use prefer it to ethylene and in many cases also to ether. It may also be used introductory to the use of ether. The Report of the Council of Pharmacy and Chemistry sums up its advantages and disadvantages. It is not irritant or unpleasant or deleterious to the liver, and pulmonary complications probably occur less often than with ether. Cardiac arrhythmias occur which are not usually seen with ether and post-anæsthetic headache is not uncommon. It is a suitable anæsthetic agent when used

cautiously by those fully informed of its properties, potential dangers and signs which indicate the stages of anæsthesia.

Henderson and Macdonald have examined several methyl and chlorine derivatives of cyclopropane but found none superior to the parent substance as anæsthetics.

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Propylene, the second member of the unsaturated hydrocarbons and having the formula C_3H_6 is a colorless gas with an odor suggesting ethylene. Its anæsthetic properties have been studied by Brown who found that anæsthesia was induced with a concentration of from 37 to 50 per cent while maintenance was carried on with from 20 to 31 per cent. Percentages over 65 were followed by toxic symptoms especially by a fall in blood-pressure. Halsey and his co-workers found that even with high and dangerous concentrations muscular relaxation was not obtained and spontaneous movements were not infrequently present. With high concentrations death might occur suddenly, usually from failure of the respiration.

In man unconsciousness followed in fifteen to twenty seconds from the inhalation of concentrations of 35 to 40 per cent and recovery may take place equally rapidly. Vomiting is not an uncommon accompaniment.

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6. Avertin.

Avertin (Tribromethanol).—Tribromethanol ($CBr_3 \cdot CH_2OH$) has been introduced into medical and surgical practice as a hypnotic and general anæsthetic under the name of Avertin. It is supplied as Avertin Fluid, 1 cc. of which contains 1 G. of tribromethanol crystals dissolved in amylene hydrate. Its action is predominantly that of central nervous system depression but occasionally excitation is observed with small doses and as an initial effect with larger doses. It is most commonly used as a basal anæsthetic in a dosage of 80–100 mgm. of avertin per kgm. of body weight, administered rectally in 2.5 3 per cent solution. This is often preceded by a therapeutic dose of some hypnotic such as morphine sulfate and supplemented as necessary by one of the volatile or local anæsthetics although with the above dosage the latter procedure is not always required. Its routine use in larger doses sufficient to produce complete surgical anæsthesia is now generally considered too dangerous to be justifiable. Rapid absorption follows rectal administration, producing anæsthesia in about five minutes which persists for from one to three hours and is usually followed by several hours of sleep, often obviating the necessity for postoperative analgesics and soporifics. Used in this manner the mental distress and irritation of the respiratory tract involved in the induction of anæsthesia by volatile anæsthetics are avoided, and it is generally agreed that vomiting is less frequent than after ether or chloroform. Furthermore an amnesia usually occurs extending from the beginning of induction until several hours after the operation. Of course

avertin has the disadvantage common to all non-volatile anæsthetics of the lack of control of its action following administration. Also close nursing attention is required for some hours postoperatively to prevent respiratory accidents such as the falling back of the tongue.

Avertin generally causes a greater depression of the respiratory center than ether or chloroform, a fact which is of some significance when it is used with preanæsthetic medicaments such as morphine. A temporary slight fall in blood-pressure is also often encountered and in one series of patients this was found to parallel a decrease in blood volume. After much larger doses a depression of the vasomotor centre and a direct injury to heart and blood-vessels have been described. Degenerative changes in the liver, kidney and colon and also acidosis have been reported after doses greater than those now recommended and some authorities consider preëxisting pathology of the above organs a contraindication to its use.

Avertin is detoxicated in the liver by combining with glycuronic acid and in this form is usually excreted quantitatively in the urine, almost all being eliminated within forty-eight hours.

No satisfactory conclusion is yet possible concerning the relative safety of avertin in comparison with other anæsthetics. A number of deaths have been reported following its use. Some of these have followed dosages greater than those now advised and in certain other cases the previous condition of the patient and associated medication may have been factors. It is now generally agreed that the risks involved do not justify the use of avertin alone as a complete surgical anæsthetic. It is chiefly used for premedication, prior to nitrous oxide-oxygen anæsthesia.

Aside from its use in general surgery it has been used successfully in smaller doses (60–70 mgm. per kgm.) in obstetrics during the second stage of labor. Favorable results have also been reported from moderate repeated doses in the control of maniacal attacks, status epilepticus and eclampsia. Recently it has been employed with good results in the treatment of tetanus. In this condition it is used for the control of the muscular rigidity and convulsions and is of course employed in conjunction with the use of large doses of tetanus antitoxin. The avertin is given by rectal injection in a sufficient dose to produce relaxation and quiet and is then repeated at intervals, usually of from six to eight hours, as may be required to control the symptoms. It may be necessary to keep the patient under the influence of diminishing doses of the drug for several days.

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III. SOPORIFICS OR HYPNOTICS.

1. Chloral Group.

Some twenty years after the introduction of the anæsthetics, a new interest was given to the methane series by the examination of chloral hydrate ($CCl_3CH(OH)_2$) by Liebreich. Henceforth the attention of investigators was diverted from the quest of anæsthetics to that of hypnotics, with the result that a number of valuable drugs have been added to therapeutics. These soporifics, or narcotics, have the same general action as the anæsthetics, but are used only to produce the first

effects of imperfect consciousness or sleep. The anæsthetics might be used for this purpose were it not for the comparatively short time during which their action persists. Narcotics are required to produce a slight but lasting effect, and for this purpose the gradual absorption from the bowel is better adapted than the rapid absorption and equally rapid elimination by the lungs. The narcotics are, therefore, less volatile than the anæsthetics, and ought to be soluble in water and not irritant in the stomach, so as to permit of rapid absorption. The most widely used members of this group are *chloral*, *barbital* (*veronal*) and *phenobarbital* (*luminal*), but many others have received attention. They all resemble each other in their general soporific action, and that of chloral may be taken as typical of all; in their other characters some differences are presented and these will be taken up for each individual drug. Larger doses of some of these hypnotics have been used to produce general anæsthesia but at the present time are more frequently used to induce analgesia and unconsciousness, prior to the administration of an inhalational general anæsthetic.

Symptoms.—Chloral in 15–30 gr. (1–2 G.) doses produces drowsiness and weariness, which soon pass into a condition resembling natural sleep very closely, from which the patient can be awakened by ordinary means, such as touching, loud sounds, or pain. The respiration and pulse are rather slower than in waking moments, but scarcely more so than in natural sleep, and the somewhat narrowed pupil and unaltered excitability of the reflexes are also common to both conditions. As a general rule, the sleep passes off in five to eight hours and leaves no unpleasant results, but sometimes headache, giddiness, and confusion are complained of. Occasionally no real sleep is produced by chloral, a condition exactly resembling alcoholic intoxication following its administration and continuing for some time.

When larger quantities (75 grs. or 5 G.) are taken, the sleep is much deeper, the patient cannot be aroused to complete consciousness, the reflexes are distinctly lessened and the sensation of pain is less acute, although no complete anæsthesia is present. The respirations are fewer and the pulse may be slow and somewhat weak. The sleep lasts very much longer (ten to fifteen hours), and nausea, vomiting, headache and confusion often remain after consciousness is regained. In still larger quantities chloral produces a condition resembling exactly the third stage of anæsthesia. The reflexes are entirely absent and no movement is elicited by painful operations, the muscles are completely relaxed, the respiration and pulse are both slow and weak, and eventually asphyxia occurs from paralysis of the respiratory centre. The heart continues to beat for a short time after the breathing ceases. The pupil is often contracted to pinhole size before death in fatal poisoning.

The first stage is the only one elicited in therapeutics. The use of chloral as an anæsthetic in man would be quite unjustifiable, because it is impossible to adjust the dose accurately enough to allow of complete anæsthesia without danger of respiratory failure.

Action.—The **Central Nervous System** is depressed and eventually completely paralyzed by chloral and its allies. Unlike the anæsthetics

and alcohol, however, chloral rarely causes excitement, but this may be due to the fact that the surroundings of the patient are less likely to cause excitement and that the drug itself causes less local irritation. The results of psychological experiments on the effects of small doses of the narcotics seem to indicate that they all depress the sensory or receptive functions of the brain, while its motor activity is much reduced by chloral and sulphonal, but may appear to be actually increased by paraldehyde; this apparent stimulation is analogous to that under alcohol and may be explained by lessened control. The sleep induced by the dulling of the perceptions may be interrupted by more intense stimuli from without. In particular, acute pain may prevent sleep after chloral, which seems to have no specific effect on pain sensation such as is possessed by morphine. In larger quantities, however, even very great disturbance of the environment produces no interruption of the sleep, and the reflex response to irritation is very much lowered. The motor areas of the brain cortex are rendered less irritable by chloral, and eventually fail to react to the strongest electrical stimulation. The reflexes of the spinal cord are depressed and finally paralyzed before the failure of the respiration; this depressant action on the spinal reflexes is much more marked than that seen under morphine. The last part of the central nervous system to be attacked is the medulla oblongata, for although the respiration is somewhat slower and shallower after small quantities, it is scarcely more affected than in ordinary sleep, and Loewy found that both the excitability of the centre and the volume of the inspired air were very similar in the two conditions. As the dose is increased, however, the respiration becomes very slow and weak, and finally ceases from paralysis of the centre.

The heart is slower after chloral in moderate doses, but scarcely more so than in natural sleep. There is often some flushing of the face and head from some obscure central action, but the blood-pressure is little affected in the therapeutic use of the drug. In poisoning, the blood-pressure is reduced by weakness of the vasomotor centre and of the heart, the latter manifesting itself also in slowing of the pulse. This action on the circulation from poisonous doses is more in evidence under chloral than under the other hyponotics which do not contain chlorine. The same difference is met with in ether and chloroform, of which the latter affects the circulation more strongly. And the action on the heart in chloral poisoning resembles that of chloroform, the auricles being affected sooner than the ventricles and the strength of contraction failing more than the rate.

Locally, chloral has an irritant action when applied in concentrated solution and this leads occasionally to nausea and vomiting when it is prescribed with insufficient fluid. This irritant action induces redness and even vesication when chloral is applied to the skin; it is said to corrode when applied to unprotected surfaces, and certainly possesses disinfectant properties like chloroform. It is rapidly absorbed when given by the mouth and is carried to the central nervous system where it is taken up by the cells until they contain more than the blood corpuscles or the cells of other organs, such as the liver. Liebreich intro-

duced chloral as a hypnotic in the belief that it was decomposed in the blood and chloroform liberated, but this has been shown to be erroneous, no chloroform being found in the blood or expired air after chloral. Chloral has no action on muscle or nerve in the living animal, but when it is applied to the exposed nerve it first irritates and later paralyzes it, and injected directly into the artery of a muscle it causes immediate rigor. The temperature falls after the administration of chloral from the lessened muscular movement, and perhaps from the increased output of heat through the dilated skin vessels.

The effects of chloral on the tissue-change have been found to correspond to those of chloroform in character, but are very slight and seldom observed; fatty degeneration of various organs has been caused in animals by prolonged administration of large doses, and the usual changes in the urine have accompanied it. The muscular movement being reduced by the narcosis, less oxygen is absorbed and less carbonic acid is excreted by the lungs. Chloral was formerly supposed to lead to glycosuria, but this has been shown to be erroneous, the reducing substance in the urine being urochloralic acid, and not sugar.

It has generally been accepted that chloral is reduced in the tissues to trichlorethyl alcohol (CCl_3CH_2OH), which combines with glycuronic acid to form urochloralic acid, and is excreted in this form in the urine but this is denied by Lehmann. Some escapes by the kidneys unchanged, however, and and some is thrown into the stomach, and this may contribute to the nausea and discomfort felt after awaking in some cases.

Trichlorethanol is itself quite a powerful hypnotic with a more prolonged action than chloral, but it has been little used clinically.

The other hypnotics of this series, with the exception of chloralose, correspond exactly with chloral as far as their action on the central nervous system is concerned. The chief difference in their effects is seen in the circulation and metabolism, which are even less affected by those which do not possess substituted chlorine atoms.

Paraldehyde ($C_6H_{12}O_3$), a polymer of acetaldehyde, resembles alcohol in its effects though it is a much more powerful narcotic and rarely induces any symptoms of excitement. It does not affect the heart directly even in large doses and has no such effects on the protein metabolism as have been observed under the prolonged administration of chloral; the pulse is slightly slower and the carbonic acid exhaled is less than normally, but these changes are due to the muscular movements being lessened, and are hardly greater in extent than occur in natural sleep. Very large quantities have been taken without fatal results and in fact without any more serious consequences than prolonged unconsciousness. It is excreted in part by the lungs, though mainly in the urine, and the odor remains in the breath for some time after the patient awakens. Paraldehyde has a most unpleasant odor and a hot, burning taste, which renders its administration somewhat difficult. It may perhaps be best given on cracked ice or in ice water. It may also be given by the rectum. The use of paraldehyde in anæsthesia is referred to later (p. 372).

Sulphonal (Sulphonmethane) $((CH_3)_2C(SO_2C_2H_5)_2)$ and its allies, **Trional** (Methylsulphonal) $(C_2H_5CH_3C(SO_2C_2H_5)_2)$ and **Tetronal** $((C_2H_5)_2C(SO_2C_2H_5)_2)$ have no immediate action on the circulation even in large doses, though it is stated that their prolonged use is deleterious to the heart, and they appear to be more uncertain in their narcotic action in cases of heart disease than in other conditions. They are practically tasteless powders, and are therefore easily taken, but their insolubility in water renders their absorption slow and uncertain, and sleep is therefore late in following their administration, while, on the other hand, depression, drowsiness and lack of energy are often complained of the day after. There is some evidence that they exercise a deleterious effect on the liver, for the relation of urea to the total nitrogen of the urine is changed and the metabolism of the purine bodies is also affected.

The use of the sulphonal group, especially when prolonged, has led in many cases to a series of symptoms, the most characteristic of which is the appearance in the urine of a reddish-brown pigment, hæmatoporphyrin, an iron-free product of the decomposition of hæmoglobin. This occurs most frequently in anæmic women, and is accompanied by constipation, pain in the stomach region and vomiting, weakness and ataxia, confusion and partial paralysis, and eventually by suppression of the urine or by collapse and death. These symptoms may appear several days after a single dose, sometimes after an interval of one or two weeks. The excretion of hæmatoporphyrin in the urine appears to be due to some obscure change in the liver; it occurs in traces in the rabbit's urine normally and in larger quantities after the animal has been treated with sulphonal (Neubauer). In other animals the prolonged administration of sulphonal often causes albumin and casts in the urine, while hæmorrhages in the kidneys have been produced by the administration of only a few doses. Very large doses are said to produce convulsive movements in animals, while ordinary ones cause sleep and subsequent drowsiness. Sulphonal is decomposed in the body and is excreted largely as ethylsulphonic acid in the urine, in which traces of the unchanged substance have also been found. The decomposition is a slow process, however, for Kast found sulphonal in the blood many hours after its administration. The ethylsulphonic acid seems to have no action whatever in itself, so that the narcosis is due to the unchanged molecule of sulphonal. Due to the fact that the drug is destroyed or eliminated so slowly there is a marked tendency to produce cumulative effects with symptoms of chronic poisoning. For this reason sulphonal is not suited for prolonged administration. Sulphonal is now rarely used except in asylum practice when it is occasionally employed to produce a mild but prolonged cerebral depression.

Butylchloral, or **Crotonchloral** $(C_3H_4Cl_3CH(OH)_2)$, was said by Liebreich to possess a specific analgesic action on the nerves of the face and head, but this has been shown to be incorrect, and, as its effects are identical with those of chloral in almost all respects, crotonchloral seems entirely superfluous.

Chloralamide, or chloralformamide $(CCl_3CHOH{-}NHCHO)$, was introduced as tending to depress the heart less than chloral, but this has not been demonstrated. It is said to be less irritant than chloral in the stomach, but to be somewhat slower and less certain in its effects. Chloral is formed by its decomposition in the body, and is excreted as urochloralic acid.

Chloralose $(C_8H_{11}Cl_3O_6)$, a sugar compound of chloral, acts much more like morphine than like chloral, depressing the psychical functions, while increasing the reflexes until convulsions resembling those of strychnine may be produced. The heart is comparatively little affected, and the respiration remains strong unless very large doses are given. In man it induces sleep, which is sometimes attended by distinctly exaggerated reflexes, especially when large doses are given.

Amylene Hydrate, or dimethylethylcarbinol $((CH_3)_2COHCH_2CH_3)$, is closely allied to paraldehyde in its effects but is twice or thrice as powerful, while it is only one-half as strong as chloral. It is said to depress the heart more than paraldehyde, but less than chloral, and to produce excitement and convulsions in the carnivora, but not in the herbivora. Even in man, it causes excitement more frequently than most other soporifics, and Harnack and Meyer state that

it first stimulates and then depresses the respiratory centre as well as other parts of the central nervous system, and that it induces a very marked fall in the temperature. It has little or no effect on the general metabolism, and is excreted in the urine in combination with glycuronic acid in the rabbit, but is exhaled by the lungs for the most part by the dog and possibly by man. It is less certain in its action than chloral.

Carbromalum, U. S. P. and B. P., brom-diethylacetyl urea, $(C_2H_5)_2CBr.CO.NH.CONH_2$, is a moderately powerful hypnotic, relatively free from after-effects and used mostly in insomnia due to worry, overwork or excitement. It is known by the trade names of Adalin and Uradal.

Urethane, or ethyl carbamic ester ($CONH_2OC_2H_5$), is too weak and inconstant in its action in man to be satisfactory. In many cases it is an almost perfect hypnotic, especially in children, producing light sleep with no after-effects, but in others it seems to have little or no hypnotic effect. It is converted in the body to urea. **Hedonal,** the amyl carbamic ester ($CONH_2OC_5H_{11}$), appears to have a greater hypnotic effect than urethane, but also fails to induce sleep in a considerable proportion of cases.

Bromoform ($CHBr_3$) has anæsthetic properties like chloroform, but is not volatile enough for inhalation. It has been used internally in whooping-cough, but in this relation it is important to remember that it gives rise to fatty degeneration when taken continuously. A number of cases of alarming poisoning in children have been recorded from its use. It has also been used occasionally in insomnia.

Bromal (CBr_3COH) differs in several respects from chloral in its action. In animals its injection is followed by restlessness and excitement, and then by stupor, which is often accompanied by dyspnœa, and ends in failure of the respiration, or in convulsions. The pupil is much contracted, and profuse salivation is observed. It acts on the heart like chloral but is much more poisonous, and is scarcely used in therapeutics.

Chlorobutanol, U. S. P., Chlorbutol, B. P. (Chloretone), trichlortertiary-butylalcohol ($CCl_3C(CH_3)_2OH$), resembles chloral in most respects, but is less liable to irritate the stomach. Very large doses have been swallowed without producing any untoward symptoms, but the hypnotic effect is obtained by the use of smaller doses than are necessary in the case of chloral. It has a reputation for prevention of sea-sickness. Like chloral, chlorobutanol has some virtues as an antiseptic, and in addition it paralyzes the terminations of the sensory nerves when it is applied locally and has proved of value as a local anæsthetic.

Many other similar bodies have been introduced as hypnotics, but have not proved to possess any advantages over those already enumerated. Among these are hypnone ($C_6H_5COCH_3$), neuronal ($(C_2H_5)_2BrCCONH_2$), isopral ($CCl_3CHOHCH_3$), bromural and brometone.

Tolerance is soon acquired toward several of these drugs, and when it is developed for one, larger doses of any of the others are required in order to produce sleep. Tolerance for alcohol also involves the use of larger quantities of the hypnotics, and in fact often leads to the complete failure of any except the most powerful.

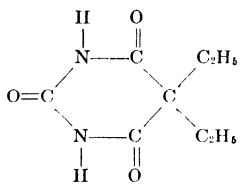
Not infrequently the hypnotics lead to skin eruptions, especially when used for some time. These assume various forms, the most common being of the erythema order, but among others urticaria, purpura, papular eruptions and blisters occur.

Habit.—Prolonged abuse of chloral leads to a condition somewhat resembling that seen in chronic alcoholism or morphinism, and marked by general depression and cachexia, with impairment of the mental powers, digestive disturbance and exanthemata. The sudden with-

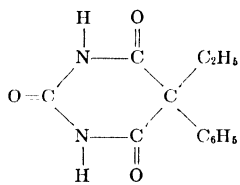
drawal of the drug in these cases has sometimes led to symptoms resembling those of delirium tremens. Cases of sulphonal and paraldehyde habit have also been reported.

2. Barbituric Acid Group.

Within the past few years a large number of barbituric acid derivatives have been synthesized and examined pharmacologically, and many of these which showed promise as hypnotics and sedatives have been introduced into the practice of medicine. The first member of this group to be introduced (under the name of Veronal) was diethyl-



Barbital.



Phenobarbital.

barbituric acid. It is now employed as a hypnotic under the name of Barbital or Barbitone. Other substances which have been used differ chemically from barbital by the replacement of either one or both of its ethyl groups by some other alkyl radical, or in certain cases an aryl substitution has been made. For this purpose, primary, secondary, iso- and unsaturated alcoholic groups have been used, the total number of carbon atoms in the two groups varying from four (barbital) to eight (phanodorn). Compounds with longer side chains have usually proved to be convulsant and of low hypnotic potency.

By various substitutions, a great number of compounds of barbituric acid is possible. Many of these have been synthesized and examined pharmacologically and the more promising have received clinical trial. While they resemble one another in action, their actions on the central nervous system are not identical. Some have more tendency than others to produce excitement and even their depressant actions are probably not quantitatively alike on every sector of the central nervous system. One of the chief differences is, however, in the duration of their actions, some like evipan being rapidly broken down in the body and having a brief hypnotic action, others like phenobarbital being more resistant and acting for a longer period.

The following list is far from exhaustive but includes most of those which have had a considerable therapeutic trial. One point which must be kept in mind with this or with any homologous series of drugs is that undesirable side actions which may occur are of the nature of idiosyncrasies which appear only in a small proportion of individuals. They can only be discovered when a drug is extensively presented. Consequently many new compounds which on a limited clinical trial are recommended as free from undesirable effects fail to live up to this reputation with more extended use.

Of many of these compounds, the sodium salts are also used. These, being more soluble, are supposed to act more quickly when given by mouth but are especially suited for parenteral injection.

Phenobarbital (phenobarbitone).
Amytal (iso-amyl ethyl barbituric acid).
Dial (di-allyl barbituric acid).
Evipan (Evipal) (methyl-cyclohexenyl-methyl barbituric acid).
Ipral (the calcium salt of isopropyl ethyl barbituric acid).
Neonal (n-butyl ethyl barbituric acid).
Nirvanol (phenyl ethyl hydantoin).
Nostal (Noctal) (isopropyl beta-brom-allyl barbituric acid).
Pentobarbital (Nembutal) (1-methyl-butyl ethyl barbituric acid).
Pentothal (ethyl-methyl-butyl thio barbituric acid).
Pernocton (butyl-bromallyl barbituric acid).
Phanodorn (cyclohexenyl ethyl barbituric acid).
Prominol (methyl-phenyl-ethyl barbituric acid).
Sandoptal (isobutyl allyl barbituric acid).
Soneryl (butyl-ethyl barbituric acid).

It is generally accepted that these compounds differ in the absolute amount necessary to produce a desired hypnotic effect, a fact indicated by the dosage advised. However, comparative studies have shown that in a general way the toxicity increases with the hypnotic potency, and a consideration of prime importance is whether or not these two factors are absolutely parallel. If hypnotic potency bears the same relation to toxicity in the various preparations, little may be gained by preparing compounds of greater hypnotic effect. However, it has been shown by various workers that in rats definite differences in the compounds are evident with respect to the ratio of minimum lethal dose to an effective hypnotic dose, or in other words, certain preparations show a much greater safety factor than others. The fact that such differences exist has been corroborated by using certain percentages of the minimum lethal dose of various of the compounds combined with nitrous oxide anæsthesia in rats. Eddy concluded that certain uniform percentages of the minimum lethal dose of various preparations showed very different effects in cats.

On the other hand, Tatum and his co-workers found that a comparative grade of surgical anæsthesia in laboratory animals required approximately the same proportion of the fatal dose in all cases and that such differences are less than the personal error in judging depression. Furthermore, they proposed the duration of action as a practical method of classification of such hypnotics. In a general way the compounds effective in small dosage are destroyed or excreted more rapidly after administration and have a shorter period of action. Pentobarbital and amytal have a comparatively short duration of action while barbital, phenobarbital, neonal, ipral and dial have been found to possess a longer period of activity. Usually such groupings hold with respect to the time of death after lethal dosage also, the shorter acting drugs causing death in a comparatively brief time by respiratory depression while the other group often brings about a delayed death due to periph-

eral effects, such as pulmonary edema and pneumonia. Furthermore, the mode of administration may play a prominent rôle in determining the action of the compound, the preparations having a short duration of action on intraperitoneal injection, behaving as the longer acting drugs on oral administration. On this account the warning is made that the oral clinical dose should not be based too closely on results obtained from intraperitoneal or intravenous toxicity in animals.

Pharmacological Action.—The action of barbituric acid derivatives is essentially sedative and hypnotic. A certain degree of analgesia is present but this is not as marked as with drugs of the antipyretic group. The localization of barbiturates in the central nervous system has been demonstrated, by numerous studies. Keeser and Keeser using barbital, phenobarbital and dial found the greatest concentration in the diencephalon—especially in the thalamus—in contrast to the cerebral hemispheres and suggest that the former region is of particular significance in the phenomenon of sleep.

Koppanyi and his co-workers in their experiments found that after intravenous injection of anæsthetic doses of sodium barbital the drug was found distributed in every portion of the central nervous system in about equal concentration, and, therefore, these drugs cannot be considered necessarily as brain stem hypnotics. This objection is answered by the Keesers who point out that the general distribution of the barbiturates is correct for the administration of large doses but does not hold good for small doses such as they employed where the kind of distribution they found seems to point to a special affinity of the drug for a definite group of cells.

Although the action on the central nervous system is the essential one in the production of the therapeutic effect, other functions of the body may be affected directly or indirectly by large doses. The effects most often described are: a fall in body temperature, slight lowering of the basal metabolic rate depending on the depth of narcosis, respiratory depression, a temporary lowering of blood-pressure on rapid injection due to vasodilation and direct cardiac effect, a depression of smooth muscle activity and, under certain conditions, hyperglycemia. Hafkesbring and MacCalmont found that the only cardiac effects of anæsthetic doses of barbital and some other barbiturates, as shown by the electrocardiograph in cats and dogs, were an increase in heart rate. Some of the barbiturates depress the endings of the cardiac vagus and diminish the depressor effect of acetyl-choline.

Poisoning, Habit Formation and Tolerance.—Much is still to be learned concerning the manifestations of idiosyncrasy and overdosage of the newer compounds, but there is no reason to believe that they differ markedly from those of barbital and phenobarbital. In fact, most of the toxic signs and symptoms described in connection with the earlier compounds have been experienced with those more recently introduced. Habit formation with barbital is now a well-recognized problem and occurs also with other preparations. Tolerance may result from the prolonged use of barbituric acid preparations but not to anything like the same degree as occurs with morphine. Fitch reported a shortening of the sleeping time in rabbits by about 50 per cent after the second or

third dose of certain of the barbiturates, and also a gradual increase in the lethal dosage.

Koppanyi and Dille also have shown that rabbits, given daily fractions of the lethal dose and excreting only about one-half of that administered, should theoretically in time store several times the fatal dose in their tissues, and yet they show no severe depression. In contradistinction to rabbits cats show continuous depression during the period of drug administration and eventually die in barbital coma. The increase in resistance in rabbits is apparently due to an enhancement in the ability of certain tissues, probably the liver, to oxidize the barbital. This destruction is further shown by the fact that only small amounts of the drug are found postmortem in the body. Also the amount which is found in the blood during the course of treatment steadily increases for a time and then begins to decline.

Excretion.—Numerous reports indicate that the barbituric acid derivatives are excreted in the urine in varying amounts, only traces being found in the feces. Apparently 90 per cent of barbital may be eliminated in this way after small repeated doses, but after the administration of larger amounts the percentage markedly decreases—possibly to from 50 to 60 per cent of the amount administered. The elimination is slow and may in certain cases extend over a period of ten days.

It has been suggested that individual tolerance may be explained by the rate of elimination. and according to certain workers animals have been protected from lethal doses of barbital by inducing diuresis. Koppanyi and his co-workers, however, deny that diuresis as produced by saline diuretics will hasten the elimination of barbitals, but have recently found that massive intravenous infusions of isotonic glucose or saline solutions can, in cats and dogs, shorten the time of anæsthesia of barbital or phenobarbital and render recovery possible from two to three times the minimum lethal dose. Although with therapeutic doses of barbital there is little effect on the kidney, signs of renal damage have been reported after large doses. Barbital and phenobarbital were found in the urine as such. Dial, pernoston, phenobarbital, ipral and allyl-isopropyl barbituric acid are also eliminated by the kidney, but apparently to a less degree than is barbital. On the other hand Herwick was unable to recover neonal and amytal from the urine of dogs, suggesting a quantitative breakdown of these substances in the body. These findings in regard to amytal and also as to pentobarbital were further confirmed by Shonle and his colleagues who could only find traces of these substances in the urine of dogs and of man, suggesting their almost complete destruction in the body.

Koppanyi and Krap however report that they were able to obtain from 3 to 8 per cent of these compounds from the urine of dogs to which they had been given and from the urine of patients who had taken poisonous doses.

The importance of the kidney in the elimination of barbital is further shown by the fact that experimental animals with severe nephrosis never recover from the depression caused by barbital, while similarly nephritic animals to which were given the barbiturates which are not eliminated by the kidneys recovered from the effects in spite of the kidney condition. Chickens, which eliminate only slight amounts of barbital in the urine, reacted in a manner similar to the nephritic animals and died from anæsthetic doses while they recovered from barbiturates other than barbital.

In the acute use of barbital the liver has little power to destroy it, as 85 per cent of that administered can be recovered from the urine, but with the continued use of the drug this power of destruction is apparently raised. The failure of the liver to destroy barbital in the acute use of the drug is also shown by the fact that injury to the liver by previous use of chloroform or carbon tetrachloride

does not affect the duration of the barbital action. On the other hand, in the case of the short acting drugs such as pentobarbital, which are almost entirely destroyed in the body, previous damage to the liver results in a prolongation of the depression produced by this substance (Pratt).

Phenobarbital, sandoptal, and chlorobutanol, substances which are believed to exert their effect principally on the brain stem, produce a marked anti-diuretic effect in narcotic doses in dogs, in contrast to so-called cortical soporifics such as paraldehyde, chloral hydrate and avertin, which have a much weaker anti-diuretic effect (Bonsmann). The possibility that certain barbiturates may effect the action of diuretics is suggested by the work of Nyary on rabbits. In contrast to chlorobutanol which markedly decreased the diuretic effect in all cases, phenobarbital usually increased the diuretic effect of such substances as caffeine, theophylline, salyrgan, hypertonic sodium sulfate, sodium chloride and urea. Schloss reported that allyl-isopropyl barbituric acid decreased salyrgan diuresis in dogs, and Epstein demonstrated that the water excretion following intravenous injection of 0.9 per cent NaCl in rabbits was increased by narcotic doses of sandoptal and phenobarbital but was unaffected by barbital.

Synergism and Antagonism.—The efficacy of barbituric acid compounds in the treatment of poisoning from cocaine, strychnine and similarly acting drugs has been demonstrated by numerous workers, both on experimental animals and clinically. Convulsions may be controlled by the intravenous injection of such hypnotics and the lethal dose of strychnine and cocaine in animals may be increased from two to four times by administration of barbituric acid preparations. In certain clinics these compounds have been used routinely previous to procaine infiltration as a protective measure and to increase the analgesic effect.

A certain relationship has also been demonstrated between barbituric acid hypnotics and antipyretic drugs and, in fact, such combinations have been used clinically in such preparations as *Allonal*, in which the hypnotic action of allyl-isopropyl barbituric acid is combined with the analgesic action of aminopyrine. Magnus found in rabbits that the stimulating action of aminopyrine was neutralized by barbital, and the depressant action of barbital was delayed and diminished by aminopyrine. Furthermore, Kaer and Loewe showed that in guinea-pigs one-half the minimal lethal dose of each (barbital and aminopyrine) did not produce death, showing a certain antagonism between the two drugs. Antipyrine and acetylsalicylic acid combinations with the barbiturates produce effects similar to those of aminopyrine.

The stimulating effect of caffeine and ephedrine in barbiturate narcosis is generally recognized, and it has been demonstrated that within certain limits the effect of picrotoxin can be neutralized by barbital. Also, Tatum and his co-workers, as well as other observers, have ascribed to picrotoxin a superiority over a number of suggested antidotes in acute barbiturate poisoning.

Barbital or **Barbitone** (introduced under the name of Veronal), diethyl-barbituric acid ($(C_2H_5)_2C(CONH)_2CO$), and its sodium salt, soluble Barbital (Sodium Barbitone or Medinal) ($NaC_8H_{11}O_3N_2$), seem to be devoid of action except on the central nervous system, and thus approach the ideal soporific more closely than some others. In ordinary doses (5–10 grs.) it induces natural sleep, frequently without subsequent

depression. Larger quantities deepen and lengthen the unconsciousness without other organs than the central nervous system being involved, though the patient may complain of lethargy and drowsiness subsequently. Fatal poisoning from barbital has frequently occurred, the smallest dose reported as having caused death is 10 grains but the average minimum fatal dose is probably about 50 grains (3.3 G.). Much larger doses have been recovered from, even as high as 125 grains (8 G.), however doses of this size usually prove fatal unless early and vigorous treatment is instituted. The symptoms are those of mental confusion, nausea, muscular weakness and incoördination. The heart and respiration are usually normal unless in very severe cases, when they are depressed. The mental depression passes into a stupor, with cyanosis, a cold skin and coma ending in respiratory failure. Bronchopneumonia may occur from the prolonged coma. Death rarely occurs earlier than twenty-four hours after the drug has been taken and more commonly not until the third day.

Owing to the widespread abuse of the drug chronic poisoning is quite common. The patient often shows an erythematous rash of the skin and is frequently cyanotic but the symptoms most commonly encountered are those due to the action of the drug on the brain. There is mental depression, drowsiness or possibly visual hallucinations. The speech may be incoherent, and rambling, or indistinct and drawling; memory is poor, and there is a defect in attention and association. The gait is ataxic. In fact the symptoms may be suggestive of a severe organic disease of the central nervous system. There is emotional instability and outbursts of temper are common, the breath is foul, the tongue coated and there is marked constipation.

Chronic poisoning with barbital is also not infrequently encountered in its therapeutic use as elimination of the drug is slow and cumulative effects such as mental and bodily weakness, tremors and dizziness soon become manifest. For this reason the drug should not be given for long periods without close supervision.

Elimination of the drug is mainly by the kidney, from 50 to 90 per cent having been recovered from the urine, the remainder apparently undergoing oxidation in the tissues.

In some animals barbital causes increased reflexes and even general convulsions, but this effect has not been seen in man.

Phenobarbital (Luminal) is a recent addition to the group of barbituric acid derivatives which possess a depressant action upon the central nervous system. It is closely related chemically to barbital, differing from it only in that one of the ethyl groups in barbital is replaced by a phenyl group. It is thus phenylethyl barbituric acid.

Its action is essentially like that of barbital in that its administration is followed usually by quietness and sleep. However for a pure hypnotic action it has not proved as efficient as some of the other members of the barbituric acid series. Its great value seems to lie in its ability to allay symptoms of motor activity thus explaining its wide use in epilepsy and in tremors or in convulsions due to strychnine or other poisons. Its relatively prolonged action is also an advantage in these conditions.

In rare instances a condition of excitement has preceded the sedative action. Symptoms of idiosyncrasy are not uncommon; the most frequent manifestation being a skin rash that is usually associated with marked itching and a slight elevation of temperature. Other less common symptoms are gastric disorders, diplopia, vertigo, and speech disturbances. Illegibility of writing and disturbances of gait have been noticed frequently.

Phenobarbital apparently is partly destroyed in the body and the remainder is eliminated in the urine. If the drug is to be used for some time the patient should be carefully watched for signs of chronic poisoning.

Soluble Phenobarbital (Soluble Luminal), the sodium salt of phenylethyl barbituric acid, is freely soluble in water and may therefore be given by hypodermic injection in a 20 per cent solution.

Pentobarbital differs from barbital in that one of the ethyl groups in the latter compound is replaced by a methyl butyl group. It is closely related to amytal, of which it is an isomer. Its action is essentially the same as that of barbital except that it is effective in smaller doses and the depression and sleep come on more promptly and are of much shorter duration. The brevity of action is probably due to the fact that it is practically entirely destroyed in the body, only very small amounts being found in the urine. The destruction probably takes place mainly in the liver because, if the liver has been injured by toxic agents such as chloroform or carbon tetrachloride, the pentobarbital depression is greatly lengthened. The amytal depression is also relatively brief, but it is more prolonged than is that following pentobarbital administration. Also the administration of amytal is not infrequently followed by a period of delirium and excitement. Both pentobarbital and amytal are relatively insoluble in water, but their sodium salts are freely soluble and therefore may be administered intravenously in case of an emergency.

Therapeutic Uses of Hypnotics.—The hypnotics are chiefly used to produce rest and sleep in cases of insomnia, and in almost every form of nervous excitement. Until the discovery of the therapeutic value of chloral, opium was used in most of these cases, and when sleeplessness is due to pain it is still preferable to the more modern remedies, which have comparatively slight influence on acute pain, except in very large doses. But in delirium, mania and convulsions of various kinds, their action on the nerve centres is preferable to that of opium, especially where these convulsions are of spinal origin or of a reflex nature; thus, in strychnine poisoning and in tetanus, chloral, phenobarbital and some of the newer barbituric acid derivatives are of great value, although in strychnine poisoning they may have to be reinforced by chloroform during the convulsions. In delirium from fever or from uræmic intoxication and similar causes, comparatively small doses often produce most satisfactory results, and in various spasmodic affections, such as cough, asthma and choreic movements, they are exceedingly useful.

Most of the soporifics have been used more or less extensively as hypnotics in simple insomnia and in insanity, but when the disturbance assumes a more violent character there is a disposition to return

to the use of chloral, as at once the speediest and surest remedy of the whole group. When there is any reason to suspect fatty degeneration of the heart, however, some hypnotic which does not contain chlorine ought to be substituted for it if it has to be given repeatedly. In other forms of heart disease, chloral may be used without danger and is often of great value as a hypnotic; the dread of its affecting the heart deleteriously in ordinary doses is quite unfounded. Paraldehyde is also a safe and effective hypnotic and would be more widely used if it were not for its objectionable taste and smell and the difficulty of prescribing it.

In recent times chloral and the older hypnotics have been largely replaced as mild sedatives of the central nervous system by barbital and its allies. Barbital itself is very efficient and is used in doses from 0.3–0.5 G. (5–8 grs.) given usually in tablet form. These should be crushed before swallowing to aid absorption. Soluble barbital may also be used but in general it has not attained the popularity of the parent drug.

More recently phenobarbital has been extensively employed especially in central nervous system disorders associated with motor disturbances. It is not so useful as a hypnotic as some of the other barbiturates but has been used in acute and chronic nervous exhaustion and in various psychoses. As a sedative in exophthalmic goitre, both before and after operation, it has proved very efficient. Doses of from 1 to 2 grains repeated once or twice daily as necessary may be given.

Perhaps its greatest field of usefulness however is in the treatment of epilepsy where in the past few years it has almost entirely supplanted the bromides. In this condition the dose of phenobarbital will need to be adjusted to the condition of the individual patient. In case the attacks are nocturnal in character a dose of 1½–2 grains given at bed time may be sufficient to prevent the convulsions. Or it may be necessary to repeat the administration of the drug in the morning giving perhaps a slightly smaller dose at that time. It is rarely necessary to give the drug three times a day but in severe cases it may be found that this is unavoidable. If drowsiness or apathy appear the dose should be reduced. Also if symptoms of idiosyncrasy (p. 369) are troublesome, the use of the drug may have to be stopped.

It is of course understood that the use of the drug is not curative in this condition but is only palliative, and that it may have to be continued for years. It is important also to remember in connection with the use of this drug in epilepsy that after it has been given for a time it must not be stopped abruptly as otherwise the attacks are likely to return in increasing number and severity. Should it become necessary for any reason to discontinue the use of phenobarbital in this disease the dose should be lessened gradually or the drug may be replaced by the bromides for a suitable time.

More recently *prominal* has been advocated as superior for the treatment of epilepsy to phenobarbital, of which it is the methyl derivative. Henderson treated a group of epileptics for one year on bromides and for a second year on prominal. The number of fits under prominal was only one-third of that which occurred under bromides. Milman

described the effect on the number of fits of changing over the treatment in an epileptic colony from phenobarbital to prominal. The mean "fit rate" under prominal was only one-third of that under phenobarbital. The dose advised was 2 to 3 grains three times a day. It is claimed that prominal produces the depression of motor excitability with less accompanying drowsiness than does phenobarbital.

Another compound, also related, but less closely, to phenobarbital, *nirvanol*, has been used especially in chorea. When given daily for seven to fourteen days, it usually produces a rash, accompanied by pyrexia and eosinophilia. When this reaction occurs the administration of the drug is stopped and in many cases the choreic movements cease. Some neurologists believe that its toxic properties outweigh its therapeutic advantages and believe that, if given, it should be restricted to intractable cases of chorea the treatment of which is under strict supervision.

Use in Anæsthesia.—Quite recently certain barbituric acid derivatives have been recommended for use in large intravenous doses to produce complete surgical anæsthesia, or in moderate intravenous doses as a basal anæsthetic to be supplemented by one of the volatile anæsthetics. In addition they have been used by mouth as preanæsthetic medication. Although many successful anæsthesias have been carried out by intravenous doses of some of these compounds this procedure is to be considered dangerous in that the dosage injected, and therefore beyond the control of the anæsthetist, must necessarily approach the lethal one, resulting in a mortality which is greater than that of the volatile anæsthetics.

Claims are made that the use of the members of this group for preanæsthetic medication is advantageous in that the patient may be anæsthetized without excitement and a period of quiet and sleep may follow the operation, but in many cases the advantage of the loss of consciousness without the anxiety or excitement involved in volatile anæsthetic induction and the prolonged postoperative analgesia may be offset by pulmonary complications resulting from prolonged respiratory depression. Also postoperative manias and excitement occasionally result, necessitating close supervision for many hours. For preanæsthetic medication, therefore, the preparations with a short duration of action are recommended so that prolonged postoperative effects will be eliminated.

One of the barbiturates which has been widely used for inducing brief anæsthesia is *evipan*, which is rapidly destroyed in the body and exercises only a brief action. It is usually administered intravenously in a 10 per cent solution, injected slowly with careful observation of the response of the patient. Unconsciousness comes on very rapidly and anæsthesia lasts usually from two to twenty minutes. Recovery is also prompt. The chief danger arises from the depressant action on the respiratory centre. *Pentothal* is recommended by many anæsthetists for a similar purpose. It produces rather better muscular relaxation and a slightly longer action than evipan. It is claimed that with it

induction is smoother and accompanied by less jactitation and muscular twitching than with evipan.

Paraldehyde has also been used for premedication purposes, usually given by rectum dissolved in saline solution. It is one of the safest basal hypnotics since it has little depressant action on the respiratory center or on the cardiovascular system. Postoperative hypnosis tends to be prolonged. It has been mostly used for children, for very elderly people and for those suffering from toxæmia or pyrexia.

Favorable results have been reported in the treatment of poisoning from strychnine or cocaine by the intravenous injection of certain of the barbiturates and such a use may be properly justified on the basis of the urgency of the condition. For this purpose the sodium salts of phenobarbital, pentobarbital or amytal have been most largely used. Recently these drugs have also been extensively used preliminary to the administration of the local anæsthetics, cocaine or procaine. They are especially valuable when the former drug is to be used as they not only allay the nervousness of the patient but also act as direct antidotes to the toxic effects of the cocaine.

Chlorobutanol (Chloretone) has been recommended in cases of gastric irritation and vomiting, which it relieves by paralyzing the terminations of the sensory nerves in the mucous membrane of the stomach.

In cases of acute **Poisoning** with the soporifics, the treatment consists in the immediate evacuation of the stomach by the stomach tube. Emetics are of less value owing to the depression of the medullary centres. The patient ought to be kept warm, and caffeine or strychnine may be given as a respiratory stimulant, while the complete failure of the breathing has to be met by artificial respiration. Picrotoxin has recently been suggested as an antidote in cases of barbiturate poisoning. When a patient has formed the habit of taking one of these drugs, it is generally necessary to send him to a retreat. It seems advisable to withdraw the drug gradually.

PREPARATIONS.

U. S. P.

CHLORALIS HYDRAS, 0.5 G. (8 grs.).
PARALDEHYDUM, 2 cc. (30 mins.).
SULFONETHYLMETHANUM, Trional, 0.75 G. (12 grs.).
BARBITALUM, Barbital, Veronal, 0.5 G. (8 grs.).
BARBITALUM SOLUBILE, Sodium Barbital (Medinal), 0.5 G. (8 grs.).
PHENOBARBITALUM, LUMINAL, 0.03 G. ($\frac{1}{2}$ gr.).
PHENOBARBITALUM SOLUBILE, Sodium Phenobarbital, 0.03 G. ($\frac{1}{2}$ gr.).
CHLOROBUTANOL, Chloretone, 0.6 G. (10 grs.).
CARBROMALUM (Adalin), 0.5 G. (8 grs.).

B. P.

CHLORALIS HYDRAS, 0.3–1.2 G. (5–20 grs.).
PARALDEHYDUM, 2–8 cc. (30–120 mins.).
SULPHONAL, 0.3–1.2 G. (5–20 grs.).
METHYLSULPHONAL, Trional, 0.3–1.2 G. (5–20 grs.).
BARBITONUM, Barbital, 0.3–0.6 G. (5–10 grs.).
BARBITONUM SOLUBILE, Soluble or Sodium Barbital, 0.3–0.6 G. (5–10 grs.).

PHENOBARBITONUM, Phenobarbital, Luminal, 0.03–0.12 G. (½–2 grs.).
PHENOBARBITONUM SOLUBILE, Soluble or Sodium Phenobarbital, Medinal, 0.03–0.12 G. (½–2 grs.).
CHLORBUTOL, Chloretone, 0.3–1.2 G. (5–20 grs.).
CARBROMALUM (Adalin), 0.3–1 G. (5–15 grs.).

CHLORAL HYDRAS or CHLORAL ($CCl_3CHO + H_2O$) is a crystalline solid, of a characteristic pungent odor, and hot, acrid taste, readily soluble in water, alcohol, ether and oils, and is almost invariably prescribed in dilute solution in syrup. Its deliquescent properties preclude its use in most of the solid preparations, and its irritant effect contra-indicates hypodermic injection.

PARALDEHYDUM ($C_6H_{12}O_3$) is a colorless fluid of strong, characteristic odor and burning taste. It may be prescribed in brandy and water or with cracked ice, or in ice water, or in capsules.

SULPHONAL ($(CH_3)_2C(SO_2C_2H_5)_2$), a crystalline powder, without taste or odor. It may be prescribed in powder form, to be taken one to two hours before retiring, but is soluble in hot water or milk, and when given in solution acts more rapidly and leaves less confusion afterward.

SULFONETHYLMETHANUM, METHYLSULPHONAL, TRIONAL, ($(CH_3)(C_2H_5)C(SO_2C_2H_5)_2$) resembles sulphonal, but is more soluble and has a bitter taste.

BARBITAL, BARBITONE (VERONAL) ($(C_2H_5)_2C(CONH)_2CO$, colorless crystals with a faint bitter taste, soluble in 145 parts of water; prescribed in powders or tablets, may be dissolved in warm water or milk.

BARBITAL SOLUBLE (MEDINAL) is freely soluble in water.

PHENOBARBITAL ($CO(HNCO)_2C(C_2H_5)(C_6H_5)$) (U. S. P.) (LUMINAL). A white crystalline powder, odorless, soluble in 1000 parts of cold water. Given in powders, capsules or tablets.

PHENOBARBITAL SODIUM (SOLUBLE or SODIUM LUMINAL) is a white hygroscopic powder; very soluble in water. May be given by hypodermic injection in a 20 per cent solution.

CHLOROBUTANOL, U. S. P., CHLORBUTOL, B. P., CHLORETONE, ($CCl_3C(CH_3)_2OH$), colorless crystals with a strong camphoraceous odor, slightly soluble in water, very soluble in alcohol; it may be prescribed in tablets. Dose, 0.3–1 G. (5–15 grs.).

CARBROMALUM $(C_2H_5)_2.CBr.CO.NH.CONH_2$. A white odorless powder, soluble about 1 in 3000 of water, usually given in tablets.

UNOFFICIAL PREPARATIONS—BARBITURIC ACID GROUP.

AMYTAL differs from barbital in that one of the ethyl groups of barbital is replaced by an iso-amyl group. It is a white crystalline powder almost insoluble in water. It is used as a sedative in doses ⅓–¾ gr. and as a hypnotic in doses 1½–5 grs. For preanæsthetic medication it is used in 3–10 gr. doses, and in convulsions due to strychnine or tetanus, doses of about an equal magnitude are used, depending upon the conditions present.

The sodium salt of amytal is freely soluble in water and may be used as a hypnotic in 3 gr. doses or for preanæsthetic medication in doses 3–10 grs. In approximately the same sized doses it may be given to control the convulsions of strychnine poisoning and of tetanus.

EVIPAN, (Evipal) a solid, freely soluble in water. The sodium salt is used for intravenous injection.

In DIAL allyl groups replace the ethyl groups present in barbital. It is a white crystalline powder almost insoluble in water. The sedative dose is about ½ gr. three or four times daily while the hypnotic dose is 1½–4½ grs. Its hypnotic action usually appears in about an hour.

IPRAL is calcium ethyl isopropyl barbiturate. It is a white crystalline powder soluble in water. It is given in doses of 2–4 grs., usually followed by hot water or milk.

In NEONAL, n-butyl ethyl barbituric acid, a normal butyl group replaces one of the ethyl groups found in barbital. It is a white crystalline powder sparingly soluble in water and is given in tablets in doses of 1–1½ grs.

NIRVANOL, a tasteless, crystalline powder, slightly soluble in water. In chorea the usual daily dose is 3–7 grs. divided into 2 or 3 doses.

In NOSTAL both the ethyl groups of barbital have been replaced; in the one case with an isopropyl group, and in the other with a substituted brominated allyl group. Its sedative action is more marked than is that of barbital and it can therefore be given in smaller doses. As a sedative it is used in doses $\frac{3}{4}$–$1\frac{1}{2}$ grs., and as a hypnotic in doses $1\frac{1}{2}$–$4\frac{1}{2}$ grs., given preferably with a hot drink.

In PENTOBARBITAL SODIUM one of the ethyl groups of barbital is replaced by a methyl butyl group. It is a crystalline powder which is freely soluble in water. Its action is relatively brief, which, as pointed out elsewhere, may be advantageous in certain conditions. As a hypnotic it is used in doses of $1\frac{1}{2}$ grs. and as a preanæsthetic sedative in a dose of about 3 grs. It may also be given, dissolved in water, by rectum.

PHANODORN contains a cyclohexenyl group in place of one of the ethyl groups found in barbital. It is a crystalline powder very sparingly soluble in water, so that it is usually given in tablets in doses of $1\frac{1}{2}$ grs. for simple insomnia or in doses 3–5 grs. in obstinate cases. The larger doses should not be repeated within twelve hours. Its action is much shorter than is that of barbital, but this may be advantageous when it is used as a hypnotic drug as it would tend to lessen any tendency to depression on the following day.

PROMINAL, colorless, tasteless crystals, freely soluble in cold water. Usually prescribed in tablets or suspension, 3 grs. once or twice daily.

SANDOPTAL is isobutyl allyl barbituric acid, differing from barbital in that both the ethyl groups are replaced; one by an isobutyl group and the other by an allyl group. The crystalline powder is slightly soluble in water. It is usually given in tablet form in doses 3–12 grs.

CHLORAL FORMAMIDUM or chloralamide ($CCl_3CHOHNHCHO$), a white crystalline powder with a faintly bitter taste; prescribed in powder or in solution in water or spirit. Dose, 15–45 grs.

ÆTHYLIS CARBAMAS, urethane ($NH_2 \cdot CO \cdot OC_2H_5$), colorless crystals, odorless, with a cool, saline taste, very soluble in water, alcohol and ether. Dose, 1–5 G. (15–75 grs.).

BROMOFORMUM ($CHBr_3$), a heavy transparent, colorless liquid with an ethereal odor, and a taste like that of chloroform, very little soluble in water, but readily soluble in alcohol. Dose, 0.2 cc. (3 mins.).

TETRONAL resembles sulphonal closely, and may be prescribed in the same dose and form.

AMYLENI HYDRAS ($(CH_3)_2COHCH_2CH_3$), a colorless liquid of pungent taste, and of an odor somewhat resembling camphor. It may be prescribed in capsules, or up to 10 per cent in water. Dose, 3–5 cc. (40–80 mins.).

HEDONAL, a crystalline powder with a taste resembling that of menthol, very slightly soluble in water. Dose, 2 G. (30 grs.) in powder or tablets.

PROPONAL differs from veronal only in having propyl substituted for ethyl, and is used in the same dose.

ISOPRAL ($C_2H_3Cl_3CHOH$), white crystals with a camphoraceous odor and aromatic biting taste, soluble in 30 parts of water; prescribed in doses of 0.5–0.75 G. (5–8 grs.).

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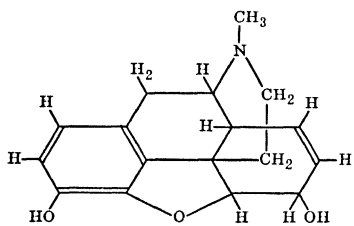
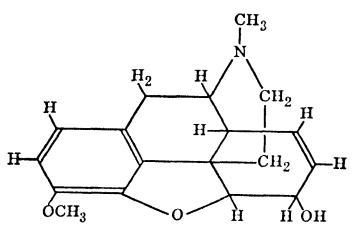
LAHOUSSE: Arch. de pharmacodyn., vol. **1**, p. 209. (Butylchloral.)
v. MERING: Therap. Monatsh., p. 249, 1887.
SCHMIEDEBERG: Arch. f. exp. Path. u. Pharm., vol. **20**, p. 203. (Urethane.)

IV. OPIUM SERIES.

Opium has been used in medicine since a very remote period, and although many substitutes have been proposed for it of late years, it still occupies a position of its own in therapeutics. It is the dried juice of the Papaver somniferum, a poppy which is grown chiefly in India, China, Egypt, Persia and Asia Minor, but has been cultivated in colder climates and is said to produce a more powerful opium there. Opium owes its activity to a large number of alkaloids, of which *Morphine, Codeine, Papaverine, Narcotine* and *Thebaine* are the most important.[1] The total alkaloids in opium vary from about 5–25 per cent, and different specimens may contain very different quantities of each alkaloid; for instance, morphine may vary from 2.7–22.8 per cent. The average percentage of morphine is 10, of narcotine 6, papaverine 1, codeine 0.5, thebaine 0.3 and narceine 0.2; the others occur in too small quantity to have any influence on the action of the crude drug.



Morphine.



Codeine.

The alkaloids are found in opium in combination with meconic, lactic, and sulphuric acids. The empirical formulæ of most of the alkaloids have been determined, those of the most important being morphine ($C_{17}H_{19}NO_3$), codeine ($C_{18}H_{21}NO_3$), narcotine ($C_{22}H_{23}NO_7$), papaverine ($C_{20}H_{21}NO_4$), thebaine ($C_{19}H_{21}NO_3$). Morphine, codeine, and thebaine are derivatives of phenanthrene ($C_{14}H_{10}$); the morphine molecule containing two hydroxyls, one of which is substituted by methoxyl in codeine, and in thebaine both are thus substituted and some other changes occur in the constitution. Narcotine, papaverine and most of the other alkaloids are derivatives of isoquinoline. The phenanthrene group of alkaloids differs considerably in action from the isoquinoline derivatives and is diametrically opposed to them in some respects.

The action of opium is mainly due to the large amount of morphine contained in it, though the other alkaloids may modify its effects. Morphine acts chiefly on the central nervous system, but it also affects some peripheral organs, such as the intestine; its action varies considerably in different animals.

Symptoms.—In **Man** small quantities of morphine ($\frac{1}{8}$ gr., 8 mgs.) lessen the voluntary movements and produce a drowsiness which soon passes

[1] Others are Pseudomorphine, Codamine, Laudanine, Laudanosine, Meconidine, Lanthopine, Cryptopine, Protopine, Papaveramine, Rhœadine, Oxynarcotine, Narceine, Hydrocotarnine, Gnoscopine (or racemic Narcotine), and Tritopine; many of these occur only in traces.

into sleep, unless the patient is continually aroused by his surroundings. As long as he is kept awake, his actions and movements show nothing abnormal, but it is impossible to keep his attention directed to any object for long, and as soon as he is left to himself for a few moments he sinks into sleep. After small quantities there is no difficulty in arousing him; in fact, the sleep seems lighter than usual and may resemble rather a state of abstraction or "brown study." In this condition (euphoria) the imagination is not depressed to the same extent as the reason; the self-control and judgment are lessened, and although the stream of thought may seem more rapid and the images more vivid than usual, the logical sequence and the ideas of time and space are lost, and the condition may rather be compared to dreaming than to a real increase of the intellectual powers. This stage of abstraction is not by any means generally observed and soon passes into sleep, but the unchecked imagination may still persist in the form of dreams. Even in this early stage pain is felt less acutely, the respiration is slow, and the pupil contracted.

In larger quantities ($\frac{1}{4}$ $\frac{1}{2}$ gr., 15–30 mgs.), morphine produces deep, dreamless sleep, from which the patient is still easily aroused, but which returns at once when he is left undisturbed. When once aroused, he can be kept awake or can be aroused again after a short interval much more easily, some time apparently elapsing before the same degree of depression is reached again. As the dose is increased, the sleep deepens into torpor, from which he can be awakened only with difficulty, and eventually all efforts to arouse his attention are fruitless and he sinks into coma, which may be reached very soon after a large dose. During this deeper sleep and coma the respiration is very slow, the pulse is regular, full, and of moderate speed. The pupils are contracted to a small point and the mouth and throat are dry. The face is purple and congested, and the skin feels warm, although the temperature may be low. The breathing generally becomes slower and weaker, and occasionally periodic (Cheyne-Stokes). The cyanosis increases, the pulse becomes smaller and often quicker, the pupils remain contracted, but dilate widely just before the final arrest of the respiration. The heart continues to beat feebly for a short time afterwards.

After small doses of morphine the patient generally awakes refreshed, and, save for occasional dryness of the throat and slight nausea, apparently quite normal. Not infrequently, however, headache is complained of, and sometimes nausea and vomiting, accompanied by marked depression. In rare cases delirium, and even convulsions, have been observed soon after its injection, but these symptoms of excitement are so rare in the human subject as to be classed as idiosyncrasies. Some skin affections, such as itching and redness, are occasionally seen while the action is passing off.

The lower **Mammals** are much less susceptible to morphine than man, and the action differs in the different species and, to a less extent, among the individuals of the same species. While in man depression of the central nervous system is the dominating feature, the lower animals often exhibit symptoms of excitation of some nervous areas. In the dog, the first symptoms are not infre-

quently vomiting and defecation, and then the animal passes into a light sleep, from which he can be easily aroused by touching or by noise, but which rapidly becomes deeper, so that greater force has to be used to waken him. When once awakened, he seems to sleep less heavily for a short time, and a much slighter stimulus is enough to arouse him if it is applied soon afterwards. When awakened he may perform apparently voluntary movements for a short time, although more clumsily than in his normal state, but no complete consciousness is present, the animal is stupid and drowsy and soon sinks back into deep slumber again. The perception of pain seems to be much lessened but not entirely abolished, and reflex movements are difficult to elicit. After larger quantities an exaggerated sensitivity to external stimulation seems present, for the animal starts convulsively at loud sounds and on pinching, but when left undisturbed lies in profound sleep. The respiration is at first quick and dyspnœic, the dog panting as if after a long run, but later it becomes slow and labored; the pupil is narrowed; the circulation seems less affected, although congestion of the skin and mouth is often observed. The reflex irritability may be distinctly increased by large quantities, and before the respiration finally ceases, convulsions generally occur, but these are asphyxial in origin and are not due to the direct action of the alkaloid.

In the rabbit and other rodents the symptoms are similar to those seen in the dog, but the depression is even more marked. An increase in the reflex irritability to external stimulation is also evident here, while the respiration is slowed from the beginning. In the cat and the other felidæ, morphine induces wild excitement which may last for several hours, the animal rushing around its cage and appearing unable to rest for a moment. This excitation is accompanied by a certain degree of depression of the intelligence, however, for no attempt to escape is made and obstacles are not avoided so carefully as by the normal animal. After large doses violent clonic and tonic convulsions may arise and prove fatal from exhaustion. Small quantities of morphine produce drowsiness in the horse, ass, and goat, larger quantities, restlessness and excitement which may pass into convulsions and death. In birds the action resembles that in the dog and rabbit.

The **Frog** is remarkably tolerant of morphine, no change whatsoever following the injection of quantities which would cause distinct symptoms in man. The first effects elicited are a diminution of the spontaneous movements, which become clumsy and ill-coördinated, and finally cease. This condition may last for several hours, when a series of symptoms of an entirely different nature appear. The reflex response to irritation is distinctly depressed during the first stage, but in this second phase it begins to return, and eventually a condition of exaggerated reflex irritability and spasms sets in, resembling that seen in strychnine poisoning, except that the frog seems more easily exhausted. The animal often dies in this phase but it may survive to pass again through a stage of depression before regaining its normal condition. In fish, morphine causes no depression, but is purely excitant, like strychnine.

Action.—The action of morphine on the **Central Nervous System** in man is mainly depressant, but it differs from the alcohol-chloroform group in its selective action on the respiration and on pain sensation, which are both much reduced by doses which have little effect on the general consciousness. The **Pain** of disease is deadened or even entirely removed, while the intelligence is almost as acute as usual, and the patient is able to answer questions and converse freely, and may seem unusually sensitive to impressions caused by loud noises or sudden flashes of light. But while a constant pain is alleviated, a sudden shock causes almost as much pain as without morphine, and when the patient is once aroused, the sensitiveness to pain apparently persists for some time. Morphine thus seems to lessen the power of attention, and under it the individual remains almost unconscious of any constant stimulus, but

he can be aroused by a sudden intense stimulus and only relapses to his former lethargy after some time. This specific action on pain indicates that morphine depresses with special power the paths by which pain stimuli reach the consciousness; it has been suggested that it may interrupt these paths at their synapses in the region of the basal cerebral ganglia (Head).

There is accumulating evidence that small doses of morphine facilitate certain mental processes, while retarding others; this is accompanied by a feeling of freedom from the restraining conditions which previously limited activity; the imagination is untrammelled by its usual controls, and this may lead to unusual brilliancy of thought and expression. In psychological experiments, it is found that the simpler responses are facilitated; for example, the reaction time to flashes of light or to sounds is shortened, fewer errors are made in the association of words or in simple arithmetical computations. This condition is the attraction which proves so fatal to the devotees of the drug, and as the results of the habit are developed, this primary stage of its action is sought as a relief from them. How far this euphoria is a true increase in the mental capacity and how far it arises from the lessened appreciation of the distresses and distractions of life is not yet clear. It is present only after small doses, and soon gives way to lessened mental activity.

The motor areas of the cerebral cortex are not affected by small doses of morphine, but larger quantities lower and eventually abolish the excitability to electric shocks. The acuteness of sensation, as indicated by the smallest distance between two points on the skin which the patient can recognize as distinct, is reduced by morphine owing to the central depression; it has hardly any significant action on the sensory organs in the periphery.

While the effects of morphine on the central nervous system in man are chiefly depressant, and this is especially marked in pain sensation and respiration, some other areas seem to be exceptionally resistant to its action. Thus the circulatory centres in the medulla are little affected directly by quantities which depress the respiration to a dangerous extent. And there is, according to one view, an actual stimulation of the nerve centre which causes contraction of the pupil.

In animals, the central nervous symptoms of morphine poisoning present an extraordinary mixture of stimulation and depression and the relative prominence of these varies widely in different species. The stimulation of the brain is best manifested in the wild excitement of the cat and its allies under morphine, while the narcotic action predominates in the rabbit and to a less extent in the dog; even in the cat some depression of the intelligence is to be made out. In the cat and rabbit the respiration is depressed as in man, but in the dog there is a stage of marked acceleration present at first. In the dog the vomiting centre is primarily excited but this stage of stimulation is followed by one of depression. If very large doses of morphine are given to dogs the depression of the centre comes on almost immediately, vomiting being entirely absent. The cardiac inhibitory centre of the medulla is also stimulated, although the action on the vagus centre is said to be

largely an indirect one from an action upon the cortex. It is impossible at present to suggest any general theory of the action of morphine on the nerve cells which covers these differences in the behavior of different animals and also in the reaction of different nerve centres in the same animal.

The effect of morphine on the **Spinal Cord** has been studied almost exclusively in the frog. The reflex irritability in these animals is first diminished to a slight extent, and then increased to the same degree as by strychnine. In all animals the cord is less depressed than in the corresponding stage of chloral poisoning, for if two animals are poisoned, the one with morphine, the other with chloral, until no voluntary movements occur, the reflexes of the one poisoned with morphine are always found more active than those of the other.

To sum up the action of morphine on the central nervous system: it produces great depression which is especially marked in the perception of pain and in the respiration; the imagination and the cerebral motor functions are less affected than the power of perception, the will, and the attention. In man the failure of the respiration closes the course of the

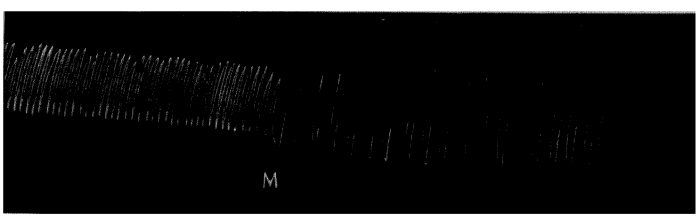


FIG. 17.—Respiration of the cat. At *M*, injection of morphine intravenously. The respiration is immediately slowed and the movement is increased in depth.

intoxication, but in the cold-blooded animals a further development of excessive reflex irritability follows which may pass into tonic convulsions. Even in the higher animals and man some indication of this action on the cord may occur, and in the feline group this stimulation involves not only the cord, but also the motor areas of the brain.

Respiration.—In man and in most other animals the respiration is slowed by morphine from the beginning (Fig. 17), and as the dose is increased, the slowing becomes progressively greater. After small quantities the breathing may be rather shallower, especially if sleep follows; but as the rate slows the depth increases, though not sufficiently to compensate for the slowing, and the total air breathed may fall to one-half the normal or less. The characteristic effect of morphine is thus a diminution in the rhythm of the centre, which remains susceptible to reflex stimulation, but is unable to accelerate the discharge of impulses to the same extent as normally. The inhalation of carbon dioxide in unpoisoned animals quickens and deepens the respiration, but under morphine, while it deepens it as much as before, it is unable to quicken it in the same measure. If morphine causes rest and sleep, less carbon dioxide is formed in the tissues and though less is excreted owing

to the slowness of the breathing, there may be no accumulation in the blood and the depth of the respiration remains unchanged or may be shallower. But if the slowing is more marked, the gas accumulates in the blood and acting on the respiratory centre deepens the breathing, as it cannot accelerate it except to a limited extent.

In the later stages of morphine poisoning, the breathing often becomes irregular, and this irregularity may have a periodic character, a series of deep respirations being followed by several progressively weaker ones and then by complete inactivity for several seconds. The breathing then recommences with a very slight movement, followed by a series increasing regularly in strength and then again decreasing (Fig. 18). This form of respiration (Cheyne-Stokes) appears to arise in part from the depression of the respiratory centre, in part from the asphyxia of the heart, which results from the inefficient respiration and which

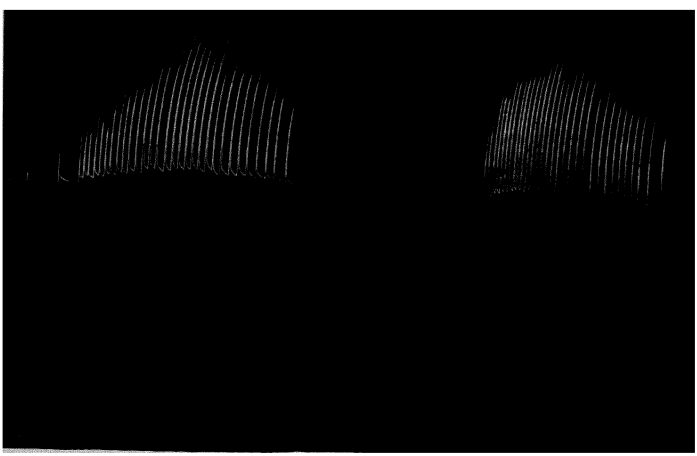


FIG. 18.—Tracings of the respiration (upper) and blood-pressure (lower) during Cheyne-Stokes respiration in a cat under a large dose of morphine. (Barbour.)

leads to periodic variations in the blood-pressure and in the blood-supply to the brain (Barbour). When the respiratory centre is once aroused by the accumulation of carbon dioxide and by the anæmia, it remains less narcotized for some time and thus a series of respirations follow which reduce the carbon dioxide of the blood and also relieve the asphyxia of the heart. The blood-supply to the brain increases, and thus the stimuli to the respiratory centre furnished by the carbon dioxide and the anæmia are both removed and the centre again becomes dormant (Fig. 18) until the carbon dioxide again arouses it to a new phase of activity.

Towards the end the respiration becomes gradually slower and weaker, and often loses its periodic character. Even after consciousness fails to be aroused by the most powerful shocks, some influence may be exerted on the respiratory centre. Thus the sudden applica-

tion of cold water may cause several deep respirations, although it fails to dispel the stupor, but the respiration finally fails to react to these applications and soon afterwards ceases.

Jackson has noticed that morphine and many of the other alkaloids of opium constrict the bronchi in animals; this appears to arise from a direct action on the bronchial muscle. It is not known that any such effect occurs in man in morphine poisoning.

Morphine has little direct action on the **Circulation** in man; the heart is often slightly accelerated at first, perhaps from the slight nausea. In the dog the heart is slow and irregular from powerful stimulation of the vagus. It is probable from the work of McCrae and Meek that in dogs, the action on the vagus is not only a direct one on the centre but is also indirect, by way of the cerebrum. This is shown by the fact that the slow irregular pulse produced by morphine in unanæsthetized dogs largely disappears when they are put under ether. Also decerebration of the animal does away almost completely with the typical vagal pulse produced by morphine. In the cat the slowing of the heart by morphine is inconstant while in rabbits it is only produced by doses which are comparatively large.

The blood-pressure remains high and the peripheral arteries in general show no change of calibre, with the exception of those of the skin especially of the head and neck, which are dilated, rendering the face flushed and hot; as asphyxia comes on the flush becomes more dusky and cyanotic, but the vessels remain dilated, so that the face is of a bloated, purple color. The dilatation of these vessels, which is due to some obscure central action, has little influence on the general pressure, but causes a sense of warmth in the skin, which is occasionally followed by itching and discomfort. It may account in part for the increased perspiration often observed, although this is doubtless contributed to by other factors. As asphyxia advances, the pulse may become slow, while the blood-pressure varies, either rising from the asphyxial activity of the vasomotor centre or falling from the slowness of the heart. These effects are entirely absent if the blood is sufficiently aërated by artificial respiration, and are, therefore, to be regarded as indirect results of the action on the respiratory centre.

The selective action of morphine is thus well illustrated in its effects on the medulla oblongata in man, for the respiratory centre is paralyzed before the centres for cardiac inhibition and vaso-constriction are affected to any marked extent.

The intravenous injection of morphine in dogs and cats is followed by a marked fall in blood-pressure, which is most pronounced in the primary injection and which may be entirely absent in later injections. The fall in pressure may be due in part to a depressant action upon the vasomotor centre but it is mainly due to a dilatation of the vessels of the skin and muscles brought about by a direct action of the drug upon the vessel walls. Tolerant dogs do not react to the intravenous injections in the same manner, there being a high degree of resistance to the depressant action of the drug. The disappearance of the reaction upon the later injections of morphine in normal dogs is due to the rapid development of resistance in the vasodilator mechanism, a condition comparable to that seen in the tolerant dogs described above. In rabbits, guinea-pigs, and rats no fall in pressure occurs when morphine is injected. (Schmidt and Livingstone).

The peripheral **Muscles** and **Nerves** are also unaffected by morphine in any except overwhelming doses. Even when directly applied to the nerve it has but little effect on the irritability (Waller). It is often stated that the sensory terminations are paralyzed by morphine, and solutions are therefore injected into the seat of pain, or liniments are rubbed into the skin over it, but as a matter of fact, morphine seems to possess only an insignificant local action. The sensibility of the skin is lowered by an injection, it is true, but this is due to the central action almost entirely.

In morphine poisoning in man, the **Pupil** is contracted to pin-hole dimensions until just before the final asphyxia, when it dilates widely. In some animals, such as the dog and rabbit, the same effects are seen, while in birds the pupil remains unaffected, and in animals in which morphine causes movement and excitement, it is dilated widely. The contraction arises from direct or indirect stimulation of the oculomotor centre, and not from any local changes in the eye, for when applied directly to the conjunctiva morphine has no effect. In dogs the miosis disappears after the cerebral cortex has been removed, indicating that the action is cortical (Amsler), and that the action upon the oculomotor centre is an indirect one. There is also some evidence that there is simultaneously a depressant action through the sympathetic innervation producing a relaxation of the radiating fibres of the iris. In the rabbit chemical changes in the blood, such as the pH of the blood and its CO_2 combining power, appear to play quite a part, factors which do not seem to be so important in the dog. Atropine applied to the conjunctiva at once removes the miosis produced by morphine. The terminal dilatation seen in man is not due to any direct action of the poison, but is a result of the general asphyxia.

As a general rule the **Secretory Glands** seem to be rendered less active than usual by morphine. When it produces nausea it may increase the saliva and the mucus, but these are the usual accompaniments of this condition and cannot be considered due to any special action. The sweat glands are exceptions to the general rule, however, for slight perspiration is generally observed from the therapeutic action, and profuse perspiration is seen before death in some cases in man from the effects of the asphyxia. The urine does not generally show any distinct alteration after morphine in man, but there is not infrequently retention in the bladder because the sphincter is powerfully contracted.[1]

The **Alimentary Canal** manifests some distinct changes under morphine, which have not yet been completely explained. In the human subject its injection is occasionally followed by some nausea, which is much more frequently present, however, during recovery from the drug. In the dog nausea and vomiting are almost invariable sequelæ of its application in any form, and seem to be due to its acting on the medullary centre. Small quantities of opium or morphine lessen the sensation of hunger in the human subject, but this is probably to be

[1] The anal sphincter is similarly contracted in some animals, and in the mouse this leads to a curious stiffening of the tail, which was at one time considered a specific test for morphine, but has been shown to be induced by many other poisons.

attributed to central action rather than to any effects on the stomach. Riegel states that in man and the dog the gastric secretion is generally retarded at first but is subsequently increased to a considerable extent. This occurs whether the drug be administered by the mouth or hypodermically and is therefore due to some change induced by it after absorption. The pancreatic secretion is lessened by morphine from direct action on the gland. The rate of absorption in the stomach and bowel appears to be unchanged by morphine.

The effects on the intestine vary with the species of animal. In man morphine induces constipation, and in most animals small quantities

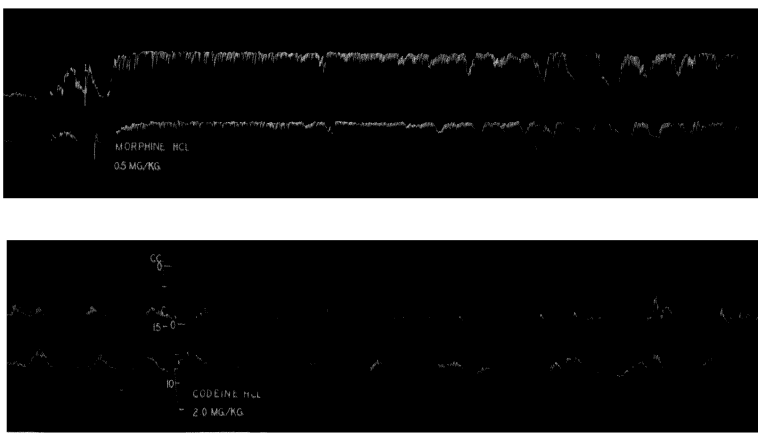


FIG. 19.—Tracings showing comparative effects of morphine and codeine upon the small intestine of an unanæsthetized dog. Each pair of tracings was taken from two balloons which were placed in a Thiry-Vella loop of the lower ileum. The upper tracing of each pair was taken from the anterior balloon, the lower in each instance from the posterior balloon. There was no open connection between the balloons. Each was connected to a Brody bellows recorder. The lower pair of tracings (codeine) show the calibration of the capacity of the balloons. The morphine tracings show the increase in tone and in strength of contractions of the intestine which result from the injection of 0.5 mg. per kilogram of body weight of morphine hydrochloride, while the lower pair of tracings show the almost complete lack of effect from a dose four times as great of codeine (2 mgs. per kilogram). The tracings were taken on different days so that lack of effect in the case of codeine is not due to the previous administration of the morphine. (Krueger.)

have this effect; opium and morphine are very extensively used in therapeutics to quiet the movements of the bowel. Magnus found that the constipating action could be elicited after all the nerves to the stomach and bowel were divided, so that it is quite independent of the action on the central nervous system. He states that the passage of food through the stomach is much delayed in the cat through a persistent contraction of the sphincter antri pylorici, which keeps the contents in the cardiac end, and later of the pyloric sphincter which delays their passage into the duodenum. Plant and Miller found in unanæsthetized dogs that the most marked gastric effect was a decrease in the muscular tone of the wall accompanied by a decrease in the frequency and ampli-

tude of the peristaltic waves. These waves may disappear for hours and the loss of muscular tone for an even longer time. On the other hand, in the small intestine they found an increase in the muscular tone and an increase in the frequency and amplitude of the peristaltic waves and in the amplitude of the rhythmic contractions. In man very similar effects were obtained as in the dog. These changes are not prevented by atropine nor by denervation of the intestine in the dog and so are due to a peripheral action of the morphine. In the colon of the unanæsthetized dog these workers also found a marked increase in tone, together with more continuous peristaltic activity.

The constipating effects of morphine, according to these views, are due in the first place to the relaxation of the stomach wall and to the changes in peristaltic waves which would delay the emptying of the stomach, and due to this slower discharge the food would be distributed in smaller quantities throughout the intestine, allowing for more complete digestion and absorption. This would be further aided by the changes in the conditions in the intestine. In the colon, again, the marked increase in tone, which at times amounts almost to a spastic contraction, also holds back the food residue from the sigmoid and rectum, allowing again greater opportunity for absorption, resulting in the contents being rendered dryer. The anti-diarrhœal action of opium would then seem to depend most largely upon the increase in tone in both small and large intestines, which in addition to delaying the progress of the intestinal contents toward the lower bowel, would also lessen the tendency to local distention of the gut, which in itself is a potent stimulus to powerful peristaltic waves which would hasten the contents on toward the rectum. Similar changes are produced by codeine and heroine, but in the case of the former, larger doses are needed to elicit equivalent effects. Papaverine acts much like morphine upon the stomach, lessening the tone of the wall and abolishing peristaltic waves, but in the intestines the effects are very slight.

Myers recently reinvestigated the action of morphine and some related alkaloids on the alimentary canal in cats and man. He found that morphine caused increased contraction of the pyloric and ileocolic sphincters. The movements of the fundus of the stomach were usually diminished, those of the small intestine diminished and then increased, while the stimulation of the colon was much more pronounced than that of the small intestine. Heroine acted in the main like morphine but was about one and a half times as powerful. The actions of dilaudid were much greater than those of morphine or heroine, those of codeine and dicodide much feebler.

In animals many forms of **Unstriated Muscle**, such as intestine, ureter, uterus, bronchial muscle and bladder, have been shown to be aroused to increased contraction and tone under the influence of morphine and the other phenanthrene alkaloids, while the isoquinoline derivatives depress their activity; after repeated injections the contractions from the phenanthrene group fail to occur, while the organ continues to respond to various other poisons. It is unknown whether the action is exerted on the muscle directly or on the peripheral nervous structure.

There is no reason to suppose that this effect occurs in man, even in poisonous doses.

Morphine frequently causes a fall in the **Temperature**, partly from the diminished movement by which less heat is formed, but mainly by the great loss of heat from the dilation of the skin vessels; sometimes a slight preliminary rise in the temperature has been seen in man. It is found that animals under morphine react less to an increase in the surrounding temperature than unpoisoned ones; *i. e.*, a normal animal exposed to a high temperature takes measures to prevent its internal temperature from rising above the normal, while, under morphine, these measures are less effective, and the temperature rises more rapidly and to a greater height; this indicates that the temperature centre in the brain is rendered less sensitive and that it is therefore important to avoid exposure to cold in cases of opium poisoning.

Metabolism.—The excretion of carbon dioxide is lessened during the depression stage, while in those animals in which excitement is produced, it may be considerably augmented from the increased muscular movement. In man the basal metabolism has been shown to be decreased about 25 per cent by 10–20 mg. of morphine in the first hour after the injection has been given. With repeated administration the diminution in the metabolism lessens rapidly. The imperfect respiration leads to an increase in the lactic acid of the blood and urine and to the disappearance of glycogen from the liver. Sugar may appear in the urine from the same cause. In dogs and cats morphine produces a marked hyperglycæmia which is prevented by removal of the adrenals.

Barbour, Gregg and Hunter have shown that dogs addicted to morphine have high metabolic rates which are reduced on withdrawal, to rise again upon resumption of the drug. This calorigenic action of the alkaloid is masked in the case of the acute administration of morphine by the neuromuscular depression which follows.

Excretion.—When given subcutaneously to rabbits morphine can be largely recovered from the stomach contents,[1] from the walls of both stomach and intestine, from the muscles of the body and from the urine. In the early hours after the injection of the alkaloid it appears in largest amounts in the stomach contents while smaller amounts are found in the urine. Later the amount in the urine is increased while the gastric excretion is lessened so that almost equal amounts may be found in both stomach and bladder. The bowel probably does not take part in the excretion, such morphine as escapes in the fæces being derived from the gastric contents. In the dog, Pierce and Plant found that the urine always contained more morphine than did the fæces and that this was true in both tolerant and non-tolerant animals. The amount found in the urine depended somewhat upon the dose administered and was influenced by the quantity of urine passed, diuresis increasing the amount. Most of the morphine therefore is eliminated from the body in the urine. Considerable amounts are found stored in the muscles

[1] In the dog and cat Hatcher and Davis were able to find only traces of morphine in the stomach. Teruuchi and Kai found considerable amounts of morphine in the stomach contents of rabbits following its injection.

and this storage is apparently of importance as it serves to protect to a certain extent the more sensitive central nervous system from excessive amounts of the drug. In acute morphinism in rabbits very little morphine is said to be destroyed in the body, as even after sixteen hours over 90 per cent of the drug administered has been regained from the various tissues and excretions (Teruuchi and Kai). In the dog, however, the condition is certainly otherwise as there is evidence that a considerable portion of the administered alkaloid is destroyed. From the tissues and excretions of non-tolerant dogs Plant and Pierce recovered 22 per cent of the amount given four hours before and 13 per cent after an interval of twenty-four hours. From tolerant dogs they recovered 19 per cent after four hours and 20 per cent twenty-four hours after the drug had been given. In chronic morphinism destruction of the morphine doubtless takes place to some extent but there is in addition a very considerable storage of the drug in the muscles and liver.

Tolerance.—The continued use of morphine or opium in man leads to a condition of tolerance, in which enormous doses of the drug are necessary to elicit their usual effects. In some animals a similar condition of tolerance has also been attained by the repeated administration of morphine and evidences of withdrawal symptoms have been encountered when the drug is stopped. In monkeys the condition of tolerance has apparently been best developed. After they receive the drug for several months they show a marked dependence upon it, together with a general deterioration in health. If the drug is stopped tolerance is lost quite rapidly, sometimes in about two weeks.

Dogs can also be rapidly rendered tolerant if large doses of morphine are given, while if small doses are used the process is a slow one. The symptoms of addiction and of withdrawal resemble to a certain extent the symptoms seen in man. In cats a moderate degree of tolerance is also said to have been gained. The mechanism by which the body gains its resistance to the large doses of morphine is not understood in spite of many laborious researches which have been carried out on the subject. It is probable that more than one mechanism may be invoked, as for instance increased ability on the part of the muscles to store the alkaloid. An increased power of the tissues to destroy the alkaloid is probably not a factor in the production of tolerance as Plant and Pierce were able at the end of twenty-four hours to recover from the tissues and excretory organs of tolerant dogs a larger percentage of the amount administered than they could from non-tolerant animals. They suggest that their results would seem to indicate that the two groups of animals, tolerant and non-tolerant, handle the drug in different ways. They found that the central nervous system of tolerant dogs contained less than that of non-tolerant dogs. They found also that the liver showed the greatest concentration of the alkaloid but that the muscles, on account of their bulk, yielded the largest amount. Teruuchi and Kai were able to isolate much larger amounts of morphine from the muscles of tolerant rabbits than from animals receiving only single injections, but the total amount recovered from all the tissues and from the excreta of the tolerant animal was only a small fraction of the morphine which

had been administered. While tolerance is easily acquired by some centres, others fail to develop it; thus dogs which have become so tolerant that even large amounts fail to induce narcosis, continue to react even to small quantities by slowing of the pulse. The cerebral nerve cells have become tolerant, as have also the cells of the respiratory centre, the vomiting centre and the nervous mechanism controlling the pupil; but the cells of the vagus centre have failed to do so. The bowel also continues to react to morphine as in the beginning. Some nerve cells thus become habituated to the presence of morphine in the blood and cease to react to it as strongly as in normal individuals, while others remain susceptible; in addition, the tissues acquire a greater power of storing morphine and apparently of destroying it. Dogs which have been rendered tolerant to morphine are also refractory to its allies, codeine and heroine. The attempt to find "antimorphine serum" has proved fruitless.

It has long been recognized that infants are specially susceptible to morphine and opium. Gibbs and Bobb found that newborn rats were approximately ten times as susceptible as adults to morphine administered subcutaneously. This susceptibility decreased until the twenty-first day of life, after which it was no greater than in the adult.

Codeine given in moderate quantities resembles morphine in its action in man but is much weaker. Thus 1 grain of codeine induces sleep and relieves pain in about the same degree as $\frac{1}{4}$ grain of morphine; the sleep is said not to be so deep and restful as that which follows the administration of morphine, and the patient is liable to be awakened by slight noises, and is restless and often unrefreshed when he awakens. Somewhat larger quantities, instead of inducing deeper sleep, may increase the restlessness and cause a considerable exaggeration in the reflex excitability. The respiration is slowed in the same way as by morphine but here again morphine is at least four times as powerful; large doses of codeine do not slow the respiration further. The pupil is slightly contracted during the codeine sleep, but dilates if the excitement stage follows. Codeine thus depresses the central nervous system in man, though there are indications of stimulation also when large quantities are used. In animals these symptoms of excitation are more obvious, however, especially in the spinal cord, in which the reflexes are rendered more acute and may finally give rise to spasms. In the cat morphine induces cerebral excitement, but under codeine this is often seen in the dog also and even to a slight extent in man. In the frog the evidences of a stimulant action are very marked.

Codeine acts less on the stomach and bowel than morphine (see Fig. 19), but when given in doses adequate to cause narcosis, it also causes constipation, and given along with morphine appears to intensify its action. It is excreted in the urine unchanged and none has been shown to undergo destruction in the tissues, as occurs in the case of morphine. Tolerance for codeine is very difficult to develop in animals, and patients may in fact appear more susceptible to the drug, a dose which at first gave relief now causing nausea and vomiting. It is possible that this may indicate a tolerance of some parts of the central nervous

system, which is not shared by the vomiting centre. As a cause of a drug habit codeine is of relatively little importance; very few cases of addiction to it have been reported. The statement therefore which is sometimes made that codeine has no addicting properties is not strictly correct.

Cases of addiction to codeine which have been described are usually not primary addiction but are more commonly secondary to the use of morphine. That is, the patient has become addicted to morphine and when for some reason he is unable to secure this drug he resorts to codeine.

Codeine is methylmorphine, and a number of similar compounds have been formed synthetically such as ethylmorphine and amylmorphine. Two of these, ethylmorphine **(Dionine)** and benzylmorphine **(Peronine)** have been introduced into therapeutics, but appear to possess no advantages over codeine.

Oxydimorphine ($C_{34}H_{36}N_2O_6$) has been found in opium by some investigators, and has a very weak narcotic action resembling that of morphine.

Heroine, diacetylmorphine, is a synthetic alkaloid formed from morphine by substituting acetyl for its two hydroxyls, and has attracted attention through its being advocated as a respiratory sedative in cough. It resembles morphine in its general effects, but acts more strongly on both cerebrum and medulla than does morphine, and is therefore more poisonous, though this is counterbalanced by its being effective therapeutically in smaller doses. The action on the respiration is the same in kind as that of morphine, and the advantages claimed for heroine by its advocates have not been confirmed by impartial investigation. Upon the intestine heroine has very little effect in the small doses usually employed but qualitatively it has the same action on the intestine as morphine. In animals large doses cause excitement and convulsions, and in man these have also been observed in cases of poisoning; the exhaustion from these convulsions is the cause of death in animals. Heroine is excreted mainly in the urine unchanged, but some is found in the stools. When it is given for some time, the tissues learn to destroy it and it no longer appears in the excretions. A certain tolerance is observed, for the narcotic action becomes less marked and may entirely disappear, but the exciting action of large doses remains unaffected. Many cases of heroine habit have occurred and this aspect of the drug's action has brought it into serious disrepute. The fact that it can be easily administered and that its dose is small makes trafficking with it easier than with some of the other narcotics. The social danger from it, moreover, seems to be greater than with morphine in that it produces a change in the personality as shown by an utter disregard for the conventions and morals of civilization. Degenerative changes in the individual progress faster than with any of the other narcotic drugs, and all the higher faculties of the mind such as judgment, self-control and attention are weakened and the addict rapidly becomes a mental and moral degenerate. The heroine habit is most difficult to cure, not only in the active withdrawal period but also in the convalescent stage, and relapse is frequent. Habitués take it either by snuffing or by hypodermic injection.

A study of the analgesia resulting from the use of members of the opium group of alkaloids showed that to produce equal degrees of effects heroine in 1.5 mg. doses was as efficient as 8 mg. of morphine or 64 mg. of codeine. Analgesia appeared in thirty minutes with heroine and codeine but not for ninety minutes with morphine, but the effect was more prolonged with the latter drug. The euphoria was least marked with codeine, being practically absent, and most marked with heroine while morphine was intermediate (Pfeiffer and Seevers).

Dilaudid. Among the newer alkaloids which have been introduced as substitutes for morphine is dihydromorphinone hydrochloride or Dilaudid. This alkaloid, which is closely related to morphine both chemically and pharmacologically,

was first described in 1923 and after a brief study was introduced into the clinic, the first report upon its action in man appearing in 1926.

Chemically it differs from morphine in that the alcoholic hydroxyl group of that alkaloid is replaced by ketonic oxygen and by the removal of an adjacent double bond by hydrogenation. The earlier experimental work showed that dilaudid produced analgesia and narcosis and acted upon the respiration in a manner similar to morphine but with the difference that it was effective in about one-quarter the dosage. In the dog, restlessness and vomiting were followed by depression, somnolence, analgesia and slowing of the respiration. In the rabbit the respiration was slowed very markedly, but some deepening of the respiration took place so that the effect of the slowing was partially compensated.

More extensive study has shown that dilaudid is six times as toxic for mice as morphine and three or four times as toxic for rabbits. The analgesic dose in cats is less than one-fourth that of morphine and one-third that of heroine. In its effect upon the respiration of rabbits it is approximately ten times as powerful as morphine and is also stronger than heroine. It slows the heart in dogs and in rabbits. Upon the intestine of rabbits its constipating effect is produced by less than one-quarter of the dose required of morphine while upon the intestine of unanæsthetized dogs it is about ten times as powerful as morphine in its ability to increase the tone of the intestine.

These studies all point to the fact that dilaudid is much more powerful in its effects than is morphine, but at the same time its toxicity is also greater. However, the ratio of the effective dosage to the toxic dose does not appear to be very different in the two alkaloids.

The resemblance of dilaudid to morphine which has been shown in the laboratory is confirmed in the clinic. In man the drug is powerfully analgesic and also markedly depressing to the respiration while nausea, vomiting and constipation are not so marked as with morphine. The question as to tolerance to dilaudid is not satisfactorily answered as yet, and while the danger of addiction does not seem to be so marked as with morphine, it is by no means absent, as already a number of dilaudid addicts have been reported, showing that the same care should be exercised in prescribing dilaudid as is used in the case of the natural opium alkaloids.

Dilaudid is used in the same manner as morphine for the relief of pain and as a sedative but in much smaller doses—usually 2–2.5 mg. For cough a dose about half that size is used. In general the dose of dilaudid to be given is about one-fifth that of morphine.

Thebaine seems to have practically no depressant action. It sometimes produces some heaviness and confusion in man, but this is accompanied by symptoms exactly resembling those described under strychnine, and it may therefore be considered as belonging to the latter series rather than to that of morphine; it is much less active than strychnine, however.

Papaverine stands midway between codeine and morphine in its action on the central nervous system, but is a comparatively weak poison. Even in large quantities it has not the soporific action of morphine, nor does it produce the same degree of excitement as codeine. Comparatively small quantities are followed by sleep and slow respiration, but this does not become deeper as the dose is increased. On the contrary, the reflex excitability is augmented, and after very large quantities some tetanic spasm may be elicited, but this seems to be of spinal origin entirely, while that produced by codeine points rather to an affection of the lower part of the brain. Papaverine has a greater tendency to slow the heart rhythm than morphine; it apparently acts directly on the heart muscle and a similar effect on the vessels dilates them when it is perfused through them; the blood-pressure is little affected by ordinary quantities, however. Papaverine has been said to have a greater action in lessening peristalsis than the other alkaloids, but recent investigations on unanæsthetized dogs show that its effect upon the stomach is much the same as that of morphine, only much weaker. Its effect upon the small intestine is very slight, while on the colon large doses decrease the frequency of the tone waves without changing the general tone level. Its action, therefore, upon the intestinal tract

of the intact animal is practically without therapeutic importance. Upon excised tissues papaverine and the other isoquinoline alkaloids relax the tone and slow the contractions of the tissue and thus antagonize morphine. It has not been shown that this action on organs and upon unstriated muscle occurs in man. Papaverine seems to undergo complete destruction in the tissues.

Narcotine resembles papaverine rather than morphine, but has even less depressant action, especially in mammals. In the frog a short stage of depression is elicited, but this soon gives place to strychnine-like exaggeration of the reflex excitability. In mammals there may be but little appearance of depression, the injection being followed by a condition of excitement immediately, restlessness and tremors with increased reflexes, which eventually lead to convulsions, during which the animal generally succumbs exactly as in strychnine poisoning. The pulse is considerably slower after narcotine injection, from a direct action of the drug on the heart. The sympathetic ganglia are first stimulated and then paralyzed, while the movements of unstriated muscle are affected in the same way as by papaverine. Narcotine is a much less poisonous body than either morphine or codeine, and very large quantities have been administered repeatedly with little or no narcotic effect. It is a compound of hydrocotarnine, another opium alkaloid, with opianic acid. **Hydrocotarnine** apparently acts very much in the same way as narcotine, but produces even less depression.

Narceine has little or no action of any kind. It is exceedingly insoluble in water, and its salts are broken up in aqueous solution, so that it is probably absorbed very slowly and imperfectly.

The other alkaloids occur in very minute quantities in opium and possess no great interest from the therapeutic point of view. Very little has been done to elucidate their pharmacological action, but those which have been examined seem to produce effects resembling those of the better known members of the group. In frogs, small doses of **Cryptopine** and **Protopine** produce a narcotic condition similar to that following the injection of morphine, but the reflex irritability does not show the same exaggeration afterward; larger quantities cause complete paralysis of the whole central nervous system and partial paralysis of the terminations of the motor nerves, which gives rise to irregular contractions and relaxations of the muscles when the nerves are stimulated (Hale). In mammals, no depression occurs, but restlessness and eventually convulsions, which do not seem to be of spinal origin but rather suggest a stimulation of the cerebrum and midbrain. The heart is slow and weak, and some depression of the vaso-motor centres is caused by large quantities of the poisons. The respiration does not seem to be depressed, but rather to be accelerated, save by the largest doses. They paralyze the terminations of the sensory nerves on local application in the same way as cocaine. The action of these two alkaloids on the heart would seem to be further developments of the heart action noted after narcotine and papaverine.

In a systematic study of the action of morphine and of the rôle which is played in bringing about this action by the various side chains attached to the central phenanthrene nucleus Eddy and his co-workers have observed the importance of the hydroxyl groups. One of these is phenolic in character and the other is alcoholic. It is the phenolic hydroxyl which is methylated in the formation of codeine, while the methylation of the alcoholic hydroxyl results in the formation of heterocodeine. Such muzzling of the hydroxyl by methylation reduces the activity of the group. Methylation of the phenolic hydroxyl, as in codeine, increases the toxicity and convulsant action of the compound but decreases its analgesic property, its effect upon respiration and the vagus centre, and upon the intestine. Codeine is a typical example of this change in the morphine picture. In addition the same type of change has been observed in fourteen other pairs of compounds. In each of these pairs the chemical difference is exactly that existing between morphine and codeine, namely methylation of the phenolic hydroxyl with a consequent reduction in its activity. It seems safe to conclude, therefore, that the free phenolic hydroxyl in morphine is

important in that it lessens the convulsant action of the compound and increases the depressant, analgesic and respiratory effects.

In another series of thirty pairs of morphine derivatives, of which heterocodeine in comparison with morphine is a typical example, the activity of the alcoholic hydroxyl has been reduced. Pharmacological activity again has varied quite uniformly with the chemical change. In this case the variation has been in the direction of increased activity. Analgesic and respiratory effects have been increased to the greatest extent by thus muzzling or removing the alcoholic hydroxyl. As a result it is concluded that the free alcoholic hydroxyl in morphine tends to inhibit the development of these effects.

Further information on the importance of the side chains of the morphine molecule in the development of the action of morphine is sought by a study of the phenanthrene nucleus and the compounds synthesized from it. In this synthesis groups related to the side chains of the morphine molecule are attached to the phenanthrene in such a way as to reveal the effect of the position of substitution, of the nature of the primary substitution, of the length of the side chain and of the simultaneous attachment of two or more groups.

For example, phenanthrene is a very insoluble crystalline substance of low toxicity which given orally to cats produces a mild hypnotic effect accompanied by decreased rectal temperature and some disturbance of locomotion resembling the effect of a small dose of a barbiturate, but in no way resembling the typical morphine picture. The attachment of so simple a group as a hydroxyl or an amino group, however, while not affecting materially the water solubility, increases toxicity and depressant action and brings out some degree of analgesic effect. The position of attachment of the group is of the greatest importance in effecting this increased activity. That compound is most active in which the primary substituent is attached in the position of the phenolic hydroxyl in morphine. In addition partial hydrogenation of the phenanthrene nucleus if carried out in such a way as to produce an asymmetric base, greatly enhances its activity in the body.

In man morphine is much the most dangerous of the opium alkaloids, because death is produced in the narcotic stage through asphyxia. In most animals, however, thebaine, codeine and laudanine are more toxic, because the failure of the respiration does not occur in the stage of depression, but during the convulsions.

Opium itself contains, besides the alkaloids already discussed, various acids with which they are in combination: meconic, lactic, and sulfuric acid, but none of these possess any action of importance. Along with these are found gums, sugars, albumins, wax and the other common constituents of plant juices, but these merely tend to delay the absorption of the active constituents, and cannot be said to play any part in the effects of opium. Of the alkaloids, morphine is present in greatest abundance, and is also the most powerful in its effects on man. According to most observers, the action of opium on the brain is practically identical with that of morphine, when due allowance is made for the slower absorption of the crude drug from the bowel; if any difference exists, it is so small as to be inappreciable in ordinary cases. But an old view that opium is a better narcotic than morphine has recently been resuscitated, and a preparation of all the alkaloids of opium in the proportion in which they exist in Smyrna opium, has been introduced under the name of **Pantopon (Omnopon)**. This has not been shown to have more narcotic action than the morphine that it contains. Being free from extractives it may be given hypodermically in doses from 0.005 to 0.02 G. ($\frac{1}{12}$–$\frac{1}{3}$ gr.). According to Straub, the alleged superior-

ity of opium over morphine as a narcotic is due to its containing narcotine, which in itself has comparatively little depressant power, but which intensifies that of morphine to a marked extent when they are administered together. He has therefore introduced morphine-narcotine meconate under the name of **Narcophine** as superior to morphine in narcotic power while less depressant to the respiration. Some later experiments seem to support Straub's view while others give the opposite result. Of late years a number of papers have been published purporting to show that one or other of the minor alkaloids strengthens the action of morphine in some direction, but no entirely convincing evidence has been adduced and such statements are to be taken with reserve. As regards their action on the alimentary tract, opium and pantopon are practically identical, while morphine is less constipating; the greater sedative effect of opium and pantopon on the intestine may be due to the presence of papaverine (Zehbe), or codeine (Hesse), or to a slower absorption and more prolonged local action.

Therapeutic Uses.—Opium is one of the most important and most extensively used drugs in the pharmacopœias at the present day as in the past. Of late years the crude drug has been largely replaced by morphine, but the action is essentially the same, and although morphine is preferable in most cases, opium is still specially indicated for certain purposes. In almost any disease, conditions which are favorably influenced by morphine may present themselves, and these conditions alone can be discussed here.

Pain.—As has been repeatedly mentioned, opium or morphine has a special analgesic action which is not shared by its modern rivals of the methane series, and which justifies the celebrated dictum of Sydenham[1] that without opium few would be callous enough to practice therapeutics. The general statement may suffice that severe pain indicates opium. Even where the disease itself is one which would in ordinary circumstances contra-indicate it, it must always be taken into consideration whether the relief of the pain and its attendant restlessness may not counterbalance the disadvantages of the narcotic. At the same time the danger of inducing the craving for morphine cannot be forgotten, for the use of morphine to subdue pain has been a fruitful cause of the habit. It is often found that comparatively small quantities of opium are sufficient to remove or at any rate to dull pain, but after repeated doses the quantity has to be increased owing to tolerance being attained. Codeine may be used instead of morphine to allay pain, but has to be given in at least four times as large doses, and is ineffective in severe pain. Some forms of pain are relieved by the members of the antipyrine series, but these are less certain and more limited in their action than morphine. On the other hand the antipyretics will often relieve pains of a neuralgic type and thus they possess a great advantage over opium in the treatment of headache, neuralgia, and similar conditions on account of the elimination of the danger of forming a morphine habit.

[1] Nollem esse medicus sine opio.

Sleeplessness.—Opium was formerly the only drug used to induce sleep, but since the discovery of chloral and its congeners, it is used much less frequently for this purpose. The soporifics fail entirely to replace it, however, where the sleeplessness is due to pain, while, on the other hand, they are more efficacious in certain conditions of excitement. Formerly opium and chloral were not infrequently prescribed together for this purpose, and the combination acted more efficiently than either of the drugs alone. Each was, of course, prescribed in considerably smaller amount than if administered separately. Opium is less efficient than certain of the hypnotics when there is apparently an increased activity of the motor functions of the brain, as in wild delirium and mania, and sometimes seems even to increase the excitement, but this general statement is subject to numerous exceptions, and morphine is still used occasionally in such disorders. In the true convulsive diseases, such as tetanus, epilepsy and chorea, the chloral group or one of the barbituric acid derivatives is preferable. In certain forms of motor excitation, especially in insanity, scopolamine or a barbiturate may be indicated as a sedative, and in cases of sleeplessness from anxiety and worry one of the barbiturates or potassium bromide is generally preferred to any of the more powerful sedatives. The beneficial effect of morphine in many acute febrile conditions is undeniable, and, as in the case of alcohol, is due to its lessening the pain and discomfort of the patient and inducing rest. A good deal of difference of opinion exists as to the advisability of administering opium or morphine in these conditions, and there is no question that the routine treatment of fever by narcotics is to be deprecated; but on the other hand, restlessness and discomfort may in themselves aggravate the condition, and morphine may be distinctly indicated under these circumstances.

The preparation chiefly used to relieve pain and promote sleep is one of the morphine salts, usually the sulfate, and given by hypodermic injection.

In **Respiratory Disorders** opium and morphine or, perhaps still better, codeine are largely used for their effects on the centre. Where it is desirable to lessen its irritability as, for example, in excessive cough and dyspnœa, opium may be indicated. On the other hand, when there is a profuse expectoration, the irritability of the centre cannot be lowered without danger, and opium is contra-indicated. Opium gives relief in cases of asthma, but there is always danger of inducing the habit. In the rapid, shallow breathing of heart disease, the administration of opium or morphine is often followed by slow deep peaceful respiration without any reduction in the efficiency of the ventilation.

Opium is often combined with expectorants in the treatment of cough, and a number of suitable preparations are provided in the pharmacopœias, such as paregoric, Dover's powder and other preparations containing ipecacuanha, and codeine phosphate. The object of combining expectorants with opium is to allay excessive coughing; the opium reduces the excitability of the centre, while the expectorant causes a secretion of mucus in the respiratory passages and thus protects the irritated mucous membrane. The combination is indicated

only in dry cough with little expectoration, and when there is abundant sputum to be removed by coughing the treatment might be unnecessary and even harmful. Codeine is usually preferred to morphine in these cases, because it reduces the excitability of the respiratory centre with less marked cerebral depression. Davenport found that, in the great majority of tuberculous patients requiring medication for the relief of cough, codeine in a dose of 10 mg. orally was a sufficient dose. Ernst found a high degree of potentiation of morphine by codeine in subduing the cough reflex, and recommended a combination of them as superior to either alone. Heroine and dionine were introduced as superior to codeine for relieving cough, but impartial investigators of these drugs have generally failed to obtain better results from them than from codeine and morphine.

In **Peritonitis and Intestinal Disorders** opium is indicated doubly; first, for its general action in allaying pain and restlessness; and secondly, for its special action upon the movements of the intestine. Opium is usually considered preferable to morphine for these purposes. In colic, especially lead colic, morphine often relieves the pain without increasing the constipation and seems to allay the spasm of the bowel without stopping entirely its peristalsis. In diarrhœa opium may be given to check the excessive peristalsis, though in the severer forms of dysentery it generally fails to have this effect, and in septic purging is to be avoided. In perforation and hemorrhage from the bowel, opium is the most efficient of all remedies, as it allows adhesions or clots to be formed which would prevent further leakage and at the same time it allays the anxiety and restlessness of the patient.

The pharmacopœias offer a number of preparations specially designed for use in intestinal disorders and especially in diarrhœa, such as paregoric, laudanum or the compound chalk powder.

In **Hæmorrhage** where the bleeding point cannot be reached, opium or morphine is most valuable. This is not from any direct effect on the vessels or blood, but because it allays the restlessness of the patient which follows the loss of large quantities of blood and thus allows the blood to clot in the ruptured vessel. The same preparations are suitable here as for pain.

In **Vomiting** morphine is sometimes used in small quantities, but it seems doubtful whether with any benefit.

Morphine is not infrequently given as a preliminary to general **Anæsthesia** in nervous patients ($\frac{1}{6}$ gr.), and for a few years some operations were performed under morphine and scopolamine alone. For this purpose $\frac{1}{6}$ gr. (10 mgs.) of morphine and about $\frac{1}{200}$ gr. (0.3 mg.) of scopolamine were injected an hour and a half before the operation, and again one-half hour before it. The anæsthesia induced was often sufficient, but, if necessary, a few drops of ether or chloroform were inhaled to complete it. The action of morphine and scopolamine on the brain is not synergistic, that is, the effects are not greater than the sum of the two alkaloids taken separately, as has often been stated. This narcosis has been used also to a certain extent in labor ("twilight sleep") but

many believe that it is dangerous to the child through depressing the respiratory centre and through prolongation of labor.

Lastly, opium is used as a **Diaphoretic**, and for this purpose it is generally combined with ipecacuanha and prescribed as Dover's powder. Although in itself it has little or no diaphoretic action, opium may augment the effects of ipecacuanha through dilating the skin vessels. Opium and its alkaloids have almost no effect when applied to the skin, and the plasters, ointments and other similar preparations are obsolete.

Codeine is perhaps less often used than morphine in therapeutics as it is of less value than morphine in allaying pain, but it is used very extensively as a sedative in cough and there is little tendency to form the codeine habit.

At the present time ethyl morphine (Dionine) is employed extensively to produce vasodilatation and edema of the conjunctiva. The chemosis is of value for its analgesic and curative effects in corneal ulcer and other inflammatory conditions in the eye. For this purpose it is usually employed in a 5 to 10 per cent solution, although a 20 per cent solution or even the dry powder is sometimes used.

For internal use for the relief of pain it may be given in doses of $\frac{1}{4}$–1 grain (0.015 0.060 G.). It is also used in coughs or colds.

Opium and morphine are contra-indicated in children at the breast, in whom even minute quantities (*e. g.*, 1 drop of laudanum) may produce the most alarming symptoms of poisoning. After one year this special susceptibility seems to pass off and the dose of morphine has not to be reduced more than that of other drugs (Döbeli). In great weakness, especially in cases where the respiration is barely sufficient to aërate the blood, or where profuse expectoration is present, morphine has to be administered with the greatest care. In cerebral congestion and meningitis the opiates are generally contra-indicated. It must be remembered also that both opium and morphine are liable to disturb the digestion and to cause nausea and want of appetite, and that these may prevent their use in cases in which they would otherwise be suitable. In some persons opium invariably causes nausea and vomiting, either soon after its administration or while its effects are passing off. For this idiosyncrasy morphine may be substituted for opium, although this is often equally nauseating, or chloral and bromides may be prescribed with opium to prevent the unpleasant after-effects. In all chronic painful diseases opium or morphine has to be given guardedly, on account of the risk of the formation of the opium habit; the patient ought to be kept in ignorance of the drug used as far as possible, and it should be alternated with others. Of course, in cases of incurable, hopeless disease, where life can only last a comparatively short time and is attended by severe suffering, this objection does not hold, and it may be necessary to administer morphine without stint and in ever-increasing quantity.

Morphine and opium are often said to be contra-indicated in Bright's disease of the kidney, but there seems no reason to believe that morphine is harmful in this condition, and in some forms of uræmia it has even been of considerable benefit.

PREPARATIONS.

U. S. P.

OPIUM contains not less than 9.5 per cent morphine. 0.06 G. (1 gr.).

MISTURA OPII ET GLYCYRRHIZÆ COMPOSITA, Compound Mixture of Liquorice, Brown Mixture, contains also opium, tartar emetic and spirits of nitrous ether. Used as a vehicle for cough syrups. 4 cc. (1 fl. dr.).

OPIUM PULVERATUM, dried and powdered opium, contains 10 per cent of morphine. 0.06 G. (1 gr.).

PULVIS IPECACUANHÆ ET OPII, Dover's powder, contains 10 per cent opium and 10 per cent ipecac with sugar of milk. 0.3 G. (5 grs.).

TINCTURA OPII, Laudanum, contains 10 per cent opium. 0.6 cc. (10 mins.).

TINCTURA OPII CAMPHORATA, Paregoric, 0.4 per cent of opium. 4 cc. (1 fl. dr.).

MORPHINÆ SULFAS, 0.008 G. ($\frac{1}{8}$ gr.). Soluble in 15.5 parts of water.

CODEINA, Methylmorphine, 0.03 G. ($\frac{1}{2}$ gr.).

CODEINÆ PHOSPHAS, 0.03 G. ($\frac{1}{2}$ gr.). Soluble in 2 3 parts of water.

CODEINÆ SULFAS, 0.03 G. ($\frac{1}{2}$ gr.). Soluble in 30 parts of water.

ÆTHYLMORPHINÆ HYDROCHLORIDUM (Dionine), 0.015 G. ($\frac{1}{4}$ gr.). Soluble in 8 parts of water.

B. P.

OPIUM contains not less than 9.5 per cent of morphine.

EXTRACTUM OPII SICCUM, contains 20 per cent of morphine. 0.015–0.06 G. ($\frac{1}{4}$–1 gr.).

OPIUM PULVERATUM, powdered opium, contains 10 per cent of morphine. 0.03–0.2 G. ($\frac{1}{2}$–3 grs.).

PULVIS CRETÆ AROMATICUS CUM OPIO, Aromatic Powder of Chalk with Opium, contains $2\frac{1}{2}$ per cent of powdered opium. 0.6–4 G. (10–60 grs.).

PULVIS IPECACUANHÆ ET OPII, Dover's Powder, contains 10 per cent of ipecac and 10 per cent of opium. 0.3–0.6 G. (5–10 grs.).

SUPPOSITORIUM PLUMBI CUM OPIO, each suppository contains 0.2 G. (3 grs.) of lead acetate, and 0.06 G. (1 gr.) powdered opium.

TINCTURA OPII, Laudanum, contains 10 per cent of opium. 0.3–2 mils. (5–30 mins.).

TINCTURA OPII CAMPHORATA, Camphorated Tincture of Opium, or Paregoric, contains 0.05 per cent of morphine with camphor, benzoic acid and oil of anise. 2–4 mils. (30–60 mins.).

MORPHINÆ HYDROCHLORIDUM, 0.008–0.02 G. ($\frac{1}{8}$–$\frac{1}{3}$ gr.).

MORPHINÆ TARTRAS, 0.008 0.02 G. ($\frac{1}{8}$–$\frac{1}{3}$ gr.). Soluble in 11 parts of water.

CODEINA, Methylmorphine, 0.016–0.06 G. ($\frac{1}{4}$–1 gr.).

CODEINÆ PHOSPHAS ($(C_{17}H_{18}(CH_3)NO_3 \cdot H_3PO_4)_2 3H_2O$), white crystals with a slightly bitter taste, soluble in 4 parts of water, much less soluble in alcohol. Dose, $\frac{1}{4}$–1 gr. (0.016–0.06 G.).

DIAMORPHINÆ HYDROCHLORIDUM, Heroine or diacetylmorphine hydrochloride, a white, crystalline powder having a bitter taste and soluble in 3 parts of water. Dose, $\frac{1}{24}$–$\frac{1}{8}$ gr. (0.0025–0.008 G.).

LIQUOR MORPHINÆ HYDROCHLORIDI, contains 1 per cent of morphine hydrochloride. 0.3–2 mils. (5–30 mins.).

SUPPOSITORIUM MORPHINÆ, each suppository contains 0.015 G. ($\frac{1}{4}$ gr.) of morphine hydrochloride.

TROCHISCUS MORPHINÆ ET IPECACUANHÆ, each lozenge contains 0.002 G. ($\frac{1}{12}$ gr.) of morphine hydrochloride, and 0.006 ($\frac{1}{10}$ gr.) of ipecacuanha.

Acute Poisoning with morphine or opium is one of the commonest forms of intoxication, with the exception of the alcoholic. It is often difficult to diagnose from other forms of unconsciousness, but the extreme contraction of the pupils gives a clue, as a general rule, and if opium has been used, the breath often has the characteristic odor.

The treatment of acute morphine or opium poisoning should consist in removing the poison from the body and in guarding against failure of the respiration.

The first object is best attained by washing out the stomach with the stomach tube, as emetics generally fail when morphine has been absorbed, owing to the depression of the centre. Even when morphine has been injected hypodermically, gastric lavage may have some value as some of the poison is excreted into the stomach. Water should be used to wash out the stomach; dilute potassium permanganate solution has been advised, but tends to oxidize the gastric mucous membrane rather than the morphine. A sharp purge may be given to remove the morphine excreted into the bowel and also to promote excretion by irritating the mucous membrane.

In morphine poisoning the danger is failure of the respiratory centre. This may be combated by the use of respiratory stimulants, of which the best is caffeine (often given in the form of hot coffee). Strychnine has also an antagonistic action to morphine and may be injected. And atropine has been used to increase the excitability and appears to be of value in small quantities; but not more than $\frac{1}{40}$ grain should be used, as larger amounts tend to weaken the respiration. Caffeine is safer and is at least as efficacious in arousing the depressed centre.

Besides increasing the excitability of the centre by these drugs, the normal stimulus may be augmented. Thus respiration may be aroused reflexly from the skin by dashing cold water on it, or by the electric current, or by flicking it with wet cloths. But the chief normal stimulus of the respiratory centre is the carbon dioxide of the blood, and an attempt should be made to increase this and thus to promote the aëration. This may be attained by keeping the patient in motion as far as is possible, in order that the muscles may supply CO_2, but as this may have to be done for several hours, it entails great fatigue both for patient and attendant. A more rational method of enriching the blood with CO_2 would be to allow the patient to breathe air containing 7–10 per cent of the gas, which might be kept in readiness in the hospitals where opium poisoning is often encountered.

Finally, if the respiration fails in spite of these measures, artificial respiration must be employed and continued as long as the heart beats. Cases of recovery from enormous doses of morphine are recorded in which artificial respiration was maintained for many hours.

Chronic Opium or Morphine Poisoning is a not infrequent condition, but, fortunately, it seems to be decreasing somewhat. Among Eastern nations, especially in China, opium is smoked, and some of the morphine is carried over in the smoke and absorbed from the respiratory tract. This habit is rare in European peoples, among whom the drug is taken by the mouth, generally in the form of laudanum or of pills, or is injected hypodermically as morphine hydrochloride or sulfate. Of the three methods the first seems to be the least harmful, for in some parts of China the majority of the adult population seems to indulge in it without the serious results which are met with in the Western opium-eaters and morphinomaniacs. This result may be due in part to race, or to the fact

that the opium-smoker never attains the immense doses taken daily in the cases of the habit met with in Europe and America. In the beginning the quantity used is small, but as tolerance is attained, ever larger quantities are required to produce any effect, until, as De Quincey states in his "Confessions of an Opium-eater," 320 grains of opium may be required to stay the craving. The effects are generally described as stimulant, but it seems possible that they consist rather in depression of the sensibility, by which the unfortunate patient becomes unconscious of the miseries of his condition, and may accordingly be able to perform his duties and maintain appearances better than when deprived of the poison. The symptoms of the opium habit are exceedingly indefinite, and the diagnosis is often almost impossible. The statements of the patient ought not to be taken into consideration, because these unfortunates seem to have lost all idea of honor and truthfulness. As a general rule they are nervous, weak in character and wanting in energy, and utterly unfit for work except when supplied with the drug. The pupils are often contracted, the heart sometimes irregular, and tremors and unsteadiness in walking may be apparent. The appetite is bad and a considerable loss of weight may occur; and the movements of the bowels are irregular, constipation alternating with diarrhœa. Eventually melancholia and dementia may follow the prolonged use of opium, and especially of morphine. Some continue the habit for many years, however, and it would seem with comparative immunity. Especially is this true if the addict is living under favorable hygienic conditions and is securing sufficient food and maintaining elimination. The marked emaciation which is often encountered in addicts is due to failure of nutrition due to the inability met with in so many of this class to supply both food and drug. If morphine is injected habitually, evidence may be obtained from the small needle marks on the front of the body, which often give rise to multiple abscesses of small size from carelessness in the disinfection of the syringe.

Upon withdrawal of the drug there is a striking change in the condition of the individual due to the appearance of the so-called withdrawal symptoms. These begin with restlessness and yawning. In a few hours the patient complains of being cold, the respiration is jerky, there is difficulty in breathing through the nose and the nasal secretion is excessive. A prolonged sleep may follow but the earlier symptoms recur with increased violence upon awakening. The patient complains of abdominal cramps and vomiting and diarrhœa may appear. Sweating is excessive. Muscular twitching is marked. Food and water are refused and sleep is unknown. Physical violence may be threatened. The severity of these symptoms increases up to about the third day, but if at any time during this period the addict should be given his usual injection his whole appearance and attitude will change and within a few minutes he will be comfortable and in less than an hour will be apparently well and strong.

The symptoms above described are apparently very largely under the control of the individual. If the addict thinks they will secure

him sympathy and an injection of his accustomed drug, they are likely to be very severe. If, on the other hand, he knows that no matter how much he apparently suffers, no drug will be given, the symptoms are usually much milder. The recognition of the ability of the patient to control his feelings is very important as he will magnify his sufferings to secure his drug or claim to be well in order to secure release from restraint.

The careful clinical studies by Light and his co-workers upon morphine addicts and carried out by all modern methods of laboratory diagnosis failed to show that in such persons there was any evidence of change in the functions of any of the organs of the body. There was no evidence of physical deterioration or of physical unfitness aside from the habit of addiction. So, too, during the withdrawal symptoms there were remarkably few and slight changes demonstrable by the ordinary diagnostic methods employed and even these were not altered by the injection of morphine which had restored a feeling of well-being.

The treatment of chronic morphine poisoning is not very promising. The will and self-control would seem completely paralyzed in many cases, and although the patient may wish to be freed from his enemy, he seems utterly unable to withstand the craving. The only means of treatment which promises success in most cases is the strict régime of an asylum or retreat, where the patient is kept under constant supervision. In the withdrawal of the drug resulting in the distressing symptoms already mentioned there are two methods of treatment available. In the one case the narcotic is withdrawn at once, while in the other method the drug is reduced in amount from day to day until none is being administered. Each method has its advocates. The withdrawal symptoms are more severe when the drug is withdrawn abruptly, but after the third day they usually begin to decrease in intensity and by the end of a week or ten days the patient is usually comfortable. In the "tapering" process the symptoms are less severe but more prolonged.

Various drugs have been used to relieve the symptoms but none has proved entirely satisfactory. Scopolamine has been used extensively but careful studies seem to demonstrate that its effect is not beneficial. The gastro-intestinal symptoms are said to be somewhat less under atropine, but certain of the other symptoms such as the restlessness are apparently worse, so that its use is not recommended. Of all the drugs suggested for the treatment of the withdrawal symptoms codeine seems to be the most promising. As the morphine is being diminished codeine can be substituted so that it will produce sleep and alleviate the discomfort to a marked degree. Later, after the morphine is withdrawn the codeine can be withdrawn rather quickly without any marked disturbance beyond some restlessness which too will disappear shortly. Unfortunately relapses are exceedingly common.

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Minor Drugs of the Opium Series.

In some other members of the poppy family (papaveraceæ) alkaloids are found which bear a close resemblance to those of opium. These are *Cheli-*

donine, α, β- and γ-*Homochelidonine*, *Chelerythrine* and *Sanguinarine; Protopine* is also found in a number of other papaveraceæ. These alkaloids are met with in very small quantities in various plants, of which Sanguinaria Canadensis (Bloodroot) and Chelidonium majus (Celandine) are the best known.

Chelidonine and α-*Homochelidonine* produce moderate depression of the central nervous system and narcosis. In the frog no secondary increase in the reflex irritability follows, but in some mammals a slight stimulation of the spinal cord may be caused. They have the same effect as papaverine on muscle and heart, and like it produce insensibility of the skin and cornea when applied locally, through paralyzing the terminations of the sensory nerves. The heart is slower through direct action on the cardiac muscle. The respiration is slightly slowed and deepened. Chelidonine has been advised in the treatment of colic and asthma in view of its depressant action on unstriated muscle. (Dose 0.1–0.2 G.)

Sanguinarine has very little depressant action, but causes tetanus and wild excitement, so that as far as its action on the central nervous system is concerned, it deserves a place between codeine and thebaine of the morphine series. It possesses the same peripheral action as protopine, however, and the heart is slowed through direct affection of the muscle. Sanguinarine paralyzes the peripheral sensory endings when applied locally, but this paralysis is preceded by a stage of irritation. It causes violent peristalsis of the bowel, and increases the secretion of saliva.

β-*Homochelidonine* resembles protopine and cryptopine closely in its effects, causing the same stimulation of the lower parts of the brain with very slight effects on the intellectual powers, slowing the heart through its muscular action and paralyzing the sensory terminations.

Chelerythrine paralyzes the central nervous system without any preliminary increase in the reflex irritability, possesses the peripheral action of protopine and cryptopine, and first irritates, and then paralyzes the sensory terminations.

None of the plants containing these alkaloids have been used to any great extent, although Sanguinaria Canadensis was formerly occasionally prescribed as a nauseating expectorant and emetic.

Anhalonium.—A number of alkaloids, some resembling morphine, others like strychnine in their effects on animals, have been isolated from different members of the Anhalonium genus (Fam. Cactaceæ). In Mexico, and along the southern boundary of the United States, where those plants are indigenous, some of them are used as narcotics in the religious rites of the Indians and are known as Pellote, Peyotl, or Muscale or Mezcal Buttons. The symptoms arise for the most part from the cerebrum and differ from those of opium and cannabis indica in the frequency with which color visions are induced, these consisting in constantly shifting flashes of brilliant tints. Mezcal eating does not induce merriment like cannabis nor sleep like morphine, but depression of some functions is indicated by the imperfect coördination of the movements, the retarded perception, and the errors in the estimation of time. The exaltation seems to be caused for the most part by one of the alkaloids, mezcaline. Very large doses have induced unpleasant symptoms through depression of the respiration. Anhalonium and pellotine, one of its alkaloids, have been used as narcotics in a few cases of insomnia.

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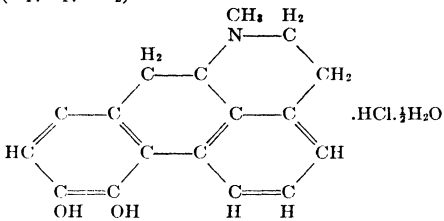
1. Apomorphine.

When morphine is acted on by acids and by some other dehydrating agents, it loses a molecule of water, and a new alkaloid is formed, *Apomorphine* ($C_{17}H_{17}NO_2$).



Through this change the action of the original alkaloid is considerably modified; apomorphine preserves the stimulant, but loses to a great degree the depressant action of morphine on the central nervous system. This stimulant action extends over the whole central nervous system in animals, but is most developed in the "vomiting centre" of the medulla oblongata.

Symptoms.—In man apomorphine in doses of 5–10 mg. ($\frac{1}{12}$–$\frac{1}{6}$ gr.) induces within ten to fifteen minutes nausea and vomiting, accompanied by the usual attendant phenomena, but with no symptoms which cannot be directly included in these. Very often the nausea passes off immediately after the evacuation of the stomach, but when larger quantities have been administered, repeated vomiting and retching may occur. Occasionally depression and sleep follow the emesis after even small doses.

The attendant symptoms are profuse salivation, increased secretion of the mucous glands of the nose, throat and bronchial passages, tears, and a cold perspiration. A feeling of depression and muscular weakness and acceleration of the pulse are also well-known symptoms accompanying nausea and vomiting, and are present after apomorphine. These are all to be regarded as sequelæ of the emetic action, however, and not as due to the direct action of the drug on the glands and other organs. In a few instances the depression and weakness have passed into alarming collapse, but no actual fatality is recorded from the use of apomorphine.

Very small doses of apomorphine may induce the secondary symptoms without actual vomiting. Thus the saliva, perspiration, tears and other secretions may be augmented by quantities which are too small to act as emetics, though there is no question that these are due to the commencing emetic action.

Apomorphine induces vomiting through changes in the medulla oblongata and not by irritation of the stomach. This is shown by the fact that it acts much more quickly and in smaller doses when it is injected hypodermically or intramuscularly than when it is swallowed, and also by the fact that if the medulla is brushed with apomorphine solution, vomiting follows immediately. The movements of vomiting

may also be induced in animals after the removal of the stomach and intestine, showing that the condition and the movements of the stomach play an unimportant part in the evacuation of its contents by apomorphine. All the phenomena in man, including the bronchial secretion, the perspiration and other attendant symptoms, are to be ascribed to medullary action.

In dogs and cats, small quantities elicit the same effects as in man, but larger doses are followed by symptoms of general nervous stimulation. In the herbivora, which are incapable of vomiting, these symptoms follow the injection of comparatively small quantities and are much more marked. The rabbit, for example, becomes restless and easily alarmed; it moves about, climbs up the walls of its cage and gnaws anything it can reach. Circus movements are developed very often, especially in the dog, the animal running unceasingly in a circle and striking against obstacles in its path, apparently unconscious of all its surroundings and overcome by the impulse to continual movement. The respiration is very much accelerated. After very large quantities the movements become less coördinated, and eventually tetanic convulsions set in, during which the respiration ceases, while the heart continues to beat for some time afterward.

Apomorphine is said to have some anæsthetic effects on the cornea when a solution is dropped upon it. It causes cloudiness and consequent dimness of sight, however, and has not been used practically for this purpose. Apomorphine is not excreted into the stomach like morphine, nor has it been found in the mucous membranes of the air passages, and it is possible that it is all decomposed in the tissues. No tolerance is acquired for it unless massive doses are employed, when a limited tolerance seems to be developed.

The symptoms induced by apomorphine resemble in some degree those following morphine in many animals, for here too the first symptom is vomiting accompanied by signs of excitement, which are, however, generally attended by those of depression of some part of the central nervous system. In man, however, the effects are very different, for apomorphine seems to have largely lost the depressant action of the parent body, although here again it must be remembered that morphine occasionally causes vomiting, so that apomorphine does not depart so far from the type of the opium alkaloids as would at first appear.

In the frog, apomorphine causes a transient stimulation of the central nervous system, followed by depression and paralysis.

Apocodeine is formed from codeine in the same way as apomorphine from morphine, but it differs entirely from apomorphine in its action and resembles nicotine in paralyzing the sympathetic ganglia. It causes purgation when injected hypodermically, apparently from removing the normal inhibition of the bowel movements (Dixon). If codeine is heated with hydrochloric acid, apomorphine is formed, and not apocodeine.

Therapeutic Uses.—Apomorphine is used chiefly as an emetic, and for some purposes presents several advantages over the older drugs employed with this object, inasmuch as it acts more promptly and can be administered by the hypodermic needle, while the other emetics cause vomiting by irritating the stomach and have to be given by the mouth, which is a serious drawback in cases of poisoning. The more important of these older drugs are ipecacuanha, tartar emetic (antimony), ammonium carbonate, the sulfates of copper, zinc and alum.

Vomiting is not now such an important method of treatment as it was formerly, and the emetics are less frequently employed to evacuate the stomach than other less heroic measures, such as the passage of the stomach tube. Emesis may be indicated in poisoning, and here

apomorphine is especially useful. But in the great majority of cases a better method of treatment is repeated washing of the stomach by means of the stomach tube, for in narcotic poisoning apomorphine not infrequently fails to act, owing to the depression of the vomiting centre, and in corrosive poisoning a certain amount of danger attends its use, as the pressure on the walls of the stomach exerted by the contraction of the diaphragm and abdominal muscles may lead to the rupture of the weakened walls of the organ. In irritant poisoning, on the other hand, the reflex vomiting set up is generally sufficient to empty the stomach, and the indications are rather to allay the gastric irritation than to increase it by causing violent movements of the abdominal walls by apomorphine. Occasionally emetics are used, especially in children to expel bodies from the air passages, as violent movements of expiration are produced during emesis. Apomorphine is comparatively rarely used for this purpose, however. In cases of choking due to foreign bodies lying in the pharynx, vomiting is often beneficial, but the emetics act too slowly to be of benefit here.

A second use of emetics is in inflammatory conditions of the respiratory passages; the object here is to induce an increased secretion without producing emesis, and very small quantities are therefore used. The special condition in which this class of remedies is of service is bronchial irritation with a sticky mucous secretion which causes cough, but can only be expectorated with difficulty. The indications are for a mild and prolonged action such as can be induced by small doses of ipecacuanha, antimony and similar bodies, rather than for the more transient effect of apomorphine, but the latter has been advised by some authorities.

Apomorphine has been used in small doses (0.002 G., $\frac{1}{30}$ gr.) as a sedative in cases of insomnia. It is given by hypodermic injection and is said to be effective in many of these cases and not to cause nausea in this dosage although doses slightly larger (gr. $\frac{1}{20}$) will do so frequently.

PREPARATIONS.

U. S. P. AND B. P.

APOMORPHINÆ HYDROCHLORIDUM, 0.001 G. ($\frac{1}{60}$ gr.), expectorant; emetic, 0.005 G. ($\frac{1}{12}$ gr.). B. P. dose, expectorant, 0.001–0.002 G. ($\frac{1}{60}$ – $\frac{1}{32}$ gr.); hypnotic or emetic, 0.002–0.008 G. ($\frac{1}{32}$ – $\frac{1}{8}$ gr.).

APOMORPHINE HYDROCHLORIDE is a grayish-white crystalline substance, very soluble in water, and turning dark green or even black, especially when kept long in solution. This change in color does not appear to impair its activity appreciably nor to alter its toxicity.

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2. Bulbocapnine.

Bulbocapnine is the most important of several alkaloids found in Corydalis cava. It is closely allied in constitution to apomorphine, being 3:4 methylenedioxy-6-methyl-apomorphine ($C_{19}H_{19}O_4N$).

It was first investigated pharmacologically by Peters (1904), who found that it produced a peculiar cataleptic condition in mammals. The limbs became stiff and, accompanying a sustained tonus of the muscles, voluntary and reflex movements were abolished, though there was no increased resistance to passive movements. The actions of this alkaloid have been more fully investigated in recent years, with special reference to its therapeutic use in certain nervous diseases.

The cataleptic symptoms do not occur in cold-blooded animals. In the frog, bulbocapnine has a morphine-like action. The action in mammals varies according to the species and the dosage. Catalepsy is more pronounced in more highly developed mammals, *e. g.*, monkeys, dogs and cats (Brucke). The stiffness of the limbs is central in origin and has been ascribed to tonic labyrinthine reflexes. Larger doses cause narcosis with eventually complete loss of motility; and the alkaloid increases the action of hypnotics, *e. g.*, luminal and paraldehyde.

Some of the symptoms suggest also a stimulant action on the parasympathetic nervous system, *e. g.*, salivation, lacrimation, micturition and defecation; but there is no marked stimulation of the isolated intestine, and the parasympathetic effects may be central.

Bulbocapnine causes a fall of blood-pressure with vasodilatation. Some of the vascular reflexes in the rabbit's ear are abolished; the pressor action of adrenaline is diminished but not reversed (Molitor).

The chief interest of bulbocapnine lies in its actions on the central nervous system, the site of which has not yet been accurately defined. It has been used especially to relieve tremor in postencephalitic conditions and in paralysis agitans and to suppress choreic movements. It has been used for the relief of vertigo in Ménière's disease (Neville) and has been suggested as a pre-anæsthetic sedative (Molitor).

A usual dose is 1½ grs. (0.1 G.) orally or subcutaneously, once or twice daily.

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V. BROMIDES.

It was formerly widely believed that the bromides had no further action than the chlorides, and that any effects observed from potassium bromide were due to the potassium ion, the bromide ion being indifferent. There is now no question, however, that the bromides

have distinctive effects, for all bromides induce changes in the central nervous system which are not elicited by the chlorides. The bromide of potassium is the salt most generally used.

Symptoms.—The local action on the alimentary tract is the same as that of sodium chloride and other salts; the bromides have a bitter salt taste and induce salivation and thirst, and, in large quantities irritation of the stomach, nausea, and vomiting. Occasionally diarrhœa has been observed from concentrated solutions reaching the intestine.

General Symptoms.—Apart from these results of local irritation, the first symptom is often a dull, heavy headache, with a feeling of lassitude, fatigue, disinclination for exertion, mental or physical, and often muscular weakness. Thought is slow and confused, the memory is indistinct, ideas are put into words with difficulty and the speech is accordingly slow and hesitating. External objects and movements are perceived, but arouse no interest in the patient, and very often this state of apathy passes into drowsiness and sleep. The bromides, however, have not the sleep-compelling power of morphine or chloral, and the sleep is never very deep and is not refreshing, the patient sometimes feeling dull and unfit for exertion after it, and some mental confusion often persisting for several hours after waking. The reflexes are much depressed by large doses of bromide, so that touching the back of the throat does not induce nausea, although the sensation of touch may persist. The mucous membranes of the genito-urinary tract are also less sensitive, or rather their irritation is less liable to set up reflex movements. After very large doses of the bromides the conjunctiva may sometimes be touched without causing winking, and lessened sensation in the skin has been noted in some cases. The pulse and respiration are slower than usual after large doses, but scarcely more so than in sleep. An increase in the urine is often observed.

Acute fatal poisoning with bromides has seldom or never occurred in man, but after enormous doses prolonged sleep or stupor has been seen, and confusion and apathy lasting for several days.

When bromide is given repeatedly in large doses, a series of symptoms is often induced to which the name of **Bromism** has been applied. It occurs much more rapidly in some persons than in others, and may suddenly appear after the patient has been taking the drug for months without any untoward results. The commonest symptoms of bromism are *skin eruptions* of various kinds, very often commencing as acne of the face. In severe cases the pustules of acne may coalesce and form small abscesses, which are followed by ulcers. Less commonly nodular lesions occur in the extremities, notably the legs, and these lesions frequently become vegetative. Some *disturbance of the digestion* and loss of appetite are often met with from the local action of large quantities of the salt on the stomach. Affections of the *respiratory passages* are not produced so often by the bromides as by the iodides, but have been met with, and consist in an increased secretion of mucus by the bronchial and nasal epithelium. The *mental symptoms* are merely exaggerations of those observed after one large dose. The memory is especially defective, sometimes sudden lapses occurring, sometimes a

general inability to remember the most recent events being met with. The patient is indifferent to his surroundings, speaks slowly and stammers, mispronounces ordinary words or misses several words out of a sentence. The gait is uncertain and tremor often accompanies any movement, the expression of the face is stupid and apathetic, and the eyes are heavy and lack lustre.

Action.—The effects of the bromides on animals can be examined only by the use of sodium bromide, as when the potassium salt is used, the action is complicated by the presence of potassium effects, which are often sufficient to obscure the slight depression of the brain which is the really characteristic effect of the bromide ion. In the frog, for example, potassium chloride is capable of inducing depression of the central nervous system, and the slightly greater depression induced by the bromide may well be overlooked; it appears, however, that bromides have very little true depressant action on the frog. The typical bromide action may be induced with greater clearness in mammals by the use of sodium bromide in repeated doses, and in dogs symptoms of depression and imperfect coördination have been observed, and sometimes stupor and death from failure of the respiration; the symptoms of central nervous depression can be elicited by a single large dose in the guinea-pig: lethargy, incoördination of movements, deep sleep passing into coma and often ending in death. The most characteristic action, however, is obtained from the administration of the drug to patients, as the affection of the central nervous system is so slight after all but extreme doses, that in order to produce distinct symptoms in the less sensitive animals, quantities must be used which entail the additional complications induced by salt-action.

The irritation of the throat and stomach, the nausea, vomiting and rarer diarrhœa must be attributed for the most part to the action of the salt in withdrawing fluid from the mucous membranes, and may be avoided by the use of dilute solutions and by their administration when the stomach is full.

The depression and other mental symptoms are due to a direct action on the **Central Nervous System.** Albertoni found that the irritability of the motor areas of the dog's brain was very distinctly reduced by the administration of bromides, and in particular that a stimulus which normally would have spread over a wide area and given rise to an epileptiform convulsion, caused only localized contractions after bromides, while convulsive poisons entirely failed to act. Loewald found some psychical processes, such as those involved in the addition of numbers, uninfluenced by bromides, while a series of figures could be learned by rote only with great difficulty; he therefore considers that the action is limited to certain definite functions. The reflexes are also reduced very considerably by bromides, and according to many observers the passage of impulses from the sensory to the motor cells of the cord is interrupted, while the connection between the cerebral centres and the motor cells of the cord is maintained intact. In man the most striking instance is the absence of reflex nausea when the back of the throat is touched. While reflex movements cannot be elicited, the sensation often remains

unimpaired, but after large doses a more or less complete anæsthesia is said to be produced. This anæsthesia extends to the skin when very large quantities are administered, and the cutaneous sensation is said to be blunted when comparatively small doses are taken; the action is purely central, the peripheral sense organs remaining unaffected.

The respiration is slower under bromides, owing to the lessened movement, but is scarcely more reduced than in normal sleep. The sexual instincts are depressed or entirely suspended, either from the action on the brain or from the lessened reflex activity.

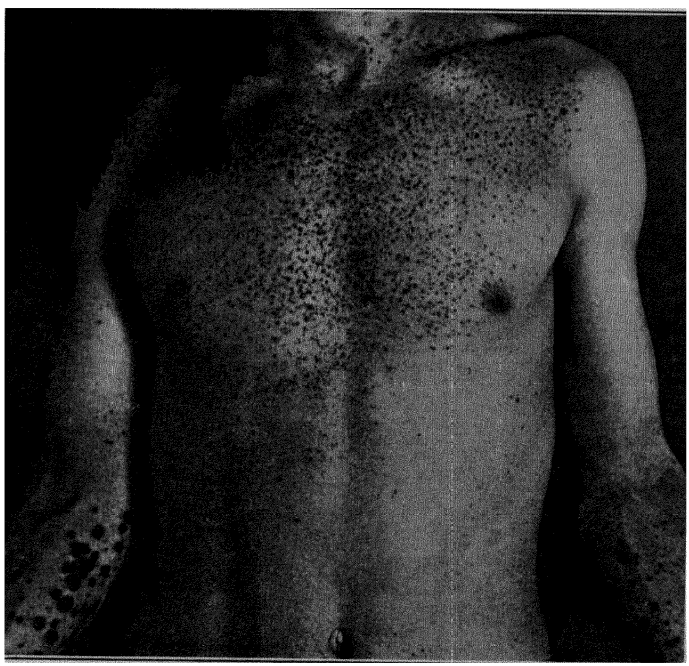

FIG. 20.—Common form of bromide eruption.

The bromide ion is almost as indifferent to most of the tissues as the chloride; for example, muscle and nerve live almost as long in solutions of sodium bromide as in those of the chloride of equivalent concentration. The heart may be perfused with saline containing bromide instead of chloride for many hours and be only slightly affected. When bromides are given by the mouth, the heart is not affected; potassium bromide injected intravenously in animals is poisonous to the heart as are the other potassium salts, but potassium bromide taken by the mouth has no effect on the heart. The vessels of the pia mater have been observed to be contracted under the bromides, but not more than in normal sleep, and this anæmia of the brain is the result, not the cause, of the depression. The temperature is often reduced in animals under

bromides from the lessened movement and consequent lessened production of heat.

Bromide has not been demonstrated in the contents of the acne pustules and the old view that the acne is due to bromine being freed is undoubtedly incorrect.

Distribution and Excretion.—The bromides are rapidly absorbed by the mucous membranes, and some bromide reaction can be obtained from the urine a few minutes after they have reached the stomach. Their distribution in the body resembles exactly that of the chloride; thus they are found in largest amounts in the blood plasma and have little tendency to accumulate in the organs. They occur in all the secretions and fluids of the body; they may be found in the form of hydrobromic acid in the stomach, and traces are found in the sweat and milk and in the hair, where chloride occurs naturally. The brain and spinal cord do not contain larger quantities than the other organs and never approach the amount contained in the blood plasma; the skin appears to contain a larger amount than most other organs.

The whole behavior of the bromides in the body indicates that most of the tissues are unable to differentiate them from the normal chloride ions, and react to a dose of bromide in the same way as to one of common salt. Thus the administration of bromide is followed by the excretion of an equivalent amount of salt, but the kidney does not discriminate between the two forms circulating in the blood but eliminates a mixture of chloride and bromide exactly in the same proportion as these occur in the blood. If it were possible to follow the course of the individual ions in the body after a dose of common salt, it would probably be found that although an equivalent amount of salt is soon eliminated in the urine, the actual chloride ions taken would only be represented in this excretion to a limited extent, the rest being furnished by that previously present in the blood and tissues; the remaining new chloride would gradually be eliminated in diminishing proportions. This is what occurs in the nearly related bromides; at first the amount excreted bears a high proportion to that of the chloride, but this falls off rapidly and some bromide appears in the urine for long afterward. Thus, after a single dose of 30 grs. the urine was found to contain bromide for two months, only about 10 per cent being eliminated in the first twenty-four hours. When the treatment is continued, the bromide therefore tends to accumulate in the body, but the proportion excreted rises with the increase of the salt in the blood, until an equilibrium is reached, exactly as much bromide appearing in the urine as is absorbed from the bowel. The excretion then continues long after the treatment is discontinued.

When the body is thus saturated with bromide, the blood plasma and all the fluids may contain as much bromide as chloride; for example, the gastric juice may contain even more hydrobromic acid than hydrochloric acid. The bromides are not simply added to the normal salts of the blood, but supplant the chlorides, which are excreted in quantity, so that the normal salt concentration of the blood is maintained, though the chloride is much diminished. During bromide treatment, therefore,

and especially in bromism, not only is there an excess of bromide in the body, but also a deficiency of chlorides, and it has been much discussed whether the symptoms of bromism and the sedative effects of bromide arise from the action of the bromide directly, or are the results of the deficiency of chloride. In favor of the latter view, it is urged that the bromide action is elicited more readily when the chloride of the food is lessened, and that the addition of chloride to the dietary often relieves the symptoms of bromism and on the other hand restores the epileptic seizures which have disappeared under bromide treatment. And Loeb finds that certain fish are depressed in bromide solution but remain normal if chloride is added. But all of these observations may be explained by the acknowledged fact that the administration of chloride promotes the excretion of bromide and thus lessens the concentration of bromide in the fluids of the body. And on the other hand it is found that animals may be narcotized with bromide quite rapidly, long before it is possible that a serious fall in the chlorides of the blood has occurred. So that the bromides appear to possess a definite action on the nerve cells, quite apart from the deficiency in chlorides. In practice, however, the bromide action is accompanied by chloride poverty and on the other hand any excess of chloride reduces the concentration of bromide and thus interferes with the treatment. The same is true of other measures which tend to withdraw bromide, such as the use of diuretics.

Wallace and Brodie found that bromides injected intravenously in dogs at once entered the spinal fluid, but that the serum always contains a lower concentration of bromine ions than the spinal fluid, while the reverse is true of the chlorine ion. They suggested that there is a selectivity factor in the passage of these ions into, and perhaps from, the spinal fluid.

The bromides of sodium, potassium and ammonium have practically identical effects in man when given by the mouth. In animals when they are injected intravenously, the potassium and ammonium bromides may present in addition the action of the potassium and ammonium ions.

Therapeutic Uses.—The bromides have been used extensively in the treatment of epilepsy, the prognosis of which was entirely changed following their introduction. In recent years, however, they have been largely supplanted by phenobarbital. In a few cases the bromide treatment was said to cure epilepsy—the attacks did not return after the treatment was stopped—but this was exceedingly rare. In the great majority of cases (90-95 per cent) the number of attacks was much smaller, or the patient might be entirely free from them so long as the treatment was persevered with, although they returned as soon as it was given up. In one large epileptic colony it was found that when no bromide was given the number of fits per patient averaged 13.3 per month, but this fell to 1.5 per month under treatment with moderate doses of bromide and no symptoms of bromism were seen; larger doses did not reduce the average of attacks further, but caused mental dulness and acne. Very often no improvement is observed during the first few days, until the tissues have become saturated with bromide, but in other cases the spasms disappear immediately. In treatment of epilepsy

it is well to begin with small doses, 0.3–0.6 G. (5–10 grs.), and to increase them if necessary, until the desired effect is attained, or some complication, such as widespread skin affections, precludes their further use.

When little chloride is taken in the food, the excretion of bromide is much retarded, and, on the other hand, the addition of chloride to the dietary accelerates the bromide excretion. The restriction of the salt in the food of epileptics under bromide treatment has therefore been suggested with the object of saturating the tissues with smaller doses of bromide than would otherwise be necessary. In practice, however, it is difficult to reduce materially the chlorides of the food, and equally satisfactory results may be obtained, with less hardship to the patient, by slightly increasing the dose of bromide. The use of bromide has to be continued for many months or years in epilepsy and the aim should be to reduce the dose to the lowest efficient one and to maintain this without variation. It may also be useful to keep the chloride of the food fairly constant and to avoid any treatment which may disturb the concentration of bromide in the blood, such as diuresis or violent purgation.

The acne is often a troublesome accompaniment of the bromide action, and in fact may prevent the use of this valuable drug in otherwise suitable cases. It may often be prevented by scrupulous cleanliness of the skin, and sometimes yields to treatment with small doses of arsenic.

The bromides are not so effective in other affections of the central nervous system, although some success has attended their use in chorea, in the convulsions of children, and in some forms of hysteria. They have also been tried in tetanus and in strychnine poisoning, but are inferior to other remedies, such as chloral and the new derivatives of barbituric acid. Neuralgia is sometimes improved by bromide treatment, especially when it arises from worry, anxiety, or overwork.

As soporifics, bromides often fail entirely, or induce such depression and confusion subsequently as to preclude their use. This prolonged action doubtless arises from the slow excretion of the bromide, the great proportion of that taken remaining in the tissues for more than twenty-four hours. In sleeplessness from anxiety they are often valuable, however and it is found that the dose of chloral may be considerably lessened if it is prescribed along with bromides. In sleeplessness from pain bromide is of little or no value. The bromides are little suited for use in a single dose unless it be a large one. On the other hand their prolonged action is very valuable in cases of exaltation and nervousness in which it is desired to allay the excitability without causing actual sleep, and in which an immediate effect is not so necessary as a prolonged slight action.

Bromides have been used with good results in sea-sickness, in the sickness of pregnancy, and, it is said, in whooping cough.

Preparations.

U. S. P.

Potassii Bromidum, 1 G. (15 grs.).
Sodii Bromidum, 1 G. (15 grs.).
Ammonii Bromidum, 1 G. (15 grs.).
Carbromalum, introduced as Adalin, 0.5 G. (8 grs.).

B. P.

POTASSII BROMIDUM, 0.3–2 G. (5–30 grs.).
SODII BROMIDUM, 0.3–2 G. (5–30 grs.).
CARBROMALUM, Uradal ($CBr(C_2H_5)_2CO{\cdot}NH\,CO\,NH_2$), 0.3–1 G. (5–15 grs.).

The bromides are all colorless crystalline bodies without odor but with a saline, bitter taste, and are very soluble in water. They are almost always prescribed in solution, which may be flavored with some aromatic syrup; they are not given hypodermically owing to the large dose necessary.

A number of other bromide combinations have been used in therapeutics. SABROMINE, the dibrombehenate of calcium ($(C_{22}H_{41}O_2Br_2)_2Ca$), has been introduced as a substitute for the alkali salts, and differs from them in being stored in the fatty tissues and in only slowly freeing the bromide ion. It is therefore not adapted for use when a rapid bromide action is desired but is recommended for use when long-continued administration is necessary or when the inorganic salts cause gastric disturbances. It contains 28.5 per cent of bromine. It is a tasteless powder, best given in tablets in doses from 0.3–1.2 G. (5–20 grs.). BROMIPIN and other bromine compounds have not proved equal to the bromides in practice. Bromipin is brominized sesame oil and contains about 10 per cent of bromine which it yields slowly. It is partly broken up in the intestines and the remainder is deposited in the fatty tissue and there is slowly split up. The dose is 4 cc. (1 dr.) which may be increased as necessary in epilepsy. Strontium bromide and hydrobromic acid are quite superfluous.

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VI. CANNABIS.

The hemp plant, especially when it is cultivated in warm climates as in India, Egypt or the southern United States, develops products which induce marked derangement of the central nervous system. Plants grown in the temperate regions possess qualitatively the same action, but the effects are much weaker than when it is grown in the warmer countries. The Indian plant was formerly supposed to be a distinct species, but it differs so little from the European form that botanists now consider them merely varieties. The old name of Cannabis Indica has, however, to a certain extent, been retained in medicine. Its introduction into Western medicine dates only from the beginning of last century, but it has been used as an intoxicant in Asiatic countries and in Africa since unknown time, and under the names of *Hashish, Bhang, Ganja, Charas* or *Churrus*, is habitually indulged in by some one or two hundred millions of mankind. Some of the preparations are smoked either alone or mixed with tobacco; others form an intoxicating drink, while in others it is mixed with sugar or honey and taken as a confection. During the last decade and especially since 1935, the practice of smoking cigarettes, containing Indian hemp under the name of "Marihuana," became increasingly prevalent in some parts of the United States and to a less extent in Canada and England. The vice was not uncom-

mon in adolescents and even in children and there seemed to be a definite association between the incidence of crime and the practice of hemp smoking. The authorities concerned have taken steps to stamp out the practice. The problem has recently been reviewed by Walton who has given a historical account of addiction to Indian hemp with an exhaustive bibliography.

The active principle of Indian hemp has been found by Wood, Spivey and Easterfield to be a red oil or resin boiling at a high temperature, which they term *Cannabinol;* this was found by Marshall to induce the typical effects of cannabis in man and animals. Fränkel states that cannabinol is a phenolaldehyde of the formula OH $C_{20}H_{28}COH$.

Symptoms.—The effects of cannabis indica are chiefly due to the changes in the central nervous system, in which it induces a mixture of depression and stimulation similar to that seen under small doses of morphine. Its action is much less constant; however, and seems to depend very largely on the disposition and intellectual activity of the individual. The preparations used also vary considerably in strength, and the activity of even the crude drug seems to depend very largely on the climate and season in which it is grown, so that great discrepancies occur in the accounts of its effects. Soon after its administration, the patient passes into a dreamy, semi-conscious state, in which the judgment seems to be lost, while the imagination is untrammeled by its usual restraints. The dreams assume the vividness of visions, are of boundless extravagance, and, of course, vary with the character and pursuits of the individual. In the eastern races they seem generally to partake of an amorous nature. The true believer sees the gardens of paradise and finds himself surrounded by troops of houris of unspeakable beauty, while the less imaginative European finds himself unaccountably happy and feels constrained to active movement, often of a purposeless and even absurd character. Ideas flash through the mind without apparent continuity, and all measurement of time and space is lost. True hallucinations may appear, but are often absent, the chief features of the action being merriment, comfort, well-being, and self-satisfaction. Often less pleasant thoughts obtrude themselves, however, such as the fear of impending death or of some imminent, indefinite danger. During this period the consciousness is not entirely lost, for the patient often feels that his dreams are unreal, his satisfaction unfounded and his movements ridiculous, but he cannot restrain them; he can give a coherent account of his condition when aroused and answers questions intelligently. The sensation of pain is lessened or entirely absent, and the sense of touch is less acute than normally. Later the dreams alternate with periods of complete unconsciousness, from which the patient can be aroused easily, and the symptoms eventually pass into tranquil sleep, from which he awakens refreshed, and, as a rule, without any feeling of depression or nausea. In the majority of cases the preliminary stage of exaltation is very short or entirely absent in Europeans, the first effects of the drug often being heaviness, drowsiness, noises in the ears and numbness of the extremities, which pass into deep sleep. According to Dixon, the drug is much more exhilarating when inhaled than when swallowed, and this may account for some of the variations in its action. In some cases, acute mania and convulsive attacks have been developed, and among the natives of India catalepsy occasionally occurs.

In animals the effects of cannabis seem to resemble those in man and present the same marked variations; a stage of exaltation with increased movement is sometimes present and is followed by depression, lassitude, and sleep. The reflex excitability is first increased and then diminished in frogs. Vomiting is often induced in dogs and cats, but cannabis differs from opium in producing no disturbance of the digestion and no constipation. The heart is generally accelerated in man when the drug is inhaled; the intravenous injection in animals slows the pulse, partly through inhibitory stimulation and partly through direct action on the heart muscle. This action on the heart is stated by Dixon to be the cause of death after poisonous quantities, for he found that respiration persists for some seconds after standstill of the heart. The pupil is generally somewhat dilated. Polyuria is stated to occur in dogs, in which cannabinol appears to be excreted by the kidneys in combination with glycuronic acid (Fränkel).

Death from acute poisoning is extremely rare, and recovery has occurred after enormous doses. The continued abuse of hashish in the East sometimes leads to mania and dementia, but does not cause the same disturbance of nutrition as opium, and the habitual use of small quantities, which is almost universal in some Eastern peoples, does not seem detrimental to them, although among Europeans it might possibly be as fatal as that of morphine. Some tolerance is rapidly acquired.

Therapeutic Uses.—Cannabis has been used as a hypnotic in cases of sleeplessness from nervous exhaustion and, less often, from pain, but on account of the uncertainty of its action, its use for this purpose has been very largely given up.

The fluid preparations are used most extensively in connection with salicylic acid in "corn" remedies, but the acid is the active ingredient in such combinations.

PREPARATIONS.

U. S. P.

CANNABIS, the flowering tops of the female plant of Cannabis sativa (hemp).

EXTRACTUM CANNABIS, 0.015 G. ($\frac{1}{4}$ gr.).

FLUIDEXTRACTUM CANNABIS, 0.1 cc. ($1\frac{1}{2}$ mins.).

The preparations vary extremely in strength and many are entirely inert, especially when they have been kept some time.

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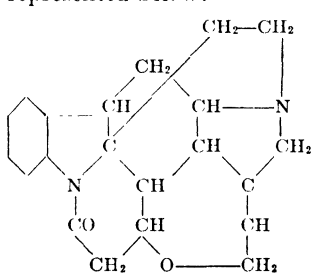
B. STIMULANTS OF THE CENTRAL NERVOUS SYSTEM.

I. STRYCHNINE.

Strychnine is the chief alkaloid occurring in several species of Strychnos, of which the best known are Strychnos nux vomica and Strychnos ignatia. Strychnine has the formula $C_{21}H_{22}N_2O_2$ and is believed to possess the structure represented below:



Strychnine

Strychnine is found chiefly in the seeds, and is generally accompanied by the alkaloid *Brucine* ($C_{23}H_{26}N_2O_4$), which differs from it in having two methoxyl groups. It seems not unlikely that they are both related to the alkaloids of curare, which is itself derived from other species of Strychnos.

The alkaloids of the strychnine group have a powerful stimulant action on the central nervous system, especially on the spinal cord, throughout the vertebrate kingdom.

Symptoms.—In ordinary therapeutic doses strychnine, like other bitter substances (page 249), improves the appetite and often leads to a distinct amelioration of the subjective symptoms, the patient feeling stronger and more hopeful. The special senses are rendered more acute by small quantities of strychnine, for differences can be recognized between shades of color which seem identical to the normal vision; the field of vision is widened, and in certain conditions of amblyopia light is rendered much more distinct. In the same way the hearing seems to be more acute, and the sense of touch is more delicate. Some cases have been noted in which disagreeable odors were rendered pleasant by strychnine, but this would seem to be a rare idiosyncrasy. In larger doses strychnine increases the reflex movements, and the sense of touch is rendered distinctly more acute.

In cases of poisoning with strychnine, these effects are present but are not generally observed by the patient, whose first complaint is of a feeling of stiffness in the muscles of the neck and face. This is soon

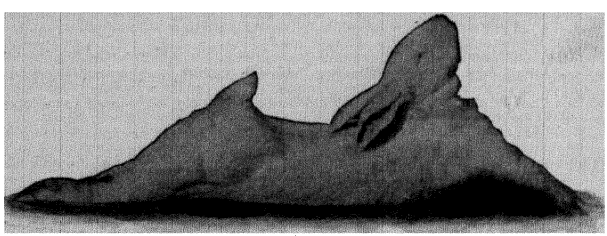


FIG. 21.—A rabbit during a strychnine convulsion.

followed by an increased reflex reaction, so that a slight touch causes a violent movement, and even a sound or a current of air is sufficient to cause a sudden start. The increased reflex irritability is generally accompanied by some restlessness, and animals sometimes seem to make attempts to escape from bright light. Some tremor or involuntary twitches may be observed in the limbs, and then a sudden convulsion occurs in which all the muscles of the body are involved, but in which the stronger extensor muscles generally prevail. In animals the head is drawn back, the hind limbs extended, and the trunk forms an arch with its concavity backward (opisthotonos) (Fig. 21). In man the same convulsions are seen and are accompanied by strong contraction of the face muscles, producing a hideous grin which has been called the *risus sardonicus*. The respiratory muscles are involved in the general paroxysm and the blood rapidly becomes deoxygenated, as is shown by the blue, cyanotic color of the lips and face in man. The muscles feel hard and firm at the commencement of the convulsion, but very soon a tremor may be made out, which becomes more distinct, and after a few intermittent contractions the animal sinks back in

a condition of prostration. The respiration generally returns, and becomes fairly regular for a short time. Immediately after a convulsion the reflex irritability may be low, but it soon regains its former exaggerated condition and a second convulsion occurs, exactly resembling the first. Mammals, as a general rule, succumb after two or three convulsions, the respiration failing to return after the spasm. In some cases, however, the convulsions become shorter and the intervals of quiescence longer, the respiration becomes weak, the reflex irritability gradually lessens and the animal dies from asphyxia. In frogs, where the breathing can be dispensed with for long periods, the alternation of convulsions and periods of quiescence may continue for hours or days, but these are of the same general character as those described in mammals. After very large quantities no convulsions may occur, the animal dying almost immediately of asphyxia from paralysis of the central nervous system.

Action.—The whole character of the intoxication points to an affection of the **Central Nervous System,** and it has been found that the symptoms are unaltered when the drug is prevented from reaching the peripheral nerves and muscles. The chief symptoms arise from the spinal cord, for the convulsions are at least as well marked in frogs and mammals in which the brain has been destroyed or severed below the medulla oblongata. The intellect in man remains unclouded until the end, except for the asphyxia produced by the stoppage of the respiration; the patient is perfectly conscious of his condition, and suffers excruciating pain from the violent contractions of the muscles.

The special senses are rendered more acute by small doses of strychnine, and this is apparently due to its effects on the central nervous system in the case of touch, taste and smell, but there is reason to believe that the increase in the field of vision and the increased sensitiveness to slight differences in light are to be attributed to its acting on the cells of the retina and not to cerebral changes. For when strychnine salts are injected in the temple or applied to the conjunctiva, the sight of the corresponding eye is improved while the other remains unaffected (Filehne); if the strychnine acted centrally it could do so only by being carried to the brain by the blood, but this would affect each hemisphere equally. The affection of one eye only is explained by the strychnine diffusing through the lymph spaces, and this is said to have occurred in the case of various dyes which were applied in the same way and were then found in the retina.

Ergographic experiments have shown that small doses of strychnine augment the capacity for muscular work, and delay the onset of fatigue; this excitation phase is followed by one in which the capacity is lowered. Electrical stimulation of the motor areas of the brain is more effective under strychnine than in unpoisoned animals, but this does not necessarily indicate that the cells of these areas are acted on directly, for the same apparently increased irritability of the cortical areas is seen when the poison acts on the cord only, and it may therefore be the result of the spinal action.

The convulsions are, as has been stated, of spinal origin, in this term

being included also those parts of the brain which correspond to the cord in performing simple reflex movements. It has been shown that in the frog they are reflex, that, provided no stimulus reaches the cord from without, no convulsion occurs. As has been already remarked, the convulsions are preceded by a stage of increased reflexes, and in fact the first convulsion is often seen to follow a stimulus, such as a blow or a loud noise. Afterwards they may seem to occur without any such impulse, but this is merely because a very slight or even imperceptible stimulus is enough to induce them. For example, a slight contraction of a muscle may induce a convulsion, as is seen very frequently in the frog, where a very slight stimulus, in itself apparently too weak to cause a convulsion, is followed by an ordinary reflex contraction, and this leads to a spasm. The absence of convulsions when external stimuli are cut off may, however, be demonstrated conclusively in various ways. Thus Poulsson found that a frog dipped in cocaine solution undergoes no convulsions after strychnine, the cocaine used being sufficient to paralyze the sensory terminations, but not to have any direct effect on the cord. Claude Bernard showed this even more conclusively by dividing all the posterior roots of the spinal nerves in the frog and then injecting strychnine, when no convulsions occurred except when the ends of the cut roots were stimulated. In mammals, however, it appears that even when all external impulses are excluded by section and degeneration of the posterior roots, convulsions still occur from strychnine; here apparently the excitability of the neurons in the cord is so extreme that they originate spasms without any impulse from without, while in the frog the advent of an external stimulus is necessary. But even in the mammal the spasms generally occur from some touch or sound or other disturbing factor.

The characteristic feature of strychnine poisoning is thus the changed response to external stimuli. In the unpoisoned animal the simple reflex movement following a stimulus is coördinated and purposive; for example, if the leg of a decapitated frog be dipped in acid it makes certain movements to withdraw the limb, and no matter how often the irritation be repeated, the same movements are produced, though it is true that if stronger acid be used the movement is more violent and a greater number of muscles are involved. In this movement certain muscles contract while their antagonists are inhibited; thus in drawing the toe away from an irritant the anterior muscles of the leg contract, while the gastrocnemius is relaxed. Under strychnine this simple reflex is stronger and is elicited by weaker irritation, and this change persists during poisoning if the external stimulus is weak and acts slowly. When a stronger or more sudden shock is applied to a poisoned animal, the response is quite different; all the muscles contract together, there being no inhibition of antagonists, and the resultant movement has thus quite a different character; the gastrocnemius being stronger than the anterior leg muscles, the foot is extended and thrust against the irritant instead of being withdrawn from it. And not only the muscles concerned in the simple reflex, but those of the whole body are involved in the movement. This tetanic contraction of all the muscles may arise from an external

stimulus which is no stronger than is required to induce a simple reflex in the unpoisoned animal. The response is the same whether the stimulus is derived from the periphery and the consequent movement is a reflex one, or from the brain. In both cases the change in the character of the movement arises from changes in the spinal cord, the impulse from the brain or periphery bearing its normal character, but changing its nature in passing through the cord.

It is often stated that this convulsive movement is a changed normal reflex, that under strychnine the spinal cord has lost its power of coördinating movement and can only respond to afferent impulses by efferent motor impulses to all the muscles. This is erroneous, however, for each form of response may be elicited alternately in poisoning; a weak stimulus is followed by a strong but coördinated purposive simple reflex, while a stronger one throws the body into general tetanus. This is not a development of the simple reflex, but is a totally different movement which is akin to the violent movement which occurs in normal persons and animals when a sudden unexpected touch or sound arouses them; here also the whole of the muscles contract together, and the resulting movement is determined by their relative strength; in man the powerful extensors of the trunk produce a violent straightening and the subject is said to "jump out of his chair." Strychnine lowers the threshold of the stimulus of this response, so that it is elicited by ordinary touch or weak sounds and becomes the response characteristic of the poisoning.

When an external stimulus is sufficient to cause this convulsive movement in a poisoned animal, the contraction is always maximal; a stronger stimulus produces no greater effect.

Houghton and Muirhead and later Baglioni stated that the cells of the anterior horn are not necessarily involved in the strychnine action. For when strychnine is applied in solution to the cord of the frog at the level of the cells connected with the nerves to the fore limbs, irritation of the hind foot produces an ordinary response in the hind limbs, while the anterior part of the body remains motionless; that is, strychnine has not penetrated to the cells connected with the hind limbs. Irritation of the fore limbs, on the other hand, produces tetanus not only of these, but also of the hind limbs, although the motor cells of the hind limbs have been shown to be outside the poisoned area. Tetanus can, therefore, be produced in parts whose motor cells are unpoisoned. The increased strength of the contraction is due, not to augmented energy in the anterior horn cell, but to the impulses which these receive being much stronger. But later investigators (Ryan, McGuigan, Barenne) state that this experiment does not hold in mammals, in which there is less chance of the results being confused by diffusion than in the small cord of the frog, and bring forward further evidence that tetanus can be induced only when the poison acts both on the motor anterior horn cells and on the sensory part of the reflex arc; the attempt to localize the action outside the motor cells cannot be regarded as successful in the light of these researches, unless the experiments on which it is based are supported by further work. All are agreed that the posterior root ganglion is not the seat of action, for convulsions may be elicited by stimulation of the posterior roots above this point. It is possible that the chief seat of action is in the synapses of the neurons intercalated between those of the posterior root and the nerve cells of the anterior horn.

An impulse travelling up a nerve in an unpoisoned frog reaches the cord and may there pass through a number of paths and in each is subjected to various influences, so that it arouses different motor cells to different degrees of activity, or actually inhibits the activity of some of them; in this way a coördinated movement follows. Under strychnine these influences, which may be figured as varying resistances in the different paths, disappear, and the impulse passes untrammeled along all available paths and reaches the motor cells in much greater force than normally and thus arouses a more powerful reaction from them and a correspondingly strong muscular contraction. But the resistance in the different paths is essential to coördinate the movement and the increased muscular contraction is thus no longer coördinated, all the muscles contracting together and the character of the movement being determined by their relative strength. The action of strychnine may thus be explained by supposing that it removes resistances to the passages of impulses through the spinal cord and thus extends the area on which an impulse acts, and also liberates it from the normal coördinating influences.

It must be remarked that while the resistance is much reduced, it is not entirely removed, and the ordinary path is still somewhat more easily traversed than the others, for weak irritation causes an ordinary reflex response in the frog, while a slightly stronger stimulus throws it into opisthotonos. In this condition a whole series of discharges occurs of longer duration than the simple reflex, and this without any further impulses reaching the cord either from without or from the muscles and joints involved in the movement; for when all movement is excluded by curare, the electrical changes can be observed in the cord corresponding to the muscular spasms in the convulsions.

Sherrington found that a stimulus which normally produces reflex contraction of a muscle with inhibition of the opposing muscle may, in an animal under strychnine, produce a contraction of both muscles; that strychnine apparently changes an inhibitory into a motor response ("strychnine reversal"). He later suggested, as another possible explanation of the phenomenon, that the apparent reversal might really be due to the exaggeration of a masked motor component in the inhibitory response. The correctness of the latter assumption was shown by Bremer, who found that strychnine only amplifies the motor element, more or less apparent, in the inhibitory component of a reflex response. Creed and Hertz have shown that the relaxation of a diaphragm slip, evoked by inflation of the lungs, is never replaced by contraction as a result of administering strychnine, and they support Bremer's conclusion that the action of strychnine is not to convert central inhibition into central excitation but to facilitate the passage of excitatory processes through reflex arcs.

Besides the spinal cord, all other regions in which simple reflexes can be produced, are affected by strychnine. Thus the medullary centres are thrown into the same condition, and their responses to stimuli are equally exaggerated; but they are in constant receipt of impulses, and

strychnine, by increasing the efficiency of these, augments the tone of the medulla oblongata when it is given in small quantities.

Artificial respiration has been shown to delay the onset of convulsions in animals, but it is still an open question whether this is due to the better aëration of the blood (Osterwald) or to the effects of the mechanical movements (Gies and Meltzer).

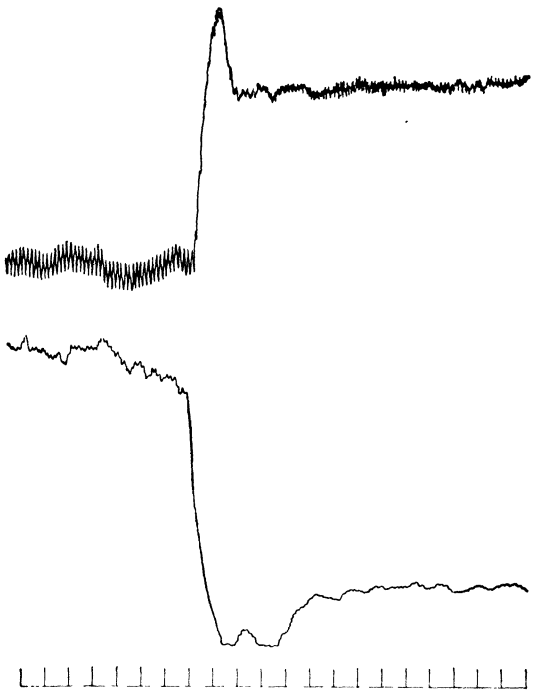


FIG. 22.—Tracings of the blood-pressure (upper) and intestinal volume (lower) from a curarized cat, showing the effect of the intravenous injection of a dose of strychnine sufficient to cause spasms in an uncurarized animal. The blood-pressure rises, while the mesenteric vessels are contracted from spasm of the vasomotor centre (Bayliss).

The stimulation of the spinal cord by strychnine is followed by depression and paralysis. Even during the first stage the stimulation is mixed with depression, for though a more violent response is induced by a sensory stimulus, this cannot be repeated so often as in the normal frog, as the cord becomes fatigued more readily. The sensory part of the spinal cord seems to be paralyzed somewhat earlier than the motor cells, but these also lose their irritability after a time and no further movement can be elicited either by reflex or by direct stimulation of the cord.

Strychnine seems to have no direct action on the voluntary **Muscles**, it is stated that minute quantities increase their tone, that is, render them more tense, so that they are prepared for immediate contraction, but this is due to action on the cord and not on the muscle fibres.

The **Terminations of the Motor Nerves** are paralyzed by large doses of strychnine in the same way as by curare. This effect is scarcely seen in mammals, as central paralysis always precedes it and destroys life, but in some species of frogs the nerve ends are paralyzed before the central nervous system. This paralysis is not due to the exhaustion of the nerve ends through the tetanus, but is a direct action on the terminations, although the exhaustion may contribute to the result.

The **Respiration** is quickened by small quantities of strychnine, especially when the centre is depressed by the previous administration of a narcotic. During the convulsions the breathing is arrested by the violent contractions of the diaphragm and the other respiratory muscles, but during the intermissions it continues fairly regular. After one or two spasms it often fails to be reinstated, and the animal dies of asphyxia; in other experiments it undergoes a gradual diminution in rate and strength, and eventually ceases from gradual paralysis of the centre.

Placing emphasis upon a depressant action of strychnine, Travell and Gold believe that death from the drug does not occur from a direct paralyzing effect of the alkaloid upon the respiratory centre. They hold that drugs which depress the centre, such as ether, alcohol and the barbiturates, are effective antidotes against strychnine preventing the respiratory paralysis, and that it could hardly be reasonable to expect one depressant drug to combat the depressant action of another. They believe, therefore, that strychnine lowers the threshold of excitability of the centre and thus the centre is exhausted as the result of its bombardment by peripheral impulses which are normally sub-threshold This view of the cause of death under strychnine has not been very generally accepted, and it has been pointed out that the antidotal effect of the depressant drugs may be due to their action against the excessive stimulant effect of the strychnine which naturally leads to exhaustion of the centre and resulting death.

Aiazzi-Mancini and Donatelli point out that to be really effective as a respiratory stimulant so as to increase the respiratory volume, the dose of strychnine must approach very close to the convulsive dose. They found that ethyl strychnine is much less toxic than strychnine itself and can stimulate respiration without producing convulsions. The minimum effective dose of the two drugs is about the same, but the toxicity of strychnine is about twenty times that of the ethyl compound. From the use of adequate doses of strychnine the change in respiratory volume is mainly due to the great increase in the depth of the respiratory movements and not so much to a change in rate.

The **Heart** is not directly affected by strychnine in mammals, though it is sometimes slightly slowed by stimulation of the inhibitory centre. During and after a convulsion it may be accelerated, as in violent exertion from any cause. Very large quantities slow and weaken the frog's heart.

The **Vasomotor Centres** in the medulla oblongata and the cord are often stimulated by small quantities, so that the splanchnic vessels are constricted, while the cutaneous and perhaps the muscular vessels tend to dilate from stimulation of the vasodilator centre. The blood is thus deflected to some extent from the abdominal organs to the skin and limbs, as well as to the heart, lungs and brain which have little or no vaso-constrictor supply. Bayliss found that stimulation of the depressor nerve caused a rise of blood-pressure after strychnine, and regarded this as an example of inhibitory reflexes being changed by strychnine

into motor ones; but both Langley and Scott believed that this effect was due to the presence of pressor elements in the nerve stimulated. Langley showed that reflex vasomotor effects in the spinal animal are markedly exaggerated by strychnine.

During the convulsions the blood-pressure is raised to an extreme height, partly owing to the activity of the vasomotor centre and perhaps partly from the blood being pressed out of the abdominal organs and the muscles by the violent contractions. Immediately after a convulsion the blood-pressure falls, probably from the exhaustion of the centre.

Strychnine stimulates the output from the adrenal glands and may thus indirectly produce sympathomimetic effects on the circulation and on other organs.

In the **Alimentary Tract,** strychnine has the same action as any other bitter substance, and it produces a flow of saliva and increased appetite if taken before meals. (See Stomachic Bitters, page 249.) It seems to be absorbed from the intestine mainly. After absorption it was thought to increase the movements of the bowel from some action on the muscle or on the ganglionic plexus in the bowel wall, but careful studies carried out on the human patient, by means of a balloon placed in the lumen of the intestine and peristalsis thus recorded, have shown that any change which is produced by the small doses usually employed is inconsequential and could readily be obtained by other less dangerous drugs.

Metabolism.—Strychnine produces an enormous activity of the muscles, and, therefore, increases very greatly the consumption of oxygen and the output of carbonic acid. This is accompanied by an increased formation of heat, which would lead to a rise in the temperature of the body were it not counteracted by an equal or even greater increase in its dissipation through the skin. As a result the temperature is generally lowered in rabbits, while it sometimes rises slightly in dogs and cats. The skin temperature, on the other hand, rises considerably because more blood flows through it than usual.

Glycosuria occurs in frogs and in young mammals, and the glycogen of the liver and muscles disappears in most animals under strychnine; the increased muscular movement and the disturbance of the respiration are probably the explanation of both of these phenomena.

Strychnine is absorbed rapidly and is distributed equally in the red corpuscles and plasma of the blood. In man from 10 to 20 per cent of that ingested reappears in the urine, in which the reaction begins usually within an hour and may remain three or more days. The rest of the alkaloid is taken up by the liver and undergoes oxidation. No marked tolerance is developed for strychnine, even after very prolonged administration; indeed, increased susceptibility may result.

The action of strychnine is almost identical throughout the vertebrate kingdom. Man is more susceptible than other mammals, and young animals are more refractory than adults, perhaps owing to the less developed condition of the central nervous system. It has been found also that females are much more susceptible to strychnine than males. At least this is true in the case of white rats. The domestic fowl tolerates comparatively large quantities without

symptoms. The convulsant action is seen in some of the higher invertebrates; in the lower it induces paralysis only.

Brucine, the second alkaloid of nux vomica, resembles strychnine closely in action but is much weaker, from 30 to 80 times as large a dose being required to produce the same effect. It differs from strychnine also in possessing a more powerful action on the nerve terminations in voluntary muscle, especially in some species of frog. Strychnine and brucine are present in nux vomica in almost equal proportions.

A third alkaloid, Vomicine, has been described, which produces clonic convulsions differing from those produced by strychnine and apparently due to an action on the cerebrum.

Therapeutic Uses.—Strychnine is used largely for its local action on the digestive organs as a *stomachic bitter*, and is generally prescribed in the form of the tincture or the extract for this purpose, as in this way it is less rapidly absorbed than when given as an alkaloidal salt. It may be combined with the cinchona preparations or with one of the simple bitters.

Small quantities of strychnine are of benefit in many ill-defined conditions of weakness, cachexia, and "*want of tone*" generally. The results are probably partly due to its stomachic effects in increasing appetite and digestion, but the action on the central nervous system cannot be overlooked. The slight increase in the irritability of the cord probably leads to an improvement in almost all of the nutritive functions through increasing the contraction of the vessels and producing greater activity of the muscles. In this way strychnine perhaps deserves the name of "tonic" more than most of the drugs to which it is applied.

As a *stimulant to the central nervous system* strychnine has found wide application in almost every form of paralysis, and as long as distinct anatomical lesions of the central nervous axis are absent, it may be of benefit; for instance, it is often valuable in lead poisoning; but where the continuity of the axis is broken by hæmorrhage or by the destruction of the nerve cells, little improvement is to be anticipated from its use, though it may serve to delay or prevent the atrophy of peripheral nerves and muscles in some of these cases. When the paralysis is due to an inflammatory process, strychnine is to be used with the greatest care, or is perhaps better avoided entirely as long as the irritation is present, as it seems to increase and prolong the inflammation when used early in these cases.

Strychnine is used as a *respiratory stimulant* in some pulmonary conditions in which it is desirable to increase the respiration or to provoke coughing. It has been advised in failure of the respiration during anæsthesia, or still more frequently, in cases of poisoning from the soporifics, and it is certainly more likely to be beneficial than a number of other drugs suggested for this purpose. In other forms of poisoning in which the respiratory centre is in danger, strychnine may also be of service. In such cases it should be injected hypodermically.

In *amaurosis* or amblyopia unassociated with atrophy of the optic nerve, and even in commencing atrophy, strychnine has frequently improved the vision. In many cases it fails to produce any benefit,

and the exact conditions in which improvement can be looked for are unknown.

Strychnine has been used in heart disease, but all exact observations agree that it has no beneficial action (Parkinson and Rowlands). In weakness of the circulation from *inefficiency of the vasomotor centre* it may act, though Crile denies it any value in the treatment of the low blood-pressure of shock, and Cabot could not find any change in the blood-pressure after its use in a number of conditions in which it is ordinarily advised. Cook and Briggs found the blood-pressure increased in certain cases of vasomotor paresis, however, when $\frac{1}{60}$ – $\frac{1}{10}$ gr. of strychnine was injected hypodermically. In rare cases this weakness of the medullary centre simulates heart disease, and this may account for the belief in the virtues of strychnine as a cardiac tonic.

Strychnine is said to be of value in chronic alcoholism in lessening the depression which forms one of the chief difficulties in the treatment.

Poisoning.—In cases of strychnine poisoning, the first treatment usually employed is evacuation of the stomach by means of emetics, or, better, by the stomach tube; it may be necessary to give chloroform, as the attempt to pass the tube is often followed by violent convulsions. Preparations of tannic acid may be given in order to form the insoluble tannate, which, however, must be removed as quickly as possible, as it is broken up by the acid gastric juice and the strychnine is rapidly absorbed. To combat the convulsions, depressants of the central nervous system should be given, and, although chloral is usually advised, chloroform or ether may have to be given at first. It is unnecessary to produce deep anæsthesia, a few whiffs of chloroform being often sufficient to allay the convulsions. The advantage of the anæsthetics over chloral is that they can be removed if any symptoms of strychnine paralysis appear. If the paralysis comes on, artificial respiration may be attempted, although the poison is destroyed too slowly by the organism to permit of much hope of recovery.

Travell and Gold found that alcohol is an effective antidote to strychnine poisoning in animals. The use of ether as an antidote has not proved to be a very successful means of preventing death, and these workers say that this unfavorable estimate of its value is due to the attempt to control the convulsions completely, and in such an attempt the depressant effect of the ether reinforces the depressant effect of the large dose of strychnine with death resulting. They therefore propose that the strychninized animal should only be lightly etherized and that a condition of reflex hyperexcitability be maintained with active corneal reflex and the voluntary movements not suppressed, giving only enough ether to abolish tetanus and convulsions.

What seems to be a great advance in the treatment of strychnine poisoning is the introduction of the intravenous administration of some of the newer members of the barbituric acid series. Those which up to the present have demonstrated their value in this condition are the sodium salts of phenobarbital, pentobarbital and amytal. These drugs have been given intravenously in doses of 7–10 grs. repeated in a few hours as may be necessary. The administration of such preparations

is followed by muscular relaxation and sleep and quite a number of cases of poisoning have resulted in recovery when so treated, even when doses of strychnine as high as 5 or 10 grs. had been taken. When these drugs are used it is even a question as to whether gastric lavage is advisable.

Some experimental work has shown that phenobarbital sodium is more efficient as an antidote than amytal sodium, the former acting against four or five lethal doses of strychnine while the latter was effective against only two and a half lethal doses. These results were obtained on rats but naturally there are no comparable figures for the relative efficiency of these two drugs in man.

Preparations.

U. S. P.

Nux Vomica, the dried ripe seeds of Strychnos nux vomica, containing not less than 2.5 per cent of the alkaloids of nux vomica. 0.1 G. (1½ grs.).

Extractum Nucis Vomicæ (about 7 per cent of strychnine) 0.015 G. (¼ gr.).

Tinctura Nucis Vomicæ (about 0.1 per cent of strychnine), 1 cc. (15 mins.).

Strychninæ Nitras (soluble about 1 in 45 of water) and

Strychninæ Sulfas (soluble about 1 in 35 of water), 0.002 G. ($\frac{1}{30}$ gr.).

B. P.

Nux Vomica, the seeds of Strychnos nux vomica, containing not less than 1.2 per cent of strychnine.

Nux Vomica Pulverata, standardized to contain 1.2 per cent of strychnine. 0.006–0.25 G. (1–4 grs.).

Extractum Nucis Vomicæ Siccum (5 per cent of strychnine), 0.015 0.06 G. ($\frac{1}{4}$–1 gr.).

Extractum Nucis Vomicæ Liquidum (1.5 per cent of strychnine), 0.06 0.2 mil. (1–3 mins.).

Tinctura Nucis Vomicæ (0.125 per cent of strychnine), 0.6 2 mils. (10 30 mins.).

Strychninæ Hydrochloridum (soluble in water about 1 in 40), 0.002 0.008 G. ($\frac{1}{30}$–$\frac{1}{8}$ gr.).

Liquor Strychninæ Hydrochloridi (1 per cent of strychnine hydrochloride), 0.2–0.8 mil. (3–12 mins.).

Syrupus Ferri Phosphatis cum Quinina et Strychnina, "Easton's Syrup" (0.025 per cent of strychnine), 2–4 mils. (30–60 mins.).

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II. PICROTOXIN.

Picrotoxin is the best known member of a group of convulsive poisons, which resemble each other very closely in action, but of whose chemistry little is known beyond the fact that they are devoid of nitrogen. It is obtained from the Anamirta paniculata (Anamirta cocculus, Menispermum cocculus), and is a neutral indifferent body. Picrotoxin ($C_{30}H_{34}O_{13}$) may be broken up into picrotoxinin ($C_{15}H_{16}O_6$), which resembles it in its effects on animals, and picrotin ($C_{15}H_{18}O_7$), which is inactive.

Other poisons resembling picrotoxin are *Cicutoxin*, derived from the Cicuta virosa, or water hemlock, and probably from other species of Cicuta, *Œnanthotoxin*, the active principle of Œnanthe crocata, water dropwort, or dead tongue, and *Coriamyrtin*, which occurs in several species of Coriaria, of which the best known is the Coriaria myrtifolia or currier's sumach; *Tutin*, the active principle of the toot or tutu poison of New Zealand, is obtained from other species of coriaria. Some of these bodies are glucosides. *Camphor* and some other volatile oil derivatives, notably the *Thujon* of absinthe, also resemble picrotoxin in their effects, and the same is true of two alkaloids *Samandarine* and *Samandaridine* isolated by Faust from the skin of the newt. Lastly, some poisonous substances inducing symptoms like those of picrotoxin have been formed by the decomposition of the glucosides of the digitalis series.

Symptoms.—The symptoms, which are often somewhat late in appearing, are very similar in all classes of vertebrates. In man vomiting is not infrequently observed, or the first symptoms may be salivation, acceleration of the respiration, and some slowness and palpitation of the heart. Stupor and unconsciousness follow and then a series of powerful convulsions, which, commencing in tonic spasms, soon change to clonic movements of the limbs, which are alternately extended and flexed in contrast with the prolonged contraction under strychnine. The respiration is interrupted during these spasms, but is reinstated during the intervals of quiet and collapse which follow them. The convulsions return after a short pause, and this alteration of spasm and quiet may continue for some time, although the respiration often fails to return after one of the spasms, and fatal asphyxia results.

Similar effects are observed in the lower mammals. After a preliminary stage in which twitching of the muscles and vomiting often occur, and in which the respiration is accelerated while the pulse is slow, a violent emprosthotonic convulsion sets in, but soon changes to clonic movements; these may last for some time, but eventually become weaker and give place to a condition of quiet and depression. An increase in the reflex excitability is noticeable during this interval; the animal is easily startled and occasional twitching of the muscles may be observed. Very soon a second convulsion sets in, and this may be fatal from asphyxia, but the symptoms often continue for an hour or more, violent spasms alternating with periods of depression and collapse. In the frog clonic convulsions are also the chief feature of the intoxication. Very often the animal becomes distended with air during the convulsions, and gives a curious cry in

releasing it. The heart is always slowed and may cease to beat altogether for a time.

Action.—The clonic convulsions of picrotoxin poisoning are different from those of strychnine and other similar bodies, which induce prolonged tonic convulsions, and it was early surmised that the members of this series act on a different part of the **Central Nervous System.** In the fish convulsions arise from picrotoxin after all the nervous system has been removed except the spinal cord. In the frog they persist when all of the brain above the medulla oblongata has been removed, although they are weaker after destruction of the optic lobes; on the other hand, they lose their typical character when the medulla oblongata is removed. In a frog ten times as much picrotoxin is required to produce convulsions after ablation of the mid-brain as is necessary when the mid-brain is intact. In mammals, the convulsions are less typical when the cerebral hemispheres are removed and disappear when the pons is destroyed. The seat of action thus seems to move upward as the higher parts of the central nervous system become more developed, the chief effects arising from the spinal cord and medulla and optic lobes in the frog and from the cerebrum and mid-brain in mammals. It is possible that in man the cerebrum is even more involved in the action than in the lower mammals. In Toot poisoning in man, it is often observed that a confused mental condition is present and that the memory is impaired after the attack and for some days later.

The stimulation of the medulla is seen in the acceleration of the respiration, in the slow pulse, which is due to inhibitory action, in a very marked rise of the blood-pressure, and in the vomiting and salivation. In many animals the reflexes are found to be increased when the medulla is severed from the cord, and this indicates that the spinal cord is also more excitable than normally. Grünwald suggests that the centres controlling the cranial and sacral autonomic nerves are especially susceptible to the action of these poisons.

The action of picrotoxin is confined to the central nervous system and nothing is known of its distribution and fate in the body. Dille has studied the detoxification of picrotoxin in rabbits and showed that in this animal at least the drug is rendered inactive quite rapidly. For example, he found that it was possible to inject repeatedly convulsive doses of picrotoxin at intervals of an hour and a half or two hours with survival of the animal. Traces of a convulsive substance were found in the urine, indicating that the large portion of the poison was disposed of in the body in some other manner than through the kidney. Like other convulsive poisons, it tends to lower the temperature when it is given in quantities insufficient to cause convulsions.

The convulsions of picrotoxin and its allies disappear when chloroform or chloral is administered and in rats are abolished by stramonium. On the other hand, the respiration, weakened by narcotic poisons such as chloral, is accelerated by picrotoxin, the blood-pressure rises, and the sleep is less prolonged. Marshall and his co-workers found that picrotoxin was effective as a stimulant to respiration which had been depressed by various means, operative such as by carotid sinus inactivation and by drugs such as chlorbutanol or avertin. It was less effective against urethane and of no value against ethyl alcohol. In normal unanæsthetized animals it was effective only when given in convulsive doses, but in anæsthetized animals it was active in non-convulsive amounts and according to the view of these workers its action upon the depressed respiration is probably due to the lessening of the depth of narcosis, bringing the animal to a more nearly normal condition. Krantz, Carr and Beck made a study of oxygen consumption during the period of the antagonistic action of picrotoxin against pentobarbital and found that in rats picrotoxin significantly antagonized the depressed oxygen consumption due to the barbiturate, but that it did not accelerate oxygen consumption which had not been previously depressed. They do not believe that the antidotal action of the picrotoxin is associated with the increased oxygen consumption but that it is due to its convulsive action, reducing the depth of the narcosis. Animals and persons are not awakened at once from narcosis by picrotoxin, but coriamyrtin has this effect.

Therapeutic Uses.—It has been proposed to give picrotoxin and coriamyrtin

by subcutaneous injection in cases of narcotic poisoning, and during the past few years the former drug has been used rather extensively following the studies by Maloney, Fitch and Tatum. In these and other studies it was shown quite definitely that animals which had been given doses of the barbiturates, which under ordinary conditions would surely have proved fatal, recovered when treated with picrotoxin.

As a result of these experimental studies the use of picrotoxin has been extended to the clinic and many reports have appeared as to its value in barbiturate poisoning.

Due to the difficulties inherent in the estimation of the value of any special form of antidotal medication in such cases, the place of picrotoxin in the treatment of barbiturate poisoning is still not established in spite of several years' experience in its employment. Some patients have recovered from very large doses of the barbiturates without the aid of picrotoxin, while on the other hand the use of picrotoxin in barbiturate poisoning has seemed to shorten somewhat the period of coma. The drug does not seem to have a direct stimulant effect upon the depressed areas of the brain, as patients receiving even large doses of picrotoxin may still remain in a comatose condition for hours while they exhibit symptoms of the effects of the antidotal drug such as muscular twitching, convulsive movements, and increased respiration. It is this last action, depending upon stimulation of the medulla, which is doubtless responsible for the drug's reputed antidotal effects. It will be seen, therefore, that while the experimental basis for this use of the drug is adequate, its value in the clinical field has not been so firmly established.

An interesting sidelight which has been encountered in connection with this use of picrotoxin is the large doses of the substance which such comatose patients will tolerate. In the normal animal, and probably also in the human patient, it is quite toxic, yet to the patient in coma relatively enormous doses have been given. While as yet no standard dosage has been established, it is the practice in poisoning to give from 5 to 10 mgs. by the intramuscular or intravenous route, such doses being repeated at short intervals, perhaps every half-hour, until signs of stimulation appear. Cases have been reported of patients receiving between 200 and 300 mgs. of picrotoxin in from twenty-four to forty-eight hours. One patient received a total of 2.134 G. in eight days. It will be seen that each case is a problem in itself and as such requires careful individual study.

The safety of the large doses which have been employed is rather unusual and would point to a rapid detoxification of the drug in the body, which view would be supported by the study made by Dille of the fate of picrotoxin in the rabbit.

Picrotoxin has had some reputation in the profuse night-sweats of phthisis, which it diminishes in a certain proportion of cases, probably by increasing the respiration and thus preventing the stimulation of the nervous mechanism of perspiration through the partial asphyxia. Dose $\frac{1}{60}$–$\frac{1}{30}$ gr. in pill or tablet. It is not official.

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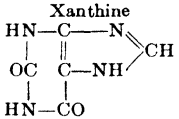
III. CAFFEINE.

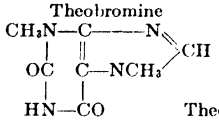
In a number of plants used in different parts of the world to form beverages and condiments, there are found the xanthine compounds, *Caffeine*, *Theobromine* and *Theophylline* (*Theocine*), which have been employed in therapeutics of late years, and have, therefore, acquired a double importance as drugs and as articles of diet. The widespread use of preparations of these by uncivilized peoples is a curious and unexplained fact, especially as they possess neither peculiar taste nor odor to guide in the selection of the plants in which they exist. Besides, caffeine and its allies in moderate quantities induce no marked symptoms, such as follow the use of alcohol, opium or hashish and explain their use among widely separated peoples. On the contrary, the only effects to be observed are a brightening of the intellectual faculties and an increased capacity for mental and physical work. Coffee, the use of which is derived from the Arabians, is the berry of Coffea Arabica and contains caffeine; tea, the leaves of Thea Chinensis, contains caffeine along with theophylline. Cacao, cocoa, or chocolate is derived from the seeds of Theobroma cacao, a tree indigenous in Brazil and Central America, and contains theobromine. In central Africa, the Cola or Kola nut (Sterculia acuminata) is used by the natives, and contains caffeine with small quantities of theobromine. In Brazil, Guarana paste is formed from the seeds of Paullinia sorbilis, and contains caffeine and theobromine, while in the Argentine Republic, Yerba Mate or Paraguay tea (Ilex Paraguayensis) is used to form a beverage which contains a small quantity of caffeine. Another species of Ilex is met with in Virginia and Carolina under the name of Apalache tea or Youpon, and also contains caffeine.

These three principles, caffeine, theobromine and theophylline, are purine derivatives closely related to the xanthine bodies found in the urine and tissues of animals; theobromine and theophylline are dimethylxanthine, and caffeine is trimethylxanthine.

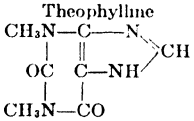
Xanthine



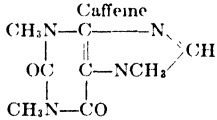
Theobromine



Theophylline



Caffeine



Action.—These all resemble each other in most points of their pharmacological action, although caffeine, and to a less extent theophylline, act on the central nervous system as well as on the kidneys, muscle and heart. Theobromine has comparatively little effect on the central nervous system.

Central Nervous System.—In man, caffeine stimulates the central nervous system, in particular that part associated with the psychical functions. The ideas become clearer, thought flows more easily and

rapidly, and fatigue and drowsiness disappear. Not infrequently, however, connected thought is rendered more difficult, for impressions follow each other so rapidly that the attention is distracted, and it requires more and more effort to limit it to a single object. If the quantity ingested is small, however, the results are of distinct benefit in intellectual work. The capacity for physical exertion is also augmented, as has been demonstrated repeatedly by soldiers on the march, and more recently by more exact experiments with the ergograph. The stimulation of the higher nervous centres is often manifested in the insomnia and restlessness which in many people follow indulgence in coffee or tea late at night. Kraepelin has investigated the effects of caffeine from the psychological point of view, and finds that both tea and coffee facilitate the reception of sensory impressions and also the association of ideas, especially in fatigue, while the transformation of intellectual conceptions into actual movements is retarded. This he regards as due to stimulation of the highest or controlling functions of the brain, caffeine acting on the same parts as are first affected by alcohol and the methane derivatives, but altering them in the opposite direction. The effect of caffeine on the acuteness of the senses has been demonstrated by the greater accuracy of touch under its influence.

Large quantities of caffeine often cause headache and some confusion and in rare cases of special susceptibility a mild form of delirium may be elicited, or noises in the ears and flashes of light may indicate derangement of the special senses. The pulse is quickened, and occasionally palpitation and uneasiness in the region of the heart are complained of. Convulsive movements of the muscles of the hand, and tremor in different parts of the body have also been recorded in some cases. These effects are induced only with difficulty in habitual drinkers of tea or coffee, so that the continued administration of small quantities of caffeine evidently gives rise to some tolerance.

In the lower mammals the injection of large quantities of caffeine is followed by symptoms closely resembling those induced by strychnine. The reflex irritability is remarkably increased, the lightest touch being followed by powerful contraction of almost all the muscles of the body. After a time these contractions occur without any apparent stimulus, and culminate in tonic convulsions which last for several seconds. During these, the respiration ceases because the respiratory muscles are involved in the spasm, and occasionally it fails to be reinstated when the convulsions pass off. In other instances the spasms become weaker and occur at longer intervals; the respiration diminishes in frequency and depth and eventually ceases.

The symptoms induced by caffeine in the lower mammals are due for the most part to its acting on the spinal cord in the same way as strychnine, though small doses may act on the brain, for they often elicit restlessness and timidity without any marked change in the reflex excitability. The centres in the medulla oblongata are also involved in the effects, as is indicated by acceleration of the breathing and occasionally by some slowness of the pulse from action on the vagus centre.

Frogs show no nervous symptoms that cannot be ascribed to action

on the spinal cord, and in some species these are elicited with considerable difficulty owing to the muscular action described below.

On comparing the effects of caffeine and strychnine on the central nervous system, it will be found that while there is a general similarity in their action, the latter causes more marked stimulation of the lower divisions and has less action on the cerebrum in mammals and man. They both produce a general increase in the activity of nerve cells, but caffeine acts more on the psychical, strychnine more on the reflex, functions.

Theophylline resembles caffeine in its action on the central nervous system, while theobromine induces few or no symptoms of stimulation. The monomethyl-xanthines and xanthine itself stimulate the central nervous system in the frog (Schmiedeberg).

The **Muscular** action of caffeine is best seen in the Rana temporaria (grass frog), although it is also induced in other species of frogs; it is less obvious in mammalian muscle and appears to be absent in invertebrates. When a few drops of caffeine solution are injected into the leg of a frog there follows a peculiar stiffness and hardness in the muscles around the point of injection, which slowly spreads to other parts of the body and induces the appearance of rigor mortis. The same effect is observed when teased muscle fibres are subjected to a caffeine solution under a high-power microscope. The fibres contract, become white and opaque, and look stiff and inflexible; the transverse striæ disappear, while the longitudinal become more easily visible. This appearance is due to the death and rigor mortis of the fibres, in which the myogen is apparently formed into myogen-fibrin; the same change occurs when caffeine is added to myogen in the test-tube.

In small quantities caffeine increases the irritability of muscle as well as its absolute strength and extensibility; that is, the muscle contracts on a weaker stimulus and against a greater load than it does normally. The amount of work done before fatigue sets in is also increased, unless when large quantities are applied, when the capacity for work is lessened; and with the first appearance of rigor it ceases to react to stimuli altogether. Sobieranski has stated that in ordinary doses caffeine increases the work done by the human muscles when they are stimulated by electric shocks. The universally recognized effect of tea and coffee in increasing the capacity for physical work and in relieving fatigue has generally been regarded as due to changes in the nerve cells, and it does not seem likely that the action on the muscle contributes to it; for theobromine, which acts strongly on muscle while it has little effect on the central nervous system, fails to remove fatigue and to increase working capacity in the same degree as caffeine.

Circulation.—In man, ordinary doses of caffeine sometimes induce some slowing of the pulse, which apparently arises from a mild stimulation of the inhibitory centre in the medulla; but not infrequently no alteration in the pulse rate is observable. The blood-pressure does not appear to be materially altered by caffeine, a slight rise of 5–10 mm. occurring in individuals, but not very frequently Sometimes palpitation is complained of in excessive tea and coffee drinkers, and this may perhaps

indicate stronger action on the inhibitory centres, but may be due to gastric disturbance. Taylor found the blood-pressure reduced by caffeine treatment in cardiac inefficiency, but this may perhaps arise indirectly from the diuresis reducing the blood volume.

When caffeine is injected in large quantities intravenously in animals, the heart is accelerated considerably without any significant change in the extent of systole and diastole. The acceleration is not dependent on changes in the regulating nerves of the heart, but arises from a direct stimulating action on the cardiac muscle, and especially on that part from which the rhythm originates. Vagus stimulation has less effect than usual, but this is due to increased irritability of the heart and not to partial paralysis of the nerve ends. A similar acceleration is induced by caffeine after division of both accelerator and vagus nerves and after the paralysis of the inhibitory terminations by atropine. Still larger quantities of caffeine injected intravenously in mammals cause weakness

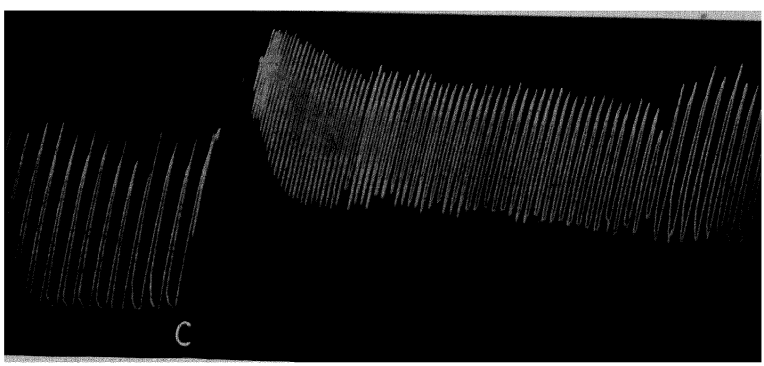


FIG. 23.—Respiration of a rabbit which had been slowed by morphine. At *C*, caffeine was injected intravenously and the respiration was at once greatly accelerated and moved toward the inspiratory position.

and irregularity of the heart. The amounts used in therapeutics in man seem insufficient to induce either the acceleration or the subsequent irregularity observed in animals. The acceleration of the heart is not always accompanied by an increase in the amount expelled per minute (Bock), for the contractions may follow each other so quickly that there is not sufficient interval for the inflow of blood.

The blood-pressure under these large intravenous injections in animals often rises to some extent, but not infrequently shows little alteration, and the increase in the blood-pressure is rarely significant. Caffeine tends to stimulate the vasomotor centre in the medulla, and this would raise the blood-pressure, were it nor for a simultaneous widening of the vessels through a direct action on the walls; this neutralizes in large part the central action on the circulation, so that the blood-pressure shows only slight changes (Sollmann and Pilcher). When very large quantities weaken the heart, the blood-pressure falls to a considerable extent, but if convulsions supervene it may again rise.

When caffeine or theobromine or theophylline is perfused through the surviving heart, the coronary arteries are dilated, and this has led to the use of these drugs in conditions in which narrowing of these vessels is supposed to be present.

In the frog's heart, caffeine in small quantities accelerates and strengthens the beat for a short time, while larger amounts slow the beat and lessen the relaxation of the heart, which finally passes into rigor resembling that seen in the skeletal muscles.

The **Respiration** is quickened by caffeine, owing to a stimulant action on the medullary centre. This is seen in the improvement of the respiration in cases of dangerous poisoning with alcohol, opium and other drugs which prove fatal by depressing the centre, but is much less marked in normal animals. The quicker respiration is often more shallow than before the administration of caffeine, but the total air breathed is increased and the blood is better aërated; the lessened content of carbon dioxide in the blood causes the breathing to be shallower through lessening the stimulus to the respiratory centre. The action of caffeine on the centre is thus diametrically opposed to that of morphine. A broncho-dilator action of caffeine has also been described.

The **Temperature** has been found to be raised by caffeine through its action on the nervous centres and perhaps on the muscles. The increase is, however, comparatively insignificant (0.5–1°C.) and is seen only in cases in which an almost poisonous dose has been used.

The **Alimentary Tract** is not often affected by theobromine and caffeine, but after either of them discomfort and loss of appetite are sometimes complained of, probably owing to changes in the gastric mucous membrane. These are much more marked after even small doses of theophylline, which has been found to produce small hæmorrhages and erosions in the stomach, both in man and animals (Allard).

Kidney.—The most important property of caffeine from a therapeutic point of view is its power of increasing the secretion of urine. It is an everyday experience that strong coffee or tea increases the urine to a much greater extent than the same amount of water, and this has been shown to be due to the caffeine contained in these beverages. Caffeine injected intravenously in the rabbit has a similar diuretic effect, though there is often a short preliminary period in which the secretion is actually diminished; this is especially marked when the injection is made rapidly, and may arise from circulatory changes or perhaps from the action of an overwhelming dose on the kidney itself.

There has been much dispute as to the method by which caffeine causes diuresis and the question is still undecided. There has been a natural desire to attempt to explain the diuretic action by a single factor, though more than one may be concerned, the relative importance of which may vary under different conditions.

According to one view the primary and essential effect of caffeine is to increase the blood-flow through the kidney by provoking dilatation of the renal vessels with or without a rise in systemic blood-pressure. In many experiments the diuresis provoked by caffeine has been found to be closely associated with an increase in blood-flow through the kidney,

but in other experiments this association has proved irregular or absent. The complicated vascular bed of the kidney offers unusual difficulties in determining changes in the rate of flow through it, and Verney is of the opinion that the possibility has still not been excluded that, even in those cases where no increase in blood-flow is revealed by ordinary methods, the diuresis produced by caffeine may be due to a relatively greater dilatation of the afferent than of the efferent vessels to the kidney.

Owing to the lack of parallelism between the blood-flow and urine-flow in the response of the rabbit's kidney to caffeine, Cushny supported the view that caffeine causes diuresis by reducing the resistance to filtration through the glomerular capsule by a specific action on its cells. According to this hypothesis, caffeine in some way alters the permeability of the glomerular epithelium.

Richards and his co-workers have shown that both the number of functionally active glomeruli and their degree of activity are widely variable under experimental conditions and are increased by caffeine. Caffeine may, therefore, increase the secretion of urine by increasing the functioning surface of the glomerular capillaries rather than by altering the permeability of the glomerular epithelium.

In the caffeine diuresis the fluid part of the urine is increased chiefly, but the solids also undergo an augmentation, though not to the same extent. Among the solids the chief increase is seen in the sodium chloride, the nitrogenous constituents undergoing less alteration, although they also rise in amount. According to some observers, caffeine increases the chloride content of the blood and causes a loss of chloride and water from the tissues, the rise of blood chloride preceding the diuresis. It is possible therefore that the diuretic action of the caffeine group is at least partly due to an action on the tissues causing a transfer of their chloride to the plasma with an increase in non-colloidal content which in turn causes the diuresis. The dilution of the urine reduces the concentration of acid, and in addition the alkali of the blood escapes through the kidney in larger quantity, so that the urine in caffeine diuresis is more nearly neutral and is less irritant to the urinary passages than normally.

The excretion of large quantities of fluid in the urine is of course, accompanied by a diminution of the fluids of the blood, but the latter soon recuperates itself from the tissues. If there is any accumulation of liquid, such as œdema, it is drained into the blood to replace the fluid thrown out by the kidney, and caffeine may accordingly be used to remove œdema or dropsy in this way. If no such accumulation exists, the blood draws on the fluids of the intestine and stomach, and their withdrawal leads to the sensation of thirst. As a diuretic, caffeine is distinctly inferior to theobromine; in the first place, because the diuresis is less certain and is often accompanied by nervous symptoms—sleeplessness and restlessness; and secondly, because the increase in the secretion is smaller and lasts for a shorter time. Theophylline acts on the kidney even more powerfully than theobromine.

The diuretic effects of the members of the caffeine group are neither so great nor so uniform as are the effects of the organic mercurial com-

pounds, but they are especially useful in cases of edema associated with severe renal insufficiency and they rarely produce toxic effects.

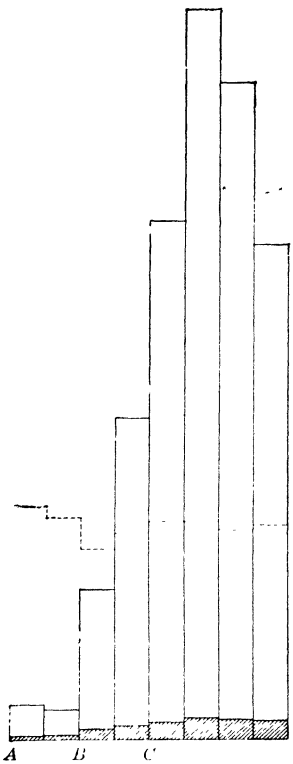


FIG. 24.—Caffeine diuresis in a rabbit. The amount of urine passed in ten minutes is represented by the height of the rectangles. The first of these, *A–B*, represent the normal secretion. At *B* a small dose, and at *C* a large dose of caffeine was injected intravenously, and the secretion is accordingly increased. The shaded part of the rectangles represents the amount of solids in the urine. It will be noted that these are increased but not in the same ratio as the fluid. The dotted line represents the average height of the blood-pressure during each period of ten minutes.

A small amount of sugar is often found in the urine of rabbits after caffeine, and this has been stated to arise from an excess of sugar in the blood; this hyperglycæmia appears to proceed from excessive action of the suprarenal glands from the excitement in rabbits, and has no clinical significance.

Excretion.—Caffeine undergoes decomposition readily in the tissues, and the whole is destroyed or excreted within twenty-four hours. During its passage through the body it loses its methyl groups and first becomes dimethyl- and then monomethylxanthine. Eventually xanthine is formed and this probably breaks up into urea. In the urine are found small quantities of the unchanged drug, accompanied by larger quantities of dimethylxanthine and monomethylxanthine. After theobromine and theophylline some of the unchanged drug is found in the urine along with monomethylxanthine. The uric acid of the urine is not increased by any of these drugs.

The exact order in which the methyl groups are lost in the tissues appears to differ in different animals; in the dog all three isomeric dimethylxanthines are formed from caffeine and appear in the urine after large doses, although theophylline predominates, while in the rabbit and in man paraxanthine is formed in larger amounts. The monomethylxanthines are also excreted in different proportions in different animals, heteroxanthine prevailing in man and the rabbit.

Tolerance.—A certain degree of tolerance is acquired from the prolonged use of coffee, tea, or chocolate, as is shown by the absence of diuresis. Apparently the caffeine and its allies undergo more rapid destruction, but this does not explain the tolerance completely; the tissues also cease to react to their presence after prolonged use.

Theobromine resembles caffeine in its effects except that it has little or no action on the central nervous system. It is often used for its effect upon the heart and has been believed to dilate the coronary

vessels, but the evidence for such an action is not convincing. It is esteemed a more powerful diuretic and generally has no other effects in man. When large doses are taken for some time, it tends to act on the stomach, causing loss of appetite and nausea. Owing to the insolubility and consequent slow absorption of free theobromine, it is generally given in the form of a soluble double salt such as theobromine-sodium-salicylate or theobromine-sodium acetate—the former containing about 47 per cent of theobromine, while the latter contains about 63 per cent. *Theocalcin* is a double salt or mixture of calcium theobromine and calcium salicylate and contains 44 per cent of theobromine. It is less soluble than are the compounds mentioned above, and on that account is said to produce less gastric irritation.

Theophylline or **Theocine** is the most powerful diuretic of the group, but in a number of cases has had a deleterious action on the stomach. Renal irritation and epileptiform convulsions have followed its use. It is more soluble than theobromine and can be given uncombined or in the form of the more soluble double salt, theophylline sodium acetate.

Like the other members of this series, theophylline has been used in cardiac conditions, especially those associated with pain. The drug acts as a cardiac stimulant and in certain cases is said to relieve the pain, but a vasodilator effect upon the coronaries has not been proven.

Theophylline has been shown to diminish greatly the local irritation produced by the injection of the organic mercurial diuretics and also promotes their absorption after they have been injected. The action of theophylline on the mercurials continues after absorption, as the percentage of mercury which is excreted within six hours after the mercurials have been administered is increased very considerably. Not only is the rate of excretion increased, but the maximum rate of excretion comes earlier. The effects of theophylline in relation to the organic mercury compounds have been ascribed, at least partially, to a reduction of the pH of the solution to one more nearly that of the blood, inasmuch as solutions of high pH are necrotic. It is also possible that a compound of the two substances is formed which is sufficiently stable to make the mercury less reactive with the tissues, thus possibly enhancing its absorption (Lehman and Dater).

Aminophylline is a mixture or double salt of theophylline and ethylenediamine, and contains about 70 per cent of theophylline. It is more soluble than other theophylline compounds, but is used for the same purposes, such as its diuretic action and for the relief of cardiac pain. Claims are also made for its effect as a vasodilator of the coronaries, but in this case also the evidence is not very satisfactory.

Therapeutic Uses.—The action of caffeine on the central nervous system has led to its employment in a number of different conditions. thus, in *nervous exhaustion* it may be used to stimulate the brain, and in collapse its action on the respiratory centre has been found of value. In *narcotic poisoning* with failing respiration, caffeine may be used to stimulate the centre and is usually preferable to strychnine or atropine; in opium poisoning more particularly, strong coffee has long been used, but caffeine might be substituted with advantage. Its

stimulant action on the brain, and more especially on the respiration, renders it an antidote in dangerous cases of alcoholic poisoning also. In such conditions it is most effective by hypodermic administration. Some forms of *migraine* and headache are relieved by caffeine, but in others it seems rather to intensify the pain; this effect probably arises from the action on the brain and may be compared to the relief of fatigue; headache is often treated by a mixture of caffeine and one of the antipyretic series, such as phenacetine.

Caffeine has been used in *diseases of the heart* on the supposition that it increases the power of the heart like digitalis; but it has not any action on the heart in such quantities as can be used in therapeutics, and its use for this purpose is not founded on any accurate clinical observations. Its reputation as a cardiac stimulant may probably arise from

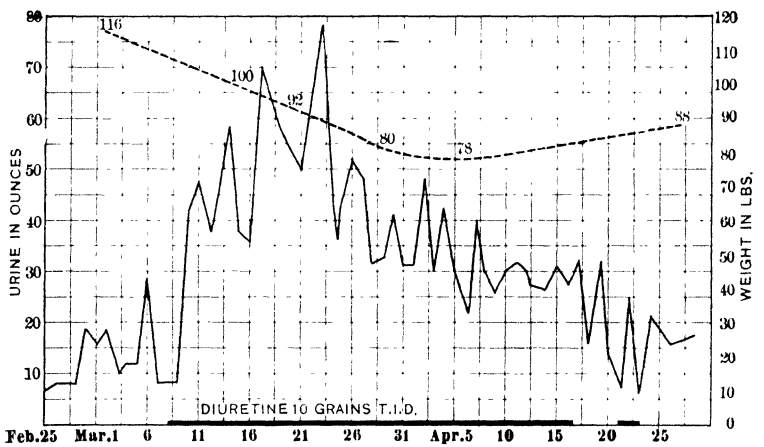


FIG. 25.—Action of theobromine in cardiac dropsy. A case of cardiac dropsy treated with diuretin (theobromine-sodium-salicylate) during the period marked with the black line below. Dose, 10 grs. three times a day. The urine per day in ounces is marked in the unbroken line. The body weight fell continuously (dotted line) as the dropsy disappeared, and when the normal weight of almost 80 pounds was reached, the diuresis became less marked, as there was no longer so much fluid to draw upon.

its efficacy in removing dropsy in heart disease, but this is the result of its renal action and the heart is not affected directly. All members of the caffeine series have been shown in animals to dilate the coronary vessels, but how far these results can be carried over to man is still an open question. As discussed earlier, the administration of theophylline is frequently followed by relief of cardiac pain but whether this is due to vasodilation bringing about a better blood supply to the heart muscle is not clear. Theobromine-sodium-salicylate has been used in *angina pectoris* and is believed to be beneficial especially in early and less severe cases. More recently theophylline-ethylene-diamine (aminophylline) has been used. It may be given orally or by intravenous injection; intramuscular injections may cause local pain. For intravenous injection

an average dose of 0.2 G., dissolved in 10 cc. of water and injected slowly has been recommended. It may cause a transient hyperpnœa.

The members of the caffeine series may under certain conditions produce a copious flow of urine. As has been explained already, theobromine is to be preferred to caffeine as a *diuretic*, and may be used in all cases in which there is a pathological accumulation of fluid in the body, whether of cardiac, hepatic, or renal origin. The results are most brilliant, however, in cases of cardiac dropsy, and here it may be prescribed along with digitalis. It must be emphasized, however, that in these cases it cannot supplant digitalis, but merely aids in the removal of the fluid. In cases of hepatic dropsy, caffeine and theobromine have also proved of service, although here the treatment can only be considered palliative. In renal dropsy theobromine has been used with somewhat variable results; it does not seem to increase the albumin in the urine, but not infrequently little or no diuresis follows its administration. This is only to be expected where the renal cells are in such a condition as to be incapable of responding. Where the disease is less developed, the members of this series produce the usual increase in the secretion. The question of the use of these diuretics in renal disease is still undecided and requires further accurate observation.

Inflammatory effusions do not seem to be lessened to any marked extent by either caffeine or theobromine.

Diuretics have often been recommended to promote the excretion of poisons and toxins from the tissues, and it is possible that they may be of value under certain conditions but usually equally good results may be attained by the administration of large quantities of water given by mouth or as physiological salt solution or one of its substitutes given parenterally.

Coffee and Tea.

Coffee is not used in medicine, but is of great dietetic importance. The coffee bean contains about 1–2 per cent caffeine, and a cup of coffee is equivalent to $1\frac{1}{2}$–3 grs. of caffeine along with some volatile substances, such as furfuralcohol, produced by the roasting; these have been called *Coffeon* and resemble in their action the volatile oils.

Tea contains a larger percentage of caffeine (about $1\frac{1}{2}$–4 per cent), but as less tea is used than coffee, each cup may be considered to contain $1\frac{1}{2}$–3 grs. In green tea there is a considerable quantity of a volatile oil which also passes into the infusion, and the flavor of black tea also arises from volatile substances (*Theon*). Both black and green tea contain about 7 per cent of tannic acid, but this is only extracted slowly, however the bitter taste in tea that has been prepared too long is due to the tannic acid.

The wakefulness and the relief from fatigue which are produced by tea and coffee are undoubtedly due to the caffeine contained in them. On the other hand, the feeling of well-being and comfort produced by coffee after a full meal is similar to the carminative effects of the volatile oils and appears to be due to the local action in the stomach of the volatile constituents of coffee. Apart from this local action, these

volatile bodies seem to have no effect whatever on the economy. There is a widespread belief that excessive tea-drinking disturbs gastric digestion and this has generally been attributed to the tannic acid contained in it. It is not unlikely that the caffeine and theophylline may also play a part in this gastric action by causing irritation of the mucous membrane. Excessive consumption of tea or coffee may produce, in addition to digestive disturbances, increased nervous excitability, tremor, palpitation and insomnia, effects directly due to the caffeine content of these beverages.

It was formerly stated that coffee lessened the tissue change and that it ought therefore to be included among foods, but it has been shown conclusively that far from lessening the metabolism of the body, coffee and tea increase it, the amount of urea and carbonic acid excreted being considerably augmented by their use. This is only to be expected from the increased activity of the nervous centres, which leads to increased movement.

Chocolate contains theobromine (0.5-1 per cent), instead of caffeine, and besides this a large amount of fat (cacao-butter, 15-50 per cent), starch and albumins. The theobromine does not possess the stimulant action of caffeine on the nervous system, and chocolate may therefore be taken where coffee or tea produces wakefulness. The starch and fat are assimilated by the tissues so that chocolate is a true food. Neumann found that cocoa retards the absorption of the proteins and fats of the food, especially those forms of cocoa in which the fat has been partially removed. On the other hand, cocoa with a large percentage of oil delays the gastric secretion and may give rise to a feeling of heaviness and discomfort in the stomach. Its continued use may cause dyspepsia, partly from this cause and partly from theobromine acting on the gastric mucous membrane. The food value of cocoa and chocolate (apart from that of added sugar) is often overestimated. It allays hunger, but this is only in part from its being a food, the local detrimental effect on the gastric mucous membrane tending to lessen appetite.

Preparations.

U. S. P.

Caffeina, as in B. P. 0.2 G. (3 grs.).

Caffeina Citrata, a white powder consisting of a mixture of about equal parts of citric acid and caffeine. It is soluble in 4 parts of water. On diluting this solution with an equal quantity of water, a portion of the caffeine gradually separates out but redissolves on further addition of water. Dose, 0.3 G. (5 grs.).

Caffeina cum Sodii Benzoate, a mixture of equal parts of caffeine and sodium benzoate, dissolves in about its own weight of water. Dose by mouth 0.3 G. (5 grs.), hypodermically 0.2 G. (3 grs.).

Theobromina cum Sodii Salicylate, introduced as Diuretin, is a mixture of sodium theobromine with salicylate of sodium in approximately molecular proportions, and is soluble in 1 part of water. It gradually absorbs carbon dioxide from the air with the liberation of theobromine, becoming incompletely soluble in water. Dose, 1 G. (15 grs.) in powder form or in solution.

Theophyllina, or Theocine, is a white crystalline powder, soluble 1 in 120 in cold water, more soluble in hot. Dose 0.25 G. (4 grs.) in powder or tablets.

THEOPHYLLINA CUM ÆTHYLENEDIAMINA, white or slightly yellowish granules, containing approximately 75 per cent of theophylline, soluble 1 in 5 of water. Dose, 0.1 G. (1½ grs.).

THEOPHYLLINA CUM SODII ACETATE, a white crystalline powder, containing about 60 per cent of theophylline, soluble 1 in 25 of water. Dose, 0.2 G. (3 grs.).

B. P.

CAFFEINA, long, white, silky crystals, without odor, but possessing a bitter taste, soluble in 80 parts of cold water, more so in boiling water. 0.12–0.3 G. (2–5 grs.). Caffeine is best prescribed either in powder or in tablets. It may also be given in water with salicylate of sodium, which aids its solution.

CAFFEINA ET SODII BENZOAS, a mixture of equal parts of caffeine and sodium benzoate, a white, odorless, slightly bitter powder, completely soluble in 4 parts of water. 0.3–1 G. (5–15 grs.); by injection, 0.12–0.3 G. (2–5 grs.).

THEOBROMINA ET SODII SALICYLAS, a white, odorless powder, with sweetish taste; soluble in 1 part of water. 0.6–1.2 G. (10–20 grs.).

THEOPHYLLINA ET SODII ACETAS, a white, odorless powder with bitter taste; soluble in 25 parts of water. 0.12–0.3 G. (2–5 grs.)

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Minor Diuretics.

A large number of vegetable drugs have enjoyed a reputation in the past as diuretics but are passing into disuse. Many of them owe their

position merely to the large quantities of water in which they are taken; and some of them, such as barley, only lend body and taste to water. Others have a slight diuretic action in themselves but are superfluous since the introduction of caffeine and its allies.

Uva Ursi, the leaves of the bearberry, Arctostaphylos uva ursi, and of allied plants, contains two glucosides, *Arbutin* and *Methylarbutin,* along with large quantities of tannin and some inactive bodies. These glucosides are decomposed by the action of acids or of emulsin into glucose and hydroquinone or methylhydroquinone, and this change seems to occur in the body, for some hydroquinone appears in the urine though most of the arbutin is excreted unchanged; it is not unlikely that the decomposition occurs from bacterial action in the intestine.

Uva ursi is found to have some diuretic action and the urine is found to undergo putrefaction more slowly than usual. Both these effects appear to be due to the undecomposed arbutin, though the hydroquinone may reinforce the glucoside in retarding putrefaction.

The urine is often dark in color after uva ursi or arbutin, and this tint deepens when it is allowed to stand, from the hydroquinone undergoing further oxidation; a similar change occurs in carbolic acid poisoning.

FLUIDEXTRACTUM UVÆ URSI is given in doses of 2 cc. (30 mins.).

Buchu, the leaves of several species of Barosma, contains a volatile oil, which is excreted by the kidneys and increases the urine slightly; it also has a feeble antiseptic action in the urine.

PREPARATIONS.

INFUSUM BUCHU CONCENTRATUM (B. P.), 4–8 mils. (60–120 mins.).

INFUSUM BUCHU RECENS (B. P.), 30–60 mils. (1–2 fl. oz.).

Scoparius, the tops of the common broom plant (Cytisus scoparius), contains a resinous substance, scoparin, which seems to act on the kidney as a mild diuretic and accounts for the reputation which broom-tops (no longer official) have long enjoyed. The alkaloid sparteine (see p. 466), which also occurs in scoparius, has no action on the kidney.

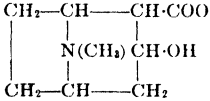
C. LOCAL ANÆSTHETICS.

I. COCAINE.

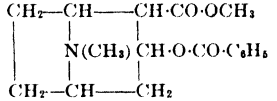
Cocaine is an alkaloid obtained from the leaves of Erythroxylon coca and other species of Erythroxylon. The coca tree is indigenous to Peru, Bolivia, and adjoining areas of South America, where it has been in use for centuries. It has been introduced into India, Ceylon, and Java. The leaves of the coca grown in Peru and Bolivia contain cocaine along with small quantities of other alkaloids, but the Indian coca and still more the Java leaves contain a smaller proportion of cocaine and a larger amount of the less known alkaloids.

Cocaine is methylbenzoyl-ecgonine. On heating it with water, methyl alcohol is thrown off, leaving *Benzoyl-ecgonine,* which may be further broken up into benzoic acid and *Ecgonine.*

Ecgonine.



Cocaine.



Ecgonine is closely related to tropine (p. 502) a constituent part of atropine, differing from it in possessing a carboxyl group.

Many artificial cocaines have been formed by substituting other radicals for the methyl or benzoyl in this formula, and several of these have since been found in the cultivated plant, as for example *Cinnamyl-cocaine*, in which cinnamyl occupies the position of benzoyl in the above formula. Various other alkaloids, such as *truxillyl-ecgonine*, and decomposition products are also present; all of these contain the ecgonine molecule in combination with various acids, and cocaine may be formed from all of them by isolating the ecgonine and combining it with benzoic acid and methyl. These alkaloids are present in the plant in very small quantities compared with cocaine. Another alkaloid which has been found in the Java coca is *Tropacocaine*, which is a combination of benzoic acid and a base $C_8H_{15}NO$.

The most important effects of cocaine are those on the central nervous system and on the sensory nerves.

Symptoms.—The symptoms of cocaine poisoning in man vary a good deal in different individuals. In most cases small quantities produce some excitement, pleasurable or disagreeable. The patient is generally restless and more garrulous than in ordinary life, often somewhat anxious and confused. But very often a small dose is followed by a calm, languorous state, somewhat resembling that induced by small quantities of morphine, but differing from it in there being less tendency to sleep. The pulse is accelerated, the respiration is quick and deep, the pupil generally dilated, and headache and dryness of the throat are complained of. The reflexes may be found somewhat more easily excited than usual and tremors or slight convulsive movements often occur; tonic or clonic convulsions sometimes supervene later, the heart becomes extremely accelerated, the breathing becomes rapid and dyspnœic and may be finally arrested during a convulsion. In most cases the convulsive seizures are entirely absent, however, and fainting and collapse occur, apparently from the rapid absorption of a large dose. The skin is cyanotic and cold, the heart slow and weak; the respiration is very much depressed and death follows from its gradual cessation. Vomiting is occasionally seen at an early stage, but is not by any means common.

In the dog, cat and rabbit the symptoms are invariably those of stimulation of the central nervous system. Soon after the injection the animal shows symptoms of great restlessness and excitement; it seems unable to keep still, the dog at first showing all the signs of affection and excitement which he displays on ordinary occasions on being unchained or taken for a walk, but afterward running continually in a circle and paying but little heed to anything around it. Still later regular convulsions occur, and these are at first clonic, but may afterward become tonic, and then resemble those seen in strychnine poisoning. Even before the convulsions appear the animal seems partially unconscious, and in the intervals between them it lies in an apathetic state, which soon deepens to coma and death from asphyxia.

In the frog a certain amount of stimulation of the central nervous system is often displayed after small doses—increased movement, exaggerated reflexes and occasionally convulsions—but these soon pass

into depression and eventually total paralysis of the central nervous system, while the peripheral nerves still maintain their function.

General Action.—Many of these symptoms point to a stimulant action on the **Central Nervous System**, resembling closely that seen in atropine poisoning. Thus the garrulity which is so often produced by cocaine, indicates augmented activity of the cerebrum, and the increased movement in the lower animals distinctly points to an affection of this part of the brain, for the movements are perfectly coördinated, and, in fact, in the early stages resemble exactly those performed by the normal animal in a condition of excitement. Further evidence of the action of cocaine on the cerebrum is offered by its effects on muscular work. The natives of Peru and Bolivia have used it for centuries to increase their endurance of fatigue. The bearers of the Andes, for example, march for hours and days with very little rest or food when they are supplied with coca leaves to chew. The effects of cocaine on the muscular power and on fatigue have been investigated also by means of the ergograph and dynamometer, and all observers are as one in asserting that much more work can be done after cocaine than before it, and that it has a surprising potency in removing fatigue. As regards mental work, its effects are less known, but on the analogy of caffeine it may be supposed to increase the mental powers also when taken in small quantities. Some travellers in South America relate marvellous tales of its producing feelings of the highest bliss and power, but these have not been confirmed by experience of the action of cocaine in less romantic regions of the globe. Cocaine in small quantities, then, increases the higher functions of the cerebrum, while in somewhat larger doses the stimulant effect spreads to the lower areas and produces a very great increase in movement, accompanied, it would seem, by a depression of the consciousness. At the same time, the coördinating or balancing powers seem affected, so that the animal generally moves in a circle, the symptoms resembling the forced movements often seen in affections of the cerebellum.

The motor areas of the cerebrum have been found to be more easily stimulated by the electric shock when cocaine is injected, though when it is painted on the surface of the brain it lowers the irritability, owing to its being present in too great concentration. Still larger quantities induce convulsions, which are not of spinal origin, but point rather to action on some undetermined part of the hind brain. At an early stage the medulla oblongata is affected, as is shown by the quickened respiration, and the exaggerated reflexes indicate stimulation of the spinal cord, which may be so great after very large doses as to cause convulsions like those produced by strychnine. The action of cocaine on the central nervous system is primarily a descending stimulation, the cerebrum being first affected, then the hind brain and medulla oblongata, and last of all the spinal cord. Perhaps it might be better expressed by saying that after small quantities the chief symptoms arise from the cerebrum, but as the dose is increased those from the lower parts of the central axis tend to become more prominent. After the stimulation there succeeds depression, which follows the stimulation

downward, affecting first the cerebrum and then the lower divisions. The two stages are not definitely divided, however, one part of the cerebrum often showing distinct depression, while another is still in a condition of excessive activity. In some cases, especially in man, when a large dose is rapidly absorbed, the stage of excitement may be very short or apparently absent and the whole course of the symptoms then points to medullary depression.

The **Respiration** after cocaine is much accelerated, owing to central stimulation. At first the depth of the movement is not changed, but as the acceleration progresses the air inspired with each breath gradually becomes less. During the convulsions the respiration is irregular or ceases, but it recovers again in the intervals, until after a very violent paroxysm it fails to be reinstated. In other cases the breathing becomes slower and weaker after a time, and eventually stops from paralysis of the centre. Periodic respiration is frequently seen, of the form generally known as Cheyne-Stokes.

Nicholson and Sobin applied cocaine to the floor of the fourth ventricle and found that it produced apnœa and death, the apnœa being preceded by a period of increased inspiratory tonus. The alkaloid paralyzed the entire central respiratory mechanism, depressing the expiratory phase more readily than the inspiratory. It also depressed or abolished the respiratory effects of inflation and deflation of the lungs, of electrical stimulation of the central end of the vagus and of sensory nerves, and of the intratracheal administration of carbon dioxide.

The **Circulation** is altered by cocaine, owing to its action on the heart and on the vessels. The heart is much accelerated in mammals, while in the amphibians this is less often observed. The quickening has been ascribed to paralysis of the inhibitory terminations, but this seems not to be the case, for stimulation of the vagus slows the heart even late in the poisoning. The heart is accelerated, then, either by direct action on the muscle or by stimulation of the accelerator mechanism. It is often slow before death, but apparently not invariably, and this is probably due to direct action on the muscle. A large dose injected intravenously may cause rapid cardiac failure. In the frog's heart the inhibitory apparatus is paralyzed, the ganglia being affected in the same way as by curare and other drugs.

The vessels are much contracted in the earlier stages of poisoning, and this, together with the increased rate of the heart, leads to a very considerable rise in the blood-pressure. The constriction of the vessels seems due to stimulation of the vaso-constrictor centre, for it is absent after section of the spinal cord. The blood-pressure subsequently falls, from peripheral action, if Anrep's assertion is correct that stimulation of the splanchnic then produces no further rise of pressure. When applied to mucous membranes, cocaine constricts the vessels from direct action on their walls, but there is no reason to believe that these are affected in general poisoning, since the necessary concentration would prove fatal from action on the heart and respiratory centre.

The effects on the peripheral **Nerves and Voluntary Muscles** are disputed, for Mosso states that small quantities increase the strength of

the muscular contractions on electrical stimulation both in man and animals, while others have failed to obtain any such effect.

Cocaine in low concentrations stimulates most forms of smooth muscle, *e. g.*, of the stomach, intestine and uterus, while higher concentrations relax or paralyze the muscle. Considerable variations have been found in different species of animals in the response of smooth muscle in particular organs. The dilatation of the pupil and constriction of the vessels suggested a stimulation of sympathetic nerve-ends, but a wider survey of the actions of cocaine provides no real parallel between its actions and sympathetic stimulation. An interesting effect of cocaine has been described by Tainter, who has shown that it sensitizes the circulation to the action of epinephrine but not to the action of some closely related compounds.

The **Urine** is sometimes said to be increased by cocaine, while in other instances its injection has been followed by total anuria lasting for several hours. This suggests that the action is not a direct one on the kidney, but is caused merely through the changes in the calibre of the vessels.

The other **Secretions** seem rather decreased than augmented, but no very marked effects are produced on them.

The **Temperature** generally rises in cases of poisoning, sometimes as much as 3–5° C., from increased heat formation caused by cerebral action. Langlois and Richet observed that the higher the temperature of the animal the more easily were convulsions produced by cocaine and the more severe their type.

It used to be supposed that cocaine retarded the **Tissue Change** and that less food was required when it was supplied. This was based on the statement of the endurance of the natives of South America when they were allowed to chew coca leaves, and on the discovery that the leaves also allay hunger to some degree. But the increase in the working power is due to the effects on the central nervous system, while the craving for food is probably lessened owing to the cocaine inducing numbness of the sensory nerves of the stomach through its local action. Careful investigation has failed to reveal any significant action on the metabolism of animals except when large quantities were given over several days, when the utilization of the protein and fats was found to be impaired.

A curious effect of cocaine, noted by Ehrlich in mice, is a widespread destruction of the hepatic cells, which become infiltrated with fat and often undergo necrosis.

Some cocaine is **Excreted** by the kidney, the amount (from 1 to 16 per cent) varying in different animals. Part of this variation has been attributed to reabsorption from the bladder.

In a case of poisoning in a woman from the administration of 800 mgs. of cocaine, 429 mgs. were obtained from the urine excreted during the first seven hours, almost one-half of this amount being excreted in the first hour. After the seventh hour none was found in the urine, nor was any found in the blood or in any of the organs after death had occurred five hours later (McIntyre).

Tolerance appears to be attained in man when cocaine is used habitually. In animals repeated injection leads to a cumulation of cocaine in the tissues and hence the animal instead of becoming more tolerant

becomes more susceptible to each new injection. As the concentration in the body increases, the amount in the urine rises (Grode).

Local Action.—Cocaine applied locally in most parts of the body produces a loss of sensation through its paralyzing the **Terminations of the Sensory Nerves,** particularly those conveying impressions of pain and touch. The exact researches of Kiesow show that at first heat and cold are recognized as readily as in the unaffected parts of the body. Cocaine applied to the tongue removes the taste of bitter substances, while sweet and acid fluids lose their taste only partially, and salt is recognized as easily as usual. A solution applied to the nasal mucous membrane paralyzes the sense of smell entirely.

The anæsthesia or insensibility to pain and touch may be induced in any of the mucous membranes that can be reached by cocaine in sufficient concentration—pharynx, larynx, œsophagus, stomach, nose, eye, urethra, bladder, vagina, and rectum. Applied to the unbroken skin its effects are less marked, as it penetrates but slowly through the horny epidermis; but when the epidermis is removed by abrasions or by skin disease, the cutaneous organs of sensation are acted on in the same way as those of the mucous membranes. The deeper sensory terminations can also be acted on by hypodermic injection, which causes a feeling of numbness and the relief of pain in the part. Hypodermic injection reaches not only the nerve terminations of the subcutaneous tissues, but also the finer nerve bundles, and these too are rendered insensible as far as the solution extends to them. The part may therefore be cut into or be subjected to other surgical treatment without pain, as long as the knife does not pass beyond the area to which the drug has penetrated, and numbers of grave surgical operations have been performed under the local anæsthesia produced by cocaine.

Injected into the neighborhood of a nerve trunk, cocaine penetrates into the fibres and induces anæsthesia of the organs supplied by the nerve, and injected into the spinal canal it causes anæsthesia over large areas of the body, sometimes over almost the whole body, from its acting on the posterior roots of the cord. It must be noted that the anæsthesia is only produced by the local application of the drug. The internal administration only leads to a partial loss of sensation in the throat and stomach, and no anæsthesia is induced by its action after it reaches the blood-vessels. The reason for this evidently is that in order to paralyze the sensory fibres and terminations a considerable amount of the drug is required, but much less is necessary to paralyze the central nervous system. Even in the frog the sensory terminations are not fully paralyzed until all symptoms of reflex excitability have disappeared and total paralysis has supervened.

Cocaine applied to a nerve trunk proves to have a distinct selective action, for the sensory fibres fail to conduct sensory impressions, while motor impulses pass through the fibres without difficulty. Similarly, when it is injected into the spinal canal, complete loss of sensation in the lower part of the body follows, but the movements are almost unimpaired. This selection is only relative, for larger quantities paralyze the motor nerve fibres also; no explanation has been given for

this difference in the reaction of the two sets of fibres. When cocaine is applied to the vagus nerve, it paralyzes the cardiac inhibitory fibres, while the afferent impulses to the respiratory centre are more resistant.

When cocaine is applied locally to a mucous membrane it produces, besides a loss of sensation, a feeling of constriction and a distinct pallor and contraction of the vessels, due to a local action on the vessel walls.

The anæsthesia produced by cocaine is comparatively short, but varies with the strength of the solution applied and with the vascularity of the part; as soon as the cocaine is absorbed, the local action disappears and sensation returns.

It has recently been observed that the prolonged muscular cramp seen in various nervous diseases and notably in tetanus, disappears when cocaine is injected into the muscles; this has been attributed to its paralyzing the sensory terminations in the muscle and thus arresting the proprioceptive stimuli which, passing to the spinal cord from the muscle, maintain its excessive activity (Magnus). But if, as is asserted, cocaine also arrests the muscular contractions induced by nicotine, guanidine, etc., even after degeneration of the nerves, this explanation is insufficient and the action must be an antagonistic one on the receptors affected by these substances (Frank).

Cocaine is applied to the **Eye** more frequently than to any other part. It produces local anæsthesia here, along with contraction of the conjunctival vessels, and this is followed by dilatation of the pupil and often by partial loss of the power of accommodation. The dilatation of the pupil is much less than that produced by atropine, and differs from it in several respects. Thus, the light-reflex is preserved, the pupil contracting in bright light and dilating further in the dark; a number of drugs which have little or no effect after atropine, contract the cocainized pupil (pilocarpine, muscarine, physostigmine), while atropine dilates it still further, and cocaine produces some dilatation after the full atropine action has been elicited. The motor oculi nerve is not involved in the action of cocaine, unless very large quantities are applied, when its terminations may be depressed in the same way as by atropine (Schultz). It is often stated that cocaine dilates the pupil by stimulating the ends of the sympathetic nerves in the fibres of the dilator muscle (Fig. 29, page 507) in the same way as epinephrine. But this is not established by any satisfactory evidence, and cocaine differs from epinephrine in not affecting the sympathetic fibres in any other organs. Another explanation of the dilatation has been suggested, namely, that cocaine acts directly on the muscle fibres of the iris and weakens the circular muscle (Kuroda).

The effect on the intraocular pressure seems to vary; it is sometimes reduced, from constriction of the vessels perhaps, while some cases are recorded in which the use of cocaine was followed by an acute attack of glaucoma, which is ascribed to the cocaine relaxing the iris and thus impairing the escape of fluid from the eye in the way which is more familiar under atropine.

General Protoplasmic Action.—The effects of cocaine on the nerve fibres and sensory terminations is so striking that its toxic action on

other forms of living matter is liable to be forgotten. The anæsthetic action is, however, merely an instance of its general toxicity, for if brought in contact with other forms of living matter in the concentration used in anæsthetizing nerve-ends, it is poisonous to all the structures which have been examined. Even concentrations too low to act on the peripheral nerves act on the nerve cells and paralyze them, so that it is impossible to induce a general loss of sensation by cocaine injected into the circulation, and local anæsthesia can be induced only by applying relatively strong concentrations and confining their action to definite areas. The ciliated epithelial cells, leucocytes and spermatozoa become motionless, the cortical nerve cells lose their excitability, and many of the invertebrates are killed by even a short exposure to cocaine. The movements of protoplasm in plants are also retarded or entirely suppressed by this poison, and the process of putrefaction is delayed considerably. In some cases, notably in the higher invertebrates, the final depression is preceded by a stage of increased movements, and vertebrate muscle cells, whether striated or unstriated, are first aroused to greater activity and then depressed and paralyzed (Kuroda). In some other instances, however, cocaine induces only depression and paralysis.

Other examples of this destructive action are also seen in the therapeutic use of cocaine, for the cornea is often rendered cloudy from its application, and its subcutaneous injection is sometimes followed by necrosis. Victims of the cocaine habit often show numerous scars on the arms and legs from this local gangrene, although this is probably often due to unsterilized syringes rather than to the solution.

An interesting analogy has been drawn by Gros between cocaine and the general narcotics of the alcohol-chloroform series, which also have some action on nerve fibres and terminations when they are applied directly. They act in lower dilution on the central nerve cells, however, and do not affect the sensory fibres more than the motor, while the concentration of cocaine which affects the nerve cell is less distant from that which acts on the peripheral fibre and it acts more strongly on the sensory than the motor nerves.

Most of the other natural alkaloids resemble cocaine in many points of their action, as far as they have been investigated, but some of the synthetic compounds present divergences from the general type. Thus a number of them do not produce anæsthesia, and some of them depart entirely from the typical cocaine action.

Truxillyl-ecgonine is often said to be a cardiac poison, but its action on the heart seems to resemble in general that of cocaine. It has, however, a more intense action on muscular tissue, which, like caffeine, it throws into rigor mortis. Its anæsthetic power is very small. Some authorities regard the muscular action of caffeine as an important factor in its preventing fatigue, and the presence of truxilline in the coca leaves might be used to explain the similar effects induced by these, but the quantity is probably too small to have any noticeable action.

Benzoylecgonine is a comparatively weak body which produces symptoms resembling caffeine—increased reflex excitability, muscular stiffness, and rigor—and *ecgonine* is still less active, but elicits similar effects in frogs.

Cocaine Habit.—Since the introduction of cocaine into general therapeutic use, numerous cases of the formation of a habit similar to that of opium or morphine, have been recorded. Some of these have been

due to the attempt to substitute cocaine for morphine in the treatment of chronic morphinism, the treatment often resulting in the development of an irresistible craving for both alkaloids; but, especially since the World War, the illicit use of cocaine, alone or with other narcotics, had increased both in Europe and America until it became a menace, and legislative measures were taken to control it. Habitués usually take cocaine as a snuff, and this practice leads in many cases to ulceration or even perforation of the nasal septum. Some tolerance is produced to it but never so high as to morphine. As a rule, the practice is indulged in more intermittently than of morphine; and the abstinence symptoms are usually less serious than those following the withdrawal of morphine. The symptoms of cocainism generally begin with digestive disorders, loss of appetite, salivation and emaciation, but the more important changes occur in the central nervous system, which apparently undergoes degeneration similar to that seen in chronic morphine poisoning. Sleeplessness, tremors and occasionally convulsions, hallucinations, insanity, and delirium have been noted after long abuse, along with indefinite disturbances of sensation and motion. The cocaine habit seems to lead more rapidly to mental, moral, and physical deterioration than the morphine habit. The treatment of these cases is the withdrawal of the drug, and this can generally be done without the production of any special symptoms, though it is sometimes followed by great depression. This treatment is much facilitated by sending the patient to a special resort, and, in fact, is almost hopeless without his isolation.

Acute Cocaine Poisoning.—The symptoms of acute cocaine poisoning vary very much, depending upon the toxic dose and the rapidity of its absorption. They can, therefore, only be treated symptomatically. In most cases convulsive symptoms are most prominent and may require to be controlled by small quantities of ether or chloroform. Especially when a large dose has been rapidly absorbed, the symptoms may be mainly depressant, and stimulation of the respiration may be necessary. Of course, the stomach ought to be evacuated first of all if the drug has been taken by the mouth. Perhaps the bladder also ought to be evacuated to prevent the possibility of reabsorption of cocaine from that viscus. In cases where cocaine is to be used in surgery as a local anesthetic the previous administration of barbital or of one of the other barbiturates has seemed to lessen to a very considerable degree the likelihood of poisoning.

II. SUBSTITUTES FOR COCAINE.

In the early days of local anæsthesia with cocaine, a number of fatalities occurred from its use. These have become less frequent with increasing experience of the margin of safety within which it can be used, but nothing can alter the fact that it is a highly toxic substance. It has also the serious drawback of habit-formation. These defects have prompted the search for less dangerous substitutes. If adequate substitutes could be found, which do not give rise to habit-formation, there would be no excuse for the manufacture of cocaine and the illicit

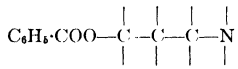
use of cocaine could be eliminated at its source. The local anæsthetics are used for a great variety of purposes, and it is not necessary that cocaine should be completely replaceable by one substitute. It would be sufficient if for each different use of cocaine some less dangerous and equally efficient substitute could be found.

In the search for substances to replace cocaine, over one hundred local anæsthetics have been introduced, but only a few have been widely used, and of these only the most important can be considered here.

1. **Tropacocaine,** a natural alkaloid found in Java coca leaves, is the benzoic ester of a base, pseudotropine.

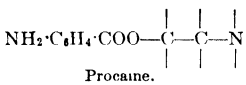
2. **Eucaine** or **Benzamine,** trimethyl-benzoyl-hydroxy-piperidine, was the first important synthetic substitute for cocaine.

Cocaine and eucaine resemble one another structurally in that both possess the grouping

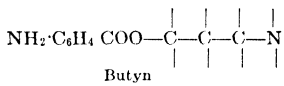


3. **Procaine** or **Novocaine** ($NH_2 \cdot C_6H_4 \cdot COO \cdot C_2H_4N(C_2H_5)_2$).

4. **Butyn** ($NH_2 \cdot C_6H_4 \cdot COO \cdot (CH_2)_3 \cdot N(C_4H_9)_2$) is closely related to procaine. These possess the groupings



Procaine.



Butyn

Procaine is probably the safest of the local anæsthetics and when injected it acts promptly and is non-irritant. Its action is usually prolonged by the addition of epinephrine to the solution. It does not penetrate well when applied to mucous membrane so that it is usually given by hypodermic injection. The hydrochloride of procaine is the salt usually employed although the borate is also used. The molecule of the latter salt is heavier than that of the hydrochloride and as it contains only 51.8 per cent of the base it has to be given in larger doses than the hydrochloride.

Procaine is destroyed mainly by the liver; although the other tissues possess some detoxifying action they act less promptly and less efficiently. Injected into the normal dog it quickly disappears from the blood, is converted into non-toxic end-products which are eliminated by the kidneys.

The toxicity of procaine for white mice increases rapidly with increase in the surrounding temperature. At 20° C. the M.L.D. is about 800 mg. per kilogram of body weight; at 43° C. it is about 200 mg., and with comparable doses death comes much earlier at the higher temperature.

Butyn was introduced as a substitute for cocaine for surface anæsthesia, particularly for use in the eye, nose and throat. It is said to be more powerful than cocaine so that a smaller quantity is required, and its action is prompt and well sustained. It does not produce drying of the tissues nor does it dilate the pupil nor contract the blood vessels. Solutions, usually 2 per cent, may be sterilized by boiling.

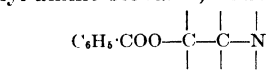
5. **Pontocaine** differs from procaine in that one of the amino hydrogens of the aminobenzoate group is replaced by a butyl group and the two ethyl groups of procaine are replaced by two methyl groups.

Pontocaine resembles procaine in its action but is more efficient when applied to mucous membranes so that it can be used in the eye, nose or throat. For the eye a 0.5 per cent solution is used and a 2 per cent in the nose or throat. Ten to 20 mg. in a 1 per cent solution may be used for special anæsthesia.

6. **Larocaine** hydrochloride differs in structure from procaine in that it has a propanol group in place of the ethanol group with two methyl groups attached thereto. It is said to be efficient as an anæsthetic whether applied locally to the mucous membranes or injected. The anæsthesia is produced rapidly and is well sustained. A 2 to 5 per cent solution is used in the eye and a 5 to 10 per cent solution in the nose or throat.

7. **Stovaine,** the hydrochloride of dimethyl-amino-benzoyl-pentanol and

8. **Alypin,** dimethyl-amino stovaine, both possess the grouping



All of these show some structural resemblance to cocaine itself, and a benzoyl group is present in them all. Many simpler benzyl derivatives have also been found to have a local anæsthetic action. This is displayed even by *Benzyl Alcohol* ($C_6H_5CH_2OH$) which has been tried as a local anæsthetic. Some near derivatives of it have been in use for a longer time, the best known being the Orthoforms.

9. **Phenacaine** (Holocaine) $CH_3\,C\langle^{N\cdot C_6H_4\,OC_2H_5}_{NH\cdot C_6H_4\,OC_2H_5}$ Phenacaine acts much like cocaine but more quickly, a 1 per cent solution applied to the eye producing anæsthesia in a few minutes.

10. **Orthocaina** (B. P.) ($NH_2\cdot HO\cdot C_6H_3\cdot COOCH_3$), is almost insoluble in water.

11. **Aethylis Aminobenzoas** (U. S. P.) **Benzocaina** (B. P.) (Anæsthesine) ($NH_2\cdot C_6H_4\cdot COOC_2H_5$) and propæsine ($NH_2\cdot C_6H_4\cdot COOC_3H_7$) are closely related to orthoform and are also insoluble.

12. **Nupercaine,** introduced as percaine, is 2-butyloxyquinolinecarboxylic acid-4-diethylethylenediamide. It acts like cocaine when applied and like either cocaine or procaine when injected. It is much more toxic than cocaine when injected intravenously into animals and is more active as an anæsthetic than either cocaine or procaine when given subcutaneously. It is said to have caused necrosis of the tissues.

13. **Diothane** (piperidinopropanediol-di-phenylurethane) acts much like cocaine but its action is claimed to be more prolonged.

14. **Apothesine** hydrochloride is the hydrochloride of diethylaminopropyl cinnamic acid. It resembles procaine more closely than cocaine in that it is more effective when injected into the tissues than when applied to the surface. It acts somewhat more slowly than procaine and has to be used in somewhat stronger solutions. Its solutions are not injured by boiling.

15. **Metycaine** [(2-methylpiperidino)-propylbenzoate] produces local anæsthesia whether applied by injection or locally to mucous membranes. Its toxicity when it is injected subcutaneously is comparable to that of procaine. For spinal anæsthesia it probably ranks next to procaine for safety. It is more potent than procaine and is also a good surface anæsthetic. A 1 per cent solution is said to act more quickly than a 1 per cent solution of procaine, and the anæsthesia is more profound and more prolonged. For use in the eye a 2 per cent solution is used, while a 2 to 10 per cent solution is used in the throat or nose.

Differing in chemical composition from any of the foregoing, quinine and many of the derivatives have been found to possess a local anæsthetic action, and of these **Quinine-urea** has been chiefly used for this purpose.

In comparing the advantages and drawbacks of the various local anæsthetics, the chief points to be considered are, the general toxicity on absorption, the power of producing local anæsthesia, the extent to which the paralysis of the nerve-ends is attended by irritation or injury of other cells in the neighborhood, and the local action on the vessels. The solubility of the substance is naturally also of importance, as is the power of penetrating the tissues.

The toxicity of a local anæsthetic varies with the animal used and with the method and rate of injection, and therefore, in a comparison of the toxicity of different anæsthetics, those factors have to be taken into account. For example, cocaine is more than five times as toxic as procaine by subcutaneous injection but less than four times by intravenous injection. This difference is partly due to the fact that procaine is destroyed by the liver, whereas cocaine is not. When given by subcutaneous injection, owing to slower absorption, time is given for destruction of procaine by the liver with a consequent diminution in its toxicity. In whatever way it is administered procaine is less poisonous than cocaine, but if procaine be injected into the tissues and accidentally gains entrance into a vein, then its toxicity approximates more nearly to that of cocaine.

For these reasons it is possible here to give only an approximate comparison of the relative toxicities of the more important local anæsthetics. By subcutaneous injection butyn and alypin are about equally toxic with cocaine, whereas eucaine and procaine, metycaine and to a less degree stovaine are markedly less toxic than cocaine. The toxic symptoms produced by them very closely resemble those produced by cocaine, but none of them have so far proved to give rise to habit formation.

In regard to local anæsthetic activity, butyn is about equal to cocaine, while nupercaine is said to be more active. Most of them have a more transient anæsthetic action than cocaine, although with some of them, such as diothane and metycaine, the anæsthesia is said to be longer than from cocaine. Eucaine, nupercaine, tropacocaine, stovaine, and especially alypin have an irritant and devitalizing action on the tissues. Procaine is especially free from this. Cocaine alone causes a shrinkage of the tissues due to contraction of the vessels; eucaine and especially butyn cause actual hyperæmia.

None of them penetrate mucous membranes so readily as cocaine, although metycaine is quite efficient when used in this manner. The effect of butyn so applied is less lasting than that of cocaine and is often followed by pain. Nupercaine seems to penetrate mucous membranes well and its effect is prolonged. Procaine produces at best delayed and incomplete anæsthesia when applied to mucous membranes and is seldom used for surface anæsthesia. All of them can be sterilized by boiling, except cocaine, which is destroyed by prolonged boiling.

The action of the local anæsthetics is quantitatively modified to an important degree by *simultaneous use of epinephrine.* By locally contracting the vessels, epinephrine produces the following effects. It relieves local congestion and lessens hæmorrhage, effects which are sometimes desirable. The contraction of the vessels also delays the absorption of the local anæsthetic. This allows longer time for excretion of the drug or for its destruction in the body and so diminishes its toxicity. By maintaining the concentration of the anæsthetic at the point of application this not only prolongs the local anæsthesia but renders this possible with a smaller quantity of the anæsthetic. It must be remembered, however, that epinephrine, especially if it should gain entrance into a vein, is a very powerful poison, and it must be used with caution.

Therapeutic Uses of the Local Anæsthetics.

The therapeutic uses of cocaine and its allies are almost all dependent on their anæsthetic action. Cocaine has been used in asthma and hay fever, but this use is dangerous from the tendency to the habit being formed. One of the advantages of the substitutes for cocaine is that none of them seem liable to produce habit-formation.

Only the general principles of local anæsthesia can be discussed here, and of these one is that the dangers of cocaine poisoning are sufficiently great and so unforseen that less poisonous anæsthetics should be substituted where possible. It will be convenient to discuss the various ways in which local anæsthetics are employed and to indicate which of them have been found most suitable for each purpose.

Surface Anæsthesia.—When applied to a surface, local anæsthetics can produce loss of sensation by their paralyzing action on afferent nerve-ends, provided that they can get access to these. They have little power to penetrate the *unbroken skin;* a 10 per cent ointment of cocaine produces only a slight dulling of sensation of the skin but no complete local anæsthesia. For *wounds* and *ulcers,* where there is no horny epithelium to oppose penetration, insoluble local anæsthetics such as the Orthoforms have occasionally been used, but they are liable to produce severe irritation and even sloughing, and they must be used with the greatest care if at all. Anæsthesine and propæsine have also been recommended for this purpose. Soluble anæsthetics are too easily absorbed and their action is too transient for this kind of use.

Many of the local anæsthetics penetrate *mucous membranes* readily, others do not.

Cocaine is still unrivalled in its power of penetrating the mucous

membranes, and this is now its chief field of usefulness; the hydrochloride is dissolved in 0.8 per cent sodium chloride solution, or better in Ringer's solution, in order to avoid the effects of water on the tissues. In ophthalmic surgery it is used very largely both during operation and to alleviate pain, and occasionally to constrict the vessels of the iris in inflammatory conditions. For complete anæsthesia a 4 per cent solution may be employed, while to allay pain one of 1–2 per cent is all that is necessary. The anæsthesia is of short duration, generally setting in after five to seven minutes and passing off twenty to thirty minutes after the application of the drug. Eucaine 2–5 per cent is not so reliable. Phenacaine has a considerable vogue in ophthalmic practice. Usually a 1 per cent solution is employed. Occasionally cocaine, especially in strong solution, produces a certain amount of opacity of the cornea, and wounds heal less readily and irritant antiseptics are more dangerous with cocaine than without it. This arises from the general toxic action of cocaine on living matter, which tends to lessen the resistance of the tissues with which it comes in contact. The usual explanation given that cocaine paralyzes sensation in the cornea, and thus prevents the reflex winking which removes foreign bodies from the surface and keeps the eye moist, is obviously insufficient, as the anæsthesia is of but short duration. The dilatation of the pupil produced by cocaine is much less complete than that under atropine, and can only be taken advantage of in diagnosis by using a very dim light, as the pupil contracts in bright light almost to its normal size. On the other hand, cocaine is less injurious in glaucoma and the dilatation can be removed at once by the instillation of a few drops of physostigmine.

In the nose, throat and larynx, cocaine is used in a solution of 4 per cent, either painted or sprayed on the surface or soaked in gauze with which the nose is packed; anæsthesia is obtained with greater difficulty than in the eye, and a considerable number of fatalities have occurred from its use in nose and throat work; this is mainly due to the use of strong solutions, such as 10 or even 20 per cent to saturate gauze. Where possible, one of the substitutes should be given by submucous injection. It is recommended that for the nose or larynx cocaine should not be used in a concentration above 10 per cent or in a total quantity above $1\frac{1}{2}$ grs. Eucaine has also been painted or sprayed in 5–10 per cent solution but is less efficacious than cocaine. More recently nupercaine (percaine) has been used for producing surface anæsthesia, and many authorities regard it as an efficient substitute for cocaine for this purpose. In the *urethra*, *rectum* and *vagina*, cocaine (1 to 2 per cent) is used either as an anæsthetic or to relieve pain temporarily, but many cases of poisoning have arisen from urethral injection where trauma or stricture existed, so that care has to be exercised.

Terminal Anæsthesia.—When cocaine is injected under the skin or under a mucous membrane, it produces local anæsthesia by paralyzing the afferent nerve-ends or the terminal nerve fibrils. In this case absorption may be rapid and full opportunity is given for the drug to exert its general toxicity. Cocaine may be used especially in combination with epinephrine, but for this purpose it should be replaced by

procaine. The latter does not penetrate sufficiently well to be useful for surface anæsthesia, but this lack of penetrating power does not affect its action when injected. When given with epinephrine its anæsthetic action is sufficiently prolonged for most purposes and its toxicity is markedly reduced. For this form of anæsthesia it is the safest and best of the local anæsthetics.

The local anæsthesia produced by cocaine or procaine, even when epinephrine is added, does not last much over an hour at most. This is sufficient for many purposes but not for relieving pain after many operations. Especially in operations for hæmorrhoids quinine-urea has been widely used, in concentrations of 0.5 to 1 per cent. This solution causes irritation and transient pain on injection, followed by local anæsthesia which may last for many hours or even several days. Quinine has little selective action on sensory nerves and the concentrations required to produce anæsthesia have an injurious action on the tissues and may even produce necrosis. Quinine-urea has therefore to be used with care.

For many years after its introduction as a local anæsthetic in 1884, the use of cocaine was practically limited to minor operations in the nose and throat and to ophthalmic surgery, few general surgeons venturing on its application except in quite minor operations which required only a small incision and no manipulation; for this purpose cocaine was injected into the site of operation, but its place has been taken by less poisonous members of the group, which are equally efficacious when injected under the skin and are less likely to cause general poisoning. Within the last few years, however, the use of local anæsthesia has undergone a wide extension, so that almost all the major surgical operations have been performed under it, and it has now become a rival of ether and chloroform. Occasionally partial local anæsthesia is combined with the administration of small quantities of chloroform or ether or one of the barbiturates which are insufficient to produce complete unconsciousness, but cause a numbing of the sensation, which, together with the local action, permits of a painless operation. Premedication with morphine or with some of the synthetic hypnotics or analgesics is said to intensify the local anæsthetic action of cocaine and its substitutes. At first strong solutions were injected to prepare the way for the knife, each step forward in the operation being preceded by an injection to induce anæsthesia of the layer of tissue to be incised. But this method, which was advocated by Reclus, is now scarcely used except for minor operations in which a single injection is sufficient.

A more satisfactory method of local anæsthesia for operative purposes was introduced by Schleich under the name of *infiltration anæsthesia*. A large quantity, generally about 100 cc. of a solution containing 0.1 per cent of procaine, 0.001 per cent of epinephrine, and 0.8 per cent of sodium chloride is allowed to permeate the tissues through a fine hypodermic needle. Only very slight pressure is required and the whole of the surrounding structures become swollen and œdematous and can be cut into without pain. Much of the fluid escapes through the incision and no symptoms of poisoning arise.

Another method (*regional anæsthesia*) is the injection of cocaine in 1 per cent solution, or preferably procaine in 2 per cent solution, into the immediate neighborhood of the nerve supplying the part to be operated on. Complete local anæsthesia is obtained, and shock is less liable to occur than when general anæsthesia is induced (Crile). This method has been used extensively in operations on the foot and hand, for which it is admirably suited; it can also be adapted to other parts of the body. The local action in both infiltration and regional anæsthesia may be augmented and the danger of general poisoning lessened by retarding the circulation in the part to be operated on. This may be done by applying an Esmarch bandage above it when a limb is involved, but the best results are obtained by using a solution of epinephrine along with the anæsthetic.

Another method of inducing anæsthesia in a limb was by means of *venous* injection. The limb is emptied of blood by elevation and bandaging and a tourniquet is applied above the point where the injection is to be made; the anæsthetic is now injected under some pressure into a superficial vein peripheral to the tourniquet and quickly penetrates by anastomosis throughout the veins of the limb, paralyzing sensation wherever it reaches. After the operation the tourniquet is slowly loosened and the anæsthesia disappears with the anæmia. The same strength of solution is used as for infiltration anæsthesia, and the quantity is too small to have any effect when it reaches the general tissues. Intra-arterial injection has also been employed in the same way in bloodless limbs. These procedures are rarely used today.

After it was found that the nerve impulses from the periphery to the central nervous system could be blocked by the injection of cocaine into the peripheral nerves, the next step was to obstruct them higher in their course by applying it to the spinal roots (*subarachnoid* or *intraspinal anæsthesia*). The first to attempt this was Corning of New York, but the development of the procedure is due to Bier and Tuffier. A long, hollow needle was passed into the spinal canal between the laminæ of the lumbar vertebræ and 1 cc. of a 2 per cent solution of cocaine hydrochloride was injected after the withdrawal of an equivalent amount of cerebrospinal fluid. The actual amount of cocaine injected was thus 0.02 G. ($\frac{1}{3}$ gr.). Under cocaine accidents were so numerous that the method was abandoned by conservative surgeons and though it received a new lease when procaine was substituted for cocaine, its use today is not very common except in certain clinics. Within a few minutes numbness begins, generally in the feet at first, but sometimes in the lower part of the trunk; it spreads upward rapidly until sensibility to pain is lost everywhere below the diaphragm and sometimes in the thorax; in some cases even the head has been found anæsthetized. The sensations induced by warmth and cold are less quickly affected, touch is preserved to some extent and the limbs can be moved readily, though the movements are carried out more slowly than usual; the consciousness is unimpaired. This condition lasts from one-half hour to one hour and then sensation returns gradually. In the beginning of the action some muscular twitching is often seen, and the muscles are never as relaxed as

they are under chloroform or ether. Vomiting occurs in a certain proportion of cases either during or after the operation, and persistent headache is often present. A more dangerous effect is the onset of collapse with very low blood-pressure and all the symptoms of cerebral anæmia. This not infrequently fatal accident is attributed to the anæsthetic paralyzing the vasomotor roots of the splanchnic nerves within the spinal canal (Smith and Porter). The anæsthesia from the intraspinal injection arises from action on the posterior nerve roots and not on the cord itself. The cerebrospinal fluid has been found to contain a large number of polynuclear leucocytes after the injection and resumes its normal limpid character only after several days. This method of anæsthesia has been used in a large number of operations, some of them of the gravest nature; it has also been substituted for general anæsthesia in labor. For spinal anæsthesia, procaine or nupercaine (percaine) is most widely used.

Of these methods, Schleich's infiltration has been most widely adopted and is admirably suited for minor operations. It is the safest method available for most of these, for the amount of anæsthetic injected is not sufficient to induce poisonous symptoms, and much of this escapes by the incision. It requires some experience to induce complete insensibility to pain by this method and the operation has to be interrupted at intervals to permit of further injections. Some headache and nausea are occasional sequelæ. When general anæsthesia is contraindicated, infiltration may be adopted in major operations, while on the other hand it is often contraindicated in minor operations where there is any possibility of complications, or where the anxiety and nervousness of the patient are likely to interfere with the proceedings. Perhaps to a greater extent than with other methods of anæsthesia, the safety and efficiency of spinal anæsthesia depends upon the skill and experience of the anæsthetist. It is usually recommended when special circumstances contraindicate the general anæsthetics, and operation is imperative. Persistent and severe headaches occur occasionally after spinal anæsthesia, and nausea is not uncommon. Fall of blood-pressure is frequent, for which some advocate ephedrine or epinephrine. More rarely serious circulatory or respiratory failure occurs during spinal anæsthesia, in some cases at least apparently due to idiosyncrasy.

Preparations.

U. S. P.

Cocaina, an alkaloid ($C_{17}H_{21}O_4N$) obtained from the leaves of Erythroxylon coca and other species of Erythroxylon, forming colorless crystals with a bitter taste followed by numbness; almost insoluble in water, soluble in alcohol. Dose, 0.015 G. ($\frac{1}{4}$ gr.).

Cocainæ Hydrochloridum ($C_{17}H_{21}O_4NHCl$), colorless, crystals very soluble in water and alcohol; prolonged boiling of watery solutions causes the alkaloid to decompose. Dose, 0.015 G. ($\frac{1}{4}$ gr.).

Procainæ Hydrochloridum (Novocaine), colorless crystals, freely soluble in water.

Eucainæ Hydrochloridum, colorless crystals, soluble 1 in 30 in water.

Phenacainæ Hydrochloridum (Holocaine) small colorless crystals, soluble 1 in 50 of water, freely soluble in alcohol.

QUININÆ ET UREÆ HYDROCHLORIDUM, colorless crystals freely soluble in water. Dose, hypodermic (one dose daily), 1 G. (15 grs.).

ÆTHYLIS AMINOBENZOAS, Benzocaine, Anæsthesine. Dose, 0.3 G. (5 grs.).

B. P.

COCAINA, methyl benzoylecgonine, an alkaloid obtained from the leaves of Erythroxylum coca and other species of Erythroxylum, or by synthesis from ecgonine. Dose, 0.008–0.016 G. ($\frac{1}{8}$–$\frac{1}{4}$ gr.).

COCAINÆ HYDROCHLORIDUM. Dose as of Cocaina.

LAMELLA COCAINÆ, each contains $\frac{1}{10}$ gr. of the hydrochloride.

OCULENTUM COCAINÆ, 0.25 per cent.

TROCHISCUS COCAINÆ ET KRAMERIÆ ($\frac{1}{20}$ gr. of the hydrochloride in each lozenge).

PROCAINÆ HYDROCHLORIDUM (Novocaine). Dose, 0.03–0.12 G. ($\frac{1}{2}$–2 grs.). By subcutaneous injection up to 1 G. (15 grs.), by intrathecal injection up to 0.15 G. ($2\frac{1}{2}$ grs.).

AMYLOCAINÆ HYDROCHLORIDUM (Stovaine), colorless crystals, freely soluble in water. Doses, by mouth and by subcutaneous injection, 0.02–0.05 G. ($\frac{1}{3}$–$\frac{3}{4}$ gr.); by intrathecal injection, 0.02–0.1 G. ($\frac{1}{3}$–$1\frac{1}{2}$ grs.).

ORTHOCAINA, Orthoform-new, a white crystalline powder, sparingly soluble in water. Dose, 0.1–0.2 G. ($1\frac{1}{2}$–3 grs.).

BENZOCAINA, Anæsthesine, a white crystalline powder, soluble 1 in 2500 in water. Dose, 0.3–0.6 G. (5–10 grs.).

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D. CURARE GROUP.

Curare, curara, woorara, urari or woorali, is an arrow poison used by the natives of South America, who prepare it by extracting the bark of plants of the genus Strychnos, such as S. toxifera.

Boehm described the types of curare—(1) tubocurare, contained in bamboo tubes, (2) calabash curare, in gourds, and (3) pot curare, in small earthenware pots. Tubocurare yields two alkaloids: (*a*) Tubocurarine ($C_{38}H_{44}O_6N_2$), which possesses the typical actions of curare, and (*b*) Curine ($C_{36}H_{38}O_6N_2$), which has only a weak curariform action, in addition to other actions on the heart and central nervous system. Curarine, obtained from calabash curare, has an action similar to, but stronger than, tubocurarine. It has been obtained directly from Strychnos toxifera. According to Boehm, pot curare contains at least three alkaloids: protocurarine ($C_{19}H_{23}O_2N$), which has a strong curare-like action; protocurine ($C_{20}H_{23}O_3N$), which has a weak action, and protocuridine ($C_{19}H_{21}O_3N$), which is non-toxic.

Curine is isomeric with bebeerine, an alkaloid found in Pareira root, which also has a weak curare-like action.

Action.—The chief effect of curare is the arrest of all voluntary movements through an interruption of the connections between the peripheral nerves and the striated muscle fibres. In the mammal the muscles give way one after the other until the animal lies helpless on the ground. It can still move its limbs, but cannot recover its ordinary position, and soon the limbs become totally paralyzed and the respiratory movements alone persist, although they too are slow, weak and jerky. Eventually the respiration ceases also, and asphyxia follows but is not betrayed by the usual convulsions owing to the motor impulses being unable to reach the muscles. The heart soon fails from the asphyxia and not through the direct action of the poison.

In the frog similar symptoms are seen, but here the arrest of the respiration is not necessarily fatal, as the skin carries on the exchange of gases, and recovery not infrequently occurs after two or even five days of complete paralysis. The cause of the curare paralysis was demonstrated by the classical researches of Claude Bernard and Kölliker. If the sciatic nerve of the frog be stimulated during the paralysis no movement follows, but if the artery of one leg be ligatured before the application of the poison this limb remains unparalyzed and reacts to reflex irritation, while the rest of the body is perfectly motionless. These facts can be interpreted only in one way; the paralysis is peripheral and not central, and may, therefore, be due to action either on the muscle, the nerve trunks, or the intermediate structures. That it is not due to the muscle is shown by the fact that direct stimulation causes the same movement as usual. On the other hand, in the experiment in which the artery is ligatured, stimulation of the nerves above the ligature, that is, where the poison has access to the nerve fibres, causes contraction, so that the nerve trunks do not seem affected. This may be shown in another way; if a nerve-muscle preparation be made and the nerve be laid in a solution of curare, contraction of the muscle still occurs on stimulation of the nerve, but if the muscle be laid in the curare solution stimulation of the nerve has

no effect, while direct stimulation still causes contraction. Curare, therefore, acts on the connection between the nerve and muscle within the muscle itself and paralyzes it without previous stimulation.

Action on Nerve-ends.—Since the investigations of Bernard and Kölliker, the action of curare has been known to be peripheral, and it has been tacitly accepted that it could be localized in the anatomical structure known as the motor end-plates. Of late years facts have been accumulating which seemed difficult to reconcile with this view, and Langley shook its foundations by showing that curare continues to act after the muscle plate has lost its function. For the action of nicotine on the muscles is opposed by curare, not only in normal muscles, but also in those in which the nerves and nerve-endings have degenerated through section. The action of curare here must be exerted, not on the end-plate, but on some undegenerated substance, which has been termed the myoneural junction and which normally serves to transfer the nerve impulse, either directly or by means of a chemical intermediary substance, from the nerve-plate to the actual contractile substance of the muscle.

The condition of "paralysis" produced by these poisons is superficially analogous to that termed by physiologists "fatigue." It is known that on stimulating a nerve rapidly by electric shocks, or otherwise, the muscle at first contracts with every stimulation, but eventually ceases to respond, owing to "fatigue" of the nerve ends, that is, to their inability to transmit impulses from the nerve to the muscle. If now the response to nerve stimulation of a muscle to which a minute quantity of curarine has been applied, be compared with that of a normal one, it is found that the poisoned one ceases to respond much sooner than the other – *i. e.*, its nerve-ends become inactive much sooner. The more curare is applied the sooner does it fail, until at last no response at all can be elicited from it. The "paralysis" of the nerve terminations by curare then has been compared to physiological "fatigue," and other conditions of "paralysis" are also analogous to those produced by overstimulation, though the exact condition of the paralyzed organ may not be the same as the fatigued one. Thus there is some reason to suppose that in the curarized terminations the substance which is normally concerned in transmission is present, but that there is a "block" produced by the curare which prevents it from acting upon the contractile mechanism of the muscle. In fatigue this substance may have been exhausted by the impulses which have already passed through.

This resemblance of the action of curare to fatigue has been so close that they were formerly believed to be accounted for by a uniform explanation. Recently, however, Rosenblueth, Lindsay and Morison have called this view into question. In their experiments carried out on cats they found that certain decurarizing agents acted differently toward indirect stimulation of curarized muscles to the way the same substances acted in the case of fatigue. They found that prostigmine and acetylcholine increased the response of curarized muscle to indirect stimulation but lessened the response of normal and fatigued muscles. Epinephrine also was more effective as a decurarizing agent than it was against fatigue. The writers therefore conclude that fatigue and curarization are really two different processes.

If the theory according to which acetylcholine is the chemical mediation between the nerve impulse and the skeletal muscle is finally shown to be correct, then it is possible to explain the action of curare as being due either to an impairment of acetylcholine production or to its preventing the action of the acetylcholine upon the muscle. The decurarizing agents such as physostigmine, prostigmine and acetylcholine either antagonize or overcome these possible actions of curare. If, for example, the curare makes the muscle relatively impermeable

to the acetylcholine, an additional amount of this chemical would raise its concentration and thus overcome the block. Physostigmine on the other hand might accomplish the same end by preventing the destruction of the acetylcholine and thus secure a supply sufficient to overcome the block.

Curare acts first on the nerves of the toes, ear and eye, later those supplying the limbs, head and neck, and, last of all, those supplying the muscles of respiration. At first slight movements can be performed, because single impulses can pass through the nerve-ends, but sustained contractions such as are necessary to preserve the equilibrium, cannot be maintained, and the animal therefore cannot support itself. The intermittent impulses to the respiratory muscles still allow time in the interval for the recovery of the terminations, but as the intoxication proceeds the number of impulses which can pass through becomes fewer and fewer, and the movement therefore assumes more and more the character of a jerk and eventually ceases.

Small doses do not affect the innervation of unstriped muscle, and the strict demarcation of its action is seen very distinctly in organs which consist partly of striated and partly of unstriated fibres. Thus in the œsophagus, the striated muscle fibres no longer contract on stimulation of the vagus after curare, while the unstriated continue to respond as usual. In the iris of the mammals, which consists of unstriated muscle, curare has no effect, while the striated muscle of the bird's iris ceases to respond to stimulation of the motor oculi, but contracts on direct stimulation. The terminations of the nerves in the heart are not affected, but the nerves of the lymph hearts of the frog are paralyzed. The nerve-ends in striated muscle in invertebrates appear to be immune to curare (Straub). The nerve fibres seem unaffected by curare, for stimulation causes the usual electrical changes in them.

The Autonomic Sympathetic Ganglia are paralyzed by large doses, and stimulation of the preganglionic nerve fibre has no effect, nor does injected acetylcholine affect the ganglia after curare although in the intact animal acetylcholine still stimulates the post-ganglionic endings. For example, stimulation of the vagus does not slow the heart, and stimulation of the chorda tympani does not cause secretion, because the impulses fail to pass the ganglia on their course. The terminations of the post-ganglionic fibres are apparently not affected, for stimulation beyond the ganglia has its usual effect.

The peripheral terminations of the afferent or sensory nerves seem unaffected, for if the artery of one leg be ligatured before the application of curare, reflex movements may be obtained in it from stimulation of any part of the body, while if the sensory terminations were paralyzed, reflexes could be elicited only by the irritation of parts to which the poison had not penetrated, *i. e.*, from the ligatured leg.

The central nervous system is stimulated by large quantities of curare, and when it is applied directly to the brain and cord without reaching the muscles, it causes violent spasms (McGuigan), which appear to resemble those of the picrotoxin series rather than those induced by strychnine. The heart is not directly affected, but large

quantities may paralyze the vagus ganglia and release the heart from inhibition. At the same time the blood-pressure may fall from paralysis of the ganglia on the vasoconstrictor nerves. The movements of the intestine, spleen and other organs are sometimes accelerated through a similar paralysis of the ganglia on inhibitory nerves.

Metabolism.—The cessation of the ordinary movements after curare and under artificial respiration naturally reduces the metabolism, but if the temperature is kept up by the external application of heat, the tissue change is not arrested in the muscles, and the CO_2 excretion and O_2 absorption are only slightly lower than those of the unpoisoned animal at rest. Sugar and lactic acid are often found in the urine after curare, but this is due to partial asphyxia and not to the direct action of the poison; the glycogen of the liver and muscles disappears from the same cause.

Curare is **excreted** by the kidneys apparently unchanged. It has long been known that this arrow poison may be swallowed with impunity, provided there is no wounded surface in the mouth or throat, and that it is therefore perfectly safe to suck the poison from a wound. This has been explained in various ways, some holding that the absorption from the stomach is so slow that the kidneys are able to excrete the poison as fast as it reaches the blood and that this prevents its accumulating in sufficient quantity to affect the tissues. Others suppose that the liver retains and destroys it, and a third view is that it is rendered innocuous in passing through the stomach walls.

The characteristic action of curare on the myoneural junction in striated muscle is antagonized to some extent by physostigmine, nicotine, and certain other chemical substances.

Feng showed that in the isolated muscle of the toad the paralyzing effect of curare was largely inhibited by the addition of calcium to the Ringer solution, or in case paralysis had taken place it was almost completely removed by the use of calcium. He concluded, therefore, that the cause of the curarization was somewhat of the nature of an electrolyte disturbance involving a loss of calcium from the neuromuscular junction.

Feng found further that calcium would antagonize the curare-like action which is characteristic of quite a number of drugs other than curare.

Potassium, too, has been shown by Wilson and Wright to exert an anti-curare effect although the antagonistic action is of a somewhat temporary character. Like prostigmine, potassium has little effect upon the fatigued muscle, thus indicating again that there must be a fundamental difference between a fatigued and a curarized muscle.

Paralysis of the terminations of the motor nerves in striated muscle—the so-called "Curare-Action"—is elicited by a large number of poisons, but in few of them is it the first effect of their application. Many drugs induce it only when injected in large quantities and at the end of a series of phenomena produced by their action on other parts of the body; it is observed much more frequently in frogs than in mammals, and is often of little importance compared to the other symptoms. Among the bodies which resemble curare more closely in their action, the peripheral paralysis playing the chief rôle in their effects, are the ammonium compounds formed from the natural alkaloids by the substitution of an alkyl, *e. g.*, methylstrychnine, amylquinine, etc. Some of the ammonium salts and many of the alkyl combinations of ammonium, phosphorus, arsenic and of several metals, also cause it. The tetraethyl ammonium salts have a much weaker curariform action than the tetramethyl compounds, and unlike the latter produce an initial increase in excitability accom-

panied by fibrillary twitches. Of greater practical importance is the fact that the venom of the Cobra and of other colubrine snakes has the same point of action as curare, from which it differs in the slowness of its action and the tenacity with which it holds the nerve ends. The toxin of botulism, a form of food poisoning, has also been shown to paralyze nerve terminations.

Therapeutic Uses.—The muscular paralysis produced by curare early suggested its use in convulsive conditions such as tetanus, tetany, strychnine poisoning, etc. The possibility of its therapeutic use depends largely upon whether an adequate degree of muscular relaxation can be obtained without arrest of respiration, and therapeutic experiments have been hampered by the difficulty of obtaining reliable preparations of curare, or of its active principles. Recently Bremer and his colleagues have shown that curare produces a selective action on nerve-endings, affecting those which are continuously in action more readily than those which are resting. Hartridge and West have found that certain specimens of curare, in doses which produce no detectable signs of weakness of voluntary muscular power, effect a measurable reduction in the muscular rigidity resulting from diseases of the pyramidal and extrapyramidal motor systems. It is not impossible, therefore, that if the active principles can be obtained and their dosage accurately determined, curare may yet find a place in therapeutics for the treatment of conditions of spasm and rigidity of voluntary muscles.

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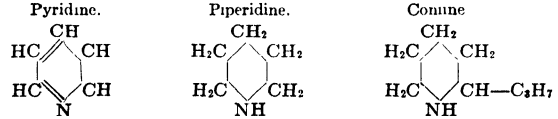
I. CONIINE.

Coniine is one of the simpler derivatives of *Piperidine*, which is obtained from *Pyridine* by reduction. A series of alkaloids may be formed from piperidine by substituting methyl, ethyl, propyl or other alkyls for hydrogen, and one of these, propyl-piperidine, is the natural alkaloid coniine and was the first alkaloid to be formed synthetically.



Coniine is found in Hemlock (Conium maculatum), along with two nearly allied alkaloids, *Methylconiine* and *Conhydrine*. The action of these and of the other simple piperidine compounds resembles that of coniine, but is much weaker.

Symptoms.—The general symptoms induced in man by poisonous doses of coniine are weakness, languor and drowsiness which does not pass into actual sleep. The movements are weak and unsteady, the gait is staggering, and nausea and vomiting generally set in, along with profuse salivation. In most cases the intelligence remains clear to the end, as is related of the death of Socrates from hemlock poisoning, but in some instances imperfect vision and hearing have been noted. The pupils are somewhat dilated. Tremors and fibrillary contractions of the muscles are often seen in animals, and some observers state that actual convulsions occur. The breathing becomes weaker and slower and death occurs from its arrest.

Action.—The terminal asphyxia and the twitching and tremor, which are sometimes seen, appear to arise from a partial paralysis of the peripheral nerves similar to that seen under curare. It also resembles curare in paralyzing the sympathetic ganglia, but this paralysis seems to be preceded by a short stage of stimulation; the ganglia are affected by quantities of coniine which are insufficient to cause paralysis of the nerves to voluntary muscle, but its action on these ganglia is not so powerful as that of nicotine, and the details of this action may therefore be left for discussion under the latter drug.

The heart is affected through the stimulation and subsequent paralysis of the ganglia on the inhibitory fibres, which lead first to slowing and later to some acceleration of the pulse. The blood-pressure is increased for a short time from stimulation of the ganglia on the course of the vasoconstrictor nerves. The respiration is sometimes accelerated slightly at first but soon becomes slow and labored, and then irregular, and finally ceases while the heart is still strong. The red blood cells of the frog show numerous vacuoles in coniine poisoning and these persist long after recovery (Gürber).

Coniine is rapidly **excreted** in the urine, so that its action passes off very soon even when quite large doses are taken. The treatment of coniine poisoning therefore consists in evacuation of the stomach and artificial respiration.

Piperidine acts in the same way as coniine, but more weakly, while methyl- and ethyl-piperidine stand between them in toxicity.

Pyridine resembles piperidine in most features but does not paralyze the ganglia nor increase the blood-pressure. It is excreted in the urine as methyl-pyridine, a combination between it and the alkyl occurring in the tissues. A similar synthesis occurs between methyl and tellurium (see Tellurium).

Quinoline and isoquinoline cause in mammals a condition of collapse similar to that seen under the antipyretics and the benzol compounds.

Hemlock or **Conium**, long widely used in therapeutics, has failed to maintain its position on more accurate investigation and has passed into disuse.

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II. GELSEMIUM.

Gelsemium sempervirens (Yellow Jasmine or Carolina Jasmine) contains several alkaloids which have not yet been fully separated and identified. A crystalline alkaloid, gelsemine, $C_{20}H_{22}O_2N_2$, is inactive in mammals but produces strychnine-like convulsions in frogs. "Gelseminine," an amorphous alkaloid which was shown by Cushny to be highly poisonous to mammals and believed to be the active principle, is regarded by Sayre as a mixture of three

alkaloids, to which the names sempervirine, gelsemidine and gelsemoidine were given. Chow has recently isolated gelsemicine ($C_{20}H_{25}O_4N_2$) highly toxic to mammals, and he considers that the poisonous nature of gelsemium is due to the presence of gelsemicine, sempervirine and possibly other amorphous bases.

Action.—The symptoms of gelsemium poisoning resemble closely those of coniine, in man the chief symptoms being double vision, ptosis, dilatation of pupils, increasing muscular weakness affecting speech and gait, and final arrest of respiration.

The pupil is very widely dilated by gelseminine when a solution is applied locally to the eye, much less so in general poisoning, in which the respiration generally fails before the pupil is fully dilated. The power of accommodation is also entirely lost when gelseminine or gelsemium tincture is applied to the eye. This mydriatic effect has not been explained, but the most plausible suggestion would seem to be that gelseminine paralyzes the terminations of the oculomotor nerve in the eye in the same way as atropine. Gelseminine differs from atropine in its behavior to other nerves, however, for it paralyzes the inhibitory cardiac fibres and the chorda tympani through acting on the ganglionic structures on their course and not on the extreme terminations. Its action on the ganglia, as far as it is known, resembles that of coniine, but it does not cause any increase in the arterial tension, such as is observed under this poison.

A tincture of gelsemium has been employed in facial neuralgia and as a cerebral sedative, and a mixture of the alkaloids has been applied locally to dilate the pupil, but has never attained any wide use.

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III. SPARTEINE.

Another alkaloid which resembles coniine closely in its action is *Sparteine*, which is found in the common broom plant (Spartium or Cytisus scoparius), and in various species of lupines. It is a pyridine derivative possessing the formula $C_{15}H_{26}N_2$, and is a fluid, but forms crystalline salts.

Action.—The general effects of sparteine are almost identical with those of coniine, but it seems very probable that the central nervous system is little affected by it, the whole of the phenomena pointing to a paralysis of the motor nerve terminations and of the sympathetic ganglia. Sparteine has more effect than coniine on the heart, which it depresses, so that the rhythm is slow and the contractions weak. A stimulation of the isolated heart by weak concentrations has been described. No increase in the arterial tension is observed from the administration of sparteine internally and even the slight rise of pressure induced by intravenous injection (especially in the spinal animal) is of only short duration. Sparteine is much less poisonous than either coniine or gelseminine; it proves fatal to animals by paralyzing the terminations of the phrenic nerves in the diaphragm.

The slow pulse and slight rise of pressure observed in experiments in animals when sparteine is injected intravenously have led some writers to ascribe to it an action similar to that of digitalis, and at one time sparteine was used to some extent as a substitute for the latter; both experimental and clinical observations, however, have failed to substantiate these claims. Experimentally it has some action in checking auricular fibrillation, like other cardiac depressants. It is still occasionally recommended for nervous palpitation, tachycardia and other functional disorders of the heart.

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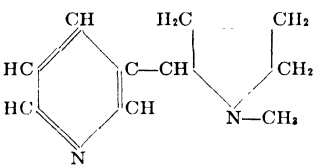
E. SUBSTANCES ACTING ON THE AUTONOMIC NERVOUS SYSTEM.

I. NICOTINE GROUP.

Nicotine, the well-known alkaloid of tobacco (Nicotiana tabacum), is a volatile fluid, possessing a strong alkaline reaction, and forming salts with acids, most of which are amorphous. It is a combination of pyridine with a hydrated pyrrol ring as shown by the structural formula—



Nicotine is the only constituent of tobacco which possesses any toxicological interest, although several other alkaloids are present in comparatively small amounts. It is accompanied by a volatile oil in dried tobacco, but this is only developed during the processes of preparation and seems to have no action apart from that of the other volatile oils. The odor and flavor, and probably the "strength," of tobacco depend in part upon the quantity and quality of this oil, in part on some products of the decomposition of nicotine. Absolutely pure nicotine has comparatively little odor, but it decomposes when kept, becomes dark colored, and acquires the characteristic odor of tobacco.

The natural or beta-nicotine is optically active, being lævorotatory, while the synthetic alkaloid, alfa-nicotine is optically inactive. In harmony with the general findings of lessened activity in optically inactive substances the alfa-nicotine is much less toxic than the natural alkaloid. It has also much less effect upon respiration and upon the circulation, although neither alkaloid has any very marked effect upon a heart-lung preparation.

The pituri plant (Duboisia Hopwoodii), the leaves of which are used by the Australian natives in the same way as tobacco by the civilized races, contains as its chief alkaloid d-nornicotine, which has similar actions to nicotine. An isomeride of nicotine, *Anabasine*, with actions similar to nicotine but weaker, has been isolated from Anabasis aphylla (Chenopodiaciæ), a native of Central Asia. Lobelia inflata, or Indian tobacco, contains several alkaloids, one of which, *Lobeline*, resembles nicotine in many of its actions.

Cytisine ($C_{11}H_{14}N_2O$), the alkaloid of laburnum (Cytisus laburnum), gorse and other plants, resembles nicotine very closely in action. A con-

stimulation of a preganglionic fibre fails to produce the usual action, as the path of the stimulus through the ganglion is interrupted. Stimulation of the postganglionic fibre by chemical or electrical stimulus will, however, still produce the characteristic effect. Nicotine acts in this way on all autonomic ganglia that have been investigated.

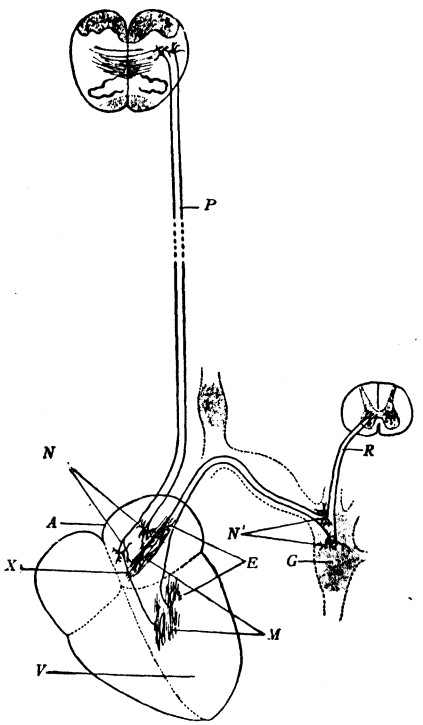


FIG. 26.—Diagram of the regulating nerves of the heart. *P*, inhibitory parasympathetic fibres (vagus), terminating around ganglion cells in the auricle (*A*). The axis cylinders issuing from these cells terminate on the muscular fibres of the auricle and ventricle (*V*). *R*, accelerator sympathetic fibres terminating around ganglion cells in the stellate ganglion *G*. The axis fibres of these ganglion cells run through the *Annulus Vieussenii* and terminate on the muscular fibres of the auricle and ventricle. *N*, *N'* points at which *nicotine*, *coniine*, *curarine*, etc., act—the ganglion cells surrounded by the terminations of the nerves. *M*, points at which *muscarine* and *atropine* act—the terminations of the postganglionic fibres which arise from the intracardiac ganglia on the parasympathetic path. *E*, points at which *epinephrine* acts—the myoneural junction on the sympathetic path.

Circulation.—The action on the circulation is extremely complex, as a number of factors are involved. After moderate quantities the heart is slow and may stand still in diastole for a few seconds, but then recovers gradually and regains its former rhythm or becomes somewhat quicker. The slow pulse is due to stimulation of the ganglia on the vagus nerve (Fig. 26, *N*), exactly the same effects being produced as by stimulation of the vagus fibres in the neck. It is not affected by section of the cervical pneumogastric, as the path from

the ganglia to the cardiac muscle fibres is still intact, but on the other hand, it is prevented by atropine, which paralyzes the terminations of the postganglionic fibres, and therefore blocks the passages of impulses from the ganglia to the muscle. It is also prevented by a number of drugs, such as curare and coniine, which paralyze the ganglia.

This stimulation of the ganglia is of short duration, soon passing into paralysis, so that on stimulating the vagus after nicotine there is no slowing of the heart but often some acceleration, due to the fact that the accelerating fibres running along with the inhibitory in the vagus nerve are postganglionic fibres to the heart, and are therefore unaffected by nicotine. Although inhibitory impulses can no longer reach the heart from above, stimulation of the venous sinus in the frog still causes arrest of the heart, since the stimulating current here reaches the inhibitory nerves beyond the paralyzed ganglia (Fig. 26, *X*), and these preserve their usual irritability. In the same way muscarine, which acts upon the postganglionic inhibitory terminations in the heart muscle (Fig. 26, *M*), can slow the rhythm even after the ganglia have been paralyzed by nicotine.

In addition to its action on the peripheral inhibitory ganglia, nicotine seems to stimulate the vagus centre in the medulla, as the slowing is greater when the vagi are intact than when they are divided. But apart from this action on the inhibitory apparatus, nicotine also at first stimulates the ganglia on the accelerator fibres, so that when the inhibitory mechanism has been put out of action by atropine, moderate quantities of nicotine increase the rate. Larger amounts paralyze the accelerator ganglia (N′, Fig. 26) and thus tend to slow the heart. A further action is said to be exercised on the heart muscle itself, which is first stimulated and then depressed (Wertheimer).

On the injection of nicotine into a vein or subcutaneously, an immense augmentation of the arterial tension occurs; this is due in part to stimulation of the vasoconstrictor centre in the medulla, in part to stimulation of the ganglia on the course of the vasoconstrictor nerves.

The constriction of the vessels can be observed in many parts of the body —mesentery, foot, rabbit's ear, etc. In these parts the pallor produced by the narrowing of the vessels is followed by redness and congestion owing to the paralysis of the ganglia, and at the same time the pressure falls to a level somewhat below the normal. In some parts of the body no constriction of the vessels occurs; for example, the dog's lip and mouth are congested first and then become pale. This flushing seems partly due to the stimulation of the ganglionic apparatus on the vaso-dilator fibres for the lips and mouth, and partly to the constriction of the vessels in the splanchnic area diverting the blood current to those parts which are less abundantly supplied with constrictor fibres, for it occurs after removal of the superior cervical ganglion containing the vasodilator fibres.

After a few minutes the blood-pressure falls to the normal level or lower, but a second injection again produces a similar rise in the arterial tension, unless the first was large enough to weaken the ganglia.

An electrocardiographic study of the effects of cigarette smoking was made on a group of adults, most of whom were normal, while a few were cardiac patients, each individual receiving about 2 mgs. of nicotine within the space of five min-

utes. In almost every case there was an increase in heart rate averaging thirteen beats per minute. In the large majority of persons there was also an increase in blood-pressure, an average systolic increase of 13 mm. of mercury and 7 mm. diastolic. The most striking change, however, was in the alteration in the *T* wave of the electrocardiogram. In a goodly percentage of cases this was either depressed or inverted. This modification in the wave usually reached its maximum four or five minutes after the smoking had been completed, after which time recovery began, with return to normal in about one-half hour. The change in the wave could not be brought about by sympathetic action, as stimulation of that system and also epinephrine administration cause increased amplitude of the wave, while stimulation of the vagus or acetylcholine causes a decrease. On the other hand, complete paralysis of the vagus has no effect on the wave. In the cases studied it is clear that the 2 mg. dose of nicotine is insufficient to paralyze the vagi, but probably merely exerts a mild stimulating effect on the nerve, the slowing of the heart which would ordinarily accompany such an action being overcome in a certain percentage of the individuals by an accelerator effect.

It is noteworthy that a majority of the individuals studied experienced certain unpleasant symptoms such as dizziness, palpitation, and gastro-intestinal disturbances.

The writers believe that the cardiac pain or angina complained of at times while smoking is probably due to the extra strain placed upon the heart by the increased rate and by the increased blood-pressure, and not by vasoconstriction as usually believed (Graybill, Starr and White).

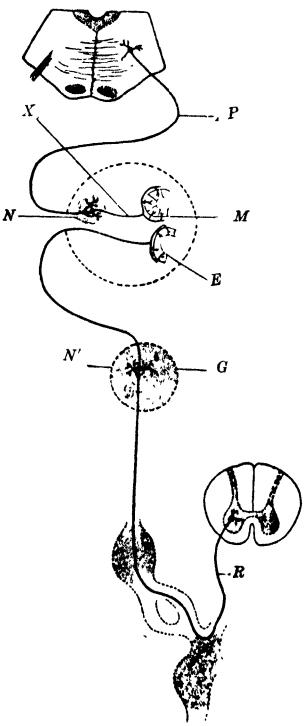


FIG. 27.—Diagram of the innervation of the submaxillary gland. *P*, parasympathetic fibres (chorda tympani), terminating around a ganglion cell in the hilus of the submaxillary gland. The axis from this ganglion cell runs to the secretory epithelium. *R*, sympathetic fibres, terminating around a ganglion cell in the superior cervical ganglion *G*. The axis from this cell runs to the secretory epithelium. In the diagram the nerves are represented as running to separate acini. *N*, *N'*, ganglion cells surrounded by the terminations of the nerves—the points at which *nicotine* acts. *M*, the terminations of the secretory fibres connected with the chorda tympani—the points at which *atropine*, *muscarine* and *pilocarpine* act. *E*, the terminations of the secretory fibres connected with the sympathetic—the point at which *epinephrine* acts.

In the rabbit nicotine tends to induce lesions of the aorta with subsequent calcareous degeneration, which resembles the atheromatous patches seen in man. This is due to the very high blood-pressure, and similar effects are seen from epinephrine and from other measures which suddenly increase the blood-pressure.

Respiration.—The respiration is at first rapid and shallow with some deficiency in the expiratory movements, but after a time, while maintaining the acceleration, it becomes deeper. It is liable to be interrupted at this stage by the convulsions, but if these do not prove fatal, it gradually becomes slower while remaining deep. Later, pauses in the

position of expiration appear, and the movements become weaker until they disappear, the animal dying of asphyxia. The respiratory centre is first stimulated and then depressed and its failure has been believed to be the cause of death, the heart continuing to beat for some time afterwards, although slowly and weakly.

There are still differences of opinion as to the explanation of the effects of nicotine upon the respiration and the part that the centre plays in this action. Several workers have found that the action of small doses of nicotine upon the respiration is not direct upon the centre, but is due to an action upon the sino-aortic nerves, and that if these nerves are severed small doses of nicotine are without any effect upon the respiration so that the early stimulation of the respiration is due to a reflex action. Wright, however, showed that larger doses do indeed exert a stimulating effect directly upon the centre.

Gold and his co-workers also showed that a dilute solution of nicotine applied directly to the centre stimulates the respiratory centre and then depresses it but apparently does not paralyze it completely. They also showed by means of phrenic potentials that the centre sends out impulses after the respiratory movements have ceased due to the curare-like action of the nicotine on the endings of the phrenic nerve on the diaphragm. These results are discussed above.

The *bronchial* muscle relaxes after a transient constriction when nicotine or lobeline is injected, these changes being brought about by stimulation of the ganglia on the course of the vagus fibres which cause contraction of the bronchial muscle, and later of those on the sympathetic fibres which cause active dilatation.

Most of the **Secretions** are increased temporarily by nicotine. The glands investigated have generally been the salivary, where it is found that the secretion is increased by the injection of small quantities, but is afterward depressed, while large doses diminish it at once. The seat of action is again the ganglionic apparatus on the secretory nerves. If the chorda tympani is stimulated in the normal animal a large secretion of saliva at once follows, but if a sufficient quantity of nicotine be injected, no such effect follows its stimulation. If, however, the nerve fibres are stimulated between the ganglion cells and the gland (at *X* in Fig. 27), the secretion again follows as before. On the other hand, nicotine increases the secretion whether the chorda is intact or not, but ceases to act if the connection between the ganglion cells and the gland is interrupted. Nicotine thus first stimulates and then paralyzes the ganglia on the course of the chorda tympani and of the sympathetic fibres supplying the gland. Pilocarpine and muscarine cause profuse salivation after nicotine because they stimulate the post-ganglionic terminations in the gland cells, and it is therefore immaterial whether the connection with the central nervous system be interrupted or not. On the other hand, the reflex secretion of saliva normally produced by irritation of the mouth or by chewing is prevented by nicotine. Atropine stops the secretion produced by nicotine by paralyzing the postganglionic terminations.

The other secretory glands are affected in the same way by nicotine, their secretions being first increased by the stimulation of the ganglia on the course of their secretory nerves, and then being lessened by their

paralysis. Thus the secretion of sweat and bronchial mucus is found to be markedly increased. The urine and bile have not been shown to be affected by nicotine, as their secretion does not seem to be so dependent upon nervous influences. The activity of the suprarenal glands is increased by nicotine, probably by its action on the ganglia on the course of the innervating fibres; this results in an augmented secretion of epinephrine into the blood-vessels, which in turn affects a number of organs, such as the iris and uterus, and introduces a new complication in the action of nicotine.

Nicotine produces extreme **Nausea and Vomiting** when taken even in comparatively small quantities, a fact which is generally recognized by tyros in smoking. This is in part central in origin, in part due to the powerful contractions of the stomach walls. This contraction extends throughout the intestinal tract, so that repeated **Evacuation of the Bowel** occurs. Somewhat larger quantities may lead to a tetanic contraction of the whole intestine with almost complete obliteration of the lumen. This exaggeration of the peristaltic contraction is probably due to stimulation of the motor ganglia in the intestinal wall, and a subsequent paralysis of these structures leads to a failure of local stimuli to induce peristalsis. A further effect of nicotine on the bowel is due to its stimulating the ganglia on the fibres of the splanchnic which inhibit the rhythmical pendulum movements. These are arrested by the injection of nicotine, but return in exaggerated form as the ganglionic stimulation passes into paralysis. The mesenteric vessels are narrowed at first from stimulation of the ganglia on the course of the vasoconstrictor nerves, but congestion follows the depression of these ganglia and the blood-pressure falls.

Similar changes are produced by nicotine in the bladder, which is thrown into tetanic contraction. The urine is therefore expelled very soon after the injection of nicotine and this probably gave rise to the erroneous view that the renal secretion was increased. The uterus is strongly contracted in pregnant animals, but is inhibited in the non-pregnant cat, in which the inhibitory nerves are more powerful than the contractor ones.

The action of nicotine on the **Pupil** varies in different animals, for while in the cat and dog its application either intravenously or locally produces marked but transitory dilation, in the rabbit partial constriction sets in immediately. In cases of acute poisoning in man contraction is generally seen at first and is followed by dilatation. In birds nicotine causes very marked contraction of the pupil, apparently owing to direct action on the muscle of the iris. The size of the pupil is regulated by two sets of nerves, the motor oculi and the sympathetic, and the ciliary fibres of both of these are interrupted by ganglia in their passage from the brain to the iris, those of the motor oculi by the ciliary ganglion, those of the sympathetic by the superior cervical ganglion (see Fig. 27, p. 471); the varying effects of nicotine may be due to its stimulating the one ganglion more strongly in one species of animals, the other in another. It is found, however, that atropine does not remove the effects of nicotine on the rabbit's eye, which would

seem to indicate an action on the muscular fibres of the iris. Several other effects on the orbital muscles are seen; thus in cats and dogs the nictitating membrane is withdrawn, the eye opens and is directed forward, while in the rabbit these symptoms are preceded by a stage in which the nictitating membrane is spread over the cornea and the eye is tightly closed; these all arise from stimulation and subsequent paralysis of the superior cervical ganglion.

Nicotine, then, first stimulates and later paralyzes all the **Autonomic Ganglia**, whether applied locally to them or injected into the circulation. In these ganglia, the characteristic formation is the basket-like arrangement of the terminations of the entering nerve, which surround a large nerve cell from which an axis cylinder runs to the muscle or secretory cell. A nerve impulse from the central nervous system passes from the basket to the cell and thence to the periphery. Langley has shown that nicotine acts on the cell of the peripheral neuron, and not on the network around it, for the same effect is obtained from the application of the poison after the network has degenerated.

In the frog nicotine produces fibrillary twitching and slow, prolonged contraction of the **Muscles**, which are not prevented by previous division of the nerves leading to them, but disappear on the injection of curare; on the other hand, the paralysis induced by curare may be partially removed by small quantities of nicotine. Langley has shown that the fibrillary twitching and slower contractions occur in muscles in which the nerve-ends have degenerated from division of the nerves, so that nicotine acts on some receptive substance peripheral to the anatomical nerve-ends and intervening between these and the contractile substance of muscle. A similar effect is seen in reptiles and birds; in mammals the twitching of the muscles is prevented by section of the nerves and is, therefore, due to central action, but large quantities of nicotine cause paralysis exactly like curare.

The convulsions seen in both cold- and warm-blooded animals evidence the influence of nicotine on the **Central Nervous System.** The spinal cord is thrown into a condition of exaggerated irritability, and the reflexes are correspondingly increased, but the convulsions do not seem to be due so much to the spinal cord as to the medulla oblongata and hind brain, for they are not tonic but clonic in character, and are much weaker after division of the cord immediately below the medulla than in the intact animal. The medullary stimulation also betrays itself in the rapid and deep respiration, and is in part responsible for the inhibitory slowing of the heart and the rise in the blood-pressure. The higher centres in the brain seem to participate but little in the stimulant action of nicotine, which is short-lived, and soon gives way to marked depression of the whole central nervous system, manifested in the slow respiration, the low blood-pressure, the disappearance of the reflex movements and the final unconsciousness.

The cause of death in nicotine poisoning has aroused considerable interest in recent years since Thomas and Franke called attention to the importance of the curare-like action of nicotine in this connection.

These workers showed that sections of the diaphragm of a dog connected

to the body of the animal by the phrenic nerve only, and therefore protected from the action of the poison, will remain active to stimulation of the nerve long after the intact portion of the diaphragm in the animal is paralyzed by the nicotine injected. They concluded, therefore, that under the conditions the death of the animal was due to a peripheral paralysis of the nerves involved in respiration rather than to a paralysis of the respiratory centre. However, in order to bring about this condition of peripheral paralysis, doses of nicotine two or three times the minimum fatal doses were given (15 mgs. per kilo of body weight), and the problem still remains as to the cause of death from the smaller doses which really constitute the M. F. D., and the work quoted does not answer that question.

Further studies on the action of nicotine on the central nervous system have been made by Franke and Denvir. They found that special reflexes could be obtained late in nicotine poisoning and that failure of the voluntary muscles to respond is due to a peripheral paralysis of the motor nerves. The authors say these studies were performed under artificial respiration in order to avoid the prompt development of asphyxia in fatal nicotine poisoning. Accordingly, while the studies show that the spinal cord is not paralyzed and that a peripheral paralysis of the motor nerves is present, they do not solve the question of the cause of death from small doses of nicotine given to the normal animal. The fact that a curare-like paralysis is brought about by nicotine is well known, but as is well shown both by the Thomas and Franke and by the Franke and Denvir studies, it is a relatively late manifestation produced by large doses of nicotine in animals under general anesthesia and artificial respiration. In support of the view, it should be emphasized that the former paper refers to the action of doses of nicotine two or three times the "minimal fatal dose," and the latter paper records the use of artificial respiration to avoid the early asphyxia, but it is the *early* asphyxia which is the cause of death in normal animals.

In a later study by Franke and Thomas (1933) it was pointed out that in unanesthetized dogs small doses of nicotine will cause death in three minutes if convulsions are produced, but that in the absence of convulsions the time elapsing before death is longer, allowing for the development of the curare-like action. The writers ascribe the early death from asphyxia to the convulsions themselves, but it might equally be true that it might result from a depression of the respiratory centre following the extreme stimulation. This explanation would be more in harmony with generally accepted pharmacological rules.

Gold and Modell (1936) attacked the problem anew by means of phrenic potentials and here again anesthesia and artificial respiration were necessarily used, although anesthesia modifies the nicotine picture greatly and rapid recovery follows nicotine poisoning if artificial respiration is maintained. It was shown that under these conditions phrenic discharges were continued for some time after all movements of spontaneous respiration had ceased. The writers, therefore, concluded that a peripheral paralysis was responsible for death.

The net result of all these studies would without doubt point to the fact that perhaps a curare-like action had not been emphasized sufficiently as a possible cause of death from nicotine. However, the evidence that the early death which follows the administration of small doses of nicotine to normal animals is not due to depression of the respiratory centre does not seem to be sufficiently established to be finally accepted, and Thomas and his co-workers make such an exclusion in their papers.

The Excretion of nicotine is probably carried on mainly by the kidneys, for it is found in the urine very soon after it enters the blood. It has also been detected in the saliva and perspiration. It has been shown repeatedly that nicotine and some other alkaloids are weakened in toxic effect or rendered entirely inactive by being mixed with an extract of

the liver or of the suprarenal capsules; but no satisfactory explanation is forthcoming, though there is every reason to suppose that much of the nicotine absorbed from the stomach and intestine is thus modified in its passage through the liver.

When small quantities of nicotine are ingested repeatedly, the body soon gains a certain **Tolerance**, and no symptoms whatever are produced by doses which in ordinary cases would produce grave poisoning. A familiar example of this tolerance is seen in the practice of smoking. The first use of tobacco in the great majority of individuals is followed by vomiting and depression, which may even amount to collapse, but after a few experiences no symptoms follow smoking, possibly owing to the cells of the body becoming tolerant of the poison or learning to destroy it more rapidly. In some individuals no such tolerance is developed, and in every case the tolerance is much more limited and more difficult to acquire than that for morphine. In animal experiments it is often found that while one application of nicotine produces considerable ganglionic stimulation, the second has much less effect. This is probably due, not to the establishment of tolerance, but to the first dose having produced primary stimulation and then depression of the ganglia, this depression, while not amounting to complete paralysis being sufficient to counteract to some extent the stimulant action of the second injection. True tolerance is attained very imperfectly by animals from the use of repeated small doses, but when larger amounts are used some tolerance is soon acquired. Animals which have acquired tolerance for nicotine also resist the action of lobeline. Certain animals have a natural tolerance against nicotine, this being strongest in rabbits. In diminishing degree appear guinea-pigs, dogs, hens and finally cats where this congenital tolerance is least.

Therapeutic Uses.—Lobelia was formerly used as an emetic, but is unreliable, and is liable to give rise to the most alarming symptoms of poisoning. It is occasionally used in the form of the tincture (Dose, B. P., 5–15 mins.), to relax the spasm of the bronchial muscle in asthma, and may also aid in this condition by rendering the mucus secretion more fluid through its nauseating action. But its effects must be carefully watched, as the preparations seem to vary in strength, and alarming symptoms and even fatal results have sometimes followed its use. In any case it is inferior to atropine and its allies in this condition. *Lobeline* stimulates the respiratory centre and has been used for this purpose in respiratory failure occurring during anesthesia, in narcotic poisoning and similar conditions. The stimulation is of short duration. It is usually given hypodermically in doses of 0.003–0.01 G. ($\frac{1}{20}$–$\frac{1}{6}$ gr.). Nicotine is not used in therapeutics.

Tobacco.

Tobacco had been in use among the aboriginal tribes of America before they became known to civilization. It was introduced into Europe soon after the discovery of America, and its use as an article of luxury, beginning in England, soon spread to the continent, and in spite of papal bulls and numerous efforts on the part of the secular authorities, has continued to enthrall a considerable portion of the human race. The most widespread use of tobacco—smoking—is also the most ancient one, having been that of the aboriginal Indians.

Snuff-taking, introduced by Francis II. of France, remained fashionable for a long time, but is now almost obsolete. Tobacco-chewing is a more modern development, but shows no signs of abatement. Curiously enough, the leaves of the pituri plant, which contains nicotine, are formed into a mass and chewed by the natives of Australia. In smoking, snuffing or chewing, nicotine is absorbed; tobacco smoke always contains nicotine, though the amount varies with different kinds of tobacco and also with the way in which it is smoked; but a large proportion of that contained in tobacco passes over in the smoke along with pyridine and some of its derivatives. In snuff the nicotine is generally small in amount, while in chewing tobacco there is generally a varying amount of foreign matter, such as molasses.

The enjoyment derived from the use of tobacco has never been adequately explained, and it is not even proved that nicotine is essential to the pleasurable results, though there seems little doubt that it plays an important part in producing them. It has been suggested that smoking gives repose and thereby improves intellectual work, but this is denied by many habitual smokers. It has also been stated, and denied, that the mental energy is reduced by the use of tobacco, and an attempt has been made to demonstrate this by measuring the amount of work done with and without tobacco; but investigators are not agreed on the results, which probably depend largely upon the individual. One fact is certain, that the tobacco habit cannot be compared with the use of such drugs as morphine, cocaine, or alcohol, for it is not taken with the purpose of producing stimulation or depression of the central nervous system, and it seems doubtful whether the nicotine ordinarily absorbed really has any action whatsoever. Perhaps the local effects on the mouth, nose, and throat play a larger part in the effects of tobacco than is generally recognized. A certain amount of rhythmic movement demanding no exertion seems in itself to have a soothing, pleasure-giving effect, for it is otherwise impossible to explain the satisfaction enjoyed by many in chewing tasteless objects, such as gum or straws. A curious fact which tends to show that tobacco smoking is not carried on solely for the sake of the nicotine absorbed, is that the pleasure derived from a pipe or cigar is diminished for many persons if the smoke is not seen, as when it is smoked in the dark; and few blind men enjoy smoking.

Most people may indulge in the moderate use of tobacco for many years with perfect impunity, but its excessive use is followed in many individuals by a number of symptoms, some of them trivial, others indicating grave changes in important organs.

One of the commonest effects of overindulgence in tobacco is a chronic inflammation of the throat and upper parts of the respiratory passages, leading to hoarseness and excessive secretion of the mucous glands. This is explained by the constant application to the throat of an irritant, alkaline vapor, and is probably not due to the specific action of nicotine. A similar irritated condition of the tongue is frequently met with, more especially when the hot vapor is constantly directed on one part, as in pipe smoking, and it is sometimes stated that the constant irritation thus produced renders the tongue and lip more liable to cancerous dis-

ease. Dyspepsia, want of appetite, and consequent loss of flesh may also be explained by the local irritation produced by the nicotine swallowed in the saliva. A symptom ascribed to the abuse of tobacco is palpitation and irregularity of the heart, which has been attributed to changes in the inhibitory mechanism. Excessive smoking is also alleged to be a cause of coronary atheroma. Another important symptom is dimness of vision, especially for colors, and imperfect accommodation, which may go on to complete blindness in one or both eyes. In early cases the retina often appears pale, and if the condition persists, atrophy of the optic nerve may result, probably following on degenerative changes in the ganglion cells of the macular region of the retina. This tobacco amblyopia is held by some to occur only when the tobacco habit is accompanied by alcoholic excess, and is especially liable to occur from smoking heavy pipe tobaccos. Smoking causes a slight rise of blood-pressure in some individuals, and this has aroused apprehensions that it may tend to favor arteriosclerosis, but the change is slight and the evidence that smoking predisposes to arteriosclerosis is not convincing. Nervous symptoms, such as tremor, exaggeration of the reflexes, headache and giddiness, are sometimes developed in workmen in tobacco factories, and may be induced to a less extent by smoking or chewing tobacco. In the great majority of cases of chronic tobacco poisoning, the symptoms disappear on abandoning the habit, or even on restricting the daily consumption. The habit of smoking does not make insistent demands on its continuance as does morphine. Withdrawal of tobacco from those accustomed to it causes a temporary feeling of loss and possibly some impairment of mental concentration. This soon disappears and is not markedly greater than occurs from the discontinuance of any established pleasurable habit.

Pearl has made a statistical study of several thousand persons to ascertain if possible the effect which moderate or heavy smoking has upon longevity. Comparing the smokers with 2000 non-smoking controls, he found that smoking impaired life duration and that the degree of impairment increased with the amount used. It is interesting to note that Pearl found that the difference between the two groups of smokers and non-smokers disappeared at the age of seventy, probably due to the "expression of the residual effect of heavily selective character of the mortality in the earlier years." Individual smokers who survive seventy are probably so resistant that thereafter tobacco does them no harm.

Esser has stated that chronic nicotine poisoning in animals induces marked disturbance of the heart, and that degeneration of the vagus fibres is recognizable histologically; changes have also been found in the nerve cells of the spinal cord and sympathetic ganglia similar to those described under chronic alcoholic poisoning.

Various symptoms have been ascribed to chronic poisoning by nicotine in persons exposed to the alkaloid in industries where it is prepared. Some of these indicate a disturbance of the vegetative nervous system such as bradycardia, arrhythmia, hyperacidity and salivation. Some symptoms appear to be due to a disturbance of the circulation in the brain, while other cerebral disturbances have been described, such as insomnia, loss of memory and various neurotic tendencies.

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II. SUBSTANCES STIMULATING PARASYMPATHETIC NERVE ENDS.

1. The Muscarine Group.

Muscarine is an alkaloid found in certain poisonous mushrooms, especially Amanita muscaria (Agaricus muscarius). The alkaloid was first isolated, and its pharmacological properties described by Schmiedeberg and Koppe in 1869. It is chemically closely related to choline (v.p.), and resembles in its actions some of the choline esters. It produces a series of effects which reproduce with almost complete fidelity the effects which result from stimulation of the parasympathetic nerves and this action is exerted on the periphery in connection with the post-ganglionic nerve terminations. This particular type of action, which is now known to occur with several other drugs, was first described with muscarine and is frequently and for convenience called a "muscarine action." Few other substances possess this action with the same purity as muscarine, many (*e. g.*, acetylcholine) combining with it a "nicotine action." Both for historical reasons and for simplicity, it is convenient, therefore, to consider muscarine first as an introduction to this group of drugs.

Symptoms.—The symptoms of poisoning in man commence with a very marked secretion of saliva, soon followed by excessive perspiration and a flow of tears. Nausea, retching and vomiting, pain in the abdomen and violent movement of the intestines causing profuse watery evacua-

tions, are next observed. The pulse is sometimes quickened, sometimes very slow and irregular; the pupil is contracted, and the sight is accommodated for near objects. The respiration is often quick and dyspnœic, and râles may be heard over the bronchi, denoting an accumulation of mucus in them. Giddiness and confusion of ideas are complained of, but the nervous symptoms are not so conspicuous as those from the peripheral organs. Eventually the respiration becomes slower and great weakness in the movements manifests itself, but consciousness remains more or less perfect till the breathing ceases.

Actions.—Though there still remain some minor discrepancies to be explained, research in recent years has tended to confirm the conception that, in its peripheral actions, muscarine stimulates the post-ganglionic terminations of the parasympathetic nerves. When circulating in the blood, or when applied locally to organs, it therefore produces all the effects associated with stimulation of these nerves. Some exceptions to this generalization are known, notably the sweat glands. Recently evidence has accumulated to show that the nerves supplying the sweat glands, though belonging anatomically to the sympathetic system, belong physiologically to the parasympathetic system. Especially it is believed that stimulation of the sympathetic nerves to these glands causes the liberation of acetylcholine, and not—as is usual with sympathetic fibres—of a substance like adrenaline. Dale has suggested the term "cholinergic" fibres for all nerve fibres which transmit their impulses through liberation of acetylcholine. With this terminology, muscarine could be more accurately described as stimulating all cholinergic nerve-terminations.

The salivary and lacrimal **Glands**, the mucous glands of the mouth, throat, nose and deeper respiratory passages, the gastric secretory glands, the pancreas, and probably the intestinal glands, all secrete copiously after muscarine. The sweat glands and the ceruminous glands of the ears are likewise roused to unwonted activity, and many other glandular structures are also stimulated.

In most cases the solids of the secretions are increased as well as the fluids, although to a somewhat less extent. The bile, the urine and the milk do not seem to be affected directly although they may be reduced in amount or otherwise modified by the withdrawal of large quantities of fluid from the body by other channels.

After a small quantity of atropine, muscarine in ordinary quantities produces no increase in any of the secretions. This indicates that the seat of action of these poisons is not the secretory cells, for it has been shown that atropine paralyzes only the myoneural junctions and leaves the cells uninjured.

Involuntary Muscle.—Nausea and discomfort in the *stomach*, followed by retching and vomiting, form some of the earliest symptoms of muscarine poisoning.

The *intestines* are also set in unusually active movement by stimulation of the vagal terminations and repeated evacuation of their contents follows. These are at first of firm consistency, but later, as the continued peristalsis carries down the contents of the small intestine, which have

not lain long enough in the bowel to allow of the absorption of their fluid, the fæces contain more water than usual. This fluidity of the stools may also be due in part to an augmentation of the intestinal secretion. Even after the bowel has been completely evacuated, the persistent peristalsis betrays itself in painful straining.

The muscle of a number of other organs contracts from stimulation of receptors similar to those in the stomach and bowel. Thus the *spleen*, *bladder*, *ureters*, and pregnant *uterus* are contracted, and in the case of the bladder repeated evacuation and straining may occur.

In some other forms of muscle, muscarine causes contraction by acting on receptors which lie on the path of the nerve impulses. Thus in poisoning and also on local application, the *pupil* becomes extremely narrowed, and at the same time the *ciliary muscle* contracts so that the lens is accommodated for short distances. Both of these phenomena are due to stimulation of the myoneural junctions in the intraocular muscles (Fig. 29, p. 507), for atropine removes the contraction and at the same time interrupts the passage of impulses from the nerve to the muscle. The intraocular pressure is reduced by muscarine although it may be increased at first. This is due to the iris being drawn up by its contraction and thus allowing free egress to the intraocular fluids (see Atropine, p. 508).

The *bronchial muscles* are contracted, an effect which, together with the profuse bronchial secretion, may cause embarrassment of respiration.

The action on the **Circulation** presents some differences in different species of animals. On application to the frog's heart, its rhythm is at once slowed, the diastolic pause being much increased in length and the contractions lessened in force. Soon the heart ceases to beat entirely, although irritation of its muscle by mechanical or chemical means elicits one or more contractions. The symptoms produced are exactly those seen on stimulation of the vagus by electrical shocks. The point of action is not the ganglia on the inhibitory fibres, for muscarine is effective after these are completely paralyzed by nicotine, and it also acts on the apex of the frog's ventricle, in which no ganglia whatever have been found. The action must therefore be localized at some point between the ganglia and the actual contractile substance, for the latter maintains its normal character responding with contractions to stimuli. Muscarine is therefore generally held to stimulate the myoneural junctions between the inhibitory fibres and the contractile substance of the muscle. Atropine removes this standstill by paralyzing the junctions, but larger quantities of muscarine will again overcome the atropine action and restore the standstill or, at any rate, the slow beat. Digitalis and its allies remove the standstill by increasing the irritability of the muscle until the inhibition can no longer hold the heart in check, but through the rhythm caused by these the activity of the vagus can be seen in the slowness of the beat and the prolongation of the diastole. When the heart is slowed by muscarine, stimulation of the vagus is more effective than normally, the action of the drug being added to that of the electrical stimulus.

In rabbits and cats similar changes are seen in the circulation after

muscarine. The heart is slowed or brought to a complete standstill, the blood-pressure falls, and all the symptoms produced by anæmia of the brain may follow, but the animal becomes again perfectly normal on the administration of small quantities of atropine.

In dogs the stimulation of the inhibitory fibres seems sometimes to be entirely absent after muscarine, and in man this is very frequently the case. Instead of a slow pulse and lessened tension of the arteries, acceleration and increased blood-pressure are then observed. This is accompanied in man by marked palpitation and discomfort in the region of the heart and by dilatation of the skin vessels, especially of those of the face. In other cases, however, the same circulatory disturbances are produced as in the cat and rabbit. The acceleration of the heart and palpitation may perhaps arise from the nausea, which may be sufficient to overcome the inhibitory stimulation, or may result from stimulation of the adrenal gland leading to an outpouring of epinephrine.

In embryo hearts muscarine, in ordinary quantities, produces no change whatever during the first one hundred and fifty hours of life (in the chick). The explanation of this phenomenon is that the inhibitory nerves have not been developed at this stage, and after their development is complete, muscarine acts on the heart as in the adult. The absence of slowing in some of the invertebrates may be due to a similar cause, although this does not hold good for the crab, in which there is a well-defined inhibitory apparatus but in which muscarine causes acceleration.

According to Straub, muscarine acts on the heart only as it penetrates into the muscle cells, and once having arrived in the interior has no further action. If dilute solutions are applied to the heart, the alkaloid may slowly accumulate in the muscle without the heart being arrested. If now the muscarine be extracted from the muscle and applied to another heart in concentrated solution, this second heart is immediately arrested. The action therefore depends on the concentration in which the drug is applied and not on the amount in the muscle; in other words, the action is exerted in the process of absorption and not after absorption. Straub holds that atropine opposes muscarine by retarding its permeation into the cell and thus producing the same result as if the concentration of the muscarine solution were lessened. On adding more muscarine so as to render the solution very concentrated the permeation is accelerated in spite of the atropine, and the muscarine action reappears.

The **Respiratory** centre is not acted on directly by small quantities of muscarine, but the changes in the circulation lessen the amount of blood passing through the lungs, and the contraction of the bronchial muscle may seriously retard the movement of the air and thus impair the aëration of the blood. The œdema of the lungs which is often observed in cats and rabbits poisoned with the members of this series, and which has also occurred in fatal poisoning in man, arises from the slowing of the circulation through the lungs from the cardiac action.

Muscarine has practically never been introduced into medical practice, because, while its action on the secretions is quite equal to that of pilocarpine, the gastric symptoms are produced more readily by it. It is also a more powerful poison than pilocarpine, and is not procurable in pure form.

Mushroom Poisoning.—The symptoms of mushroom poisoning are often definitely suggestive of muscarine, *e. g.*, gastro-intestinal irritation, slow pulse and labored respiration. Consciousness may be unaffected, but delirium, convulsions or coma may ensue. Atropine will remove the symptoms due to the peripheral actions of muscarine. Active principles other than muscarine have been described in certain species of mushrooms and the poisonous effects are not invariably due solely to muscarine.

In Siberia the Agaricus muscarius is used to form an intoxicating beverage. The symptoms produced are hilarity and jollity, and the victims declare themselves to be more capable of fatiguing exertions than they would be without the preparation. Eventually giddiness and somnolence are produced, and after large quantities vomiting and convulsive attacks may follow and eventually prove fatal. The exhilarating effects are probably due to the presence of a poison discovered by Harmsen and not to the muscarine. This new poison seems to play a rôle at least as important as that of muscarine in cases of amanita poisoning; it is not antagonized by atropine, and its chemical nature is unknown.

2. Choline, Acetyl-choline, and Other Choline Esters.

Choline is a constituent of lecithin and is otherwise widely distributed in animal and vegetable tissues. A liter of blood plasma may contain 160 to 300 mg. of choline combined as lecithin. It is believed that small amounts of free choline exist in the circulating blood, but the amount occurring in blood or in extracts from tissues after death increases owing to autolysis of lecithin. The actions of choline were early found to resemble in many respects those of muscarine, to which it is chemically related. Thus it causes cardiac slowing, increased intestinal movements and increase of lacrimal, salivary and other secretions. In 1908 Reid Hunt described the actions of a number of esters of choline synthetically prepared. He found acetyl-choline especially active, having (in respect of its depressor action on the circulation) 100,000 times the activity of choline itself.

In 1914 Dale showed that choline and, with varying degrees of intensification, certain esters and ethers of choline, possess two distinct types of action—a "muscarine" action, paralyzed by atropine, and a "nicotine" action, paralyzed by excess of nicotine. Later Riesser showed that acetyl-choline could provoke contracture of skeletal muscle of amphibia.

These three types of action of acetyl-choline have assumed great importance in connection with the chemical transmission of nervous impulses. The outstanding impetus to this conception, which had been earlier foreshadowed, was given by Loewi's demonstration (1921) that the vagus nerve produces its effect on the frog's heart by liberating an inhibitor substance. He showed that this substance (later identified with considerable certainty as acetyl-choline), obtained in the fluid filling the heart, could be transferred to another heart and there reproduce the vagus effect. This conception has recently been extended by many workers, notably by Dale and his collaborators, and the view has

now been put forward that acetyl-choline may act as a "chemical transmitter" of nervous impulses, not only at the terminations of the post-ganglionic fibers of the parasympathetic nerves but at the autonomic ganglia and possibly at the terminations of the motor nerves in skeletal muscle. This view offers a new conception of the effect of nerve stimulation, which necessarily also alters our conception of the method of action of many drugs. The action of choline esters, therefore, possesses a new importance not only for physiology, but for pharmacology, immediate and remote. Here they can be considered merely as pharmacological agents.

The chemical formulæ of choline and of some of its more important derivatives are given below.

Choline	$(CH_3)_3{\equiv}N{\cdot}CH_2{\cdot}CH_2OH.$ HO/
Acetyl-choline	$(CH_3)_3{\equiv}N{\cdot}CH_2{\cdot}CH_2O{\cdot}CO{\cdot}CH_3.$ HO/
Muscarine	$(CH_3)_3{\equiv}N{\cdot}CH(CHO){\cdot}CH(C_2H_5)OH.$ HO/
β-methyl-choline	$(CH_3)_3{\equiv}N{\cdot}CH_2{\cdot}CH(CH_3){\cdot}OH.$ HO/
Acetyl-beta methyl choline	$(CH_3)_3{\equiv}N.CH_2.CH.CH_3O.CO.CH_3$ HO/
Homocholine	$(CH_3)_3{\equiv}N{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2OH.$ HO/
Carbaminoylcholine	$(CH_3)_3{\equiv}N{\cdot}CH_2{\cdot}CH_2O{\cdot}CO{\cdot}NH_2.$ HO/

Acetyl-choline.—Acetyl-choline is an unstable substance. It is rapidly hydrolyzed in the presence of alkali to choline and acetate, and has a maximum stability at pH 3.9. In presence of blood or extracts of most tissues, hydrolysis occurs very rapidly, due to a specific cholinesterase. The amount of this esterase varies widely in blood and different organs of different species, the activity of human blood or serum being very great. Physostigmine has a powerful inhibitory action on cholinesterase and a preliminary injection of physostigmine enhances the pharmacological effect of most choline esters. Acetyl-choline has a double action on the autonomic nervous system, producing effects (*a*) like muscarine and (*b*) like nicotine.

"Muscarine"-Action.—These effects are due to a stimulation of the terminations of the post-ganglionic fibres of the parasympathetic nerves and are, so far as is known, identical with those produced by muscarine. As these effects have already been described under the latter alkaloid, they need only be briefly recapitulated. Acetylcholine causes an increased secretion from the glands innervated by parasympathetic nerves, *e. g.*, salivary, lacrimal, intestinal, as well as of the sweat glands, which are innervated by the sympathetic. It causes a fall of blood-pressure due to dilatation of the vessels, slowing of the heart, and contraction of most forms of involuntary muscle, *e. g.*, of

the stomach, intestine, bronchi and uterus. All these effects can be prevented by a small dose of atropine.

"Nicotine"-Action.—These effects are due to a stimulation, followed by paralysis of all the autonomic ganglia of the body, including therefore those connected with the sympathetic as well as those on the course of the parasympathetic nerves. Clearly the result of this action will vary with the dosage. Among the effects under this heading may be mentioned a rise of blood-pressure after atropine. Atropine paralyzes the parasympathetic terminations and prevents both the slowing of the heart and the vasodilatation. Acetyl-choline stimulates the parasympathetic and sympathetic ganglia, but atropine prevents the effects of the former. Hence after atropine, acetylcholine stimulates only the sympathetic ganglia and consequently produces a rise of blood-pressure similar to that produced by epinephrine. Large doses of nicotine, by paralyzing these ganglia, prevent the rise of blood-pressure produced under these conditions. The rise may be augmented by an outpouring of epinephrine from the adrenal glands, which are stimulated by acetyl-choline.

Another action which acetyl-choline shares with nicotine is a stimulant action on voluntary muscles, most readily displayed on the normal muscles of some lower vertebrates and on the motor-denervated muscles of mammals. In the latter, the contraction is slow, but a rapid type of contraction has recently been shown to occur in the normal mammalian muscle (Simonart). This rapid contraction is readily inhibited by curare and is very sensitive to the action of ether and some narcotics. The muscle of the body wall of the leech is stimulated by acetyl-choline and this reaction, especially when sensitized by physostigmine, is one of the most delicate biological tests for acetyl-choline.

Following the fundamental demonstration by Loewi that stimulation of the vagus nerve to the heart causes the liberation of a substance later identified as acetyl-choline, the liberation of this substance has been shown to occur in many organs as the result of parasympathetic stimulation, *e. g.*, in the stomach, bladder, lungs and salivary glands. Evidence has also been brought forward to show that there is a liberation of acetyl-choline in ganglia when the preganglionic fibres are stimulated and in voluntary muscle when the motor nerves are stimulated.

The superior cervical ganglion of the cat perfused with Locke's solution containing glucose and physostigmine can synthesize acetylcholine during prolonged stimulation. If the perfusion fluid contains only inorganic salts, the synthesis will fail after a time due to fatigue of the ganglion. The fatigue can be overcome by the addition to the perfusion fluid of glucose, mannose, galactose, lactate, or pyruvate, as these substances promote the synthesis of the acetylcholine.

When an animal is curarized, the curare apparently forms a block between the acetylcholine and the receptive element of the muscle, or at least renders the receptive element resistant to the chemical. However, even with full curarization, acetylcholine is still formed upon nerve stimulation in quantitatively normal amounts. The relation of curare to acetylcholine formation and action in the case of the sympathetic ganglia is the same as is found in the skeletal muscles. When exhaustion occurs from repeated stimulation, no acetylcholine is released. Also in denervated muscle no acetylcholine is formed.

In the isolated sinus and auricles of the hearts of frogs and turtles extremely dilute solutions of acetylcholine cause weakening of the contractions without

any change in rate. On the ventricle of the turtle the drug is without effect, whereas on the basal, middle or apical portions of the ventricle of the frog it causes inhibition indicating the presence of vagal fibres in all these portions of the ventricle. On cultures of the chick heart which are contracting under the the conditions without nerves, acetylcholine has no effect.

The administration of acetylcholine brings about a lowering of blood sugar, which effect has been explained by stimulation of the islets in the pancreas through the vagus nerve producing an increased output of insulin.

Other Choline Compounds.—Acetyl-choline has been more carefully studied than any other ester of choline. Compared with it, propionylcholine has weaker muscarine-actions, but stronger nicotine-actions. With butyrylcholine the muscarine-actions are still feebler but the nicotine-actions remain about the same.

Carbaminoylcholine has an activity on the blood-pressure about equal to that of acetylcholine but it is much more stable and is effective when given by mouth. Administered to man intravenously in doses of 0.25 to 0.5 mg., carbaminoylcholine causes a rapid fall in both systolic and diastolic blood-pressure with a marked rise in pulse rate. These changes reach their maximum in about thirty seconds and then pass off equally rapidly. They may be accompanied by flushing of the head and neck and a feeling of heat throughout the body and a sensation of constriction in the throat and chest. These symptoms also pass off quickly.

When the drug is given by intramuscular injection, the symptoms are much the same as those described, except that their onset is slower and their duration more prolonged. The flushing and feeling of heat may be accompanied by salivation, lacrimation, sweating, a feeling of constriction in the throat, nausea, and a feeling of unrest in the abdomen. These symptoms, like the circulatory changes, usually pass off in about one-half hour. In some cases, they are quite severe and may lead to collapse. In such cases, prompt recovery follows an injection of atropine.

Carbaminoylcholine has been employed to a limited extent in clinical medicine, principally to lower blood-pressure and for its stimulating effect upon the gastro-intestinal tract. In the eye in glaucoma, dilute solutions (0.75 per cent) instilled into the conjunctival sac will cause a marked constriction of the iris and lowering of the intraocular pressure. For this purpose it may be combined with a very small amount of physostigmine, the latter drug intensifying and prolonging the action.

In general, the action of this compound in man is much the same as that of acetylcholine itself, except that the action is more prolonged and can be induced by intramuscular and subcutaneous administration as well as by the oral route, although the latter method is less reliable. Hunt and Taveau and later Simonart found that acetyl-β-methylcholine had a powerful muscarine-action, but that its nicotine-action is feeble or absent.

Acetyl-Beta-Methylcholine (Mecholyl or Mecholine).

Acetyl-beta-methylcholine (mecholyl or mecholine) has been shown to resemble acetylcholine quite closely in its effects, but differs from it in being a more stable compound, being less readily hydrolyzed than the acetyl compound. It can be administered by oral as well as by

parenteral avenues and is employed also for its local effects by means of electrophoresis.

On animals it produces effects similar to those of acetylcholine dependent mainly upon parasympathetic stimulation, as the nicotine-like effects are comparatively feeble. The drug produces changes in the heart characteristic of vagus stimulation, an increase in intestinal peristalsis and tone, constriction of the bronchi and contraction of isolated strips of uterine muscle. There is also salivation and vasodilatation.

In the normal human being doses from 10 to 25 mg. given by subcutaneous injection produce flushing, a feeling of heat, sweating, salivation, lacrimation, increased intestinal peristalsis, discomfort in the epigastrium, palpitation and a feeling of constriction under the sternum. The effects appear in two or three minutes and last for about thirty minutes. With the onset of the symptoms the blood-pressure falls and the heart rate increases. In certain individuals the symptoms appear very rapidly and the blood-pressure fall is so severe that a condition of collapse seems imminent necessitating the immediate injection of atropine, which alkaloid quickly removes the effects of the choline compound.

Slowing of the heart may be very marked when the drug is given intravenously and in some cases it has led to complete stoppage so that this method of administration is strongly contraindicated. The point of injection should not be massaged, as such manipulation will hasten absorption and possibly unduly intensify the symptoms. The blood-pressure fall may be rapid and marked, so that the patient should be in the recumbent position when the drug is given in order to prevent fainting. The drug is contraindicated in cases of hyperthyroidism, asthma, or in any severe illness. In persons susceptible to asthma it has not infrequently brought on typical attacks.

Therapeutic Uses. Acetyl-beta-methylcholine has been found useful in stopping attacks of paroxysmal tachycardia of auricular or supraventricular type. In general, smaller doses of the drug are needed in order to stop an attack in young persons than in persons of advanced years, doses of from 10 to 30 mg. being sufficient in those under middle age as against 30 to 50 mg. for the older group. The drug may be given orally or by injection in cases of chronic ulcers, Raynaud's disease, and other vasospastic conditions of the extremities. It has been found, however, that while the oral method of administration is beneficial at times in such cases, and also as a palliative in chronic arthritis, the method of administration by means of the galvanic current (electrophoresis, iontophoresis, or common ion transfer) is usually much more efficient.

In this method the direct or galvanic current is used to deposit the ions of certain salts which are in solution either on or in the tissues, where they may be taken up into the blood stream and exert systemic effects. Moreover, when it is desired to get the penetration of the drug into deeper tissues than is possible by simple topical application, the galvanic current has been employed recently and has proved efficient as a mode of administration of acetyl-beta-methylcholine in the treatment of certain vasospastic conditions of the extremities, in chronic ulcers, and as a palliative in rheumatoid arthritis.

To utilize the galvanic current in these conditions the active electrode is saturated with a 0.5 to 2 per cent solution of the acetyl-beta-methylcholine and

applied to the part to be treated. This is then wrapped (if an extremity or a joint) with a narrow strip of metal foil arranged to convey the current uniformly to the whole surface to be treated. This foil is connected to the positive pole of the electrical appliance while the negative pole is applied to the patient's back by means of a large dispersive electrode in order to complete the circuit. The strength of the current and the time of its flow will regulate the effectiveness of the ionization. Usually a strength of 40 to 50 milliamperes applied for perhaps twenty minutes is most satisfactory.

This method of application of acetyl-beta-methylcholine (and also of histamine) has been shown to produce local effects, such as vasodilation, which are not obtainable by the use of the drug orally or by injection. Also, while at times general systemic symptoms are obtained when this method is employed, these symptoms are less serious than when it is given by injection.

This method is of value especially in the treatment of chronic ulcers, scleroderma, Raynaud's disease, and other vasospastic conditions of the extremities. It has also acted as a palliative to the discomfort in some cases of chronic rheumatoid arthritis.

The methyl-, ethyl-, vinyl-, and butyl-, ethers of choline are less active than acetyl-choline, especially in respect to nicotine-actions. Acetyl-homocholine is much less active than acetyl-choline.

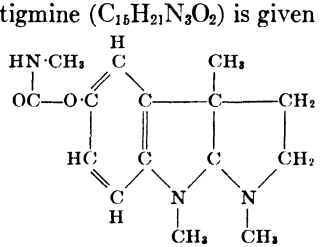
Muscarine can be regarded as choline with an aldehyde group in the α-position and an ethyl group in the β-position. It is possible that the ethyl group is responsible for the absence of nicotine-action, as Simonart has shown that the substitution of a methyl-group in the β-position deprives acetyl-choline of its nicotine-action.

Therapeutic Uses of Acetyl-choline.— Acetyl-choline has been tried, usually by subcutaneous injection, in a variety of conditions in which benefit might be expected from stimulation of parasympathetic nerves, *e. g.*, in high blood-pressure, Raynaud's disease, tachycardia, hypochlorhydria. Its action is evanescent, but some other compounds, especially acetyl-β-methylcholine, with a more prolonged action have been found more satisfactory for clinical use.

Choline and Fat Metabolism.—Choline administered subcutaneously has been found by Best to produce a curious effect on fat metabolism. It prevents the accumulation of fat in the liver of starved animals or of dogs kept alive by insulin after removal of the pancreas. This effect does not seem to be related to the purely pharmacological actions of choline or its compounds.

3. Physostigmine.

Physostigmine or Eserine is the chief alkaloid of the Calabar bean, or Ordeal bean (Physostigma venenosum), which grows in Western Africa and was employed there by the natives in the trials by ordeal for witchcraft. Either physostigmine itself, or a nearly allied alkaloid, occurs also in the Kali or Cali nuts, the seeds of Mucuna urens. The constitution of physostigmine ($C_{15}H_{21}N_3O_2$) is given below.



The actions of physostigmine were first examined in detail by Fraser who described (1863–1868) the constriction of the pupil, slowing of the heart, and increase of glandular secretions produced by this alkaloid. Later it was classed with muscarine in that its effects could be partly explained by its stimulating parasympathetic nerve-ends. Hunt (1918) found that it had a sensitizing effect on the actions of acetylcholine and later Loewi showed that minute amounts of physostigmine inhibited the activity of the specific esterase which inactivates acetyl-choline. The peripheral actions of physostigmine are therefore partly indirect, due to its prolonging the action of acetyl-choline liberated at the nerve-ends and probably partly to a direct action of the alkaloid itself. (See page 484.)

A number of other alkaloids have been stated to occur in Calabar bean, but their existence is not sufficiently established in most cases and little is known of their action. They have been named *Calabarine, Isophysostigmine, Geneserine, Eseredine,* etc. According to Heathcote, eseridine possesses about one-tenth of the activity of physostigmine and acts similarly.

Symptoms.—The symptoms of poisoning vary but little in different animals; in the dog and rabbit the first results of a large dose of physostigmine are weakness in the voluntary movements and a curious tremor and muscular twitching, beginning in the hind legs, but soon extending over the whole body. The animal falls on one side and cannot raise itself again, although it makes efforts to do so when touched. The saliva and tears are increased, the bowel is often evacuated and in the dog vomiting is common. The respiration is at first rapid and deep, and later slow and dyspnœic, the heart is weak and slow, and the pupil is contracted to a small point. These symptoms become more marked as more of the poison reaches the blood, until the respiration ceases. In cats these symptoms of depression and paralysis are preceded by a stage of increased movement and evident anxiety, but the later symptoms resemble those in the dog. In man physostigmine elicits practically the same results as in the dog, vomiting and pain in the stomach region, dyspnœa, giddiness and muscular weakness, contraction of the pupil, salivation, and perspiration. The heart is slow, muscular twitching may be present, and complete collapse follows. In frogs the voluntary movements disappear soon after the injection of physostigmine, the respiration ceases, and last of all the reflexes are paralyzed.

Central Nervous System.—In cases of poisoning in man, the consciousness is preserved until late, which indicates that the highest functions of the brain are not directly affected by physostigmine. The motor cerebral cortex is apparently rendered more excitable, for in epileptics the number and intensity of the seizures increase under its use, and in guinea-pigs rendered epileptic by operative procedures the same aggravation is seen after it. In the dog epileptiform convulsions occur occasionally, while in the cat a stage of excitement is generally present, and irregular muscular movements, such as nystagmus, are seen in these and other animals. It is possible, however, that some of these

effects may arise from the peripheral action of the poison, for example from the partial asphyxia from broncho-constriction; they all disappear after the injection of atropine. The depression and muscular weakness which are seen in animals under large doses probably arise from affection of lower parts of the central nervous system and resemble the condition known as collapse more than that of narcosis.

Quite apart from these central effects, physostigmine causes twitching of the voluntary muscles which is not prevented by division of the nerves and is therefore peripheral in origin; this symptom is not marked in the frog, but may be so developed in mammals as to simulate convulsions. It is arrested by curare, but not by atropine. Curare and physostigmine are mutual antagonists, for the paralysis of curare may be removed by physostigmine and on the other hand the twitching induced by physostigmine is arrested by curare; and this suggests that they act at the same point Acetyl-choline produces a similar effect on muscle which is accentuated by physostigmine and Simonart suggests that the fibrillary twitches produced by physostigmine are really due to acetyl-choline.

Physostigmine has also been shown to remove the paralyzing effect of nicotine and curare upon the gangha of both sympathetic and parasympathetic systems. Soon after the stimulation of the peripheral ends of the vagus or of the cervical sympathetic nerves has ceased to have an effect due to the paralyzing action of either of the two drugs, the nerves will once more display normal activity if a small dose of physostigmine is injected. This action of the physostigmine is due to its removal of the block produced by the curare or nicotine to the acetyl-choline transmission of the nerve impulse through the synapses, either by lowering the threshold of the ganglionic cells to acetyl-choline or by increasing the amount of acetyl-choline available by preventing its destruction by the choline esterase.

There is also a mutual antagonistic action between atropine and physostigmine as relatively small doses of atropine will protect the animal against the action of physostigmine on the secretory system, on the smooth muscle, and also prevent the clonic convulsions characteristic of toxic doses of the drug. It does not prevent the muscular fibrillation of physostigmine, and its antagonism against the effect on the respiration is incomplete.

The **Respiration** is at first somewhat accelerated and then becomes slow and weak. The preliminary acceleration may arise from central stimulation, or possibly from partial asphyxia due to constriction of the bronchi. The subsequent weakness and slowness of the breathing is undoubtedly of central origin, and death follows from the failure of the respiratory centre.

The changes in the **Circulation** require further investigation. Small doses slow the pulse and increase the blood-pressure, while larger doses are followed by greater slowing of the heart and a fall in the blood-pressure. In the dog the slowing of the heart is due to stimulation of the vagal terminations and is prevented by atropine, but in the rabbit and frog this does not occur (Heathcote). According to several observers, the irritability of the terminations of the inhibitory fibres in the heart is increased, so that stimulation of the vagus is more effective after physostigmine—an observation that readily falls into line with the view that vagus stimulation causes an output of acetyl-choline and that physostigmine augments this action by inhibiting the effect of cholinesterase.

The increased blood-pressure has also been the subject of some discussion. It seems independent, in part at least, of the vasomotor centre, for it is not prevented by section of the spinal cord or of the splanchnic nerves, operations which prevent impulses from the centre reaching the vessels. It may be partly due to the powerful contraction of the intestines expelling the blood from the mesenteric area, or to a stimulation of the vasomotor ganglia.

The frog's heart beats more slowly after physostigmine, but here the individual contractions are said to be strengthened and prolonged, and there is definite evidence of stimulation of the heart muscle, which is not seen in mammals. If the vagus be stimulated in the frog after physostigmine, it produces slowing but no complete standstill of the heart, because the irritability of the muscle is so much augmented that the inhibitory apparatus can no longer entirely control it. If such a poison as muscarine produces complete standstill, physostigmine removes it, not by depressing the inhibitory apparatus, but by increasing the irritability of the muscle.

The **Secretions** are increased by physostigmine as by pilocarpine and muscarine; thus the *saliva*, the *tears*, the *perspiration*, the *mucus* secretion and the *pancreatic juice* are all augmented.

Muscle.- Physostigmine produces powerful contractions of the *Stomach*, *Intestine*, *Uterus*, *Ureter*, *Bladder*, *Spleen* and *Bronchial Muscle* resembling those elicited by muscarine and pilocarpine.

The *Intraocular Muscles* also undergo contraction, and their movements under physostigmine have been the subject of a large number of investigations and of a good deal of controversy. The pupil contracts when physostigmine is employed either locally or internally, and this contraction may be lessened by the subsequent application of atropine, but is not altogether removed except by large quantities. On the other hand, the dilatation of the pupil produced by small quantities of atropine may be diminished by physostigmine, but the resulting contraction is much less than that caused by physostigmine applied to the normal eye. The ciliary muscle is acted on in the same way as the iris, so that the eye becomes accommodated for near distance, and atropine induces the same modifications. The effects of physostigmine, then, on the secretory organs, pupil and ciliary muscle are strictly analogous, and are generally attributed to the alkaloid stimulating the terminations of the nerves in these organs. The antagonism of physostigmine to atropine is more complete than that of pilocarpine, for a renewal of the contraction can be elicited more easily by the former alkaloid. The intraocular pressure is reduced by the application of physostigmine to the eye and this has generally been attributed to the contraction of the pupil facilitating the escape of the fluid by allowing it freer access to the spaces of Fontana. Another factor may be contraction of the intraocular vessels, which lessens the secretion. In the *stomach* physostigmine produces an increase in tone in from three to ten minutes, the organ becoming smaller and the outline sharper. This increased tone may last for an hour. The peristaltic waves are deep and powerful and force the gastric contents through the pylorus

more rapidly than normal. These effects of physostigmine on the stomach may be of considerable value when roentgenological examinations of the organ are being made.

Peripheral Action.—It has been discussed whether physostigmine actually stimulates the myoneural junctions, that is, causes impulses to be emitted by them as pilocarpine does, or whether it merely renders them more sensitive to stimuli descending the nerve fibres; the latter seems to be the case in some instances, for it is found that when the chorda tympani nerve is cut physostigmine often fails to cause secretion, though electrical stimulation of the nerve is more efficient than before. In other instances physostigmine appears to act after the impulses from above are excluded, so that here it has the same action as pilocarpine. It is possible that the failure of physostigmine to contract the pupil after degeneration of the postganglionic ciliary branches may be due to the exclusion of the impulses from the centres (Loewi and Mansfeld). Another explanation of the action of physostigmine is provided by Loewi, which relates it to the humoral transmission of parasympathetic impulses (v. Acetyl-choline, p. 483). He found that acetyl-choline is readily destroyed by an esterase in the blood and tissues and that physostigmine has a specific effect in preventing this destruction. This would explain its failure to act on denervated organs in which no acetyl-choline is liberated. Stedman has found that, of a series of compounds related to physostigmine, those which exhibited miotic activity also possessed the property of inhibiting the activity of esterases. This supports the probability that the actions of physostigmine are due to its inhibiting the activity of cholinesterase. Whether this effect on esterases accounts for the entire pharmacological activity of physostigmine or whether the alkaloid has an additional direct action has been recently investigated by Manning, Lang and Hall who have shown that amounts of physostigmine which are too small to produce demonstrable pharmacological effects will yet be sufficient to inhibit the cholinesterase and at the same time enhance parasympathetic excitability.

The alkaloid itself does not elicit its own specific pharmacological response until a sufficient dose is given to exceed the quantity necessary to inhibit the esterase to a maximal degree.

The effect of the inhibition of the cholinesterase is to prevent the rapid destruction of acetyl-choline with resulting exaggeration of the effects of vagus stimulation or of amounts of acetyl-choline which might be injected. When the saturation point of the enzyme system by physostigmine is reached, inhibition is maximal and now additional amounts of the alkaloid will produce parasympathetic effects.

The action of physostigmine is further complicated by its increasing the amount of epinephrine secreted into the blood. This may act in the same direction as physostigmine, for example, on the motor fibres of the uterus, or may oppose it, for example, by inhibiting the movements of the intestine which physostigmine augments; in some conditions the injection of physostigmine may actually arrest peristalsis from this secondary effect.

Physostigmine increases the blood sugar of rats, the maximum

increase being in one hour with return to normal in two hours. This action is prevented by the previous administration of atropine.

Physostigmine and strychnine are said to act synergistically in the production of hyperglycemia in rats, the combination of both drugs producing a greater increase in blood sugar than the sum of effects of each given separately.

Some physostigmine is **Excreted** in the urine, but most of that ingested is destroyed in the tissues. It has also been found in the saliva and bile.

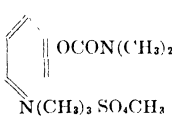
The symptoms of poisoning with Calabar bean are identical with those caused by physostigmine, except when an old preparation is used, when some stimulation of the spinal cord may be induced.

Therapeutic Uses.—In recent years physostigmine has been given in cases of atony of the intestine leading to tympanites and meteorism. However, it is used chiefly for its action on the intraocular muscles and tension. For this purpose a solution of $\frac{1}{3}$ to 1 per cent is dropped in the eye, 2 to 4 drops at a time, or small discs of gelatin impregnated with the alkaloid may be applied to the conjunctiva (B. P.). The pupil begins to contract in five to fifteen minutes, and attains its smallest size in half an hour. It remains contracted twelve to fourteen hours; according to some observers a difference in the size of the two pupils may be made out for several days. The ciliary muscle contracts along with the iris, and vision becomes accommodated for short distances. This action on the accommodation passes off in two to four hours, but the sight is often rendered indistinct for some hours. The action of physostigmine on the eye differs from that of muscarine, for the former acts more on the pupil, the latter on the ciliary muscle, and the pupil is often contracted by physostigmine while the accommodation is practically unchanged. The intraocular pressure is somewhat increased at first but subsequently sinks. Its action in narrowing the pupil after atropine has been made use of to remove the dilatation produced so frequently in ophthalmological practice. It antagonizes the dilatation of the pupil after homatropine and cocaine much more successfully than that due to atropine. Physostigmine is extensively employed to reduce the intraocular pressure in glaucoma. Physostigmine is useful in roentgenological examination of the stomach as by increasing the tone it makes the outline sharper.

Recently physostigmine, or one of its analogues, has been much used in the treatment of myasthenia gravis. The paresis of voluntary muscles in this disease resembles that which occurs in curare poisoning and physostigmine can to a certain extent remove the paralysis produced by curare. Anticipating that physostigmine might have a similar restorative effect in myasthenia gravis, Walker tried the alkaloid as a remedy (1934) with striking results. In most cases physostigmine produces a remarkable strengthening of the paretic muscles. The effect lasts for a few hours. Atropine, given previously or simultaneously largely prevents the disagreeable symptoms of parasympathetic stimulation produced by physostigmine, without diminishing the action of the latter alkaloid on voluntary muscles. Prostigmine and some other

members of the physostigmine group act similarly and seem to possess some advantages over physostigmine itself for this purpose (*v. i.* below).

Analogues of Physostigmine.—Stedman investigated a large number of synthetic compounds related to physostigmine and showed that the pharmacological activity of physostigmine depends on the presence in the molecule of the methyl-carbamic ester group—$CH_3NH \cdot COO$. Other substances containing this group were found to possess a miotic action similar to that of physostigmine, and, generally, all compounds of the general formula $RNHCOOC_6H_4R'$, where R was a methyl or ethyl group and R' a basic substituent such as $-N(CH_3)_2$. The activity was greatest when R was a methyl group, as occurs in physostigmine itself. Aeschlimann and Reinert investigated a further series of such compounds and showed that one of these (the dimethyl-carbamic ester of m-hydroxyphenyl-trimethylammonium-methylsulphate) was as active as physostigmine in stimulating intestinal peristalsis but had less effect on the heart and circulation. This compound has the following formula:



Sold commercially under the name "*Prostigmin*," this compound has been extensively used as a substitute for physostigmine in the treatment of intestinal atony. More recently it has been employed in the treatment of myasthenia gravis with successful results. Walker found that a dose of 2 mg. hypodermically relieved the paresis in eight minutes, the effect lasting five to six hours. As with physostigmine, atropine given at the same time prevents the colic and nausea, without affecting the action on the nerve-ends in voluntary muscle. Given by mouth, physostigmine in corresponding doses caused more nausea and the effect on voluntary muscles was delayed and less intense. It is claimed that prostigmine has advantages over physostigmine in being less depressant to the heart, less excitant to the stomach and probably safer in effective doses.

On the human stomach Veach, Laner and James found that prostigmine exerted an inhibitory action and that atropine following it produced a motor effect. However, if atropine were given first exerting its usual inhibitory action, a subsequent injection of prostigmine had a stimulating effect. Prostigmine is constantly motor to the colon and this action is removed by atropine.

Prostigmine exerts a definite synergistic action on the effects of mecholyl (acetyl-beta-methyl-choline chloride) on the sweat glands, flushing, gastric secretion and cardiovascular system in man. For instance, prostigmine itself produces no sweating, flushing or lacrimation, and mecholyl produces these effects only to a minor degree but if mecholyl is given a few minutes after a small dose of prostigmine, it is followed by a very marked reaction. This reaction may take the form of local sweating, or in case of the gastric secretion, the acid content drops very suddenly and the quantity of gastric juice increases greatly.

In the cardiovascular system the synergistic action is equally well marked. Doses of 5 mg. of mecholyl may cause a slight increase in heart rate and blood-pressure; rarely a fall in pressure. If the mecholyl is given a few minutes after 0.5 mg. of prostigmine, the reaction is usually very pronounced, even leading

to collapse. There is a very pronounced fall in blood-pressure together with an increase in pulse rate followed by a marked fall. With larger doses of mecholyl following the prostigmine, the cardiac changes are more severe with sinus bradycardia and partial or total heart block. These effects can be prevented or removed by the use of atropine.

Certain substances which are related to physostigmine other than prostigmine have also an anticurare action. Perhaps the best known is the methylphenyl carbamic ester of 3-oxyphenyl trimethyl ammonium methyl sulfate (substance 36). This compound has been shown to act antagonistically to curare and like prostigmine it has been used successfully in myasthenia gravis.

Guanidine, $CNH(NH_2)_2$, and methylguanidine, $CNHNH_2NHCH_3$, two bases occurring in animals and plants, resemble physostigmine in their effects, causing fibrillary twitching of the muscles, which is opposed by curare and obviously arises from stimulation of the same myoneural receptors as are affected by physostigmine. Vomiting, salivation, bronchial spasm also occur as under physostigmine. On the other hand the central nervous system is more distinctly stimulated, for violent convulsions are induced by guanidine, these arising partly from the brain and partly from the cord. These bases are of special interest as they are regarded as the poisons involved in the idiopathic tetany of children and in the similar convulsive attacks in animals after the removal of the parathyroid gland (Paton). Collip, however, has found that the convulsive attacks produced by injection of guanidine are not relieved by the parathyroid hormone and the available evidence suggests that parathyroid tetany is due chiefly to lowering of the blood calcium.

Paton and others observed that guanidine may produce hypoglycæmia and Frank and his co-workers made an extensive study of guanidine derivatives with a view to finding a substance with a more pronounced hypoglycæmic effect but lower toxicity. As a result they introduced decamethylene-diguanidine ($NH_2 \cdot NH:C\ NH(CH_2)_{10}NH\ C:NH\ NH_2$) **(Synthalin)** as a remedy for diabetes mellitus, and it has had a fairly extensive trial in this disease. It lowers the blood sugar and acts when given by mouth. It is not nearly so effective as insulin and does not act in the same way; for example, the hypoglycæmia produced by synthalin does not respond to epinephrine as does that produced by insulin. It may produce anorexia, nausea, vomiting, diarrhœa and jaundice. The available evidence goes to show that synthalin produces hypoglycæmia by a toxic action on the liver. A number of analogues of synthalin have been investigated and hypoglycæmia has been found to run parallel with liver damage, due to a toxic action on the liver. The dosage of synthalin is difficult to regulate and, on the whole, the results with it have been disappointing. Its use is still advocated by some authorities, especially in milder forms of diabetes, and if insulin be contraindicated or refused. The dodecamethylene compound (Synthalin B) has similar hypoglycæmic properties but is said to produce fewer side reactions. The toxic symptoms are lessened by the simultaneous administration of decholin (Adler).

Preparations.

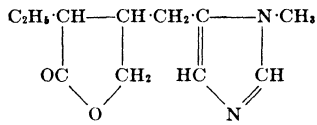
Physostigminæ Salicylas, eserine salicylate (U. S. P.), 0.002 G. ($\frac{1}{30}$ gr.); B. P., 0.0006–0.0012 G. ($\frac{1}{100}$–$\frac{1}{50}$ gr.).

Lamellæ Physostigminæ (B. P.), each containing $\frac{1}{1000}$ gr. of physostigmine salicylate.

The salicylate of physostigmine forms colorless or faintly yellow crystals, without odor, but possessing a bitter taste. The salicylate has usually a slight acid reaction, and is soluble in about 100 parts of cold, or 30 parts of boiling water. It undergoes decomposition when kept in solution and then assumes a reddish-brown color; the addition of boric or sulphurous acid to the solution is said to retard this decomposition.

4. Pilocarpine.

Pilocarpine is an alkaloid found with Isopilocarpine in the leaves of several species of Pilocarpus. It has the following structural formula:



Pilocarpine stimulates the terminations of the postganglionic fibres of the parasympathetic nerves. It therefore acts in the same way as muscarine and the symptoms produced by both are nearly identical. Pilocarpine does not potentiate the actions of acetyl-choline as does physostigmine.

Pilocarpine stimulates the secretion of all *glands* innervated by the parasympathetic nerves, *e. g.*, salivary, lacrimal, gastric, intestinal and bronchial glands. The salivary secretion may amount to one-half litre or more in the course of two or three hours after an injection of pilocarpine, while the skin and lungs excrete even a larger quantity of fluid in the same time. The weight is thus considerably reduced by pilocarpine, owing to the loss of fluid, which may, according to some authors, amount to 2–4 kilograms after a single dose. The increased activity of the glands is accompanied by an acceleration of the blood current through them. This may be partly due to the increased activity of the glands, though pilocarpine may also have a direct dilator effect on the vessels supplying them.

Pilocarpine produces a profuse secretion from the bronchial glands. Large doses may produce dangerous pulmonary œdema from aspiration of fluid as well as from the depression of the circulation.

The sweat glands, though innervated by the sympathetic, are also stimulated by pilocarpine. In man it is found that, in cases of complete interruption of the nervous paths in the cord, small doses of pilocarpine cause no sweating in the lower part of the body. This does not seem due to the division of the secretory fibres proper, for division of the sympathetic nerves alone does not impair the sweating under pilocarpine; more probably the failure of pilocarpine to cause sweating in these cases arises from the disturbance of the circulation through the break in the afferent and vasodilator path (Burn). All those effects on glands are prevented by atropine, as is shown for the gastric secretion in Fig. 28.

Salivary glands which have had the chorda tympani cut respond to the injection of pilocarpine more promptly and more vigorously than do the normal intact glands. This increased response which appears in two or three weeks after cutting the nerve was found to exist undiminished for a year afterwards. No explanation can be given for this increased response to the drug.

Pilocarpine also stimulates the parasympathetic terminations in involuntary muscle, *e. g.*, of the alimentary canal, bronchi, spleen, bladder, ureters, etc. Repeated evacuations of intestines may occur from stimu-

lation of both muscle and glands. There may be frequent emptying of the bladder with straining. Retching and vomiting occur less often with pilocarpine than with muscarine. Pilocarpine causes contraction of the pupil, and of the ciliary muscle, with a lowering of intraocular pressure. The pupil of the rat is exceptional in being dilated by pilocarpine. Pilocarpine has no effect on the pupil in birds, in which the muscle of the iris is striated.

In normal dogs pilocarpine promoted the emptying of the stomach during the earlier part of the process, but later it caused some delay. In dogs with denervated stomachs it shortened both the initial and the final emptying time, hastening the progress of the intestinal contents along regardless of their state of digestion. In dogs with intact sympathetic nerves pilocarpine failed to shorten the emptying time.

In the normal human subject pilocarpine favored initial emptying of the stomach, but as in dogs the final emptying was somewhat delayed. The early favorable effect on evacuation appeared to be due to an increased gastric tone due to heightened vagal activity.

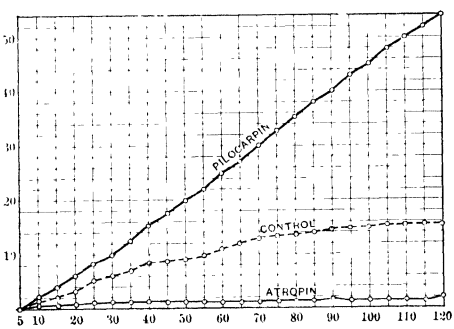


FIG. 28. - Chart of the gastric secretion in the dog under pilocarpine and atropine. Three observations were made in one milk alone was given, in another milk with pilocarpine, and in a third milk with atropine. The amount of secretion was noted in a small isolated pouch of the stomach, and is indicated graphically in the chart. (Riegel.)

The effects produced by pilocarpine on the **circulation** are somewhat variable according to the species as well as the dose administered. They differ in some respects from those produced by muscarine. Like muscarine, pilocarpine locally applied causes slowing or actual diastolic standstill of the heart from stimulation of the vagus endings, an effect prevented by atropine. When injected intravenously pilocarpine produces, in rabbits and cats a fall of blood-pressure due to slowing of the heart and dilatation of the arterioles. Pilocarpine differs from muscarine here in several particulars, for it soon depresses the inhibitory fibres and the heart regains its former rhythm, but the cardiac muscle is then affected, so that the contractions rapidly become weaker and slower again, and this secondary slowing is not removed by atropine; the vasomotor centre also becomes gradually weakened by large doses, so that the blood-vessels remain somewhat dilated, and the arterial tension remains low even after atropine. In the decapitate (but not in the decerebrate nor in the anæsthetized) cat, the fall of blood-pressure which

follows on the injection of pilocarpine, is succeeded by a secondary rise of considerable height and duration. This may be due to a stimulant action on the preganglionic sympathetic fibres (Heaton and MacKeith), which may explain some of the anomalous effects on the circulation produced by pilocarpine. In dogs and in man, the stimulation of the inhibitory fibres seems sometimes to be absent, and acceleration of the pulse occurs, accompanied by palpitation, with a rise of blood-pressure.

It has been found that pilocarpine increases the **Leucocytes** of the blood, from its action on the spleen and other leucocyte-forming tissues; it is possible that the leucocytes are pressed out of the spleen by the contractions of the smooth muscle. Both polymorphonuclear and mononuclear cells are increased in the blood. Ruzicka states that the Malpighian corpuscles of the spleen are increased in number after pilocarpine.

Administered to normal rats pilocarpine causes a marked increase in *blood sugar*, the maximum effect being attained in fifteen minutes with return to the normal level in one hour. These changes in blood sugar are prevented by the administration of atropine.

The **Temperature** is said to be increased by pilocarpine, although only to a very small extent, and the carbonic acid excretion is increased through the drug increasing the activity of the glands and other organs. After the perspiration is fully developed the internal temperature is generally reduced, especially in fever.

Some symptoms occur in cases of poisoning which point to some action of the alkaloid on the **Central Nervous System.** Thus frogs develop well-marked convulsions, and even in the higher animals and man tremor and slight convulsive movements, such as hiccough, have been observed. The collapse which is seen in the later stages may be central in origin but probably is largely the result of the peripheral action, and the convulsions, which occur in some cases, arise from anæmia of the brain as the result of the cardiac weakness.

Therapeutic Uses of Pilocarpine.—Its action on the sweat glands renders pilocarpine much the most powerful sudorific in the pharmacopœia, and it is used internally almost exclusively for this purpose. In various conditions in which excess of fluid accumulates in the body, pilocarpine may be exhibited to remove it. In dropsy, especially that due to renal disease, a few injections frequently reduce the fluid and remove the effects of the accumulation, although they do not, of course, affect the diseased tissues directly. By unburdening the blood and tissues of their excessive fluid, however, pilocarpine may improve the nutrition of the kidney, and thereby promote its recovery. In dropsy due to heart disease pilocarpine must be used with caution, owing to its action on the heart. In some other exudations pilocarpine has also been advised, as in pleural, pericardial, and subretinal effusion. It must be remembered that after the sweating produced by pilocarpine there usually sets in a period of depression, weakness and languor, and this may be sufficient to counteract the improvement obtained by the removal of the fluid. It is still a disputed point whether pilocarpine

possesses any advantage as a sudorific over the other means of producing sweating, such as hot or cold packs. Its advocates point to the fact that much less disturbance of the patient is required, and that the subsequent depression is not greater, while its opponents assert that the hot or cold pack produces less depression and is not accompanied by the unpleasant salivation and occasional nausea of pilocarpine. Accumulations of fluid in the body may also be removed by way of the bowel by the use of a hydragogue cathartic or preferably a saline purgative, or the kidney may be stimulated to special activity by the use of such diuretics as theobromine and caffeine. The last method of treatment is that generally preferred as it induces less weakness and depression subsequently than either of the others. The sweating induced by pilocarpine is much more profuse than that seen after the nauseating diaphoretics such as ipecacuanha, and no such effects are claimed for pilocarpine as for these in fever.

In uræmia pilocarpine sometimes proves of great benefit if exhibited early, and it has been supposed that this was due to the skin taking up the renal function vicariously and eliminating the poison. Some support has been given this explanation by the discovery of traces of urea in the perspiration after pilocarpine, but it is now recognized that the urea is not the poisonous principle in uræmia, and the beneficial effects are probably due rather to the removal of fluid and the relief of the overstrained circulation. It has also been suggested that pilocarpine acts directly on the kidney, and an increase in the urine is not infrequently seen after several injections; but this is to be ascribed rather to the changes in the circulation following the removal of the fluid than to any direct action on the renal epithelium, for which there does not exist any satisfactory experimental evidence.

In ophthalmology pilocarpine has been employed as a substitute for physostigmine, to contract the pupil and reduce the intraocular pressure. For this purpose a dilute solution of the nitrate (2 per cent) may be used, or gelatin lamellæ may be prescribed, each containing $\frac{1}{4}$ mg. ($\frac{1}{250}$ gr.), to be laid on the conjunctiva. The contraction of the pupil generally attains its maximum in about one-half to one hour, and passes off in three to five hours; it is less complete and of shorter duration than that seen after physostigmine. Pilocarpine is said to first increase and then lower the intraocular tension.

In various diseases of the ear, pilocarpine has been used with good effects in some cases, but it is quite unknown how it acts here. The conditions in which it is of service are various forms of labyrinthine disease, and some forms of effusion into the tympanic cavity.

Pilocarpine is frequently prescribed in lotions for the hair, and a renewed growth of the hair has been frequently seen in alopecia treated in this way. This has been explained by its action on the glands of the skin, increasing the moisture of the scalp and improving its circulation and nutrition, but Tappeiner found that the local application of pilocarpine to the skin produces no increase in the secretion of the glands.

In cases of atropine poisoning, the use of pilocarpine is quite unjustified as the danger arises from the central nervous system in which the action of atropine is not antagonized by pilocarpine. In poisoning from pilocarpine or muscarine small quantities of atropine are the antidote recommended alike by pharmacological experiment and by clinical experience.

PILOCARPINÆ NITRAS (U. S. P., B. P.) ($C_{11}H_{16}N_2O_2.HNO_3$), the nitrate of an alkaloid obtained from Pilocarpus leaves, forms a white crystalline powder, which is soluble in about 8 parts of cold water. 0.005 G. ($\frac{1}{12}$ gr.); B. P., 0.003–0.012 G. ($\frac{1}{20}$–$\frac{1}{5}$ gr.).

Arecoline ($C_8H_{13}NO_2$), one of the alkaloids contained in Betel nut (Areca catechu) resembles pilocarpine in its actions but is more powerful.

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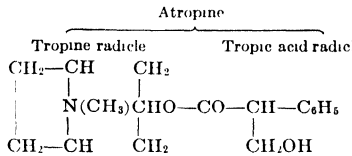
III. SUBSTANCES DEPRESSING PARASYMPATHETIC NERVE ENDS.

1. The Atropine Series.

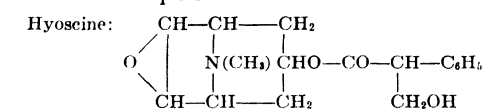
The atropine series contains a number of very closely allied alkaloids of which the chief are *Atropine*, *Hyoscyamine* and *Hyoscine* or *Scopolamine*. They are found in many plants of the Solanaceæ order, and in most cases several of them occur together.

Atropine ($C_{17}H_{23}O_3N$) may be broken up by alkalies into an alkaloid, *Tropine*, and *Tropic Acid*. The former is a pyridine compound very closely allied to *Ecgonine* (see Cocaine) as may be seen by its structural formula, while the latter is an aromatic acid.



Atropine is racemic hyoscyamine, that is, it consists of equal parts of lævohyoscyamine and dextrohyoscyamine, but, as the latter is only feebly active in the body, the action of atropine is practically that of its lævohyoscyamine half. Lævohyoscyamine is formed in the plants, but is readily changed to atropine in the plant cells and also in the process of extraction, so that the relative proportion of the isomers in the plants and in the preparations varies. Indeed, it is quite probable that atropine itself does not exist as such in the plants but that it is formed from the l-hyoscyamine in the process of extraction.

Hyoscine or *Scopolamine* ($C_{17}H_{21}NO_4$) is very closely allied to atropine, and is decomposed into tropic acid and *Scopoline* (*Oscine*), which is nearly related to tropine.

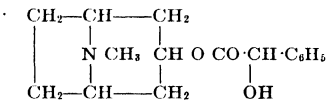


A number of other alkaloids have been described in different plants, generally associated with one or more of those already mentioned. But on examination these have generally proved to be mixtures of atropine, hyoscyamine and hyoscine. Thus the *Duboisine* of Duboisia myoporoides, the *Mandragorine* of Mandragora (Mandrake) and the *Daturine* of Datura stramonium have all failed to maintain their position as new bases and have proved to be mixtures of the established alkaloids in varying proportions. *Atropamine*, *Belladonnine* or *Apoatropine*, is found along with atropine in some plants (belladonna), and may be formed synthetically from atropine by the removal of a molecule of water; it is a compound of tropine and atropic acid. *Pseudo-hyoscyamine* is said to differ from atropine and hyoscyamine in some of its chemical relations, but has not been the subject of much work as yet. *Atroscine* is isomeric with hyoscine and the same relation exists between them as between atropine and hyoscyamine.

After atropine had been found to be a compound of tropine and tropic acid, a number of other acids were attached to tropine in the same way as tropic acid. These artificial alkaloids are known as *Tro-*

peines, and in action resemble atropine in some points while differing from it in others. The only artificial tropine which has as yet been used in medicine is the ester of tropine and mandelic acid known as *Homatropine*. *Scopoleines* have been formed by substituting other acids for the tropic acid of scopolamine, but none of them has proved of value in therapeutics as yet.

Homatropine·



It must be understood that the combination of tropine and its allies with tropic acid does not partake in any way of the nature of the combination of an ordinary alkaloid, such as morphine, with an acid. The bond is the much closer one seen in the compound ethers, and the resulting substance is alkaline and combines with acids to form salts exactly as other alkaloids do.

The chief plants containing these alkaloids are Atropa belladonna (Deadly nightshade), Hyoscyamus niger (Henbane), and Datura stramonium (Thornapple).

Of less importance are Duboisia myoporoides, Scopola atropoides, and Mandragora autumnalis, or Atropa mandragora (Mandrake); another species of Duboisia contains nicotine.

A number of other Solananceæ—*e. g.*, tobacco and potato leaves, are said to contain small quantities of the atropine alkaloids but the quantity present here is too small to be of any importance.

These alkaloids all resemble each other closely in the effects produced by them in animals. Some differences in the symptoms exist, however, and the action of atropine alone will first be described and later the points in which that of hyoscyamine and of scopolamine differ from it.

Atropine acts as a stimulant, and in toxic doses as a depressant, to the central nervous system. It also affects a number of organs, especially those containing smooth muscle or secreting glands, producing its effects largely by paralyzing the terminations of the parasympathetic nerves.

Symptoms.—In man, $\frac{1}{100}$ gr. (0.6 mg.) causes some dryness of the mouth and throat, and thirst; the skin also feels dry, and the heart may be accelerated after a short period of slowing. Doses of $\frac{1}{25}$ gr. (2.5 mgs.) are followed by marked dryness of the skin and throat, thirst, difficulty in swallowing and hoarseness in speaking. There is often nausea, and in some cases vomiting, headache, and giddiness; the pupils are wider than normal and the sight may be indistinct, especially for near objects. The respiration may be quicker and the pulse often beats at one hundred per minute or more. A symptom that is often present, though by no means invariably so, is redness of the skin, especially of the head and neck; the conjunctiva may also be congested. After larger doses the same symptoms are observed, but are soon followed by others of graver import. The patient can no longer swallow, although suffering from intense thirst, the heart is generally extremely rapid, speech

is difficult and hoarse, and the pupils are dilated until the iris almost disappears. Restlessness and garrulity point to an increase in the irritability of the brain; the patient at first talks in a perfectly normal way but soon becomes confused, begins a sentence and does not finish it, often bursts into laughter or sobs, and in short becomes delirious and eventually maniacal. Often marked tremor of different muscles may be observed, and eventually convulsions set in and may be the cause of death through the failure of the respiration. As a general rule, however, the stage of excitement passes into one of depression, the patient sinks into a sleep, which deepens into stupor and coma, the respiration and heart become slow, weak and irregular, and death eventually occurs from asphyxia.

In the frog the injection of small quantities of atropine is followed by a period of depression and paralysis of the peripheral nerve terminations resembling that seen under curare; after a few days there supervenes a stage of increased reflex excitability and tonic convulsions indistinguishable from those seen under strychnine. This stage slowly passes off and the animal again becomes normal.

Action.—These symptoms in man and other mammals, indicate stimulation of the **Central Nervous System** followed by depression. Those observed in man sometimes resemble those seen in the excitement stage of alcohol poisoning, and it has been suggested that in both the cause is rather a lessening of the control normally exercised by the higher powers over the lower motor areas than a true stimulation of the latter. But this is shown to be incorrect by the fact that in atropine poisoning the motor area is more easily stimulated by the electric current than normally. The stimulant action of atropine is also seen in the increased reflex response to irritation of the skin, as well as in the augmented activity of the centres in the medulla. The nervous symptoms under atropine, therefore, arise from true stimulation of the central nervous system, but they are wholly different from those produced by strychnine, because the latter acts especially on the lower parts of the nervous axis, while atropine acts more strongly on the higher divisions. The most marked symptoms of strychnine poisoning arise from the spinal cord and medulla oblongata, and consist in increased reflex movements and convulsions, while those caused by atropine are rather to be referred to the brain, and consist of increased coördinated movements, such as talking and delirium, the exaggerated reflex being of minor importance.

Atropine differs from caffeine, on the other hand, in its effect on the brain, for under the latter the psychical functions are those affected first of all. It would seem probable, then, that each of these three stimulates the whole of the central nervous system more or less, but that while strychnine acts more strongly on the lower divisions, the spinal cord and medulla, and caffeine on the highest functions, the psychical, atropine occupies a midway position, and exercises its chief action on the motor divisions of the brain. These are rendered so excitable that the controlling areas can no longer keep them in check, and an increase in movement occurs somewhat resembling that seen when the controlling areas are depressed by alcohol. The stimulant

action spreads downward when large quantities have been absorbed, and involves the medulla oblongata and spinal cord, so that symptoms resembling those seen in strychnine poisoning may make their appearance. After the stimulation has lasted some time, depression sets in and may go on to complete paralysis of the central nervous system, which is fatal to mammals through cessation of the respiration. Even during the stimulation stage some symptoms of depression are to be made out, exactly as has been described under strychnine.

The peripheral action of atropine involves a number of secretory glands, organs containing unstriped muscular tissue, and the heart.

Generally this action can be described as a paralyzing action on the post-ganglionic terminations of parasympathetic nerves, and is an action antagonistic to that of the muscarine group. Atropine prevents the peripheral actions of acetyl-choline, although it does not interfere with the liberation of acetyl-choline which occurs at the nerve-ends upon nerve stimulation. It rather renders the tissues insensitive to the action of acetyl-choline. Atropine acts on the terminations of some nerves (*e. g.*, to the sweat glands) associated anatomically with the sympathetic, rather than the parasympathetic, division, but in such cases there is reason to believe that these sympathetic nerves exceptionally transmit their impulses by discharge of acetyl-choline, and that they are, in Dale's terminology, "cholinergic" rather than "adrenergic" nerves.

Most of the **Secretions** are decreased by the application of atropine —salivary, gastric, pancreatic, mucus, and sweat. This is due, not to any action upon the secretory cells, but to the failure of nervous impulses. It has been investigated most carefully in the salivary glands, but enough work has been done on the others to show that the process is the same in all. The *secretion of saliva* in the normal animal seems to occur only when impulses reach the gland cells by one of two paths—through the chorda tympani, or through the cervical sympathetic fibres. If the chorda tympani be divided and put on electrodes and a cannula be passed into Wharton's duct, a rapid flow of saliva occurs on stimulation of the nerve, which ceases or is very much diminished on stopping the stimulation. If now atropine be injected, stimulation causes no increase in the secretion, and atropine, therefore, seems to paralyze some part of the peripheral secretory apparatus. The chorda tympani passes through ganglion cells on its way to the gland cells, and the impulses might be hindered in their passages through these, as actually occurs under the action of some drugs. But this is not the explanation of the inefficiency of chorda stimulation, as is shown by the fact that if the electrodes be pushed into the hilus of the gland so as to stimulate the nerve fibres beyond the ganglia no secretion follows. Another explanation would be that the gland cells themselves are paralyzed by atropine, but this is shown not to be the case, for on stimulating the sympathetic, which supplies the same cells as the chorda tympani, the usual secretion follows. The site of action of atropine, therefore, seems to lie between the ganglion cells on the course of the chorda tympani and the secretory cells, that is, the point of attack is the terminations of the nerve fibres in the gland cells. The secretion of saliva seems to occur generally only on the arrival of impulses

by way of the chorda tympani, so that on the paralysis of its terminations the secretion ceases entirely.

In the same way the other *glands of the mouth, throat, nose and respiratory passages* cease secreting after atropine, and the effect is the characteristic dryness of the mouth, the hoarseness of the voice, and the thirst and difficulty in swallowing complained of after its administration.

The secretion of the *gastric juice* has been shown to be diminished or entirely arrested by atropine, which paralyzes the terminations of the secretory fibres of the pneumogastric nerve in the stomach (Fig. 28, p. 497). The hydrochloric acid of the secretion is more reduced than either the pepsin or the fluid as a whole. The secretion of *pancreatic juice* is reduced after atropine, and stimulation of the pneumogastric has no effect on it, while in the normal animal it accelerates the flow. The secretion induced by the specific pancreatic hormone, secretin, continues, showing that atropine does not act on the cells of the pancreas, but only isolates them from the pneumogastric nerve. But as the formation of secretin depends on the passage of hydrochloric acid into the duodenum, and this is lessened by the action on the gastric glands, the pancreatic secretion is further reduced in this indirect way.

Gray, investigating the possible relationship of histamine to gastrin, showed that while atropine will completely abolish the gastric secretory response to a meal, which secretion is presumably due to gastrin (or histamine), it will not completely prevent the secretion produced by an equivalent amount of histamine. This discrepancy would seem to show either that histamine is not the humoral gastric secretory excitant, or that the atropine prevents its formation when a meal is taken.

The secretion of *tears* is diminished by atropine, presumably from the interruption of the nervous connections of the lacrimal glands. The *bile* is also said to be somewhat lessened by atropine. The interchange of glycogen and sugar in the liver is not affected by atropine, according to recent investigations (McGuigan), but on the other hand some forms of hyperglycæmia seem to be lessened by it.

The same paralysis is produced in the terminations of the nerves in the *sweat glands*. Stimulation of the sciatic nerve as a general rule causes perspiration in the foot of the cat and dog, but after atropine this effect is absent, because the impulses cannot reach the cells through the paralyzed terminations, and the skin therefore becomes dry and hot. The local application of atropine to the skin has no effect on the sweat secretion, as it does not penetrate to the glands. The secretion of *milk* is not materially changed by atropine, whether the alkaloid is carried to it by the blood or is applied locally. This is in accord with the physiological observation that the mammary gland continues to secrete after all its nerves have been cut and allowed to degenerate; in other words the mammary secretion is largely independent of the nervous system.

The *kidney* is not controlled by secretory nerves, and atropine causes little or no change in the amount of urine except through the arrest of the other secretions. The *secretion of lymph* is not altered by atropine, so that it also is not controlled by nerves in the same way as the true

secretions. The secretion of the suprarenal glands is not affected by atropine though it is controlled by nerves more directly.

All **Organs Containing Unstriped Muscle** (apart from the arterial wall) seem to be altered by atropine. Thus the movements of the pupil and œsophagus (except in animals in which these consist of striped muscle), stomach, intestine, bladder, uterus, spleen and thoracic duct are affected by atropine.

The dilatation of the *pupil* occurs on internal administration as well as on the application of minute quantities locally, and is due to paralysis

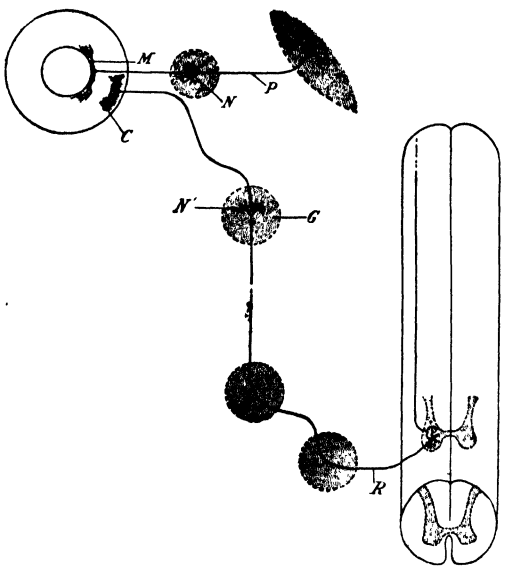


FIG. 29.—Diagram of the innervation of the iris. *P*, A fibre of the motor oculi passing from the brain to the ciliary ganglion (*N*), in which it terminates around a nerve cell, which sends an axis cylinder to terminate, *M*, in the circular fibres of the iris. *R*, A sympathetic nerve fibre issuing from the lower cervical cord, running through the stellate and inferior cervical ganglia and terminating around a ganglion cell in the superior cervical ganglion, *G*. The axis cylinder from this nerve cell runs to the iris (passing the ciliary ganglion) and terminates, *C*, on the radiating fibres. *M* is the point acted on by atropine and muscarine. *N*, *N'*, The ganglion cells, are the seat of action of nicotine. *C*, The terminations in the dilator fibres, that of epinephrine.

of the myoneural junctions in the circular muscle of the iris. This is shown by the fact that stimulation of the motor oculi nerve or of the postganglionic fibres from the ciliary ganglion is without effect. This limits the paralysis to the periphery, and that the muscle is not acted on is shown by its reacting to electrical stimulation. The local nature of the action may be further shown by carefully applying a minute quantity of the drug to one side of the cornea, when dilatation of one half or less of the pupil occurs, the rest remaining contracted. The motor oculi (Fig. 29) constantly transmits impulses through the ciliary nerves to the sphincter muscle of the iris and keeps the pupil moderately

contracted, and when these impulses can no longer reach the iris owing to the interruption of the path, the sphincter relaxes and the pupil dilates. The contractile substance does not seem to be affected by the ordinary application of atropine, but if strong solutions be continuously applied, it may be paralyzed by it as by many other drugs. Atropine antagonizes the action of pilocarpine in the pupil after degeneration of the motor oculi, and the receptor for these alkaloids therefore does not undergo degeneration and must be situated in the muscle between the nerve ends and the contractile substance.

The constrictor muscle is constantly opposed by dilator fibres, and when the former is thrown out of activity by the paralysis of the terminations of the motor oculi, the radiating fibres cause an active dilatation. If, however, the radiating muscular fibres be separated from their innervating centre by section of the cervical sympathetic nerve in the neck, they also cease to contract and there is no active dilatation, so that atropine causes less widening of the pupil than it would if impulses continued to reach the radiating muscle. After the application of atropine to the eye, the iris often relaxes with sufficient force to tear weak adhesions to the lens, and if the iris be attached at two points to the lens, atropine causes a bow-shaped dilatation between them, the concavity being directed inward. The dilatation is therefore an active movement, accomplished by the contraction of the radiating muscular fibres, but these are not put in motion by the action of atropine on the radiating muscles of the iris, or their nerves, but by the normal impulses descending from the central nervous system, which after atropine are not counterbalanced by impulses reaching the circular fibres.

The dilatation of the pupil effected by atropine is not quite maximal, for stimulation of the cervical sympathetic trunk generally increases it, though but slightly. It differs considerably in different animals, being more complete in man, the dog and the cat than in the rabbit, entirely absent in birds and reptiles, and elicited with difficulty in the frog. In birds and reptiles the iris consists of striped muscle fibres, and accordingly atropine has no action on the nerve terminations.

When complete dilatation is attained, the pupil ceases to contract in bright light, as the impulses descending from the central nervous system are prevented from reaching the muscle, although the rest of the reflex arc is intact. The retina is unprotected from bright light and this often gives rise to pain and discomfort in the eyes and headache.

Besides the dilatation of the pupil, a further result of the application of atropine to the eye is the paralysis of the *accommodation*. Near objects are no longer seen clearly, while distant ones are as distinct as formerly or may be even more distinct to some eyes. The action is here again on the myoneural junction, in this case in the ciliary muscle. On local application the paralysis of accommodation occurs later, and disappears earlier, than the dilatation of the pupil, and larger quantities are required to produce it.

The *intraocular pressure* appears to be unchanged by atropine in the normal eye, but when there is a tendency to hypernormal pressure, atropine often augments it considerably, whether it is applied locally or is carried to the eye by the circulation. This is apparently the indirect result of the dilation of the pupil, by which the lymph outflow

is obstructed; in the normal eye this is not sufficient to raise the pressure, but in eyes in which the outflow is already deficient the additional hindrance may suffice to increase the tension and precipitate an attack of glaucoma.

The *bronchial muscle* normally contracts when the pneumogastric nerve is stimulated, but makes no response after atropine, which paralyzes the myoneural terminations; the sympathetic fibres which inhibit the bronchial muscle and dilate the bronchi are unaffected by atropine.

The terminations of the nerves in the unstriped muscle of the *œsophagus* are affected in the same way as in the bronchial muscle. A curious contrast has been noted by Luchsinger in the behavior of the œsophagus in rabbits and cats, in the former of which the muscle is striated, while in the latter the upper part is striated, the lower is unstriated. Atropine, he found, paralyzes the vagus in those parts which are unstriped, while

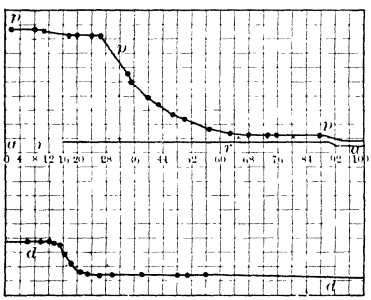


FIG. 30

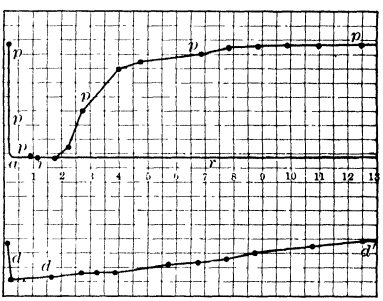


FIG. 31

FIGS. 30 and 31.—Charts of the changes in the accommodation (*pp*) and in the pupil (*dd*) under atropine. The impairment of the accommodation and the widening of the pupil are indicated by downward movements of the lines, while the return to the normal is shown by an upward movement. In Fig. 30 the time from the application of atropine is given in minutes to show the beginning of the action, in Fig. 31 the time is in days to show the gradual recovery. (After Donders.)

leaving unaffected those in which the fibres are striped. Exactly the opposite occurs after curare, which paralyzes the nerve supply of the striped muscle, while leaving the unstriped active.

It is possible that the difficulty in swallowing, which is present in cases of poisoning by atropine, may be due in part to the paralysis of the motor nerve, but it is generally attributed to the absence of the mucous secretion and consequent dryness of the passages.

Atropine has generally a sedative effect on the movements of the *stomach* and *intestine*, though vomiting has sometimes been observed in cases of poisoning, and less often free evacuation of the contents of the bowel. After very small quantities the normal peristalsis is not affected, and the movement induced by ordinary doses of the purgatives is not arrested, but the griping pains resulting from large doses or from the more violent purgatives are absent or less marked if atropine is given along with them. Similarly, the violent peristaltic and

tetanic contractions seen after such poisons as pilocarpine and muscarine are prevented by the preliminary injection of atropine.

These results suggested that atropine paralyzes the terminations of some of the extrinsic nerves of the stomach and bowel in the same way as it paralyzes the oculomotor terminations in the iris. But this proves to be incorrect, for the vagus and splanchnic nerves continue to exert their ordinary influence after atropine. In fact, these small doses of atropine appear to arrest only certain abnormal violent forms of contraction, and as they do this without interfering with the normal peristalsis and without interrupting the path of nervous impulses from the brain to the bowel, it must be accepted that these abnormal forms arise from some mechanism which is distinct from that presiding over the ordinary peristalsis, and which does not lie on the path of the nerve impulses.

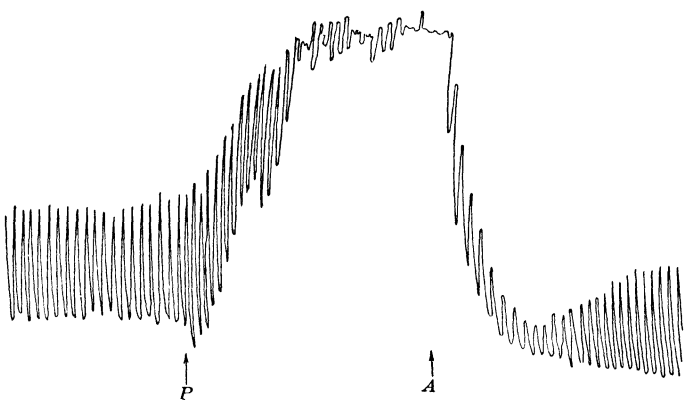


FIG. 32.—Movements of the intestine. At *P*, pilocarpine causes a violent tetanic contraction, which is maintained until at *A* atropine is applied, when the spasm is immediately relieved. The normal pendulum movements continue afterwards. (Magnus.)

This action on abnormal contractions is the only one induced by therapeutic doses of atropine, but in animal experiments large quantities tend to increase the peristalsis from some action exerted on the plexus of Auerbach (Magnus). It is possible that this increased peristalsis may account for the vomiting and purging sometimes seen in cases of poisoning. Finally, very large quantities paralyze the muscle fibres, but this probably does not occur in the intact animal.

Atropine exercises the same sedative effect on the movements of other organs as on those of the bowel. Thus, the *spleen, uterus, gall-bladder, ureters, urinary bladder* and the *other ducts* of the genito-urinary tract react like the stomach and bowel, several poisons failing to induce contractions after atropine, while stimulation of the nerves continues to be effective. It has been observed frequently in cases of poisoning that the urine is ejected soon after the ingestion of the poison, and subsequently there is a desire to micturate without the ability to do so.

Atropine paralyzes the **Inhibitory Terminations of the Vagus in the**

Heart, and stimulation of this nerve therefore causes no change in the pulse after its administration. Nicotine in large doses also removes the inhibitory power of the vagus, but acts on a different part of the nerve, namely, on the ganglia. That atropine does not act here but on the terminations has been shown by a number of observations. Thus, in the normal frog's heart, and even after paralysis of the ganglia on the course of the vagus, electrical stimulation of the sinus venosus causes slowing and standstill of the heart, because the stimulus reaches the postganglionic nerve fibres (Fig. 26, p. 469); but after atropine, no slowing follows stimulation of the sinus. Again, several drugs stimulate the ends of the vagus in the heart and act on parts in which no ganglia exist, but these drugs have no effect whatever after atropine. Small quantities of atropine have no further action on the heart than the paralysis of the inhibitory nerve ends. The terminations of the acceler-

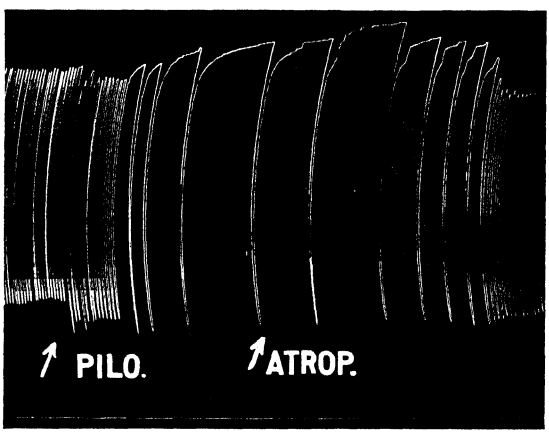


FIG. 33.—Tracing from heart of a turtle showing the effect of pilocarpine and atropine applied directly to the heart. Rather slow absorption. Lever moves down in systole.

ator nerve are unaffected, exactly as the terminations of the sympathetic in the salivary glands, and the heart muscle is neither stimulated nor depressed. The heart is therefore placed in the same position as if the vagus were divided in the neck, and, accordingly, it is accelerated in some animals, while in others the rhythm is unchanged. In the dog there is marked quickening of the heart after atropine, because normally impulses are constantly transmitted from the inhibitory centre in the medulla, and these prevent the heart from beating as rapidly as it would if freed from the nervous control. In the cat the tone of the vagus is less, and the changes produced by atropine are correspondingly smaller, while in the rabbit and frog there is generally no inhibitory retardation of the heart, and atropine therefore produces little change. In man the effects vary considerably with the age of the patient. The inhibitory fibres seem almost inactive at birth, but their tone increases with age up to twenty-five to thirty-five years, and from this time lessens again.

Atropine does not quicken the heart in the newborn child, but up to about thirty the acceleration increases with the age, and from this point onwards it lessens again until the heart is accelerated by only 4 to 5 beats per minute in patients between eighty and ninety years. Along with the acceleration of the pulse the other effects of vagus section are also produced—increase in the extent of systole, decrease in the diastole and augmentation of the output of the heart per minute.

Stimulation of the vagus causes no retardation of the pulse after an ordinary dose of atropine, but, on the contrary, is not infrequently followed by acceleration from the presence of accelerator fibres which are not affected by atropine. But it is found that if a minimal amount of atropine is given, so that slight vagus stimulation has no effect, a very strong current may still slow the heart; the terminations are so weakened that feeble impulses fail to reach the heart, but strong impulses can still force their way through the block. (Pilcher and Sollmann.)

Large quantities of atropine, besides paralyzing the vagus, weaken and depress the heart muscle, and the contractions consequently become slower and weaker and the output of the heart is less than normal. Even therapeutic doses injected hypodermically in man slow the pulse for a short time, possibly from direct action on the heart muscle, but more probably from stimulation of the vagus centre before the nerve terminations are paralyzed; the first effect is thus a fall in the pulse rate followed by marked acceleration.

The **Peripheral Action** of therapeutic doses of atropine is due to its paralyzing receptors in a number of organs. Some of these are normally put in action by nerve impulses, which they transmit to the contractile or secretory cells, and their paralysis by atropine leads to the failure of part of the nervous control of the organ (many glands, pupil, bronchial muscle, œsophagus, and heart). In other organs the receptors do not lie in the path of nerve impulses and their paralysis by atropine therefore does not affect the nervous control of these organs (muscle of stomach, intestine, spleen, uterus, and bladder). The effect of atropine on these organs is in fact only detected by the cessation of unusual movements induced by certain poisons and by some pathological conditions (see also muscarine and pilocarpine, p. 479). The organs thus affected receive their innervation from the autonomic system, and, with few exceptions, from the parasympathetic division. Atropine prevents the actions of acetylcholine on parasympathetic nerve ends, but not the action on voluntary muscle.

The voluntary **Muscles** are not directly affected by atropine. An action similar to that of curare is seen in the frog under large doses. In mammals the twitching induced by physostigmine through its action on the myoneural junctions is, according to some authors, antagonized by large doses of atropine; but no true curare action is induced by atropine in mammals.

The terminations of the **Sensory Nerves** are depressed by its local application. Thus, when atropine is applied to an irritated surface of the skin or to a mucous membrane, numbness is produced and the sensation of pain is lessened; no such effect occurs when atropine ointment is rubbed on the unbroken skin and the local anæsthetic effect is not elicited by its internal administration.

Circulation.—The changes in the circulation under atropine arise for the most part from the changes in the heart. The blood-pressure often falls for a few minutes at first and then rises above the normal from the acceleration, when this is marked. But the rise in pressure from the acceleration is not great unless there is unusual activity of the inhibitory mechanism previously. There is no evidence that the vasoconstrictor centre in the medulla is excited by atropine. In normal animals there is thus no evidence that atropine acts on the vessels or on the nerve ends in them; but in animals whose vessels are dilated by acetylcholine, atropine immediately counteracts this effect, which indicates that it possesses some vascular action. Very large amounts of atropine depress the heart and consequently the blood-pressure falls; the respiration fails in cases of poisoning before the heart is seriously injured. In poisoning there is often flushing of the skin of the head and neck and a rash resembling that of scarlet fever, and these have been regarded as due to dilatation of the arterioles from stimulation of the vasodilator centre; the flush is said to disappear on section of the cervical sympathetic cord, which would suggest its central origin. The rash usually disappears after a few hours, but is sometimes followed in a day or two by desquamation.

The action of atropine on the **Respiration** has been the subject of much discussion. In therapeutic doses, its only effect is to relax the bronchi, and the respiratory centre is unaffected; larger amounts accelerate the breathing from stimulation of the centre and increased formation of carbon dioxide. In severe poisoning this quickened breathing is frequently interrupted by convulsive movements, and such an interruption often proves to be final. If it returns, the movements become shallower and slower in the stage of depression of the nervous centres, and the failure of the respiration is the cause of death in fatal cases of poisoning.

Atropine often induces a marked rise in **Temperature**, the cause of which cannot be said to be definitely known. According to Ott, the dissipation of heat is increased, but the heat formation undergoes a still greater augmentation. This seems to be independent of the circulatory changes and also of the convulsions, and is attributed by him to direct action on the heat centres of the brain.

Distribution and Excretion.—Atropine is rapidly absorbed and may be found in most organs. It is excreted in the urine in man and most animals, partly as unchanged atropine, partly broken up into tropine; from a third to a half of that ingested reappears in the urine, and traces have been found in the milk and also in the fœtal blood. The rest of the atropine undergoes oxidation in the body, apparently in the liver; in some rabbits, which show a very high congenital tolerance, much of the atropine ingested undergoes decomposition in the blood plasma, being apparently hydrolyzed into tropine and tropic acid. In other rabbits no such action occurs in the blood and these do not acquire this power even when treated for a long time with atropine; they may be endowed with it, however, by the injection of the serum of an animal which already possesses it, and even cats which do not normally destroy atropine in the plasma are also enabled to do so by the injection of the

active serum of a rabbit (Schinz); the blood of man, the dog and many other animals does not seem to possess this property.

Tolerance.—Most animals withstand much larger quantities of atropine than man, and an especial degree of tolerance is met with in the herbivora; rabbits, for example, may be fed for weeks on belladonna leaves without showing any symptoms; this is undoubtedly the result of the active decomposition of the alkaloid which occurs in their plasma. It has also been observed that the action of atropine on the heart and other organs passes off more quickly in rabbits than in other animals and this again arises from the atropine being destroyed so rapidly. A certain degree of tolerance may be acquired by other animals through the continued administration of atropine, which ceases to elicit the symptoms from the central nervous system in the doses previously sufficient and later seems to have a weaker and shorter action on the peripheral organs.

In his studies upon the rôle played by the liver in the disposal of atropine and indirectly upon the question of tolerance, De Saram found that the amount of atropine which could be tolerated by rabbits, if the injection were made into the portal vein, was about twice the amount which would prove fatal if it were injected into an ear vein. He concludes, therefore, that the liver is important as a detoxifying agent. In *in vitro* experiments with emulsions of liver cells there was no evidence of destruction of the alkaloid by the cells themselves, so that it would seem that the atropine must be stored in certain cells of the liver from which it is taken up slowly and excreted by the kidneys. According to De Saram, there is little evidence of a specific detoxifying action by the liver apart from its ability to temporarily store the drug.

Hyoscyamine is rarely obtainable in pure form, as it is almost always mixed with atropine, into which it changes when kept in solution and perhaps even when dry. It paralyzes the same peripheral mechanisms as atropine, but acts almost exactly twice as strongly on them. Its action on the central nervous system in mammals resembles that of atropine and the fatal dose is the same, but in the frog it has less tendency to cause convulsions. No narcotic influence is exercised on either frogs or mammals; the belief that it induces sleep is founded on observations in which scopolamine was mixed with the hyoscyamine employed.

The action of atropine, as has been stated, is compounded of that of natural or lævorotary, hyoscyamine with that of its dextrorotary isomer. The latter does not exist free in nature and possesses little or no action on the nerve terminations, while it stimulates the spinal cord of the frog more than either atropine or hyoscyamine. The peripheral action of atropine is thus due to its containing *l*-hyoscyamine, and as a grain of atropine contains only half a grain of *l*-hyoscyamine the former naturally exercises only half the effect of a grain of *l*-hyoscyamine. On the other hand, the half grain of dextrorotary hyoscyamine in a grain of atropine is almost inert on the nerve terminations, but exercises the same effect on the central nervous system as its lævorotary complement. Atropine thus acts on the central nervous system in mammals in the same strength as hyoscyamine, but only half as strongly in the periphery.

Von Oettingen and Marshall found that the ratio of potency of atropine and its two isomers differed according to the species of animal employed and the structure studied, and even that sera of different rabbits varied in their ability to destroy the alkaloids. They explain this as being due, in part at least, to

the relative rates at which the alkaloids are destroyed in the body. They showed that rabbit serum may destroy the laevohyoscyamine the most rapidly of the three alkaloids and the dextrocompound more slowly than the racemic atropine which stood intermediate in this respect. Thus there might be quite a variation in responsiveness of different rabbits to these alkaloids and therefore to the relative ratio of potency assigned to the different members of the series.

Scopolamine or **Hyoscine** resembles atropine closely in its peripheral action, except that it passes off more quickly. The inhibitory terminations in the heart are paralyzed; but the therapeutic dose in man is too small to elicit this effect, and the pulse is therefore unaltered in rate or may be slower, owing to the hypnotic action. Applied to the conjunctiva it produces mydriasis and loss of accommodation more quickly than atropine, but for a much shorter time; pure scopolamine acts about twice as strongly on the nerve terminations as atropine, or about equally strongly with hyoscyamine. The effects on the central nervous system present the greatest divergencies from those described under atropine, for the characteristic stimulation is absent in the great majority of cases. As a general rule, scopolamine produces a marked sensation of fatigue and drowsiness, the patient moves about less and speaks less, and a condition in no way dissimilar to the natural sleep follows. In many cases, however, a short stage of excitement with giddiness, uncertain movements and difficult and indistinct speech precedes sleep, and occasionally symptoms exactly resembling those produced by atropine follow the administration of scopolamine, especially if large doses are employed. Sleep generally lasts from five to eight hours, and the patient may then remain quiet for several hours longer. As a general rule, after small doses no confusion is complained of on awakening, but dryness of the throat and thirst are often present. Larger doses do not cause deeper sleep but give rise to delirium and excitement resembling those following atropine. In one or two cases collapse has been observed after scopolamine. The respiratory centre does not seem to be stimulated as by atropine, the respiration generally becoming slower from the beginning.

In the lower mammals scopolamine reduces the excitability of the motor areas as tested by electric shocks, while the reflex excitability in the frog is not increased as by atropine. Scopolamine appears to be excreted or destroyed in the tissues much more rapidly than atropine, for its effects last a shorter time.

The action of scopolamine, then, seems to correspond with that of atropine, save that the central nervous system is here depressed, while the action on the peripheral nerve ends is of shorter duration. It depresses the brain in very small quantities, $\frac{1}{2}$ mg. ($\frac{1}{120}$ gr.) being generally sufficient to induce quiet. The therapeutic dose is well below the fatal dose but medicinal doses occasionally produce toxic symptoms, apparently a form of idiosyncrasy. A certain degree of tolerance is produced after repeated use, so that the dose has to be increased after a week or two.

Scopolamine is much less reliable as a hypnotic than morphine or the members of the chloral group. It is most effective when sleep is

prevented by motor excitement, and the sleep seems to arise from the relief of this condition and not from depression of the consciousness.

Scopolamine is lævorotary to polarized light; the racemic form, which is often present in commercial scopolamine, acts only one-half as strongly on the peripheral organs, because in it the lævorotary alkaloid is mixed with the dextrorotary isomer, which is almost inactive. The cerebral action is equal, however, in the two forms.

The other natural alkaloids have been less carefully examined than the three foregoing and possess no therapeutic interest.

Among the artificial tropeines only one has received much attention at the hands of either experimental or practical therapeutists. This is **Homatropine**, a compound of tropine and mandelic acid, which resembles atropine in its action, but is much less poisonous. When applied to the eye, it dilates the pupil almost as rapidly as atropine, but less completely, and the action passes off much sooner. It has less tendency to increase the intraocular tension than atropine owing to its shorter action.

Methylatropine or **Eumydrin**, a synthetic compound of atropine, has been used to some extent in ophthalmology. Its mydriatic action is more prompt and less enduring than that of atropine and it is less poisonous.

Homatropinemethylbromide (Novatropine) has been introduced as a substitute for atropine in the treatment of gastro-intestinal spasm and hyperchlorhydria. The advantages claimed for it are that it is less toxic than atropine, that its cerebral effects are less marked and that side effects, such as cycloplegia and dryness of the mouth and skin, are also less pronounced. The ratio of toxicity of atropine to novatropine as reported by different investigators has differed somewhat, but it would seem to be in the neighborhood of 1 to 33. Slight cerebral symptoms have resulted from the use of maximum doses, but no cumulative effects have been reported. Novatropine is a white crystalline powder easily soluble in water and is usually prescribed in tablet form, each tablet containing $\frac{1}{24}$ gr. (2.5 mg.), 1 to 2 tablets being taken three times daily before meals.

Syntropan, the phosphate of the tropic acid ester of diethylaminodimethyl propanol, is used as a substitute for atropine, especially for those purposes for which an action on smooth muscle is concerned. For most animals it is less toxic than is atropine. Its mydriatic action on the eye of the cat is much weaker than that of atropine, as is also its action in suppressing salivation. Its action as a depressant of the parasympathetic nervous system is also much weaker than is that of atropine. However, as a depressant of spasm of smooth muscle, its potency approaches much closer to atropine in that it not only possesses an action on the nervous mechanism similar to that of atropine, but also exerts a direct action on the muscular tissue itself. Judging from these experimental findings, it would seem that the drug would be useful in cases of spasm of smooth muscle.

The field of usefulness of syntropan has not been definitely established

as yet, but it has been used in such conditions as are associated with spasm of the blood-vessels such as coronary spasm, and angina.

It is also recommended in gastric spasms, and colic due to cholelithiasis and in spastic conditions of the bladder and ureters.

Syntropan is a white crystalline powder soluble in water. It is administered in 50-mg. doses in tablet form– 1 tablet being given three or four times daily. It can also be given by intramuscular or subcutaneous injection in 10-mg. doses.

The other tropeines vary in their action on the lower animals, some of them failing to act on the peripheral organs, while others have the peripheral action of atropine but in a weaker degree; the compounds of tropine with the acids of the methane series possess much less peripheral atropine action than the others. The peripheral action is most developed in the compounds of tropine with acids of the benzene series possessing hydroxyl and an asymmetric carbon atom, the whole molecule being lævorotary. A considerable variation also exists in the effects of the tropeines on the central nervous system, some causing excitement like atropine, while others act as depressants and therefore resemble scopolamine.

Tropine itself is a weakly toxic, basic substance, which in large quantities stimulates the frog's heart, but does not paralyze the vagus nor the oculomotor terminations on local application. After the injection of large quantities, dilatation of the pupil has been observed, it is true, but this does not seem to be of the same origin as that produced by atropine.

Some synthetic scopoleines have been found devoid of action on the nerve ends in the pupil and heart and on the salivary secretion. They possess a certain stimulant effect on the heart muscle like some of the synthetic tropeines, and all produce more or less depression on the central nervous system and narcosis.

The action of the **Crude Drugs** is very similar to that of the active principles already discussed. The peripheral action of all of them is therefore almost identical in kind, though varying in degree. In considering their effects on the central nervous system it must be remembered that preparations containing much atropine are more stimulant, those with scopolamine more sedative. But as the relative amount of the different alkaloids changes with various conditions such as the age of the plant and the methods of preparation, it is obvious that accurate results can be obtained only by the use of the pure principles. Even when a preparation is accurately standardized in the content of alkaloids, as in the U. S. P. and B. P., its power may vary very widely according to the proportion of lævorotary alkaloid (hyoscyamine) to racemic (atropine).

Therapeutic Uses.—The numerous changes produced by atropine and its congeners on the organism would indicate for them a very wide sphere of usefulness were it possible to elicit their action on one organ without affecting others, and this difficulty is being overcome to a certain extent as the different individuals of the series have been more carefully compared, and new tropeines and other modifications of the tropine radical are being made available in therapeutics.

The peripheral action of the natural alkaloids of the group is so uniform that any member might be used to elicit it, but the only one that has come into general use for its peripheral effects is atropine. The purposes for which atropine is employed may be divided into groups as follows:

To Arrest or Lessen Secretions.—In rare cases of excessive *salivation* atropine has proved of service, but it is much more frequently used to lessen the *perspiration*, especially in the later stages of phthisis. For this purpose comparatively small quantities, such as a $\frac{1}{4}$ mg. ($\frac{1}{250}$ gr.) given by the mouth or hypodermically, are generally sufficient, or the extract or tincture of belladonna may be used instead. In local sweating, atropine is often applied locally in the form of an ointment, liniment, or plaster, although Tappeiner has found that it has no effect when thus employed. It is also used to arrest the secretion of the *milk*, a belladonna plaster being strapped over the gland, but this acts mainly as a mechanical support and the same result may follow the application of simple adhesive plaster. Some forms of excessive secretion of *gastric juice* have been treated by atropine with success. It is also of value in *bronchitis* with profuse expectoration and has been used sometimes with success in edema of the lung.

To Paralyze the Cardiac Inhibitory Terminations.—For this purpose a slightly larger quantity is required than is necessary to stop the secretions, and the administration of sufficient atropine to paralyze the vagus (1 mg.) therefore involves unpleasant dryness of the throat and difficulty in swallowing. In cases where slowing of the heart tends to be dangerous in itself, more especially in poisoning with muscarine, pilocarpine and their allies, atropine is indicated. It may also be used for diagnostic purposes, to find if bradycardia is due to disease of the heart muscle or to inhibition. It may be repeated here that the resultant quickening is much less in old than in middle-aged people, and in many cases of old aortic lesion the administration of atropine is followed by little acceleration. In typhoid fever atropine accelerates the pulse comparatively little owing to the heart muscle being involved in the action of the toxin. The use of atropine to paralyze the vagus terminations in the bronchi before the administration of an anæsthetic has been discussed already. (See p. 340.)

To Paralyze the Terminations of the Motor Nerves in the Iris and Ciliary Muscles.—It is used for this purpose largely in ophthalmology as a means of diagnosis and of treatment, and the precise conditions in which it is indicated may be treated better in text-books on this subject than here. For these objects, solutions of the alkaloidal salts are generally applied to the conjunctiva, when enough of the alkaloid diffuses into the eye to produce marked local effects without affecting more distant organs. In order to dilate the pupil, extremely dilute solutions are used; a few drops of a solution of 1 in 1000, or even of 1 in 10,000 are quite sufficient. Much stronger solutions are required to paralyze the accommodation, and as a general rule 1 per cent is used. These strong solutions produce complete paralysis in one-half to one hour, and the accommodation does not recover completely until after five to seven days, while the pupil may not regain its normal size for ten to fourteen days. The application of even weaker atropine solution renders the sight imperfect for an inconveniently long period, and hyoscyamine and homatropine are therefore much used in its stead. The symptoms produced by a 1 per cent solution of homatropine pass off or, at

any rate, become very much less marked in the course of thirty-six hours. These are consequently preferable for diagnostic purposes, while atropine is rather to be used where it is desirable to produce a paralysis of longer duration, as in various inflammatory conditions of the iris or cornea. Atropine is also preferable where complete paralysis of the accommodation is necessary, as homatropine often fails to effect this. Atropine and its congeners are contraindicated where there is any suspicion of glaucoma, as, owing to their action on the intraocular pressure, they may either aggravate the disease already present or precipitate an acute attack.

When dilatation of the pupil is necessary and there is reason to apprehend the results on the intraocular pressure, homatropine should be employed, as its effects can be readily controlled by eserine. Numerous cases of poisoning have arisen from the extensive use of atropine in disease conditions of the eye. It is often asserted that it passes down with the tears through the lacrimal duct and is absorbed from the nose, throat and stomach, but it may be absorbed from the conjunctiva itself. The symptoms are generally only the milder ones of atropine poisoning—dryness of the throat and slight excitement—but dangerous and even fatal poisoning has also arisen from its local application. In many cases this is due to the application of unnecessarily strong solutions to the eye, but, on the other hand, some patients seem abnormally sensitive to the action of atropine, and scopolamine 0.5 per cent or homatropine, ought to be preferred. In rare cases a curious inflammatory condition of the conjunctiva is set up by atropine, and this is often supposed to be due to the use of irritant preparations, but sometimes seems to follow the application of the absolutely pure alkaloid, and is apparently an idiosyncrasy; it may, perhaps, be explained by the arrest of the ordinary secretions of the lacrimal gland and conjunctiva in these cases. Sometimes discs of gelatin impregnated with atropine or homatropine (B. P.) are applied to the conjunctiva instead of solutions of the salts.

To Relax Spasm of the Stomach and Intestines.—In various forms of colic atropine is of very great service in lessening pain and allowing the passage of the intestinal contents; for instance, it is preferable to morphine in lead colic, as it does not cause constipation. It sometimes relieves the pain of gastric ulcer by preventing the reflex contraction of the stomach wall, and similarly spasmodic contraction of the pylorus may be released. Belladonna in the form of the extract is often prescribed along with purgatives in order to lessen the griping which they produce, and has been used as a laxative in some forms of constipation with considerable success. The object of prescribing an impure preparation instead of the alkaloid is to allow of a strong local action on the intestinal wall along with a slow and imperfect absorption, as the pure alkaloidal salts are liable to be absorbed in the duodenum.

To Relax Spasms of the Involuntary Muscles of Other Organs.—In the spasmodic contraction of the ureters and bile ducts due to calculi, atropine is occasionally prescribed either in the form of a pill or in solution for internal use, or by hypodermic injection. In some

forms of asthma due to contraction of the bronchial muscles, atropine has been applied locally by means of a spray or given internally, and stramonium leaves are often found of benefit when made up into cigarettes and inhaled when the attack comes on; the smoke has been shown to contain small quantities of the alkaloids. Another ingredient of these asthma cigarettes is often nitrate of potassium, which is reduced to nitrite in the course of combustion and passing into the lungs in this form dilates the bronchi by action on the bronchial muscle. Perhaps this action in relaxing spasmodic contractions may also explain the beneficial effects obtained in cases of incontinence of urine in children, in which belladonna has long been the most reliable remedy.

To Lessen Pain.—Belladonna liniment, plaster and ointment have long enjoyed a considerable reputation as local anodynes, but have been less used of late years.

The Effects on the Central Nervous System of the members of this group are very different, and the purposes for which they are used are diametrically opposed. Atropine is used as a stimulant in various conditions of depression of the brain and medulla oblongata. Thus, in collapse its hypodermic injection has been advocated to stimulate the respiration. In dangerous poisoning from narcotic and hypnotic drugs, more especially in opium poisoning, atropine has been largely used. It may be questioned whether atropine may not be replaced by caffeine with advantage. The former stimulates the medullary centres, but subsequently paralyzes them, while caffeine, even in comparatively large quantities, does not seem to have a depressant action in man.

In some spasmodic diseases, such as whooping-cough, belladonna preparations have long enjoyed a wide reputation; this may possibly be explained either by the scopolamine reducing the excitability of the respiratory centre, or by atropine relaxing bronchial spasm.

Scopolamine or *hyoscine* has been used as a narcotic to depress the central nervous system; it is of great efficacy in *insanity*, producing sound and refreshing sleep, but is of less value in controlling the excitement during the day, and may in fact increase it. Scopolamine is also used with benefit in various forms of *tremor of central origin*, and is said to lessen sexual excitement. Its hypnotic action does not seem to be of the same nature as that of opium, for in sleeplessness produced by pain it is of comparatively little value, and it has no power to relieve pain itself. It differs from chloral in not inducing deep sleep, for patients under the influence of scopolamine can always be aroused and are much less confused than after chloral. The special indications for scopolamine seem to be sleeplessness due to abnormal activity of the motor areas and some forms of tremor.

It is very useful in relieving the tremor of *paralysis agitans*. In post-encephalitic *Parkinsonism* it often produces a remarkable improvement: diminution of the generalized muscular rigidity, lessening of the tremors of the face and extremities, disappearance of excessive lacrimation and salivation, improvement of speech and a general brightening of mental outlook. It is usual to commence with small doses, *e. g.*, $\frac{1}{150}$ gr. per day subcutaneously, which may be gradually increased to $\frac{1}{50}$ gr.

or more, if required. By mouth, larger doses are required. Preparations of stramonium have also been extensively used for this purpose.

On the use of scopolamine with morphine as a surgical anæsthetic see p. 340.

Poisoning.—In cases of poisoning with belladonna and its allies the treatment is purely symptomatic. In the excitement stage sedatives may be used; perhaps chloroform and ether are best, as their effects are more transient than the others. Morphine has been advised, but its action on the respiratory centre renders its use dangerous, as in severe atropine poisoning the stimulation soon passes into depression, and the effects of the poison and its so-called antidote therefore supplement each other. Chloroform and ether, on the other hand, may be used to control the spasms and then stopped when these pass off. In the depression stage caffeine may be used, and eventually artificial respiration. Pilocarpine is of course useless, as it does not antagonize the actions of atropine on the central nervous system, which is the point of danger.

Preparations.

U. S. P.

Belladonnæ Folium, the leaves of Atropa belladonna, containing 0.3 per cent of alkaloids. Dose, 0.06 G. (1 gr.).

Extractum Belladonnæ (1.25 per cent), 0.015 G. ($\frac{1}{4}$ gr.).

Tinctura Belladonnæ (0.03 per cent), 0.6 cc. (10 mins.).

Unguentum Belladonnæ (10 per cent).

Belladonnæ Radix, the root of Atropa belladonna, containing 0.45 per cent of alkaloids. Dose, 0.045 ($\frac{3}{4}$ gr.).

Fluidextractum Belladonnæ Radicis (0.3 per cent). Dose, 0.06 cc. (1 min.).

Emplastrum Belladonnæ. The belladonna plaster mass must yield between 0.25 and 0.30 per cent of the alkaloids of belladonna.

Hyoscyamus. The leaves of Hyoscyamus niger (henbane) yield not less than 0.040 per cent of alkaloids. Dose, 0.2 G. (3 grs.)

Extractum Hyoscyami (0.15 per cent of alkaloids), 0.05 G. ($\frac{5}{6}$ gr.).

Tinctura Hyoscyami (0.004 per cent of alkaloids), 2 cc. (30 mins.).

Stramonium, the dried leaves and flowering tops of Datura stramonium, containing 0.30 per cent of alkaloids.

Extractum Stramonii (1.2 per cent of alkaloids). Dose, 0.02 G. ($\frac{1}{3}$ gr.).

Tinctura Stramonii (0.03 per cent of alkaloids). Dose, 0.75 cc. (12 mins.).

B. P.

Belladonnæ Folium, the leaves and tops of Atropa belladonna, containing 0.3 per cent of alkaloids.

Belladonna Pulverata, powdered belladonna leaf adjusted to contain 0.3 per cent of alkaloids, calculated as hyoscyamine, 0.03-0.2 G. ($\frac{1}{2}$–3 grs.).

Extractum Belladonnæ Siccum (1 per cent of alkaloids), 0.015-0.06 G. ($\frac{1}{4}$–1 gr.).

Tinctura Belladonnæ (0.03 per cent of alkaloids), 0.3–2 mils. (5–30 mins.).

Belladonnæ Radix, the dried root of Atropa belladonna.

Extractum Belladonnæ Liquidum (0.75 per cent of alkaloids), 0.015–0.06 mil. ($\frac{1}{4}$–1 min.).

Emplastrum Belladonnæ (0.25 per cent of alkaloids).

Linimentum Belladonnæ (0.375 per cent of alkaloids).

Hyoscyamus, the dried leaves and flowering tops of Hyoscyamus niger, henbane.

EXTRACTUM HYOSCYAMI SICCUM (0.3 per cent alkaloids), 0.016–0.06 G. ($\frac{1}{4}$–1 gr.).

TINCTURA HYOSCYAMI (0.005 per cent of alkaloids), 2–4 mils. (30–60 mins.).

EXTRACTUM HYOSCYAMI LIQUIDUM (0.05 per cent of alkaloids), 0.2–0.4 mil. (3–6 mins.).

STRAMONIUM (0.25 per cent of alkaloids), 0.03–0.2 G. ($\frac{1}{2}$–3 grs.).

TINCTURA STRAMONII (0.025 per cent of alkaloids), 0.3–2 mils. (5–30 mins.).

Alkaloids.

ATROPINÆ SULFAS (U. S. P.), Atropinæ sulphas (B. P.), a white crystalline powder, with a very bitter taste, soluble in water and alcohol. Dose, 0.0005 G. ($\frac{1}{120}$ gr.); B. P., $\frac{1}{60}$–$\frac{1}{60}$ gr.

LAMELLA ATROPINÆ (B. P.), gelatin discs, each containing $\frac{1}{600}$ gr. of atropine sulphate.

OCULENTUM ATROPINÆ (B. P.) (0.25 per cent).

HYOSCINÆ HYDROBROMIDUM (B. P.), SCOPOLAMINÆ HYDROBROMIDUM (U. S. P.) ($C_{17}H_{21}NO_4HBr,3H_2O$), the hydrobromide of hyoscine or scopolamine. It is obtained from hyoscyamus, scopola and other Solanaceæ, and forms colorless, transparent crystals with an acrid, bitter taste, and is very soluble in water, less so in alcohol. 0.3 mg. ($\frac{1}{200}$ gr.); B. P., 0.0003–0.0006 G. ($\frac{1}{200}$–$\frac{1}{100}$ gr.).

HOMATROPINÆ HYDROBROMIDUM (U. S. P., B. P.) ($C_{16}H_{21}NO_3HBr$), the hydrobromide of an alkaloid prepared from tropine by condensation with mandelic (oxytoluic) acid, a white crystalline powder soluble in 6 parts of cold water. Dose (U. S. P.), 0.0005 G. ($\frac{1}{120}$ gr.); B. P., 0.001–0.002 G. ($\frac{1}{34}$–$\frac{1}{32}$ gr.).

LAMELLA HOMATROPINÆ (B. P.), gelatin discs, each weighing $\frac{1}{50}$ gr. and containing $\frac{1}{100}$ gr. of homatropine hydrobromide.

METHYLATROPINÆ NITRAS or EUMYDRIN (unofficial) an alkaloid prepared from atropine, forms a white crystalline salt readily soluble in water. Dose, 1–3 mgs. ($\frac{1}{60}$–$\frac{1}{20}$ gr.).

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Compare also the Literature of pilocarpine and muscarine, nicotine, and physostigmine.

Agaricin.

White Agaric (Agaricus albus, Boletus Laricis), a fungus growing on the European larch tree, was formerly a purgative and antihydrotic of some repute. Its use to lessen the perspiration (antihydrotic) has been revived of late years, or rather a preparation known as agaricin and containing the active principle has been introduced into therapeutics. Agaric acid, the active constituent, has the formula $C_{16}H_{30}O_5$.

Action.—Both the acid and its sodium salt irritate the mucous membranes and wounded surfaces, and cause inflammation and even suppuration when injected subcutaneously. Large quantities irritate the stomach and intestine and cause vomiting and purging, but these are more liable to arise from the impure agaricin owing to its containing resinous acids. Injected into the frog, agaric acid paralyzes the central nervous system, slows the heart, and stops the secretion of the skin glands. In mammals the intravenous injection of agaric acid is followed by depression, weakness, dyspnœa and death. Animals can only be poisoned with difficulty by the subcutaneous injection of agaricin, and no general symptoms are elicited when it is administered by the mouth. The action resembles that of the saponin series, except as regards the sweat secretion.

The most interesting feature of the action of agaric salts is the arrest of the sweat secretion, which is caused by peripheral action, for stimulation of the nerves of the cat's foot fails to elicit perspiration after its ingestion. It thus acts on the same peripheral mechanism as atropine in all probability, that is, on the terminations of the secretory nerves, but differs from atropine in acting only on the sweat glands, for the saliva, tears and other secretions are not hindered by it, and may, in fact, be increased by its causing nausea. It is also devoid of action on the nerve terminations in the heart and pupil. Atropine acts much more powerfully than agaric acid, at least twenty times as much of the latter being required to arrest the sweat secretion.

Uses.—Agaricin is used in the night sweats of phthisis and other similar conditions and is generally given in pill form in doses of 5–60 mgs. ($\frac{1}{12}$–1 gr.). The commercial agaricin often contains a large percentage of impurities and has to be given in larger quantities, but the treatment ought to be begun with small doses. Tolerance is said to be acquired after some time, and the dose has then to be increased. The best results are got when the pills are taken five to six hours before retiring, as the acid is only slowly absorbed. If agaricin causes intestinal irritation and diarrhœa, it may be given with opium, but as in phthisis all irritation of the bowel is to be avoided, the remedy ought perhaps to be stopped when any such disturbance arises. Camphoric acid, which was formerly advised to lessen the secretion of sweat in phthisis, appears to have little or no effect and should be discarded (Vejux-Tyrode).

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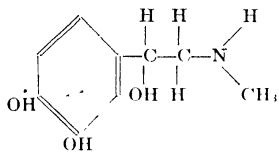
IV. STIMULANTS OF SYMPATHETIC NERVE ENDS.

1. Epinephrine (Adrenaline).

The suprarenal glands of all vertebrates have been shown to contain a body which possesses a powerful action on the organism, and which the glands normally secrete into the blood-stream. The active prin-

ciple in the form of a benzoyl compound was first isolated by Abel and named *epinephrine*, but as a pure crystalline compound it was first isolated in 1901 by Takamine and by Aldrich and named *adrenalin*. It is also known under the trade names of *adrenine*, *suprarenine*, etc. It has also been found by Abel in the external neck glands of a tropical toad. It is a feebly basic derivative of benzene, corresponding to the formula $C_6H_3(OH)_2—CHOH—CH_2—NHCH_3$. Epinephrine has been



Epinephrine

formed synthetically, and a number of other amine compounds similar to it in structure have proved to resemble it also in action in many features; other amines less closely related chemically tend to depart further from the typical epinephrine action (Barger and Dale). Epinephrine is lævorotary to polarized light; the dextrorotary isomer has only about one-twelfth of the activity of the natural substance (cf. Atropine and Scopolamine).

The characteristic action of epinephrine is best elicited by its injection into a vein, when it stimulates the myoneural junctions of the post-ganglionic fibres of the sympathetic nerves. The effects of epinephrine are thus for the most part identical with those of stimulation of the sympathetic nerves and the group of amines of which it is the best known member have therefore been termed the sympatho-mimetic amines. The symptoms show certain analogies with those induced by nicotine, but the latter affects a wider area from its involving the parasympathetic autonomic nerves as well as those of the true sympathetic. And the point at which nicotine acts is the ganglion cell, while epinephrine involves the other end of the peripheral neuron. It should be added that some of the sympathetic terminations are not involved in the action of epinephrine; the secretory fibres in the sweat glands are not affected, for example, although they are of sympathetic origin.

Circulation.—On the intravenous injection of epinephrine a very marked rise in the arterial blood-pressure occurs, accompanied at first by acceleration, then by slowing, and later again by acceleration of the heart. This rise in blood-pressure is for the most part due to constriction of the vessels of the abdominal cavity, but an increase in the efficiency of the heart often plays a part, though a subordinate one. The sudden increase in pressure occurs after destruction of the vasomotor centre and cord, or after section of the splanchnic nerves and paralysis of the ganglia on the vaso-constrictor nerves, so that it is obviously due to direct action on the muscle of the vessel walls, or on the terminations of the nerves in them. The greatest constriction is seen in the vessels of the splanchnic area, but most of the other vessels are also involved in lesser degree. Thus the limb vessels are narrowed less than those

of the intestine, and the pulmonary and cranial arterioles are so slightly constricted that there has been some difficulty in proving that they are involved in the general action; most observers now hold that there is narrowing in these regions also. The effect on the coronary artery of the heart has also been the subject of dispute, most investigators finding that it is dilated by epinephrine; but though this is often the prevailing effect, very small concentrations of epinephrine cause distinct contraction of the coronary artery and slow the passage of blood through the heart (Brodie and Cullis).

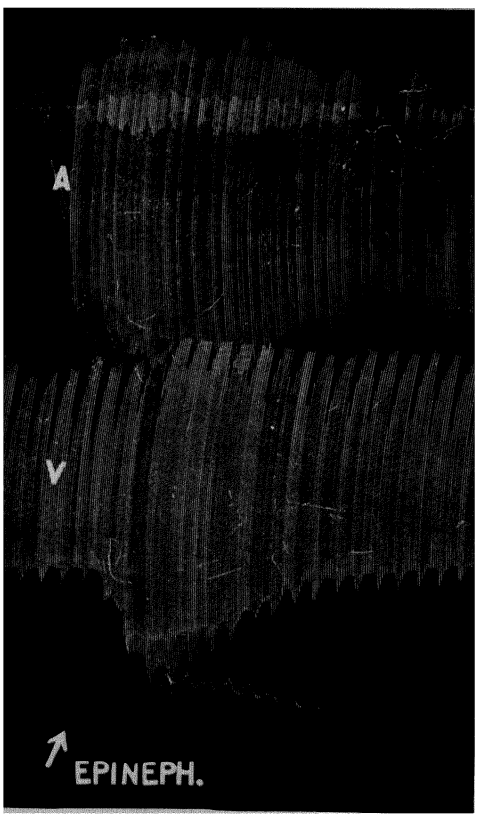


FIG. 34.—Effect of very small dose of epinephrine upon the dog's heart and blood-pressure. *A*, Auricle; *V*, ventricle. Lever moves down in systole. Lower tracing. Blood-pressure. The very small dose gives almost pure muscular action with practically no vagus effect.

Observations made upon the unanæsthetized dog by means of a thermo-stromuhr placed upon the circumflex branch of the coronary artery showed that the intravenous injection of 0.05 to 0.1 cc. of a 1 to 1000 solution of epinephrine causes an immediate but transient increase in coronary blood flow. This increase which may be as great as from two to four times the control value lasts for about seven minutes.

characteristic of inhibitory activity. This second phase of slowing of the heart beat is not observed if the vagi are divided or if atropine is given before epinephrine, so that it obviously arises from excitation of the vagus centre; this is not entirely a direct epinephrine action but is largely a secondary result of the high blood-pressure, which induces congestion of the brain and arouses the vagus centre to activity. After a short time, the blood-pressure beginning to fall, or, the vagus centre becoming exhausted, the accelerator stimulation again gains the upper hand and the pulse is again much accelerated.

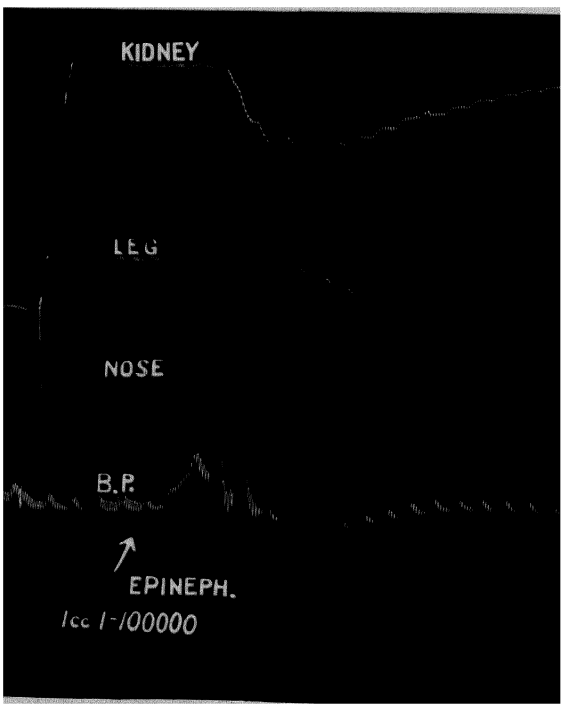


FIG. 35.—Change in distribution of blood in dog from small dose of epinephrine. With the increase in blood-pressure there is marked decrease in volume of kidney from constriction of its vessels. There is also constriction of vessels in mucous membrane of the nasal cavity. At first there is a passive dilatation of the leg vessels as blood is diverted to muscles from the splanchnic area, and as blood-pressure returns to normal the leg volume decreases (Nelson).

The effect of epinephrine on the mammalian heart is thus in small doses to accelerate and strengthen it; in large amounts the acceleration may be excessive and impair its efficiency, or the acceleration may be temporarily replaced by inhibition which also reduces the output. Epinephrine increases the irritability of the heart and thus predisposes it to pass into fibrillary contractions. The frog's heart is less easily affected than that of the mammals, but similar changes have been observed.

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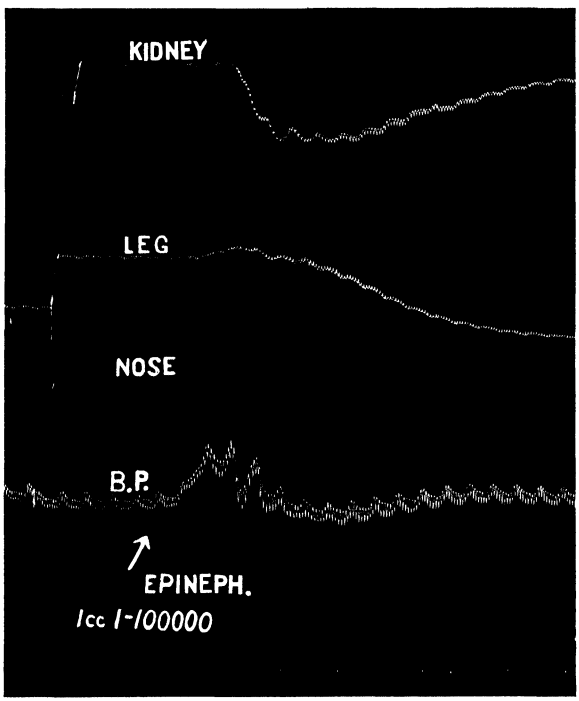

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The effect of epinephrine on the mammalian heart is thus in small doses to accelerate and strengthen it; in large amounts the acceleration may be excessive and impair its efficiency, or the acceleration may be temporarily replaced by inhibition which also reduces the output. Epinephrine increases the irritability of the heart and thus predisposes it to pass into fibrillary contractions. The frog's heart is less easily affected than that of the mammals, but similar changes have been observed.

The action on the heart may be demonstrated by perfusing very dilute solutions of epinephrine through the vessels of the excised heart, and the same method is used in investigating its action on the vessels of other organs. In the excised heart the accelerator and augmentor action alone is visible, the stage of slowing being absent. The contraction of the vessels in such organs as the kidney is shown by the diminished outflow from the veins when epinephrine is added to the perfusing fluid; and different organs respond in different degrees, little retardation of the flow occurring in the lungs, brain and heart compared with that in the intestines, limbs, and kidney. A similar constriction of the vessels may be observed when a solution of epinephrine is applied to a mucous membrane, for the part becomes pale and anæmic from the constriction of the vessels; this is well seen when the drug is applied to the congested conjunctiva or to the mesentery. Painted on the unbroken skin epinephrine has no effect, as it fails to penetrate it, but denuded surfaces become blanched, and hæmorrhage ceases from small vessels.

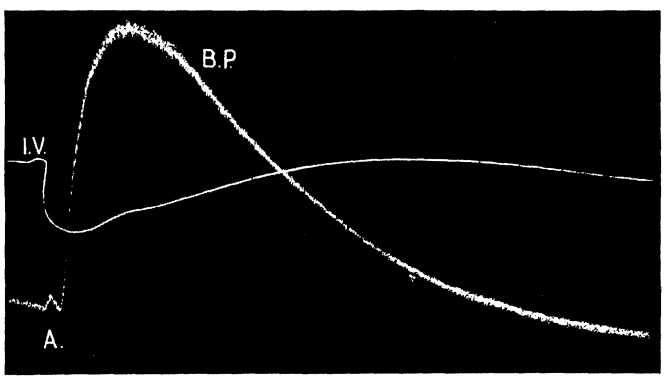


FIG. 36.—Blood-pressure (*B.P.*) and bowel volume (*I.V.*) of cat. At *A* injection of epinephrine. The blood-pressure rises and bowel volume diminishes, indicating constriction of the mesenteric vessels. As these relax again the blood-pressure falls. The vagi had been divided previously, so that there is no secondary slowing of the heart. (See also Fig. 35.)

When it is injected hypodermically, the skin and subcutaneous tissues around the point of injection become pale and anæmic and may be cut into without bleeding, and when it is applied to a bleeding surface, the hæmorrhage is arrested unless some large artery has been opened. But even the direct application of epinephrine to a lesion of the lung or brain has little effect in stopping the bleeding, the vessels in these organs not being constricted by epinephrine to the same extent as those of other organs.

The **Respiration** sometimes becomes irregular during the period of high blood-pressure, and periods of strong and rapid breathing may alternate with apnœa; this is probably a result of the high blood-pressure and not of any direct action on the centre.

Stomach and Intestine.—The intravenous injection of epinephrine is followed by immediate cessation of the movements of the stomach and intestine, which become relaxed to their full extent. This is in accordance with their innervation, for the splanchnic fibres are the inhibitory nerves of those organs and their stimulation also arrests peristalsis and causes relaxation (Fig. 37). But certain specialized parts of the bowel wall receive motor fibres from the sympathetic—the pyloric, ileo-colic and internal anal sphincters and the muscularis mucosa—and these are thrown into contraction by epinephrine. The movements of the gall-bladder are inhibited and those of the bile-duct are increased by sympathetic stimulation and also by epinephrine.

The reaction of the **Bladder** to epinephrine differs in different species of animals according to the nature of the dominant impulses of the lumbar sympathetic nerves.

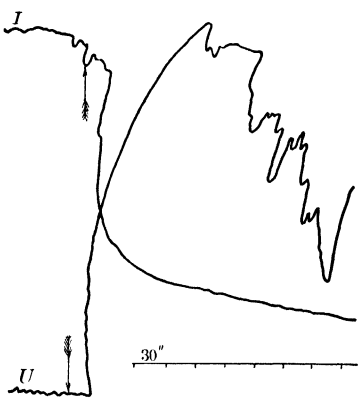


FIG. 37.—Tracing of the movements of intestine (*I*) and of the uterus (*U*) of a rabbit under epinephrine injected at the point marked with an arrow. The intestine relaxes while the uterus contracts powerfully.

Uterus.—The reaction of the uterus to epinephrine differs in different animals and even in the same animal at different periods. In the non-pregnant cat, epinephrine generally causes inhibition of the movements and relaxation, while in the pregnant cat its injection is followed by powerful contractions; in the rabbit epinephrine almost always causes contraction whether the animal is gravid or not, while in the dog the uterus first contracts and then passes into a position of relaxation and inhibition. In each case the action of epinephrine is identical with that of stimulation of the hypogastric nerves which carry both motor and inhibitory fibres to the uterus; the relative power of the two sets of fibres varies in different animals and in different conditions in the same way as the action of epinephrine (Fig. 37).

The Eye.—The intravenous injection of epinephrine is followed by dilatation of the pupil, the eyelids are widely opened, the eyeball is protruded, and the nictitating membrane withdrawn; the action corresponds exactly to the effects of stimulation of the cervical sympathetic

fibres; it occurs when these have been cut, and is even intensified when they have been allowed to degenerate. Applied locally to the eye, it constricts the vessels of the conjunctiva and often dilates the pupil and reduces the intra-ocular tension for a short time.

Bronchial Muscle.—Epinephrine injected intravenously dilates the bronchi widely, an effect which is especially noticeable when they have been previously constricted by pilocarpine or physostigmine. In bronchial asthma the subcutaneous injection of small doses of a 1 to 1000 solution of epinephrine (0.2–0.5 cc.) will usually give relief through its relaxing effect upon the bronchial musculature. This action is not the same as the dilation caused by atropine, but arises from epinephrine stimulating the terminations of the bronchial sympathetic fibres, which cause relaxation of the muscle.

Other Organs containing unstriated muscle are similarly affected, some undergoing contraction, while others are inhibited under epinephrine, and in each case the result corresponds with the effect of stimulation of the fibres of the sympathetic supply. A curious instance of the action of epinephrine has been described by Spaeth, who found that it induces contraction of the pigment in the scales of the small fish, fundulus.

The **Secretions** do not present such marked changes under epinephrine, though they are also generally increased when they are controlled by the sympathetic nerves. This is due to the fact that the blood supply is simultaneously reduced by the vaso-constriction, for Edmunds has shown that the secretion of the pancreas is arrested by epinephrine causing ischæmia of the gland. The saliva under epinephrine corresponds in character with that secreted on stimulation of the cervical sympathetic trunk, not with that from stimulation of the chorda tympani, which is a cranial autonomic nerve and is therefore not susceptible to epinephrine. The *sweat* glands provide the most notable exception to the rule that epinephrine has the same effect as sympathetic stimulation, for though they are innervated by sympathetic fibres whose stimulation causes secretion, epinephrine has no effect on the sweat secretion, whether it is injected intravenously or applied locally. The nerves to the sweat glands are anomalous in another feature, for their terminations are the only example in which atropine paralyzes sympathetic terminations.

The secretion of the *urine* is often arrested immediately on the injection of epinephrine and is then considerably augmented. This appears to be due to the vascular action, the renal vessels being constricted at first but relaxing sooner than those of the other organs; the flow of blood through the kidney is thus reduced at first and the urinary secretion falls or stops altogether; then an abnormally large flow occurs from the renal vessels dilating while the blood-pressure is still high, and more urine is accordingly secreted.

In the pithed frog with one ureter cannulated the injection of epinephrine is followed by the same sequence of events, *viz.*, oliguria coinciding with the diminished blood flow in the kidney followed by polyuria associated with the improved circulation in the organ (Adolph).

The glycogenic function of the *liver* is disturbed by the presence of excess of epinephrine and the result is an unusual hydrolysis of glycogen and an unusual amount of sugar in the blood and tissues, which may give rise to glycosuria. This is not generally seen when a single intravenous injection is made, apparently because the action is too short; but it may be induced by the prolonged intravenous infusion of dilute epinephrine solutions, and very frequently arises from the subcutaneous injection of large amounts. This accelerated breaking down of glycogen appears to arise from epinephrine stimulating the terminal mechanism of the sympathetic nerves in the liver that control the glycogenic function. The action is thus of the same character as that in other organs and perhaps differs only in being slower and thus requiring a longer period of action than is necessary to induce obvious changes in the blood-vessels and unstriated muscle. The statement is sometimes made that the glycosuria does not occur after epinephrine in animals in which the thyroid glands have been excised previously, but this is not generally correct; the glycosuria is not a constant feature after epinephrine even in normal animals, and inferences from its absence ought to be drawn only with the greatest reserve.

The urea excretion is lessened during the stage of diminished urinary flow but during the stage of polyuria it is increased, the urea and also the chloride excretion rates varying directly with the water excretion rate.

Epinephrine thus acts in the same way as stimulation of the sympathetic nerves and is held to induce its effects by stimulating the mechanism lying between the nerves and the muscle. It obviously does not act on the contractile muscle itself, for some involuntary muscle contracts under it while in other organs it relaxes. And it is found that after ergotoxine, an alkaloid which antagonizes the action of epinephrine in some organs, the muscle remains active though the receptor on which epinephrine acts is paralyzed. Epinephrine therefore does not act on the contractile mechanism of muscle. On the other hand it does not act on the anatomical nerve ends, for after these have degenerated and disappeared, the usual effects of epinephrine are elicited by its injection. It is obvious that the action is exercised on some substance intermediate between the nerve and the contractile material of muscle and this has been termed the "myoneural junction or receptive substance."

Epinephrine injected intravenously acts in very small quantities, $\frac{1}{1000}$ mg. often sufficing to raise the blood-pressure in the dog. The effect is of very short duration, but it may be repeated indefinitely by fresh injections, and this is generally agreed to be due to the rapid destruction of epinephrine in the tissues. Elliott states that this destruction takes place more rapidly in those organs in which epinephrine acts strongly than in others, and it certainly is not destroyed in the blood-plasma. When the blood-pressure regains its normal level after an injection of epinephrine, none of the alkaloid can be detected in the blood or tissues, the whole having undergone oxidation.

The rapidity of disappearance of epinephrine from the blood has been repeatedly demonstrated and it is stated that 75 per cent of the injected material disappears in fifteen seconds but traces may still be found for three minutes. No individual organ can be held responsible for the destruction of epinephrine as ligation of the blood supply to the liver, spleen or kidneys does not essentially alter the blood-pressure response to the injected drug. It is probably oxidized in the tissues to some inactive compound, possibly protocatechnic acid.

Straub classes epinephrine among the "potential" poisons and holds that it acts only in the process of permeation into the cells which are affected by it; when it has reached the interior it is at once destroyed and the action, therefore, lasts only so long as there is epinephrine in the blood in excess. A new injection by increasing the concentration in the blood causes further permeation into the cells and renews the action.

Epinephrine applied locally induces such vaso-constriction that it is only slowly absorbed; and it, therefore, has only local effects when it is given by the mouth. Injected hypodermically it causes local ischæmia, and after large doses compared with those necessary by intravenous injection, a distinct rise of blood-pressure and some dilation of the bronchi often occur; injected intramuscularly it seems to have stronger general effects.

Animals are poisoned by large amounts injected hypodermically, and even smaller quantities induce glycosuria and diuresis. Larger quantities cause prostration, collapse and paralysis of the central nervous system, ending in failure of the respiration and œdema of the lungs. Similar symptoms arise from the intravenous injection of very large doses, but here the effects of the high blood-pressure are also in evidence in numerous hæmorrhages. The intravenous injection of epinephrine in the rabbit often leads to atheromatous degeneration of the aorta, apparently from the strain caused by the high arterial pressure; it does not occur in other animals.

Cannon and his co-workers first demonstrated that the stimulation of a sympathetic nerve in an intact animal will release into the blood stream a substance having many of the characteristics of epinephrine and to this substance they have given the name *sympathin.*

While epinephrine and sympathin have similar actions in many instances, they show certain differences in action which should preclude their identity. One of these differences is in their relation to ergotoxine which produces the well-known vasomotor reversal effects with epinephrine, but with sympathin there is no such phenomenon. Sympathins derived from the stimulation of different sympathetic nerves, such as those going to the heart or liver, or from stimulation of the hypogastric nerve differ, therefore, not only from epinephrine, but also from each other. On this account, the sympathins have been put into two groups —sympathin E or sympathin I, depending upon whether they stimulate the structure to which the nerve is distributed (heart or blood-vessels) or depress it as in the intestine.

It is suggested that the sympathin is released in the immediate vicinity of the reacting mechanism and probably within the cell itself. It is possible that this production of sympathin may be entirely respon-

sible for the transmission of the sympathetic nerve impulse to the affected mechanism and that there may not be any necessity for direct electric transmission, but further evidence will be needed to definitely establish this point.

Therapeutic Uses.—Disease of the suprarenal gland leads to a series of symptoms known as Addison's disease, and it was hoped that the extract of the gland or the dried gland itself might counteract this condition by supplying the substance whose deficiency induced the symptoms. As a matter of fact, however, little or no success has attended its use for this purpose, and there is evidence that in Addison's disease the tissue at fault is not the medulla, from which epinephrine is obtained, but the cortex of the gland. (See Adrenal cortex, p. 559.)

The general action of epinephrine on the circulation may be induced in such emergencies as heart failure, in which its powers of restoring the circulation have been proved both in animals and in man; for example, in animals in which the heart has been arrested by excessive doses of ether, the circulation may be restored by the intravenous or intracardiac injection of epinephrine. The dose suggested for intravenous injection is 0.2 cc. of the solution well diluted. In this connection it is to be borne in mind that epinephrine may tend to cause fibrillation of the ventricle at an earlier stage of chloroform anæsthesia. The intracardiac injection of epinephrine has been frequently carried out with success but the procedure is not without considerable danger. In some cases reported excessive doses were certainly employed and there is danger of dilatation of the heart and permanent damage. In certain cases, however, it has without doubt been life-saving.

Epinephrine has also been employed in "shock" to constrict the vessels. Where the symptoms are largely nervous in origin, this may be good practice, but when true secondary shock has developed with capillary distention and reduced blood volume, epinephrine appears to be of no service and indeed it may be harmful if large doses are used. The treatment should aim at increasing the volume of the blood in circulation by the transfusion of blood or the infusion of glucose solution.

The great use of epinephrine is, however, due to its local effects on the vessels. No other body is known which induces such complete contraction of the vessels in any part to which it is applied, and in addition it has practically only local effects, unless it is injected into the blood. Complete bloodlessness of a part may thus be elicited without significant alteration of the general blood-pressure, and in fact without any appreciable effect upon other parts of the body. This local ischæmia has been largely employed to allow of bloodless operations on the eye and to remove congestion of the conjunctiva from various causes. It is often administered with the local anæsthetics in operations on the eye, being used especially with cocaine and procaine. Here it not only gives a bloodless field of operation but also limits the absorption of the anæsthetic and prolongs its action. In congestion of the nasal mucous membrane and in operations on the nose it is also used extensively and with much success; the 1 per mille solution may be sprayed into the nose, or cotton soaked in it may be packed into the cavity. In epistaxis

and in operations on the nose or throat, the hæmorrhage ceases almost completely and the contraction of the mucous membrane permits of a clearer view of the field of operation. Hay fever is often temporarily relieved by similar treatment.

Grünbaum first suggested its administration by the mouth in gastric hæmorrhage, in which the action is confined to the mucous membrane of the stomach, but the chances of its being effective are not great. Similarly it may be injected into the rectum, bladder and uterus in congestion or hæmorrhage from these organs, and Schäfer recommends it especially in post-partum hæmorrhage, in which it acts not only on the uterine vessels but also on the muscular walls, and arrests the bleeding by causing a tonic contraction. In all of these cases the epinephrine has to be applied directly to the bleeding organ. The local contraction of the vessels lasts very much longer than that induced by intravenous injection, for even dilute solutions cause ischæmia lasting from thirty minutes to two hours, according to the rapidity with which the epinephrine is absorbed. The vessels of some organs scarcely contract under epinephrine, and no benefit is to be expected from its application in hæmorrhage from these; spraying epinephrine into the lungs in case of hæmoptysis, for example, is quite useless, and similarly hæmorrhage in operations on the brain cannot be controlled by it.

The constriction of the vessels in a part to which epinephrine is applied retards the absorption of local anæsthetics injected with the epinephrine, and at the same time permits of their exercising a more marked local effect. This fact is being utilized in surgery to prevent the absorption of cocaine and to intensify its local action, and the method is usually quite successful. A few drops of the 1 per mille solution are added to the Schleich's solution of cocaine, and blanching of the tissues results; instead of cocaine, any of its substitutes such as procaine may be used, as epinephrine does not interfere with their action.

The hypodermic injection of 0.3 to 0.5 cc. of the solution often gives relief in asthmatic attacks immediately; apparently enough of this large dose is absorbed to stimulate the dilator nerve fibres in the bronchi. The dose may be repeated in fifteen minutes if required but the effect usually lasts much longer than that.

In urticaria, angioneurotic œdema, and serum sickness the drug may be given in the same way and it often produces a great improvement in the symptoms.

Epinephrine may also be used in the same manner and dosage to prevent the occurrence of the nitritoid crises following the use of arsphenamine or indeed to treat this condition in case it has occurred. Also 0.5 to 1 cc. of the solution may be injected subcutaneously to offset the symptoms of hypoglycemia produced at times in a diabetic patient by insulin.

Preparations.

U. S. P.

Epinephrina, *l*-Methylaminoethanolcatechol. 0.0005 G. ($\frac{1}{120}$ gr.).

Liquor Epinephrinæ Hydrochloridi, 0.1 of 1 per cent solution of epinephrine hydrochloride. 0.5 cc. (8 mins.).

B. P.

ADRENALINA, Epinephrine. 0.0001–0.0005 G. ($\frac{1}{1000}$–$\frac{1}{120}$ gr.).
LIQUOR ADRENALINÆ HYDROCHLORIDI, 0.1 of 1 per cent solution of adrenaline hydrochloride, 0.12–0.5 mil. (2–8 mins.).

Extracts were at first made from the fresh glands, but soon the dried glands were introduced—*Suprarenalum siccum*—and a watery solution made from these has been used. At present the active principle under the name of EPINEPHRINE or ADRENALINE[1] has almost entirely supplanted the cruder preparations.

EPINEPHRINA or ADRENALINA, $C_9H_{13}NO_3$, is a light brown or nearly white powder very slightly soluble in water; it may be obtained from the suprarenal glands of animals or may be formed synthetically.

A number of other substances are known which resemble epinephrine in action and in chemical structure. Many of these are formed by chemical synthesis, but some are found in nature, being produced from the amino-acids by the removal of the carboxyl group; the amino-acids are formed in the decomposition of proteins and where this occurs in the presence of putrefactive organisms these bases are liable to occur. The best known of these is **Tyramine** or **hydroxy-phenylethylamine** which is formed from the amino-acid tyrosin.

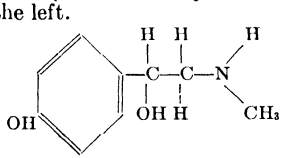
$$\underset{\text{Tyrosine}}{C_6H_4OH\cdot CH_2CH(COOH)NH_2} = \underset{\text{Tyramine}}{C_6H_4OHCH_2CH_2NH_2} + CO_2$$

These bases are all less active than epinephrine but otherwise present no significant divergence from it in their effects on the organism. Tyramine is said to have slightly less action on the terminations of the inhibitory nerves, and to increase the blood-pressure more when it is injected hypodermically. Tyramine occurs in the ergot preparations and was first identified in putrefying flesh.

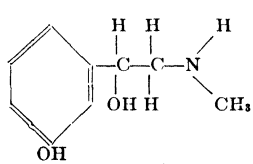
Synephrin and Neosynephrin.

In the past few years a study has been made of the action of various compounds which are more or less closely related chemically to epinephrine and ephedrine. In general the changes which have been made in the molecule have rendered the compound more stable so that it is not so easily broken down in the body, thus prolonging its action and at the same time lessening its activity and toxicity.

Two of these compounds which have been introduced into medicine are Synephrin and Neosynephrin, the two differing from epinephrine in that they have only one hydroxyl attached to the benzene ring instead of two as in epinephrine. They differ from each other in that in Synephrin the hydroxyl is in the para position while in Neosynephrin it is in the meta position. The former compound rotates polarized light to the right while neosynephrin rotates it to the left.



Synephrin



Neosynephrin

[1] Other names applied to this substance are adrenalin, adrenine, suprarenaline.

Synephrin was the first of these compounds to be introduced and was employed mainly for its local effects as a vasoconstrictor. Its action was much weaker than epinephrine but the constriction was more prolonged. In general it appeared that it was from one fiftieth to one one-hundredth as strong as epinephrine. Through an action upon the smooth muscle it caused relaxation of the intestine and of the bronchial muscle. It dilated the pupils and increased the tone of the uterus. Applied locally it constricted the smaller vessels, thus reducing congestion and swelling and in the nose it caused little irritation and sneezing. It was used in combination with procaine and other local anæsthetics to cause local vasoconstriction and thus prolong the anæsthesia. In hay fever and asthma it was given in 1–3 grs. doses either orally or by hypodermic injection.

Neosynephrin is a still more recent addition to the group and on account of certain advantages which it possesses over the older compound it has largely replaced it. Injected into cats it causes an increase in blood-pressure which is considerably more prolonged than is that produced by epinephrine, and in man the pressure increase may be quite prolonged. Ergotamine, which will reverse the rise produced by epinephrine through paralysis of the motor receptive substances, has little effect in the case of neosynephrin, indicating that the constrictor effect is largely limited to the muscle in the vessel walls.

Applied locally to mucous membranes in a 0.25–0.5 per cent solution it constricts the smaller vessels and reduces congestion and swelling and it may therefore be used in rhinitis and hay fever. It is also used to prolong the anæsthesia produced by procaine and the other local anæsthetics.

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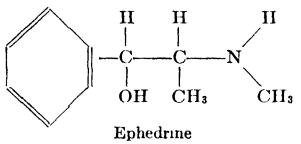
2. Ephedrine.

Ephedrine is an alkaloid obtained from Ma Huang, a drug which has been used by the Chinese from early times. The alkaloid, which was

first isolated by Nagai in 1887, is closely related both chemically and pharmacologically to epinephrine as will be seen by the following formula:



Ephedrine

Solutions of ephedrine are more stable than are those of epinephrine and the drug is active when given by mouth.

In man the drug in doses of from 20 to 50 mg. given by mouth produces an increase in blood-pressure with decreased heart rate, associated at times with some throbbing in the head and a feeling of palpitation and anxiety. These effects may last for two hours. In certain persons the anxiety complex is so marked as to serve as a contraindication to the use of the drug.

Injected into animals the alkaloid produces an increase in heart rate and in the strength of the contractions and a prolonged rise in blood-pressure. The increase in the rate of the heart is due to an action upon the accelerator mechanism but in man this action may be overcome by increased activity of the inhibitory mechanism and slowing of the heart often results together with an increase in both systolic and diastolic pressure.

The action of ephedrine upon the heart of the unanæsthetized dog has been studied by Meek and Seevers. They found that when injected in small doses there was at once a marked bradycardia which was followed by extrasystoles and a slow rhythm. These two stages are the result of a primary followed by a reflex stimulation of the vagus nerve, the reflex action on the vagus being the result of increased blood-pressure. Tachycardia followed the stage of slowing and in case atropine had been given at the beginning of the observations the tachycardia came in early. They found too that these cardiac phenomena were largely prevented or removed by the administration of sodium barbital, which acted to lessen the vagal effects by a certain degree of paralysis and also probably by some depression of the automatic centers.

Ephedrine, in doses of 5 mg. per kilogram of body weight, administered to normal dogs for several days at six-hour intervals, produced a considerable rise in blood-pressure together with slowing of the heart, these changes lasting several hours. Return to normal occurred soon after the discontinuation of the drug administration (Ogden and Teather).

In animals vaso-constriction occurs, especially in the splanchnic area, resembling that produced by epinephrine except that it is more prolonged. Inhibition of the intestine has been reported by some workers while others find contraction occurs not infrequently. The results are therefore very contradictory. Contraction of the uterus is produced in all species of animals examined. Upon the normal bronchial muscles there is little effect, but relaxation follows if the tone of the muscles has been increased by histamine or by physostigmine. The pupil is dilated due to an action upon the iris and, occurring after the iris has been denervated by section of the cervical sympathetics and when cocaine is no longer active, it must act peripherally to the latter drug.

The alkaloid has little effect upon secretions such as the sweat, nor does it alter body temperature, although it was for these two effects that it has been employed by the Chinese for so long.

The drug resembles epinephrine closely in its effect and has been believed to act upon the same structures in the body, but, according to the views of some, the point of attack is not the receptive substance as with epinephrine, but is rather upon the muscle cell itself, or it is not unlikely that both structures may be affected. From the clinical standpoint the main difference in its action from that of epinephrine is that it is active when given by mouth and its effects are more prolonged than are those of epinephrine.

As has been shown there is some difficulty in explaining the various effects of ephedrine by assuming an action upon any one specific structure. An attempt has been made to overcome this difficulty by ascribing some of its effects to an action in relation to epinephrine similar to that which exists between physostigmine and acetylcholine. In the latter case, as was discussed under the general subject of physostigmine, this drug was shown to inhibit the action of the enzyme which is responsible for the rapid destruction of the acetylcholine which is liberated when parasympathetic (cholinergic) nerves are stimulated.

In like manner a substance probably related to epinephrine is believed to be liberated when sympathetic (adrenergic) nerves are stimulated, and this substance like epinephrine is said to be destroyed quickly in the body through the action of an enzyme which has been designated as amine oxidase. Now, according to Gaddum, ephedrine which is closely related chemically to epinephrine and at the same time is not destroyed by amine oxidase, may inhibit the destruction of epinephrine in the same manner that physostigmine protects acetylcholine, and in this way certain of the ephedrine actions may really be due to epinephrine. The action of epinephrine is definitely potentiated by ephedrine when the ephedrine is in low concentration, but it is antagonized by high concentrations. This latter effect is explained by the theory that the ephedrine combines with the motor receptors and blocks them up.

Ephedrine has also been employed to aid in securing larger quantities of the substance which is liberated by the "adrenergic" nerves so that its properties can be more fully studied.

Methyl ephedrine is a tertiary amine which is related to ephedrine. It was first prepared by Negri and later isolated by Smith from Ephedra. On the blood-pressure the effect of the methyl compound is about one-tenth as strong as ephedrine and the heart is less accelerated. In dogs under luminal it will slow and deepen the respiration, but it does not antagonize the action of morphine upon the respiration. It does not stimulate the central nervous system as does ephedrine, and while it is less toxic for dogs and rabbits, the symptoms produced are much like those from ephedrine.

Methyl ephedrine will dilate constricted bronchi but the action is slightly weaker than with ephedrine. Inasmuch as it is less toxic and has less effect upon the heart and blood-pressure and lacks the central nervous system stimulating action, it would seem that it might be substituted for ephedrine in the treatment of asthma. (Pak and Read.)

Therapeutic Uses.—Ephedrine in the form of its salts is being used for the relief of asthma, where success has been reported in a certain percentage of the cases treated. It seems to be more active in preventing

an attack than in relieving one already present. It is also used in hay fever, rhinitis, and sinusitis, usually in the form of a spray or in solution.

It is also recommended for the treatment of shock and hæmorrhage and other conditions associated with low blood-pressure where its action in accelerating the heart may be helpful. In the low blood pressure sometimes seen in spinal anæsthesia its administration has been found helpful. In serious circulatory collapse it is probably valueless.

Preparations.

U. S. P.

Ephedrina, Ephedrine $C_{10}H_{15}ON$. An alkaloid derived from various species of ephedra. It is soluble in water, alcohol, and liquid petrolatum.

Ephedrinæ Hydrochloridum. The hydrochloride of ephedrine is soluble in water and in alcohol. 0.025 G. ($\frac{3}{8}$ gr.).

Ephedrinæ Sulfas. The sulfate of ephedrine is soluble in water and with difficulty in cold alcohol—more freely in hot alcohol. 0.025 G. ($\frac{3}{8}$ gr.).

B. P.

Ephedrinæ Hydrochloridum, 0.016–0.1 G. ($\frac{1}{4}$–$1\frac{1}{2}$ grs.).

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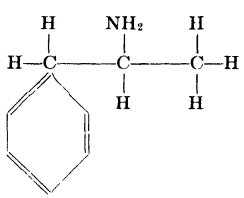
F. BENZEDRINE.

Benzedrine (B-Phenylisopropylamine, Amphetamine), $C_6H_5—CH_2$, $CHNH_2.CH_3$, is a synthetic preparation belonging to the sympatho-



mimetic group of drugs and closely related to epinephrine and ephedrine. It is a colorless liquid which on exposure to air rapidly changes into the carbonate, both the base itself and the carbonate being volatile. The sulfate of benzedrine, on the other hand, is non-volatile and is used for both local and general effects.

Benzedrine may be used as a spray in the form of a 1 per cent solution

in liquid petrolatum or by inhalation of the vapor of the base or of the carbonate. Applied thus locally it produces shrinking of the mucous membranes with a lessening of the nasal secretion. Excessive inhalation of the vapor will produce certain toxic symptoms such as stimulation of the central nervous system with wakefulness, an increase in blood-pressure and some cardiac weakness. Diuresis also occurs at times in susceptible persons. Such toxic symptoms are rarely serious and are seen only when the dosage is distinctly excessive.

Benzedrine sulfate is a white odorless powder freely soluble in water and may be used in solution for its local action, or it may be given orally in tablets for its general action.

Administered to man, benzedrine sulfate produces a stimulation of the central nervous system as shown by an increase in alertness and in motor and psychical activity, together with a decrease in fatigue, accompanied at times by insomnia. There is usually a rise in blood-pressure which may be prolonged and some slowing of the heart with irregularities such as extrasystoles or paroxysmal tachycardia. The drug has little effect upon the tone of the normal gastro-intestinal tract but will relax the organ if it is in a condition of hypertonicity. A moderate increase in basal metabolic rate occurs together with some loss of weight and an increase in the cellular content of the blood is explained by a possible vasoconstriction in the blood reservoirs in the body. Toxic doses produce hyperexcitability and insomnia followed by depression. There may be abdominal cramps and hematuria followed by collapse, convulsions and coma.

Injected into animals the drug produces a stimulation of the central nervous system with an increase in the rate and depth of the respiration. There is a marked increase in blood-pressure.

With toxic doses there is a dilatation of the pupil, erection of the hair, salivation and tonic and clonic convulsions. On excised tissues the drug in high dilutions has little effect except some inhibition upon the intestinal musculature of the cat. In slightly more concentrated solutions it causes contraction of all smooth muscle.

Therapeutic Uses.—Benzedrine is used in a 1 per cent solution in liquid petrolatum for its vasoconstrictor effect in the upper respiratory passages. It is also used by inhalation combined with menthol and a flavoring oil. Used in this form it should not be employed at too frequent intervals as excessive use may cause restlessness and insomnia. Benzedrine sulfate (amphetamine sulfate) is often used in conjunction with homatropine as a cycloplegic. Internally in the form of tablets it is employed in doses of from 5 to 10 mg. for the treatment of narcolepsy, resulting usually in relief from the attacks of sleep and cataplexy. In some cases the doses named may have to be increased in order to produce the desired effects. In postencephalitic Parkinsonism used in conjunction with stramonium or scopolamine it has proved of value. It is also valuable in certain depressive psychopathic conditions, but such use should be confined to cases in institutions. It is not to be recommended as a remedy for sleepiness or fatigue, not only because of the danger of the formation of the habit, but also because it

would remove a warning signal of overwork or overstrain in the individual. Then, too, the possible vasopressor effects would be undesirable and cases of collapse have been reported from such use. For the same reasons it should not be used as a central nervous stimulant to develop a sense of increased energy or increased capacity for work.

The drug has been used in various spastic states of the gastro-intestinal tract and as an aid in the roentgenolographic study of this structure, but the evidence as to its value in these conditions is somewhat contradictory. The use of benzedrine sulfate is definitely contraindicated in conditions associated with hypertension, coronary artery disease and in states of excitement.

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G. ERGOT.

Ergot is a parasitic fungus (Claviceps purpurea) which grows on the rye (Secale cereale) and occasionally on other kinds of grain; more rarely on other plants. It is of some importance in therapeutics and also in toxicology, as the use of bread and meal containing it has frequently given rise to widespread epidemics.

The chemistry of ergot has been the subject of a large number of investigations and various alkaloids have been described in addition to certain amines which possess a powerful action but which are not specific for ergot.

The first specific active alkaloid in ergot to be isolated was discovered by Barger and Dale and their co-workers and was named Ergotoxine, $C_{35}H_{41}O_6N_5$. Practically at the same time it was also isolated by Kraft and named Hydro-ergotinine. This alkaloid differs from the inactive alkaloid isolated many years before by Tanret and named Ergotinine, $C_{35}H_{39}O_5N_5$, only in that ergotinine contains one less molecule of water than ergotoxine. Either alkaloid can be transformed readily into the other and this may explain some of the discrepancies in the literature of the subject. Stoll isolated still another alkaloid from ergot which he named Ergotamine. It has the empirical formula $C_{33}H_{35}N_5O_5$ and it crystallizes as a free base and in addition forms crystalline salts. It can be easily transformed into another alkaloid Ergotaminine which is apparently an isomer possessing the same percentage constitution.

The physiological action of ergotoxine and of ergotamine is much the same both qualitatively and quantitatively, the main point of difference, according to Rothlin, being in the action on the medullary centres.

In spite of the isolation of these various alkaloids which were the product of many years of arduous research the chemistry of ergot was still only partially solved, and it was still generally recognized that these alkaloids did not entirely replace the crude preparations. This was emphasized by the late onset of the effects on the uterus when the alkaloids were given as compared with the galenical preparations. When ergotoxine or ergotamine was administered, no contraction of the uterus appeared for almost an hour while with the crude preparations strong contractions would often be induced in from six to ten minutes. This difference between the two groups of preparations was forcefully emphasized by Moir, who, employing a method which registered the contractions of the human uterus, was able to show that preparations made by watery extraction of the crude drug and therefore devoid of the commonly known alkaloids, were still active. In fact, powerful contractions of the uterus appeared within a few minutes after the drug had been given by mouth. It would seem, therefore, that there must be some active principle in ergot other than those which had been discovered and which was responsible for this early uterine response.

Research stimulated by Moir's findings resulted in the discovery of a new alkaloid, to which various names have been applied, viz., Ergobasine, Ergometrine, Ergotocin and Ergostetrine, but it has been shown that these all represent one and the same principle—an alkaloid with the formula $C_{19}H_{23}O_2N_3$ to which the name Ergonovine has been given. The molecule is seen to be much smaller than that of Ergotamine, which has a formula $C_{33}H_{35}O_6N_5$. It differs from the latter alkaloid, too, in being easily soluble in water but soluble in chloroform only with difficulty. Inasmuch as it gives some of the color reactions common to the older ergot alkaloids and yields on decomposition some of the same products, it has been suggested that it is a step either in synthesis of ergotoxine or ergotamine or is a product of their breaking down. Jacobs and Craig have shown that the new alkaloid is the hydroxyisopropylamide of lysergic acid. The same workers had already shown that this acid is present in several of the other alkaloids of ergot, thus showing the close relationship existing between them. As a further step in our knowledge of the chemistry of ergonovine, Stoll has reported that he and Hofmann have synthesized ergonovine from lysergic acid and 2-aminopropanol-l producing ergobasinin which was converted into ergobasine (ergonovine).

Smith and Timmis also described a new alkaloid with the formula $C_{19}H_{23}O_2N_3$, to which they gave the name Ergometrinine. This has proved to be an isomer of the alkaloid Ergonovine, found recently, into which it can be transformed. These new alkaloids, therefore, add another pair to the group of substances which include the long known alkaloids, ergotinine—ergotoxine and ergotamine and ergotaminine.

In the ergot preparations there are found in addition various amines, *Tyramine* (page 535), *Ergamine* (*Histamine*) (page 552) and several other bases such as *Isoamylamine* and *Acetylcholine* (page 484). These are often present in other conditions as products of the putrefaction of protein, and it is not yet determined whether they are formed by the ergot fungus itself or by the microbes which infest it. In any case they do not ordinarily exert any significant action when ergot is applied in usual therapeutic procedures. The effective agents are primarily the ergotoxine, ergotamine and ergonovine.

Ergot has rarely given rise to serious **Acute Poisoning** in man, but in some cases in which it was taken to procure abortion the symptoms consisted in collapse, with a weak, rapid pulse, tingling, itching and coldness of the skin, unquenchable thirst, vomiting and diarrhœa, confusion or unconsciousness, hæmorrhage from the uterus, abortion and often icterus. Ecchymoses were found in the subcutaneous tissues and in many internal organs. Occasionally, after a single small dose, gangrene has supervened in small areas such as the toe-nails.

Given in therapeutic doses ergot has generally no effect except in pregnant women, in whom it often induces contraction of the uterus and evacuation of its contents. In some cases of fatal poisoning no abortion occurred.

Chronic Poisoning was formerly not uncommon, and in fact frequently gave rise to widespread epidemics, from the use of bread containing ergot after poor harvests and especially in wet seasons. Of late years these epidemics have become rare except in Russia, but some of the "plagues" of mediæval Europe may have been due to ergot poisoning.

The symptoms of ergotism are sharply divided into two groups: those of gangrene and those of nervous disorders. In some epidemics both the gangrenous and the convulsive forms are present, but, as a general rule, the epidemics in Western Europe were almost exclusively gangrenous in type, while in Eastern Europe the convulsive form almost invariably prevailed. The gangrene is generally developed in the limbs, especially in the fingers and toes; sometimes the whole arm or leg becomes cold and anæsthetic, dark in color, and then dry, hard and shrunken, and falls off with little or no pain and no hæmorrhage. Symptoms of such severity are rare, however, and in milder cases only the skin necroses. Gangrene of internal organs also occurs, resulting in cataract in the lens of the eye, or ulcers in the bowel and stomach, and sometimes affecting a whole organ such as a lung or the uterus. Abortion is seldom mentioned in the accounts of chronic ergot poisoning, and pregnancy seems in many cases to have run its ordinary course.

In spasmodic ergotism the first symptoms are depression, weakness and drowsiness, often with headache and giddiness, painful cramps in the limbs and itching and formication of the skin. In severe cases paroxysmal convulsions set in, generally clonic, and often epileptiform, but leaving as sequelæ contractures in the limbs, or less often in the trunk muscles. Some intellectual weakness often follows recovery from ergot poisoning, this not infrequently amounting to complete dementia, but the disease was immediately fatal in a large proportion of cases in earlier times. The characters and distribution of these two forms of ergot poisoning have given rise to much discussion. The gangrenous

form appears to be the more characteristic, and it has been suggested that the spasmodic form may have arisen in cases where ergot poisoning was complicated by starvation and possibly by epidemic nervous disease such as poliomyelitis or meningitis.

In mammals treated with ergot, restlessness, salivation, sometimes vomiting and purging have been observed. Depression and weakness, ataxia and clonic convulsions follow on larger doses, which prove fatal by paralyzing the respiratory centre. Gangrene is common in the pig, in which the ears, the extremities, and patches of the skin of the trunk become dry and hard, and finally fall off. Extravasations

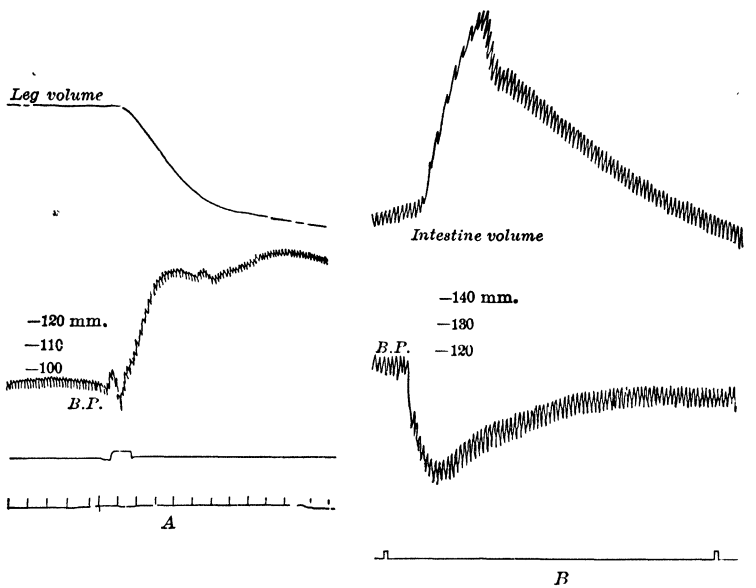

FIG. 38.—Figures illustrating the effects of ergotoxine on the blood-pressure (Dale). In *A* the injection induces a rise of blood-pressure (*B.P.*) with constriction of the vessels of the leg. In *B* a large dose of ergotoxine had been injected previously, and epinephrine injected at the point indicated now causes a fall of blood-pressure with dilatation of the intestinal vessels, illustrating the phenomenon known as vasomotor reversal.

of blood into the stomach and bowel and other organs have frequently followed the exhibition of ergot in mammals. In pregnant animals abortion is often induced, but not invariably, even when very large doses are given.

In fowls a characteristic train of symptoms is induced, and these animals have frequently been used as tests for the activity of ergot preparations. The cock becomes drowsy and dyspnœic, and the comb and wattles become dusky purple in color. Vomiting or purging may follow and a curious ataxia is observed, the animal swaying to and fro and evidently maintaining its balance with difficulty. After large or repeated doses the comb becomes dry and hard and falls off, and a

similar gangrene may attack the legs, tongue, or wings. The animal refuses food and becomes weak and somnolent, but may recover if the treatment be stopped. The gangrene of ergot poisoning arises from the prolonged constriction of the vessels by the ergotoxine and ergotamine.

Action.—The study of the action of ergotamine and ergotoxine in the living organism has shown that these alkaloids resemble epinephrine in some of their effects, and like it act on the myoneural junctions of the true sympathetic nerves. But while epinephrine stimulates these junctions indiscriminately whether they are motor or inhibitory in character, the ergot alkaloids act on the inhibitory junctions only to a slight degree but stimulate the motor myoneural junctions in small doses and paralyze them in larger amounts. They are less powerful than epinephrine, but the effects last longer and can be elicited by hypodermic injection or by administration by the mouth.

Circulation.—Ergotoxine and ergotamine injected intravenously cause an abrupt rise in blood-pressure which is obviously due to action on the peripheral vessels, for it occurs after section of the splanchnic nerves, and is accompanied by constriction of the vessels of the abdominal cavity and the limbs, as may be shown by oncometer and plethysmographic records (Fig. 38, *A*). The heart is often accelerated at first and then slowed, partly from the vagus centre being stimulated by the high blood-pressure and partly by a direct action on the heart muscle. Sometimes the slowing of the heart may be so marked as to lower the blood-pressure and thus to conceal the effects of the vaso-constriction on the tracing.

The rise in pressure is to be ascribed to stimulation of the constrictor nerve terminations in the vessel walls and is strictly analogous to that observed under epinephrine. The extent to which it is developed varies in different animals, being well marked in the cat, dog and fowl and observed only with difficulty in the rabbit and monkey.

Ergot preparations injected intravenously sometimes fail to increase the blood-pressure if they contain little of the specific alkaloids and large proportions of histamine, which dilates the capillaries (p. 554). As a general rule an intravenous injection of a crude ergot preparation, as distinguished from the alkaloids, is followed by some fall in pressure, and then by a slower rise above the normal.

The ergot alkaloids have little effect in constricting the vessels when applied locally, therefore, absorption is not so much retarded as by epinephrine and ergot action may thus be elicited by oral administration.

The heart is not acted upon so strongly as the vessels by ergotoxine but the contractions are strengthened while the rhythm is slower in some degree; it is uncertain how far this arises from direct action on the cardiac muscle and how far the accelerator terminations are involved. Crude ergot preparations generally slow and strengthen the heart when injected intravenously; sometimes a muscarine action is induced by the presence of acetylcholine. The terminations of the inhibitory nerves of the heart are not paralyzed or weakened in any way by ergot and indeed according to Rothlin the activity of the vagus is augmented by ergotamine while in the case of the depressor nerve the reverse is true.

Ergotamine causes a moderate increase in the pressure of the cerebrospinal fluid following the intravenous injection of small doses. An increased flow of blood through the brain is also found, this increase being in all probability secondary to the increase in general systemic blood-pressure.

Stomach and Intestine.— Ergotoxine[1] in small doses has little effect on the movements of these organs, since the sympathetic nerves are inhibitory and therefore escape its influence; under ergot vomiting and diarrhœa often occur in animals; in man the action on the digestive organs is seldom noticeable.

The **Pupil** undergoes a powerful constriction when ergot is injected intravenously, sometimes after a momentary dilatation. This constriction is not affected by atropine and arises from the direct action

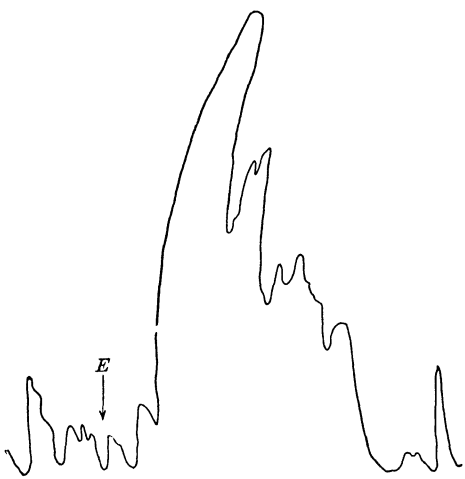

FIG. 39.—Tracing of the movements of the uterus under ergot injected intravenously at the point *E*. Contraction is indicated by an upward movement of the lever.

of ergotoxine on the muscle fibre; in the rabbit, however, the pupil is dilated, perhaps owing to the excitement and increased movement.

The **Respiration** is often greatly accelerated in poisoning in animals apparently from stimulation of the centre, though this may be aided by the increased movement and high temperature.

The **Temperature** rises greatly in the cat and rabbit under ergotoxine (but not from ergotamine, Rothlin), while in the rat and mouse it often falls. The fever temperature is partly due to increased heat formation, partly to imperfect heat-loss (Githens); it is absent after removal of the brain, presumably owing to the destruction of the heat-regulating centre.

In some animals the hair rises owing to the stimulation of the sympathetic terminations in the pilomotor muscles.

The most important effect of ergot, however, is exerted on the

[1] As stated above, the actions of ergotoxine and ergotamine are practically alike.

Uterus, in which it causes a powerful contraction which lasts for a short time and is followed by a slow relaxation interrupted by numerous new contractions, a lasting effect on the irritability being induced (Fig. 39). The innervation of the uterus, both motor and inhibitory, is derived from the sympathetic; but ergotoxine, stimulating only the motor fibres, always causes contraction, the inhibitory ones remaining unaffected by it.

The uterus thus reacts to ergot in a way precisely analogous to the arterioles, and it is noteworthy that from therapeutic doses it is from the uterus alone that any obvious symptoms are elicited. The alimentary tract is but little affected, and the rise of blood-pressure is not easily observable in the circumstances in which ergot is usually exhibited. The contraction of the uterus in pregnant animals causes the descent of the fœtus toward the os, and in suitable doses ergot induces abortion. If the dose injected is small, the rhythmic contractions are accelerated and strengthened, or if the uterus is at rest, ergot may arouse it to rhythmic contraction. As the dose is increased, the contractions become more powerful and last a longer time, until with a large injection the uterus may contract very powerfully and remain in this position for many minutes.

The secondary paralyzing action of ergotoxine and ergotamine on the myoneural junctions is elicited only by large doses and does not occur in the therapeutic use of ergot; large quantities of ergot often elicit this effect in experiments, however. This paralysis was originally believed to affect only the motor sympathetic neurons, while the inhibitory ones were, according to this view, left unaffected and stimulation of a mixed motor and inhibitory nerve, or the injection of epinephrine, caused inhibition only. This view of action of the ergot alkaloids being confined to the motor sympathetics is undoubtedly true when applied to the use of moderate doses of the drugs but with the employment of large doses a further action upon the inhibiting nerves is also seen as described below. Thus, after a moderate dose of these alkaloids, epinephrine may lower the blood-pressure (Fig. 38, *B*), where previously it increased it by stimulating the constrictor nerve ends; these are now unable to react due to the paralyzing action of the ergot alkaloids, but the dilator nerve ends are more resistant, and epinephrine stimulating them dilates the vessels. Epinephrine also acted on the dilators before the ergotoxine injection, but the effect of this stimulation was masked by the simultaneous stimulation of the more powerful constrictors. The same reversal of effect by ergotoxine is seen if the splanchnic nerves be stimulated. The motor splanchnic fibres to the intestinal sphincters and bladder and other similar motor sympathetic fibres are similarly paralyzed by ergotoxine in fairly large doses, and stimulation of the nerves or the injection of epinephrine has now no effect on them. The fibres from the cranial and sacral nerves, however, are uninjured. Similarly, stimulation of the cervical sympathetic no longer dilates the pupil or elicits salivation in ergotoxine poisoning because the connection with the muscle and gland is broken, but the motor oculi and chorda tympani, being cranial nerves, remain normal. Both motor and inhibitory nerves of the uterus are sympathetic, and ergotoxine in certain amounts paralyzes the motor while leaving the inhibitory intact, and stimulation of the hypogastric nerve or epinephrine now causes inhibition and relaxation. The accelerator nerves to the heart are sympathetic, but it is difficult or impossible to throw them out of action completely with ergotoxine.

In contradistinction to the view of the action of the ergot alkaloids being exclusively confined to the motor sympathetic endings as described above, Rothlin showed that ergotamine not only paralyzes the motor sympathetic fibres but also acts on the inhibitory terminations as well. It thus prevents not only the motor but also the inhibitory effects which follow the injection of epi-

nephrine. This was shown by allowing solutions of ergotamine to act upon certain excised tissues which were normally inhibited by epinephrine. Following the use of such solutions the action of epinephrine was entirely absent. In the case of the intestine of the guinea-pig and of the rabbit a concentration of ergotamine twice that of the epinephrine was needed in order to offset the action of the latter drug. In the intact animal the same reaction was also shown. For instance in the case of the intestine of the dog and the rabbit, minimum amounts of ergotamine are sufficient to prevent the normal inhibitory epinephrine effects. The ease with which the endings are affected by ergotamine differs considerably in different animals, the guinea-pig and the rat being especially resistant. According to Rothlin, therefore, ergotamine and epinephrine occupy the same relationship in respect to the sympathetic nerves that atropine and pilocarpine do for the parasympathetics.

Some **Tolerance** is acquired for ergotoxine when it is injected repeatedly into animals.

The new alkaloid *Ergonovine*, which was recently discovered, resembles in many of its actions the older members of the group, ergotoxine and ergotamine.

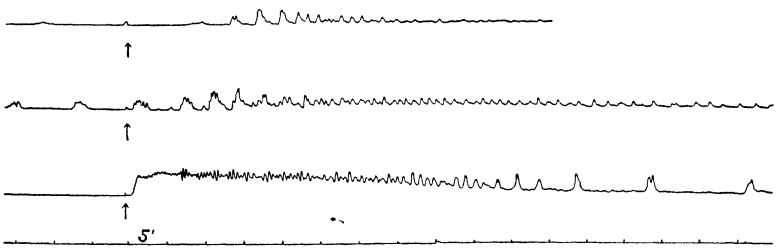

FIG. 40 – Ergonovine upon the human uterus. Tracings obtained from 3 patients each on the seventh postpartum day. In each case a rubber balloon was placed within the uterine cavity and connected with a bellows recorder. To each patient 0.2 mg. of ergonovine tartrate was administered. To patient yielding the top curve it was given by mouth; to patient giving the middle curve, by subcutaneous injection, and the lowest curve, by intravenous injection. The time intervals are five minutes. In the last 2 cases the effects lasted more than two hours, while in certain other patients the increased contractions were plainly observable for a much longer time. (Gardner and Bradbury.)

In general ergonovine is approximately one-fourth as toxic as ergotamine for mice and rabbits and one-tenth as toxic for cocks, but nearly equally toxic for cats. The toxic symptoms resulting from its use resemble closely those produced by the older alkaloids and are apparently due to the lysergic component of the molecule judging from the toxicity of ergine, an amide of lysergic acid. The symptoms from ergonovine are mainly those due to central nervous stimulation, weakness, tremors, excitement, convulsions, together with signs of sympathetic stimulation such as mydriasis, exophthalmos, erection of the hair and tachycardia. The symptoms resulting from sympathetic stimulation seem to be due almost exclusively to central action. Its most important action is upon the uterus where its effects are prompt and vigorous whether it is administered by mouth or intravenously. Apparently the outstanding features of the action of ergonovine on uteri are shown in the puerperal period where its prompt action and effectiveness in small doses distinguish it from the alkaloids studied earlier. Not only is this action on the uterus seen in animals, but it has been also shown to occur in the human subject, where after oral or subcutaneous administration strong contractions of the uterus appear within a few minutes.

On the isolated quiescent strips of human uteri and Fallopian tubes ergonovine has little effect, but it induces vigorous contractions in similar strips of the postpartum uteri of guinea-pigs. The difficulty of demonstrating an action of the

alkaloid upon the isolated uterus has suggested that its action on the uterus is not entirely peripheral (McLachlin).

It raises the blood-pressure in rabbits and spinal cats but usually lowers it in anæsthetized cats and dogs. It has little effect upon the heart. It quickens the respiration but lessens the respiratory volume. The temperature is lowered in rats and mice, but it causes hyperthermia in rabbits whereas in these animals ergotamine in small doses leads to hypothermia and in large doses to hyperthermia. Ergonovine exhibits some signs of a peripheral action upon the sympathetic system, such as mydriasis, relaxation of the isolated intestine of the rabbit and some increase in the blood sugar of rabbits and dogs, but the symptoms seen in the intact animal ascribable to a sympathetic action are mainly central in origin.

The principal difference in action between the ergonovine and the old alkaloids is that the new principle exerts no paralyzing effect upon the sympathetic nerves so that while the sympathetics are stimulated, causing the increase in blood-pressure, they are not paralyzed so that the vasomotor reversal phenomenon is not seen. Nor are the other effects of sympathetic nerve stimulation inhibited by it as they are by the older alkaloids. A striking point of difference between the new principle and the older alkaloids is that while the former will produce cyanosis of the cock's comb it has been possible thus far to produce gangrene with it in only a few instances. It will be seen, therefore, that judging by the studies of the newly described active principle which have been carried out thus far its greatest clinical value would seem to lie in the field of obstetrics and that it would be without value in those conditions in which an action upon the sympathetic nerves might be required.

Therapeutic Uses.—Ergot is used very extensively in obstetrics to promote the contraction of the uterus, but considerable divergence is met with in the views of different authorities as to the special indications for its exhibition. Thus, those who believe that ergot increases the irritability of the uterus and produces rhythmical contraction without tetanus, advise that it be given whenever the pains seem insufficient, and more especially when this occurs in the later stages of labor. Others are apprehensive of the prolonged uterine contractions, which they consider delay labor and tend to cause asphyxia in the child, and therefore advise that ergot be used only to preserve the uterus in a contracted condition after the child and placenta have been expelled. In every case the attendant should of course satisfy himself before giving ergot of the absence of all actual impediments to the passage of the child, such as contracted pelvis, abnormal presentation, or great rigidity of the soft parts, and when it is administered before the head emerges, the dose ought to be small, as otherwise the tonic contraction may be induced. When the placenta is delivered, on the other hand, a larger dose may be given to promote the permanent contraction of the uterus and thus to prevent postpartum hæmorrhage. Whenever there is atony of the uterus and postpartum hæmorrhage, pituitary extract may be given at once by intramuscular injection and a preparation of ergot or ergonovine administered by mouth at the same time. The pituitary action coming on rapidly will be passing off when the ergot action is becoming manifest, although as shown in the ergonovine tracings reproduced above the action of this alkaloid appears very quickly, especially when it is given parenterally. Probably in the near future one of the alkaloids will replace the crude preparations in practical obstetrics as a rapid stimulant of the uterine contractions or even for more prolonged

administration. In the latter case care must be taken that the alkaloids are not given for more than a brief period as several cases of gangrene of the extremities have already been reported due to neglect of this precaution.

Ergot hinders postpartum hæmorrhage, chiefly by promoting the contraction of the uterus. In other forms of hæmorrhage—from the stomach, intestines, kidneys, lung or uterus—in which the bleeding point cannot be reached, it is often advocated in the belief that it contracts the walls of the vessels and thus arrests the flow of blood, but it may be questioned whether ergot exerts any influence whatsoever in these cases. The essential treatment is rest with or without morphine.

The effect of ergot in inducing contraction of the uterus has been used in the treatment of subinvolution and the process certainly seems to be favored by it. The prolonged treatment of this, or of any other condition, with ergot is to be deprecated, for if the drug is active at all, it may induce gangrene. This is especially true when the alkaloids are employed.

In the past few years ergotamine has been introduced as a treatment for migraine and severe headaches of a periodic type. Its administration has been followed by relief in a large proportion of cases, although in a certain number no improvement follows. Lennox and Leinhardt say that in 90 per cent of cases the administration of ergotamine is followed by disappearance of the migraine headache and of all other symptoms. Ergonovine is not so efficient as in only about 40 per cent of the cases when this alkaloid was used was the pain entirely stopped while a further 40 per cent were improved by it.

There is no entirely satisfactory explanation as to how the ergot alkaloids relieve the migraine headaches. However, Graham and Wolff say that the intensity of the headache is closely related to changes in the amplitude of the pulsations of certain branches of the external carotid artery. They believe that the pain of migraine attacks is produced by distention of cranial arteries and that the termination of these attacks by ergotamine is due to its action constricting these arteries and thus reducing the amplitude of the pulsations. Factors which decrease the pulsation amplitude decrease the headache and *vice versa*. They showed that ergotamine reduces the pulsation by about 50 per cent, at the same time reducing the headache, and observations and photographs made before and during the action of ergotamine show vasoconstriction of the temporal and meningeal arteries. Lennox and Leinhardt also ascribe the beneficial effects of ergotamine in this condition, at least in part, to its bringing about an increased tone in arteries where it may have been impaired. They also point to an increased rate of blood flow through the peripheral tissues, together with a decrease in viscosity. These two studies would appear to point to an action of ergotamine upon certain arteries of the head as being responsible for its beneficial effects in attacks of migraine.

When the alkaloid is administered intravenously in 0.2 to 0.5 mg. doses relief usually follows in less than one-half hour, but nausea, vomiting and some muscle pain are not uncommon side effects. These accompanying symptoms are not as likely to occur if the drug is given by intramuscular injection, although vomiting is fairly common. The occurrence of emesis is not necessary for the relief of the headache as

the vomiting, if it is present, comes on earlier than the relief of the migraine.

Ergotamine may also be given by mouth in 1 to 3 mg. doses for this effect, but it is usually not so efficient as when given parenterally.

Serious complications from the use of ergotamine in migraine rarely, if ever, occur provided proper care is used to avoid overdosage. No more than one injection should be given in a day nor more than two a week.

Preëxisting sepsis or obliterative vascular disease, especially of the coronary vessels, is a contraindication to the use of the alkaloid. It should also be used with caution in the presence of marked arteriosclerosis.

Preparations.

U. S. P.

Ergota, 2 G. (30 grs.).

Fluidextractum Ergotæ, 2 cc. (30 mins.).

Ergonovine (non-official).

B. P.

Ergota.

Ergota Præparata, Prepared ergot. 0.3–1 G. (5–15 grs.).

Extractum Ergotæ Liquidum, Liquid extract of ergot. 0.6–1.2 mils. 10–20 mins.).

Ergotoxinæ Æthanosulphonas, Ergotoxine Ethanesulphonate, is the ethanesulphonate of ergotoxine. 0.0005–0.001 G. ($\frac{1}{120}$–$\frac{1}{60}$ gr.).

Ergometrina, Ergometrine, $C_{19}H_{23}O_2N_3$ (Ergonovine in United States), is an alkaloid obtained from ergot. Dose: Oral, 0.0005–0.001 G. ($\frac{1}{120}$–$\frac{1}{60}$ gr.); intramuscular, 0.00025–0.0005 G. ($\frac{1}{240}$–$\frac{1}{120}$ gr.); intravenous, 0.000125–0.00025 G. ($\frac{1}{480}$–$\frac{1}{240}$ gr.).

Ergota, ergot of rye, the sclerotium of Claviceps purpurea replacing the grain of rye The U. S. P. requires that ergot shall be subjected to bioassay by the cock's comb method and shall be of such a potency that each gram of ergot shall have a strength equivalent to not less than 0.5 mg. of ergotoxine ethanesulphonate. The B. P. requires a colorimetric method of assay.

The fluid or liquid extracts are probably the best of the crude preparations. A very large number of preparations, such as ergotin, etc., are simply more or less purified extracts and have no advantage over the pharmacopœial preparations.

The pure alkaloid, ergotoxine phosphate, was put on the market, and later this was supplemented by another salt, the ergotoxine ethanesulphonate. Ergotamine tartrate has been introduced under the name of Gynergen. It is recommended to be given in doses of $\frac{1}{2}$ mg. by hypodermic or intramuscular injection or in 1- or 2-mg. doses in tablets or solution by mouth. Ergotamine is also available as the methanesulphonate.

Ergonovine is not official in the United States, but is on the market in the form of the malate under the name of Ergotrate. In the B. P. it is official under the name of Ergometrine.

The crude preparations of ergot vary greatly in activity and appear to deteriorate on keeping. This deterioration in the fluid preparations of ergot has not been explained, various factors possibly contributing thereto. Among these factors, the most important seem to be the temperature under which the preparation is stored, a low temperature favoring stability, and the hydrogen-ion concentration, increased acidity apparently enhancing its keeping qualities. At present ergot preparations can be standardized biologically by comparing their activity with that of a standard preparation or with that of the alkaloids.

It is not unlikely that in the near future the crude preparations of ergot will be replaced to a greater or less extent by the pure alkaloids.

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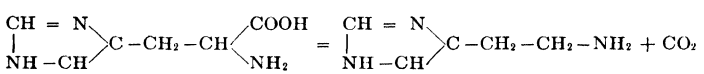
II. THE HISTAMINE GROUP AND ANAPHYLAXIS.

Histamine is an amine derived from the amino-acid histidin by the removal of the carboxyl group, and structurally is β-iminazolylethylamine.



Histidin Histamine

Histamine may be found wherever protein is broken down into its component amino-acids in the presence of putrefactive organisms; thus it occurs in some quantity in the intestinal contents and in the putrefaction of meats and has been isolated from preparations of ergot, though it is doubtful if it occurs in the fungus itself, and the quantity present is too small to modify the action except when the ergot is injected intravenously.

The action of histamine is very similar to that of a number of protein derivatives of unknown structure, such as peptones, the "split protein" produced by the action of alkalies (Vaughan), and the extracts of various organs and muscles. A very slight modification of the protein molecule is sometimes enough to change it to a poison having the characteristics of this group; thus Bordet showed that serum shaken with agar agar induces poisonous symptoms of this type when injected intravenously, although it presents no other features which distinguish it from ordinary serum.

The symptoms of **Secondary Shock** from severe injury in man may also be included in the group, for they resemble those induced in animals by histamine so closely that it has been suggested that they are due to the liberation of histamine or similar poisons in the injured tissues.

Another form of poisoning which resembles that of histamine very closely was first described by Richet and called by him **Anaphylaxis.** If an animal receives an injection of any harmless foreign protein, it presents no symptoms whatever; but if the same protein is injected again after an interval of about fifteen days, severe or fatal poisoning may result. This anaphylactic reaction is very specific for each protein; for example, if the first, or sensitizing injection consists of horse serum, then the second injection must contain horse serum, that of any other animal causing little or no reaction. The sensitiveness to a second injection remains for many months, in man perhaps throughout life, and this has become of great importance of late years, since an injection of one of the antitoxic sera in childhood may suffice to induce fatal poisoning in adult life if a second treatment is necessary with serum from the same species of animal. When an animal recovers from even slight anaphylactic shock, no reaction occurs from a further injection; the animal is said to be desensitized.

Many unusual reactions presented by individuals to certain foods or to exposure to dusts and pollens which are harmless to most people, are now believed to be due to their having been previously exposed to these and having become sensitized to them. Anaphylaxis is induced only by proteins.

Several explanations of anaphylactic shock have been given; according to one of these, the first or sensitizing injection leads to the development of a ferment-like substance which modifies the protein injected (antigen); on the second injection this ferment decomposes it rapidly into a poisonous "anaphylotoxin" which produces the symptoms, just as such a drug as histamine does. On the other hand, Dale holds that the sensitizing injection leads to the formation of a new antagonistic body, precipitin, which penetrates into the cells of unstriated muscle and other tissues; when the second injection is made, the antigen penetrating into the cells reacts with the precipitin, causing cellular injury and freeing histamine and other substances, the action of these other substances being responsible for those symptoms which occur in anaphylactic shock and are not produced by histamine. This view is in harmony with many other facts known about the behavior of antigens and has been supported by experiments in which the involuntary muscle reacted to the second injection after all trace of protein had been washed out of the vessels, and in which any anaphylotoxin in the blood must have been removed also. In anaphylaxis the cells are peculiarly sensitive to the presence of the antigen; it is true that this sensitiveness arises from the formation of a precipitin in the blood and tissues as a result of the first injection, but this is not toxic in itself, but only reacts with the antigen. This precipitin may be transferred by transfusion to a second animal, which then becomes sensitive to the antigen, though it has never come in contact with it directly. After the shock has been recovered from, no second attack is caused by a second injection of antigen, since all the precipitin has been combined already.

The similarity of the symptoms induced by all of these has suggested that they arise from a single substance, and histamine has been looked

the heart and the arterial side of the circulation. The pulmonary vessels remain constricted however, and this is another factor in disturbing the circulation. In the cat the capillary action is diffused fairly evenly throughout the systemic circulation; in the dog it is more marked in the liver than elsewhere, as is shown by the swollen and tense condition of that organ.

In the herbivora, the action on the capillaries is absent, so that histamine increases the blood-pressure through constriction of the arterioles; later it becomes irregular through the asphyxia.

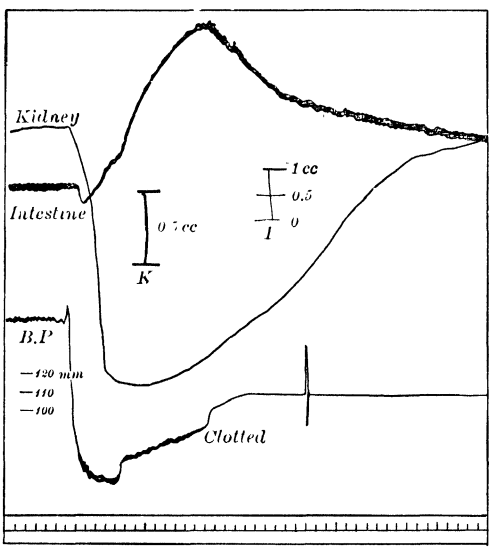


FIG. 41.—The action of histamine on the blood-pressure (*B.P.*) and on the volume of the intestine and kidney in the cat. The injection causes a marked fall in the blood-pressure which is due to dilatation of the intestinal capillaries. The kidney vessels are constricted. (Dale.)

The capillary action is not developed when histamine is added to the fluid perfused through surviving organs of the cat in the ordinary way, apparently because some receptor in the capillaries has become unresponsive through the failure of the oxygen and epinephrine supply; in these experiments, histamine lessens the flow through the vessels by constricting the arterioles. When special measures are taken, however, the dilation of the capillaries can be shown in these experiments also (Dale and Richards). The shock symptoms in carnivora are increased by anæsthetics, and this is true also of secondary shock from injury. The heart is increased in strength though it may be slowed in rate from a direct action on the heart muscle, but as the fall of pressure is developed, the beat may become slower from an insufficient supply of blood.

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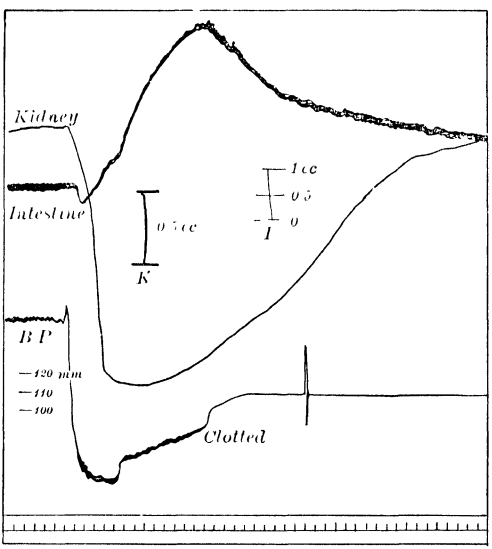

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In the excised perfused hearts of both rabbits and cats histamine causes both augmentation and acceleration, diminishing the coronary outflow in the rabbits, but increasing it in cats. This latter action may be due to dilatation of the capillaries (Gunn).

The **Respiration** does not seem to be affected through the centre; the asphyxia in the herbivora is induced by constriction of the bronchi from histamine acting on the bronchial muscle directly; this action is hardly affected by atropine, showing that it is not dependent on the nervous mechanism; on the other hand, it is antagonized to some extent by epinephrine, which inhibits the bronchial muscle, and by anæsthetics, especially urethane, which has a special weakening action on the bronchi.

The **Stomach, Intestine and Uterus** contract more powerfully or may pass into spasm, and as this effect is not counteracted by atropine, it probably arises from direct action on the muscle; the uterus especially is exceedingly sensitive to the presence of histamine.

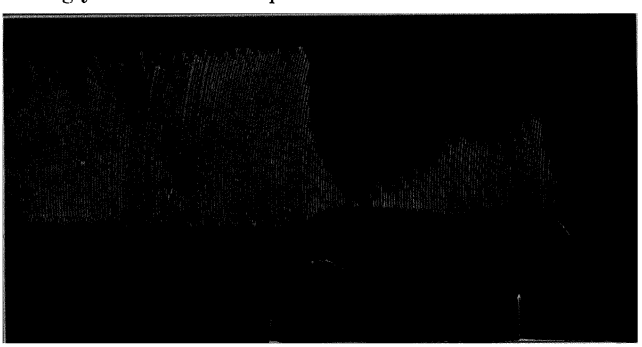

FIG. 42.—Action of histamine on the bronchi and blood-pressure of a rabbit. The expansion of the lungs on inflation is greatly reduced (upper tracing) from the contraction of the bronchi. The blood-pressure rises with each injection. At the arrows, intravenous injection of histamine. (Gunn.)

The pupil is contracted, apparently from central action, for this does not occur under anæsthesia.

The accumulation of the blood in the capillaries and increased permeability of the capillary walls facilitate the escape of the plasma of the blood, so that the red cells are increased in proportion. There is an increase in certain of the chemical constituents of the blood, such as the calcium, phosphate, non-protein nitrogen, and sugar; but the increased concentration of the blood will probably account for some of these changes but there are probably other contributing factors involved.

Many **Glands** secrete under histamine—the salivary, gastric, pancreatic and lacrimal; this action is prevented or greatly diminished in the salivary glands, and presumably in the others, by atropine, but not by section of the parasympathetics, so that the secretion is probably caused by stimulation of the ganglia or the terminations of the post-ganglionic fibres. In the case of the gastric secretion the increase is

mainly one of water, hydrochloric acid, and other inorganic constituents without affecting the secretion of the enzymes.

Histamine has been isolated from acid extracts of the pyloric mucosa and is probably the sole secretory excitant active subcutaneously in such extracts. A histamine-like substance has also been found in the gastric juice of normal persons but the amount present was so small that it could not be identified by chemical means. According to Brown and Smith the amount contained in 1 litre of gastric juice was about 0.7 mg. Histamine has also been demonstrated to be present in various other tissues, among them being the liver, lungs and the intestinal tract, in which organs it was present in largest amounts. It has also been found in the heart and spleen and in the urine. In various other localities, such as the skin, a histamine-like body has also been found but in too small quantity to allow for chemical identification.

Histamine apparently is destroyed in certain tissues by an inactivating substance which has been designated histaminase. This enzyme has been found in many tissues and organs, the largest amount being in the intestines and kidneys while none was found in the stomach, heart or skin.

Histamine which is liberated in the body by cell destruction or by nerve stimulation, or which is injected intravenously, is taken up by the tissues and then slowly passed into the blood. The heart-lung preparation of a dog can inactivate large amounts of histamine. The major part of blood histamine in the dog has been shown to be held in combination in the white blood cells. In the rat injected histamine disappears rapidly from the blood. In the various tissues, aside from the kidney, histamine disappears rapidly during the first half hour after its injection. In the kidney during this time the amount remains almost unchanged, but in the second half hour and subsequently the amount drops very rapidly.

Adrenalectomized rats are less resistant to histamine than normal animals, but such animals showed a distribution of histamine in the tissues and blood much as in the intact animals, the main point of difference being that in each instance there was a definite retardation in the rate of disappearance. This interference with destruction of the histamine in the adrenalectomized rats is probably not due to any specific action of the adrenals upon the metabolism of the histamine, but rather to a general decrease in bodily resistance characteristic of this condition.

According to Anrep and his co-workers the white cell layer of centrifugated unclotted blood is rich in histamine, containing about one-half of the total amount, the remainder being found in the red cells and plasma. On clotting the white cell layer disappears and the entire amount of histamine is found in the clot or in the fibrin.

Both white and red cells take up histamine only when the amount of this substance in the surrounding plasma or serum exceeds their own. The amount which is taken up is retained by the cells quite tenaciously.

During contraction of a voluntary muscle there is a release of histamine which is proportional to the strength and duration of the contraction and is derived from the preëxisting store in the muscle. Similar observations have been made upon the heart muscle and upon prepara-

tions of smooth muscle from the digestive tract and from the bladder. The histamine is probably derived from the cells of the contracting smooth muscle, the nervous elements not being involved. This is also shown by the observation that after section and degeneration of the motor nerve to a muscle direct stimulation of the muscle will still cause an increase in histamine in the venous blood. Drugs such as strychnine and picrotoxin when given in convulsive doses will also increase the histamine output from the muscles.

The local action of histamine is seen when it is applied to a scratch on the skin or by subcutaneous injection, and consists in dilation of the capillaries, leading to redness, swelling, and the exudation of plasma into the skin; this is apparently due to local capillary dilation and suggests that the wheal caused by local injury may arise from the liberation of bodies with similar action.

Lewis has described the local skin reaction as a "triple response;" a vaso-dilatation, a diffuse flare with a diameter of about 3 cm., and an area of local edema. The maximum response is attained in about five minutes and the effects have passed off in about an hour. When the nerves of the skin have degenerated the flare does not appear but the edema is present. These phenomena have been ascribed by Lewis as being due to the H-substance; the action of which is not unlikely to be due, at least in part, to histamine.

The characteristic action of histamine is the powerful contraction of the unstriated muscle, which is developed in the uterus,[1] and in the bronchi in some animals. The muscle of the alimentary tract and arterioles responds less strongly and the iris and bladder are not affected directly. In the carnivora there is extreme dilation of the capillaries, except those of the lungs, apparently from direct action on the walls. The peripheral nervous mechanism of the glands is stimulated to some extent, and there is some narcotic action on the brain.

Histamine has recently been employed extensively in clinical medicine as a gastric secretory stimulant, especially as a diagnostic agent to distinguish between true and false achylia. The change in secretory activity which it produces is, as pointed out earlier, entirely confined to an increase in the acid component of the gastric juice. Histamine is a very efficient agent to employ in such tests but care must be taken not to give doses which are too large. In certain cases this has been done and they have been followed by disagreeable symptoms such as a severe occipital headache and an anginal pain in the chest. The face becomes cyanosed, and the vision blurred, and the blood-pressure drops very rapidly. At times the patient may appear to be dying.

The usual dose to employ is from 0.3 to 0.5 mg., the same to be given by subcutaneous injection. On account of the dangerous symptoms sometimes encountered in the use of histamine some authorities recommend that it should never be used, as they believe equally valuable information can be gained as to the condition of the gastric secretory

[1] A remarkable exception to this contractor action has been observed by Guggenheim in the rat's uterus, which is inhibited by histamine.

mechanism from the use of less dangerous remedies such as 7 per cent alcohol.

The action of histamine and of other bodies resembling it in effects does not suggest any use in therapeutics which is not more safely attained by other less dangerous measures. It has been tried as a uterine stimulant in doses of about 2 mgs. ($\frac{1}{30}$ gr.) given hypodermically, but even this dose causes unpleasant symptoms in some instances.

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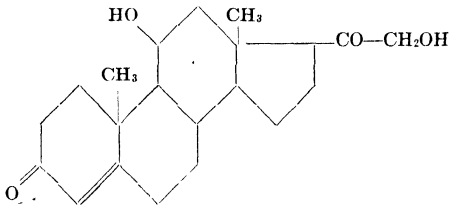
I. DRUGS OF INTERNAL SECRETION.

I. ADRENAL CORTEX.

Brown-Sequard in 1856 showed experimentally that adrenalectomy invariably resulted in death in the course of a few days, a finding amply confirmed by later investigators. Furthermore, it has been shown that death is due to the removal of the cortex rather than the medullary portion of the gland. Various measures of treatment of adrenalectomized animals were successful in prolonging life for only a matter of days. However, in 1930, after numerous partially successful attempts, certain groups of investigators prepared active cortical extracts which restored the normal metabolism of moribund adrenalectomized animals, and on continued administration prolonged life for an indefinite period. Such characteristic postoperative effects as gastro-intestinal disturbances, muscular weakness and lethargy, lowered metabolism, lowered resistance to exposure to heat and cold, hypotension, anhydremia, hypoglycemia and increases in blood phosphate and non-protein nitrogen were successfully combated by the extract.

Our knowledge of the chemistry of the active principle or principles of the adrenal cortex is still incomplete, although recently much light has been shed upon the subject. Many crystalline substances belonging to the group of steroids have been isolated from cortical extracts. Some of these are apparently

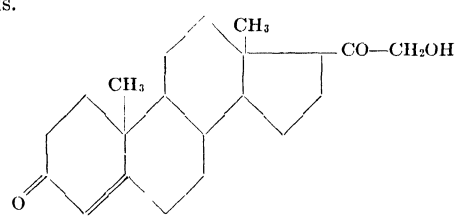
inactive, while others exert a very definite effect in maintaining the life of adrenalectomized animals. The two most active of these compounds have been named corticosterone and dehydrocorticosterone. These compounds are



Corticosterone.

capable of maintaining the life of adrenalectomized dogs when given in doses of 1 to 1½ mg. daily. They will induce retention of sodium and excretion of potassium and other reactions which are characteristic of extracts of the cortex. However, no single compound equals in activity that of the extract from which it is obtained and it is probable that the potency of an extract is the summation of the activity of several cortical steroids present.

The production of cortin-like effects is not limited to products which have been isolated from the adrenal cortex, as somewhat similar effects are obtained from some of the sex hormones. One of these, progesterone (page 600), which is obtained from the corpus luteum, will not only affect the sodium and potassium excretion, but it also has some effect in maintaining the health of adrenalectomized animals.



Desoxycorticosterone.

The first synthetic compound which exhibited cortical-like actions was desoxycorticosterone, prepared by Reichstein. This compound in the form of the acetate and dissolved in oil has several times the activity of corticosterone in maintaining the health of adrenalectomized dogs and, in addition, it has been used successfully in daily doses of from 4 to 6 mg. in the treatment of human cases of Addison's disease. It is quite possible that in the not distant future this compound or one more or less closely allied to it may be used in the treatment of human adrenal insufficiency.

In the use of desoxycorticosterone care must be used not to give excessive doses as several unfortunate results have followed such usage. In these cases cardiac failure has been reported with death. Some of these accidents have appeared to be due to the fact that unnecessarily large doses were given.

Considerable amounts of vitamin C, ascorbic acid, have been isolated in crystalline form from the adrenal cortex, but the significance of its presence here is unknown.

Various theories have been advanced to explain the function of the adrenal cortical hormone (sometimes called cortin or interrenalin). Swingle and his co-workers believe that it is responsible for the regulation and maintenance of the volume of the circulating blood, and that in its absence fluid is lost from the circulation by capillary transudation, the other effects following secondarily. They ascribe the lessened volume of blood to a loss of capillary tone with resulting dilatation, stasis and circulatory stagnation. According to them, therefore,

the hormone is concerned with the maintenance of capillary tone and in a regulatory control of volume capacity of the circulatory system. They do not believe that the urinary loss of sodium and chloride are necessary accompaniments of severe adrenal insufficiency, although in uncomplicated cases there is such an increased output of these electrolytes together with retention of potassium. They point out that adrenalectomized dogs which have been maintained in a normal state by the use of cortical extract pass into a condition of severe insufficiency when the extract is withdrawn and, at the same time, may be anuric and so cannot lose the electrolytes, and such a loss could not be invoked as a cause of the insufficiency in this type of case. With administration again of the extract, diuresis and elimination of potassium occurs. They believe, therefore, that the hormone mobilizes accumulations of intracellular water and electrolytes, shifting them to extracellular compartments and the blood stream, thus bringing about dilution of the blood and relief of the symptoms.

Britton and Silvette believe that the hormone is necessary for normal carbohydrate metabolism and that a failure of this, characterized by hypoglycemia and a marked decrease of muscle and liver glycogen, results in the characteristic picture of adrenal cortical insufficiency. On the other hand, due to the widespread physiological changes in this condition and a suggested relation to gonadal function, Hartman and his associates prefer to characterize it as a general metabolic hormone. Loeb and Harrop believe that the cortical hormone is involved in the metabolism of sodium chloride, inasmuch as soon after adrenalectomy in animals the rate of sodium excretion through the kidney is increased with a resulting decline in concentration of sodium, chloride, and bicarbonate in the blood serum. With the loss of sodium there is an increased loss of water, leading to a condition of dehydration and lessened blood volume, a lessened rate of blood flow, and essentially what amounts to a state of shock. This disturbance in sodium metabolism is also seen in patients with Addison's disease, both in the effects of the withdrawal of an adequate amount of salt and in the beneficial effects of adding it to the diet. Wilder, Power and Cutler have shown that adrenalectomized dogs excrete excessive amounts of sodium and chloride and retain potassium, and that the administration of potassium will provoke an increased excretion of sodium and chloride and precipitate adrenal crisis. The average value of sodium in the plasma in Addison's disease is lower than that for normal subjects and the same is true for plasma chloride. The urinary sodium and chloride is considerably increased over the normal, a condition which is all the more remarkable in view of the lowered concentration of these substances in the blood. As Kendall has pointed out, it is necessary to give a dog weighing 15 to 20 Kg. from 5 to 6 G. of sodium chloride a day in order to obtain a normal level of this substance in the blood, and he and Allers succeeded in keeping such adrenalectomized dogs in good condition for weeks by the administration of sodium chloride and sodium bicarbonate without giving any cortical extract. They do not believe the hormone is concerned with the metabolism of carbohydrates, proteins or fats since a normal condition can be maintained without cortin if a diet satisfactory in mineral content is used. Selye has advanced the view that under certain conditions, such as exhaustive muscular work, toxic metabolites are formed and that in the absence of the adrenals these are not detoxified but are stored in various organs such as the lymphatic glands and that this condition may be one of the causes of adrenal deficiency symptoms. It is clear therefore from the statements regarding the different views held concerning the functions of the adrenal cortex that at present there is no general agreement and that further investigation is undoubtedly necessary for a final answer in this regard. A high level of the cortical extract in the body apparently suppresses the secretion of the adrenotropic hormone of the anterior pituitary lobe as atrophy of the adrenal cortex results from the injection of large amounts of cortical extract into normal rats. Simultaneous administration of the adrenotropic hormone will prevent the regression of the cortex. (Ingle.)

Grollman has shown that while cortical extracts will replace the hypoglycemia of adrenalectomized animals and maintain a normal level of carbohydrate, these

extracts do not induce hyperglycemia in normal animals. He concludes that the hypoglycemia seen in adrenal insufficiency may possibly be due to pathological changes in other organs.

In connection with the weakness and fatigability so characteristic of Addison's disease, Missiuro, Dill and Edwards have studied the effect of cortical extracts upon the performance of work in the normal human subject. They found that small doses had little effect in resting subjects, but that the efficiency of the performance of easy walking was increased for some days after the period of injection. The most characteristic change seen in severe work was the earlier return to normal of the blood-pressure. This was true of both systolic and diastolic pressures.

The pathological involvement of the adrenal glands in Addison's disease and the similarity of this syndrome to the findings following experimental adrenalectomy have led to the use of adrenal cortical extracts in the treatment of this condition. Beneficial results have been produced in seriously affected patients and a definite prolongation of life has been reported as a result of such treatment. It appears that better results are obtained when the administration is begun early in the disease and when it is supplemented by general palliative measures.

In patients who respond well to the injection of potent cortical extracts there is a disappearance of anorexia, vomiting and the development of a feeling of hunger. There is an increase in energy and relief from fatigue, an improvement in sleep, decrease in pigmentation, and a gain in weight. There is elevation of body temperature, some elevation of blood-pressure, and in general a greater or less degree of rehabilitation. Not all patients will respond equally well to the effects of the extract, as some will be suffering from some primary disease, possibly tuberculosis, to which the adrenal condition may be secondary. Then, too, irreparable damage may have taken place in other organs before the extract was administered. While, therefore, cortical extracts are often of great benefit in Addison's disease, each case is a separate problem and requires individual consideration, depending upon the severity of the symptoms and the existence of possible complications. In a certain number of failures the trouble may have been due to the use of a weak extract or to insufficient dosage of a potent preparation.

The administration of sodium chloride at the same time as the extract is being administered is usually very beneficial and may allow the amount of extract to be diminished and in certain cases of the disease the use of sodium chloride alone will at times maintain the patient temporarily in good condition.

The extract has been tried in a number of other conditions such as neurasthenia, asthma, and acute infections, such as diphtheria, but with little avail, and, indeed, a scientific basis for such uses is lacking.

Oral Use.—Some success has attended the use of concentrated extracts administered orally. Such extracts when accompanied by adequate amounts of sodium chloride have been used to a limited extent for maintenance of patients, but they should not be used in acute Addisonian crises.

One of the great advantages claimed for desoxycorticosterone is that it is effective when given orally.

Adrenal Medulla.—Epinephrine or adrenaline is obtained from the medullary portion of the adrenal glands. Since the action of this substance is that of a stimulant of the sympathetic nerves the effects of its administration and its use in therapeutics are discussed under that heading. (Page 523.)

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II. PITUITARY ANTERIOR LOBE.

The earliest ideas regarding the function of the anterior lobe came from the association of clinical pictures with pathological findings. Gigantism and acromegaly were interpreted as being due to excessive secretion of the anterior lobe in the period of active growth and adult life respectively. Deficiency was held to be responsible for adiposogenital dystrophy. The development of modern methods of surgical removal, however, has made possible the demonstration that the latter syndrome is due to the combination of injury to the tuber cinereum with anterior pituitary deficiency. Removal of the anterior lobe results in almost complete cessation of growth in young animals, and loss of weight in the adult, atrophy or failure of development of the genital system, and atrophy of thyroid, parathyroid, and adrenal cortex. The basal metabolism falls, to an extent not exceeded by that following complete ablation of the thyroid. When fresh glands are transplanted into hypophysectomized animals, there is a restoration of the normal rate of growth, sexual activity and normal histology of the genital system, thyroid, and adrenal cortex. These results cannot be produced by feeding the gland.

In young normal female rats, mice, or rabbits, transplantation of anterior lobe or injection of certain extracts results in the rapid attainment of sexual maturity, as shown both by the behavior and by the

development of ovaries, uterus and vagina. The uterine and vaginal changes are, however, apparently indirect, since they do not occur in castrated animals. A similar acceleration of maturity can be produced in young males. When the sexual apparatus of young hypophysectomized animals is brought to maturity by such replacement therapy, the animals will mate and produce normal litters.

Recent studies have indicated that there are several factors present in extracts of the anterior lobe. Among those which have been demonstrated most satisfactorily are (1) a growth factor, concerned with the development of the body; (2) probably two gonad stimulating factors, one of which promotes the growth and maturation of the ovarian follicles, which in turn bring about the changes in the uterus and vagina characteristic of estrus, and one which causes luteinization of the ovarian follicles even before ovulation has occurred; (3) a thyreotropic factor which causes restoration and even hyperplasia of the thyroid epithelium and an increase in basal metabolism in hypophysectomized animals. The thyreotropic hormone exerts its action only when the thyroid is present, in the absence of this gland all its effects being absent. It is still unknown just what part the underproduction of this hormone may play in conditions of hypothyroidism, or even in such states as cretinism or myxedema. In the latter conditions it is not to be expected that this hormone would be of value clinically, as all the evidence points to the fact that it can only act upon or through a normal thyroid, a condition not present in myxedema or cretinism. (4) A lactogenic factor (prolactin) upon which the activity of the mammary gland depends; and (5) an adrenotropic factor which acts upon the cortex of the adrenals have also been described.

It will be seen from this list of hormones, to which others may be added when their existence becomes better established, what an important position this gland holds in the maintenance of body functions, and this is further emphasized by a closer study of the actions of these hormones.

The effects of a lack of the growth hormone are especially noticeable in young animals which, under these conditions, are unable to increase their skeletal dimensions or to maintain proper bodily growth. Certain types of human dwarfism have been ascribed to a similar deficiency in this hormone. The cachectic and rapidly wasting disease described by Simmonds is probably not associated with lack of the growth hormone; in fact, little is known of the effects of a dearth of this substance in the adult human subject. On the other hand, an overproduction of the hormone is apparently associated with gigantism, in which there is symmetrical overgrowth of the body, and with acromegaly, in which the overgrowth is not symmetrical. In both these conditions the pituitary has been found to be hypertrophied.

It is perhaps only fair to say that Riddle questions the existence of a separate and distinct growth hormone, believing that the growth effects following the use of pituitary extracts are due to the lactogenic and thyreotropic hormones. This view is denied by Evans who still holds to the opinion, which is generally held, of a distinct growth hormone.

Injection of anterior pituitary preparations into immature animals brings about a rapid development of the ovaries and other signs of sexual precocity, due to the presence in the extracts of the gonad-stimulating hormone. In the ovaries there is growth of the follicles, with ovulation and formation of corpora lutea and early luteinization of the walls. These changes have been ascribed to two hormones, the "follicle-stimulating" and the "luteinizing" hormone. The luteinizing factor has been found in the urine of pregnancy, while the follicle stimulating principle, which is probably the true pituitary hormone, is found in menopause urine.

Lack of the gonadotropic hormones both in animals and in the human subject is associated with sexual infantilism. In pregnancy there is an abundance of the gonadotropic luteinizing factor in the urine, the maximum amount being found in the fourth or fifth month. In the very early stages there is a definite excretion of the substance, the presence of which in the urine is the basis of the Aschheim-Zondek test for pregnancy. The follicle-stimulating substance present in the urine has been designated Prolan A and the luteinizing factor, Prolan B. Prolan is assumed to come from the anterior lobe, which is known to hypertrophy during pregnancy. It does not seem, however, that the gonadotropic factors of pregnancy urine and of anterior pituitary extracts are the same, since a number of investigators have found that there are distinct differences in the reactions to Prolan and to anterior pituitary extracts, and the luteinizing factor is now known to be the product of the chorionic villi.

The lactogenic hormone (prolactin) of the anterior lobe is primarily responsible for activity of the mammary gland. While the estrogenic substance provides for the growth of the duct system of the gland, it does not affect the development of the secretory alveoli, as the functional activity of the gland depends on prolactin. During pregnancy the secretion of prolactin is inhibited by the estrogenic substance, but with the expulsion of the placenta the inhibition is removed and full development of the mammary gland and lactation follow. Prolactin administered to pigeons brings about a development of the crop gland and secretion of crop milk.

Certain workers claim that in the absence of the pituitary gland estrogen has no effect upon the growth of the mammary gland. They postulate the existence of a "mammogenic hormone" which is produced by the pituitary under the influence of the estrogen. This hormone they do not find in the pituitaries of non-pregnant cattle, differing in that respect from the lactogenic factor. (Gomez and Turner.)

Disturbances in prolactin production are rarely simple matters, as they are usually associated with abnormalities in the production of one or more of the other hormones, so that the clinical picture is often confused. For example, abnormalities of the mammary glands and also diabetes may be found associated with gigantism or acromegaly.

A relationship between the anterior pituitary and the adrenal cortex has apparently been established through the mediation of still another hormone known as the adrenotropic or the interrenotropic hormone.

Following hypophysectomy in animals, atrophy of the adrenal cortex develops, and this can be corrected by the injection of anterior pituitary extracts. Injection of these extracts into normal animals brings about hypertrophy of the adrenals.

In addition to the action of the various hormones which have been mentioned, the anterior lobe apparently has certain relationships with the metabolism of carbohydrates and of fats. Hypophysectomized dogs are very sensitive to insulin, and it is also of great interest that this operation greatly lessens the severity of the diabetes due to pancreatectomy. In turn, the condition of diabetes in those dogs which have been subjected to the two operations is made worse by the injection of anterior lobe extracts. The injection of such extracts also counteracts the action of insulin and increases both pancreatic and phlorhizin diabetes and even produces diabetes in normal animals (Young).

Evidence is also becoming available that this lobe has certain relationships to fat and to protein metabolism, but these effects are not sufficiently well understood at the present time for the formulation of a satisfactory statement concerning them.

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III. PITUITARY POSTERIOR LOBE.

The extract of the pituitary body was shown by Oliver and Schäefer to exercise a pronounced effect upon non-striated muscle when it was injected intravenously; the anterior lobe proved devoid of this action, which arises only from extracts of the posterior lobe or infundibulum and the intermediate tissue. It is probable that the activity of extracts of the gland depends upon more than one principle, but as the active substances have not been isolated in pure form as yet little is known of their character. The active principles are probably comparatively simple bodies which can be dialyzed and boiled without losing their activity. According to one view previously held there is in the gland one principle which can be hydrolyzed by boiling in dilute acid with the formation of a number of physiologically active but dissimilar cleavage products. Exponents of this unitarian view held that those who support the dual theory have split off that part of the original molecule which affects primarily the uterus from the remaining portion of the molecule which acts upon the blood-vessels and upon the kidney secretion. These two products or, according to the other view, prin-

ciples are known as pitocin (oxytocin) and pitressin (vasopressin), the former acting upon the uterus and the latter upon the blood-vessels. Still other workers believe that there may be even a third principle present which is concerned with the antidiuretic effect of pituitary extracts. These principles act in minute doses, smaller than those of any known substance except perhaps the protein poisons.

In connection with the pituitary gland, as also with certain of the other ductless glands, the question has from time to time been raised as to whether the active principles which are extracted from it are hormones which are elaborated in the gland and passed out into the body fluids to be carried to distant organs to perform a specific function, or whether they are merely potent chemical substances which are extracted through chemical manipulations but which may have no specific function in the body. An important argument in favor of the former view has been furnished by the work of Haterius and Ferguson who carried out experiments in which the stalk of the pituitary was stimulated electrically at the same time as the uterine movements were being recorded. They found that when the stalk was stimulated there was an immediate increase in uterine movements, both increased frequency and increased amplitude, resembling in every way the changes produced by the injection of the oxytocic hormone itself. The response persisted after spinal transection, after cutting of the splanchnics and of the vagi, but was lost after the stalk of the gland was destroyed by burning. On the basis of these findings, it would seem safe to conclude that the oxytocic principle is really a hormone which is produced by the cells of the posterior lobe and then passed out into the body fluids to be carried to the uterus.

Action.—The administration by mouth of the dried gland or its extract is not attended by any obvious result, while the intravenous or intramuscular injection of the aqueous extract causes pronounced effects in a number of organs, especially in those containing involuntary muscle. The administration of pituitary extracts by other avenues, such as the nasal cavity, is at times effective but in general is uncertain and not to be depended upon.

Circulation.—When the extract is injected intravenously into anæsthetized animals, the blood-pressure rises rather slowly and remains elevated for some time. The rise is usually preceded by an abrupt fall during which time the heart is accelerated, probably as a compensatory measure. The rise in pressure is due to constriction of the peripheral arterioles, as is shown by the lessened volume of the organs, and as this constriction occurs after the vasoconstrictor nerves have been divided and even after their connection with the muscular coats of the arterioles has been interrupted by ergotoxine, the pituitary substance must act directly on the muscle fibre. The rise in pressure under pituitary extract is smaller and less abrupt than that under epinephrine but is maintained longer. The constrictor action on the vessels may be shown by perfusing them with saline containing pituitary extract, when the venous outflow is at once reduced. All the arterioles examined appear

to be constricted when thus perfused, but in the body they vary in their response, some being narrowed more than others and the renal vessels even being dilated. In the normal animal, as well as to a less degree in the etherized, the injection of pituitary extract produces a marked pallor of the skin and mucous membranes lasting from fifteen minutes to an hour or more. The capillaries are powerfully constricted.

The heart is generally slowed by the injection, and this partly through direct action on the cardiac muscle, and in smaller part from inhibitory action; the slight inhibitory stimulation probably arises partly from the increased blood-pressure flooding the brain and arousing the inhibitory centre. But the extract also slows the excised heart perfused with Ringer's solution, which indicates that the muscle is directly affected. The sudden fall of blood-pressure which is often observed immediately after the injection appears to be due to cardiac action, spasm of the coronary vessels being mainly responsible for the cardiac weakness.

After the blood-pressure has returned to its normal height, a second injection of pituitary extract is found to have no effect or a much slighter one than the first, the vessel walls apparently having lost their power of response to the active principle. The highly active preparation of the posterior lobe prepared by Abel and his co-workers, following the rise resulting from the primary injection, causes a marked fall in pressure even with the second injection unless a considerable period of time has been allowed to elapse after the first. In man the intravenous or subcutaneous injection of preparations of the posterior lobe is sometimes followed by an increase in blood-pressure, which may be maintained for a considerable period. However, in a certain number of persons the rise may be slight and in many cases, in place of an increase, there may be a very definite lowering of pressure. The diastolic pressure is usually raised, so that there is commonly a reduction in pulse pressure. Following the injection in man there is also a decrease in pulse rate, in cardiac output, and in oxygen consumption. These changes last for a brief period, when they are replaced by a more prolonged rise in all three phenomena. The decreased cardiac output is probably reflex in origin.

Respiration.—The respiration is generally strengthened at first, but later becomes shallower and slower, and these phases may recur several times. After repeated injections of the extract, it ceases to have any effect. The centre is acted on directly, the action beginning at the same time as that on the blood-pressure. In the rabbit and guinea-pig the bronchial muscle is strongly contracted but this effect is probably due to histamine contamination of the pituitary preparation. Highly purified preparations are said to have no constrictor effect on the bronchi. In the unanæsthetized animal the intravenous injection of the extract causes apnœa alternating with periodic panting and marked acceleration of the respiration. These changes, which are ascribed to impairment of the circulation to the respiratory centre through vaso-constriction, are much

less marked in the etherized animal and also when it is given to the normal animal by the subcutaneous route.

The **Stomach and Intestine** are aroused to stronger contractions under pituitary extract. The tone of the intestine is increased and defecation soon follows in the case of the unanæsthetized dog. The action on the intestine has been shown to occur in man. In the dog the pressor factor seems to be more important in its effect upon the intestine than the oxytocic principle—the roentgen-ray showing a distinct contraction of the wall. The action of the oxytocic fraction is not so clear when it is studied in like manner, although in the normal animal the injection is followed by defecation. In many studies using methods other than the intact dog inhibition of the intestine has been described as resulting from the administration of either pressor or oxytocic principle. Variation in technique and differences in reaction between different species of animals probably explain the many discordant results which have

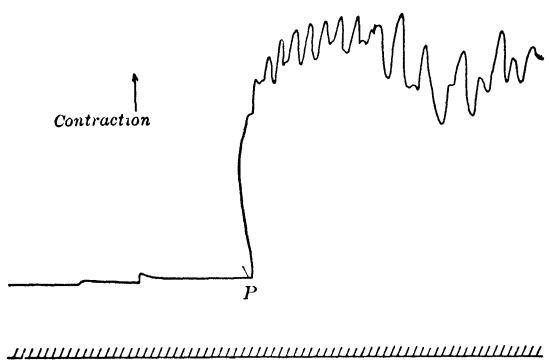

FIG. 43.—Contraction of the isolated uterus suspended in Ringer's Solution; pituitary extract was added at *P*. (Dale.)

been reported in the study of this question. In cats which had been injected with thorium dioxide, rendering the colon opaque to the roentgen-rays, pitressin produced in certain cases a marked colonic contraction which reached its maximum in fifteen minutes. The animals differed in their susceptibility to the pitressin and negative results followed the use of the oxytocic principle. The bladder undergoes changes similar to those in the intestine.

The isolated **Uterus,** submerged in a warm saline bath, contracts more strongly and relaxes less completely after pituitary extract, and this change differs from that seen under epinephrine in that the stimulating action occurs in all animals, whether pregnant or not, and therefore cannot be attributed to an action on the nervous mechanism but must arise from direct muscular effect. In the intact animal and in the human patient the action of pituitary extract on the uterus is not so simple, and its effect is apparently modified by various factors, such as the condition

of the uterus itself, whether it is in the non-pregnant state or, if pregnant, whether in the early or late stage. (See Fig. 44.) Whether the organ is quiescent or actively contracting is important, as it responds much more strongly to pituitary if in the latter condition. The organ *in situ* would also be influenced by hormones from the ovaries and from the anterior lobe of the pituitary and the effects of these will doubtless determine to some extent its reactivity to the oxytocic principle of the pituitary. In general the uterus seems to be most reactive to pituitary in late pregnancy and during labor, so that preparations of the gland have to be given with caution in order to avoid tetanic contraction of the uterus, with suffocation of the child, or even rupture of the organ. The action on the uterus is more marked than the motor action on the alimentary tract.

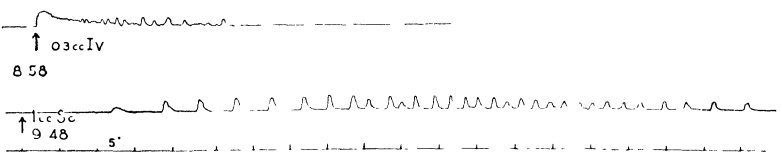

FIG. 44.—Pituitary extract upon the human uterus. Tracings taken from a patient on the eighth postpartum day. A rubber balloon was placed in the uterine cavity and connected with a bellows recorder. Upper tracing taken at 8.58 shows the effect of 0.3 cc. of pituitary extract given intravenously. Lower tracing taken from the same patient at 9.48 following administration of 1 cc. of pituitary extract subcutaneously. Time intervals, five minutes. (Gardner and Bradbury.)

Morgan has analyzed the effect of extracts of the pituitary gland upon the uteri of anæsthetized rabbits, comparing the effect of the extract with that of its two components, as illustrated by pitressin and pitocin. The oxytocic principle caused a contraction of the uterus followed by augmented activity, while the contraction caused by the pressor principle was followed by a period of lessened activity which is accompanied by a fall in volume of the uterus due to a spasm of its vessels. The effect of the injection of the whole extract is the sum of the two components, the presence of the pressor principle being responsible for the late depression of activity sometimes seen.

Melanophores.—When frogs are treated with pituitary extract, a distinct darkening of the skin is observed from dilation of the melanophores or pigment masses; this appears to be due to a direct action on the pigmented cells. The anterior lobe of the gland of most animals is apparently devoid of the substance which produces this effect as it is confined to the neuro-intermediate lobe. The melanophore-stimulating principle has been named *Intermedin*.

By means of tissue culture of the different portions of the pituitary gland, Geiling and Lewis obtained evidence that the melanophore expanding hormone is elaborated in the pars intermedia, but that this portion of the gland does not form the pressor hormone, as extracts of the pars intermedia tissue possess no blood-pressure raising property. The tissue cultures from the anterior lobe

gave neither blood-pressure raising nor melanophore-expanding effects. The armadillo pituitary has no intermediate lobe and the anterior lobe is separated from the posterior by a connective tissue septum. Extracts prepared from the anterior lobe possessed melanophore-expanding activity, while the posterior lobe furnished oxytocic, pressor and antidiuretic principles. The stalk contains only traces of the four activities. The posterior lobe in these animals contains glia-like cells and "glandular" cells, and it is possible that these are the cells which are responsible for the elaboration of posterior lobe hormones (Oldham).

Geiling has shown that in the finback and sperm whales, which possess no pars intermedia, the melanophore hormone is derived from the anterior lobe. A similar condition is to be found in domestic fowl, which also have no pars intermedia, and in these too the melanophore hormone is derived from the anterior lobe. On the other hand, from the posterior lobes of the whales the pressor, oxytocic and antidiuretic hormones are obtained. The potencies of the whales' posterior lobes in pressor and in antidiuretic hormones is about the same as that found in cattle, but the oxytocic activity in the case of sperm whale is only about 10 per cent and with the blue whale about 30 per cent of that of cattle.

The **Pupil** appears to vary in its reaction and shows no very marked change as a general rule; in the excised eye of the frog some observers obtained dilatation, others contraction; in the rabbit contraction generally occurs from intravenous injection, dilatation from instillation.

Kidney.—One of the earlier observations was that pituitary administration to anæsthetized animals was followed by a profuse secretion of urine, this is accompanied by an accelerated flow of blood through the kidney, while the amount of oxygen used in the organ is not increased. The period of diuresis in the rabbit, which lasts about one-half hour, is often preceded by a brief period of lessened flow of urine which has been ascribed to the action of the extract upon the ureters producing a constriction. It is doubtful if this action is of any importance. Various explanations have been given for the diuresis which may follow the administration of the pituitary preparations. It seems clear that it is not due to a direct action of pituitary upon the kidney, and from the fact that the urine is rich in salts it is believed that the diuresis, in part at least, is in reality a saline diuresis, the increased fluid of the urine being necessary to eliminate the salts. An improved renal circulation is doubtless an important factor in bringing about the diuresis, as there is usually an increased renal blood flow and an increased kidney volume. A contraction of the efferent arterioles has also been found which would increase glomerular pressure and thus favor diuresis. After the period of diuresis has passed off there usually follows a stage of diminished urinary flow which may last for a considerable time. In man and in unanæsthetized animals the effect of the extract is to lessen urinary flow—this action is especially marked in cases of polyuria, notably in cases of diabetes insipidus. In this condition the urine is enormously increased, as much as 10–15 litres being passed in twenty-four hours or many times the normal amount; this is accompanied by intense thirst and large amounts of water are drunk. There is often some lesion in the pituitary or in neighboring parts of the brain. The hypodermic injection of pituitary extract reduces the urine to within ordinary limits, and by repeated injections this may be maintained but the

diuresis returns as soon as the treatment is stopped. It is possible that this antidiuresis may be due either to a lessened glomerular activity or to an increased reabsorption of fluid as it passes over the tubules. In man and other mammals the action is probably due to increased water reabsorption, the site of this reabsorption being according to some workers located in the thin loop of Henle.

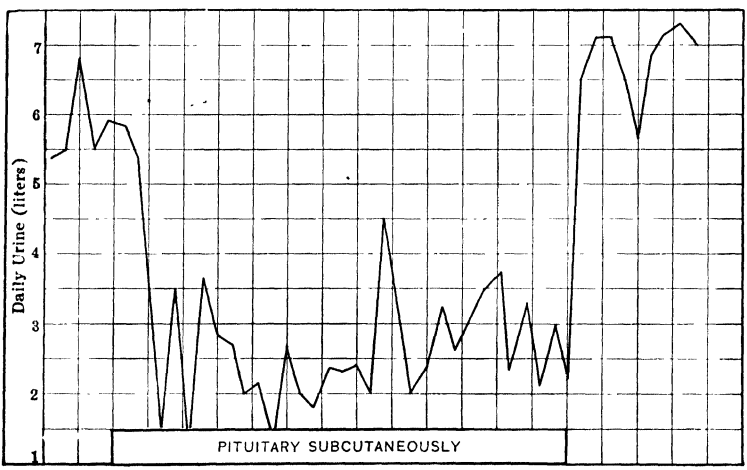

FIG. 45.—Urine in a case of diabetes insipidus in a child. The subcutaneous injection of pituitary solution, at first 0.25 cc. three times daily, later 0.05 cc. twice daily, reduced the urine from about 6 litres to 2.5 litres; the intake of fluid fell in the same proportion. (Christian.)

In human beings the drinking of large amounts of water does not alter the percentage of hæmoglobin, but if the taking of the water is preceded by an injection of pituitary extract a definite lowering in hæmoglobin per cent follows and may last for two hours. (Craig.)

Nelson and Woods have shown that in mice small doses of pituitary possess an antidiuretic action, but that if larger doses are given a diuresis may result associated with an increase in absolute amount of chlorides.

It was shown some years ago that the injection of pituitary extracts into frogs produced a temporary gain in weight due to the uptake of water. Boyd and Brown have investigated the matter anew, studying some of the factors involved. It had been known from the earlier work that it was necessary to inject the extract into the frog in order to get the increase in weight, as merely to add the extract to the water in which the animal was submerged had no effect. Isolated muscles submerged in salt solution to which extract has been added do not increase in weight, whereas if the drug is injected, the muscle may increase in weight as much as 25 per cent in an hour or two. The greatest increase in weight occurs when the animals are kept in the dark and the smallest increase when they are in direct sunlight. Increases in the temperature to which the frogs are exposed inhibits the increase and markedly shortens its duration. Increase in dosage of extract increases the gain in weight up to a certain point, after which the larger doses have no greater effect. The pressor principle of the gland has much less effect than does the oxytocic principle. No explanation has been offered for this phenomenon.

The hydremia is accompanied by a fall in hematocrit, a decrease in specific gravity, and an increase in plasma volume. It is probable that the increased

water in the blood is derived from reservoirs of extracellular fluid with a probable flow of both water and potassium from the cells into the blood plasma (Yanagi).

The administration of massive doses of pituitary extract to rabbits is followed by a marked anemia which reaches its highest development about the fifth day following the injection of the extract. According to Gilman and Goodman, this anemia is not due to a specific action of the pituitary, but rather is caused by water retention produced by the antidiuretic action of the drug. The lowered osmotic pressure of the serum presents an abnormal environment for the red cells and causes their destruction.

Milk-secretion.—One unique property of pituitary extract is its power of apparently increasing the secretion of the mammary glands. The rate of outflow may be increased as much as eighty times by an intravenous injection of pituitary extract and Schaefer states that even the glands of a non-pregnant cat may be induced to expel some serous fluid under its influence. However, pituitary extract does not actually increase the amount of milk formed, but merely causes its rapid expulsion by arousing the unstriated muscle of the gland to contract; this is not prevented by atropine, the muscle fibres being affected directly. While the secretion is increased immediately, the total amount of milk per day is not augmented in cows. In the human subject pituitary extract injected intramuscularly causes tingling in the breasts and then free secretion. The extract of the pituitary of birds and fishes is also galactagogue in mammals.

The Central Nervous System does not seem to participate in the action of pituitary extract except after very large doses, which are followed by some somnolence and muscular weakness. The cerebrospinal fluid is increased, apparently from a direct action on the choroid plexus.

The action of pituitary extract is apparently a direct one on the terminal organs in each case and not on the nervous mechanism. The failure of a second injection to induce effects comparable to the original one has not been explained in any way. The most typical effects are obtained by the intravenous injection of the extract, but subcutaneous injection also elicits them in a less marked degree. Little or no effect follows the administration of the gland or its extracts by the mouth. A general action of the drug is also obtained from its application to the nasal mucous membrane. For this purpose a pledget of cotton moistened with a dilute solution is placed in the nasal cavity.

General Metabolism.—The administration of extracts of the pituitary is followed by hyperglycæmia, this action apparently being due to the oxytocic principle acting directly upon the liver.

Neither of the hormones of the pituitary seems to be of any particular significance in determining the blood sugar level in rabbits. While some hyperglycemia does follow the injection of the pressor substance in these animals, the dosage necessary is too high to be considered physiological. In dogs, however, mild states of hypoglycemia which have been produced by insulin can be abolished by the oxytocic hormone of the pituitary, while the pressor principle has no such action. Large doses of the oxytocic principle will not only remove the insulin hypoglycemia, but will also cause a condition of hyperglycemia (Ellsworth).

The pressor principle has also been shown to produce a fatty change in the liver of certain animals, an action which is almost absent from the oxytocic fraction.

Further changes in metabolism following the injection of the pressor principle into unanæsthetized animals are indicated by the arterial hue of the blood returning from the muscles during the early period following the administration of the drug. The lessened oxygen consumption is accompanied by an increase in lactic acid in the blood, together with a lowered carbon dioxide tension. This period during which the tissue is apparently not taking up oxygen and occurring when the output of the heart is lowered, is followed by the period of recovery when the conditions are reversed, the blood being of a dark color, with increased use of oxygen in the tissues, with a rising production of carbon dioxide, and return of lactic acid to its normal level. Whether these changes are brought about through an action on the cells or through the vascular changes produced by the drug is unknown.

The **Excretion** of the pituitary principle appears to be slow and to be performed by the kidney. Some experimental work seemed to suggest the presence of pituitary secretion in the cerebrospinal fluid, but the oxytocic effect produced by this fluid has more recently been shown to be due to its calcium content.

Therapeutic Uses.—Pituitary preparations are used extensively in obstetrics to arouse or to strengthen the contractions of the uterus. The effects come on in from two to three minutes after subcutaneous or intramuscular administration of the extract, reach their maximum strength quickly and begin to decline in ten or fifteen minutes. The usual effect is to increase the number and the strength of the individual contractions but sometimes a tetanic spasm of the muscle supervenes which may be a source of danger to the life of the child.

The drug may be used in the second stage of labor in case there is no contra-indication such as a disproportion between the size of the pelvis and that of the fœtus and if the cervix is fully dilated. In case the cervix is not dilated or if there is some obstruction to delivery the strong contractions of the organ which would be caused by the extract might result in rupture of the uterus with death of the child and grave danger to the mother.

The extract is also very useful following the delivery of the child when there is postpartum hæmorrhage due to an atonic condition of the uterus. When used in such cases in full doses it usually proves very effective. When it is given during the course of labor, however, it should be used in very small doses which may be repeated at intervals if necessary. The small divided doses lessen the likelihood of spasm of the uterus with danger of rupture of the organ or laceration of the other soft tissue. Pituitary is also used to some extent to induce labor during the last few weeks of pregnancy.

The extract has been used to increase the blood-pressure, especially in shock, but the results are disappointing. In atony of the intestines such as may occur following surgical operations or as a complication of some of the acute infections, it has been used at times with success.

An important use of pituitary is in diabetes insipidus where the polyuria can be controlled by the hypodermic use of the extract. The relief is only temporary, lasting only so long as the extract is being given. It has to be administered in this condition by hypodermic or intramuscular injection once or twice daily although some favorable results have been reported from its application to the nasal mucous membrane and also when it is given by the rectum. When given by the latter method its effect is more transitory. Administration of the extract by mouth is without value. Pituitary preparations may also be used to treat the effects of an overdose of insulin, inasmuch as the two drugs are antagonistic to each other in their relation to the sugar in the blood.

PREPARATIONS.

U. S. P.

PITUITARIUM POSTERIUM, dried posterior lobe of the pituitary.

LIQUOR PITUITARII POSTERII, solution of pituitary. 1 cc. (15 mins.). The dose, as noted above, must be greatly reduced if it is given during the course of labor before the child is born or the placenta delivered. One cubic centimeter of the solution of Pituitary is equivalent in strength to 0.005 G. of the standard pituitary powder. It therefore contains 10 international units in 1 cc.

B. P.

EXTRACTUM PITUITARII LIQUIDUM, pituitary extract. 0.2-0.5 mil. (2 to 5 units).

PITUITARIUM, the powdered posterior lobe of the pituitary body of cattle, is a yellowish or grayish powder only partially soluble in water.

LIQUOR PITUITARII, or the liquid extract, is a solution of the water-soluble principles of the fresh posterior lobe of the pituitary body of cattle. It must be assayed biologically.

Various extracts of the posterior lobe are on the market under the names Pituitrin, Infundibulin, Hypophysin, Pituglandol and Hypophysin sulphate, Pitressin and Pitocin, the latter two being the pressor and oxytocic principles.

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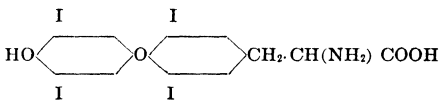
IV. THYROID GLAND.

The treatment of certain diseases by the administration of thyroid gland and its extracts is one of the most satisfactory examples of rational therapeutic progress, and the steps which led to its adoption may therefore be briefly mentioned. In 1882–3, Kocher and Reverdin published observations made on patients whose thyroids had been totally extirpated, and who had subsequently presented a series of symptoms to which these observers gave the name of cachexia thyreopriva. They pointed out that this condition resembled in many of its features myxœdema, a disease discovered by Gull some years before and associated with atrophy of the thyroid gland. These observations were confirmed by a number of authors, who removed the thyroids from animals, and found cachexia appear in them. The next advance was the discovery that these symptoms in animals could be removed, or at any rate ameliorated, by grafting pieces of thyroid in the peritoneal cavity or subcutaneous tissue. Horsley suggested that myxœdema should be treated in the same way, and Murray soon afterward introduced the treatment of this disease by the subcutaneous injection of thyroid juice. Even in his first case, the results were eminently satisfactory, but it was soon found that the same results could be obtained by administration by the stomach, and a large number of cases have now been recorded in which very favorable results, or even the complete disappearance of the symptoms has followed this medication. These include not only myxœdematous patients, but also cases in which the thyroid was removed by surgical operation, or where its disease gave rise to symptoms. That the favorable results are due to the treatment is proved conclusively by the return of the symptoms when it is abandoned.

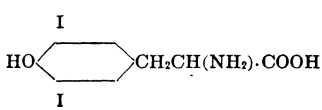
The effect of the thyroid treatment could be explained only by the presence of some chemical principle, for the preparation of course contained no living cells. A globulin, *thyreoglobulin*, was extracted from the gland, which had the therapeutic action and gave the ordinary protein reactions but was characterized by containing a small percentage of iodine; Baumann's detection of this element in the thyroid gland was the first intimation that it existed in the tissues of the higher animals

and man. More recently a crystalline substance was isolated from the gland by Kendall and named by him *Thyroxin*. By improving the method of isolation, Harrington has succeeded in greatly increasing the yield of thyroxin to be obtained from the gland and has shown that the substance is a tetraiodo derivative of the hydroxyphenyl ether of tyrosin with an empirical formula of $C_{15}H_{11}O_4NI_4$ and a structural formula as follows:



The correctness of this view was later confirmed by synthesis of the product by himself and Barger. Basing his calculation upon the fresh gland, Harrington obtained a yield of thyroxin of 0.027 per cent, or 0.12 per cent of the dried gland. The synthetic thyroxin has been tested on patients by Lyon and found to possess the effects upon the basal metabolism which are characteristic of the natural product and of the dried gland itself.

Thyroxin is a white crystalline substance existing in the gland in protein combination; it is believed, however, that it is secreted into the blood and lymph and carried to the tissues. The whole specific action of the thyroid preparations is probably due to the presence of thyroxin, although recently a second compound containing iodine has been isolated from the gland. This compound has been shown to be diiodotyrosin, possessing the formula



It will be seen that the compound is very closely related chemically to thyroxin, it being an intermediate product in the synthesis of the thyroxin in the thyroid. Previous to the isolation of this compound it had been suggested that thyroxin had probably been derived from tyrosin and now with the finding of this substance the relationship between tyrosin and thyroxin is established with diiodotyrosin as the intermediate product. The activity of the gland, however, seems to be dependent upon the thyroxin (probably as iodothyroglobulin) content, although a complete parallelism between thyroxin content and physiological activity has not been shown to exist. This discrepancy can easily be understood when it is realized that the fate of pure thyroxin in the alimentary canal may not be the same as that of thyroxin in its protein combination in the gland. The properties of thyroxin are such as to make it probable that its absorption would be erratic and inefficient (Harrington and Salter). It has been shown that in the normal gland approximately 40 per cent of thyroid iodine is in the form of thyroxin and 60 per cent as diiodotyrosin, but while this proportional distribution may hold good for the normal it will, without doubt, show wide varia-

tions in cases of abnormal glands. So, too, in normal glands great variations in activity may be encountered, due to the extent to which the synthesis from tyrosin through diiodotyrosin to thyroxin has progressed, inasmuch as it is the completed thyroxin which alone is active. The content of iodine, and of thyroxin, varies greatly in different glands according to the supply of iodine in the food, and is much increased by treatment with iodides or iodine. Compounds of iodine which are administered are very rapidly taken up and stored in the thyroid, but the synthesis to thyroxin is much slower, eight hours being the shortest time in which this transformation has been observed.

Action.—The thyroid preparations and thyroxin often have little obvious effect in normal persons or animals unless given in what would be large doses for others; symptoms develop slowly and the maximum effect of a dose may not be reached for several days. Undesirable effects are more liable to be induced by repeated doses than by a single large one. These symptoms are partly subjective and indefinite, such as headache, wandering pains, or general weakness, while others indicate circulatory changes, and consist of a feeling of fullness and congestion of the head, palpitation of the heart, and acceleration, sometimes weakness, of the pulse. Tremors in the arms and legs point to changes in the central nervous system, while loss of appetite and diarrhœa indicate that the alimentary canal is not exempt from its influence. Perspiration is often complained of, especially in myxœdema, and a rise of temperature also occurs not infrequently. The most striking effect in the majority of cases is a rapid loss of weight.

If to a completely myxœdematous patient with a basal metabolism of about −30 a dose of 2–4 G. of desiccated thyroid is given, no subjective symptoms may be experienced for about twelve hours. After this time there may set in headache, loss of appetite, nausea and perhaps vomiting, pain in the back, legs and joints and an increase in pulse rate and in metabolism. The temperature rises to normal or perhaps to a little above normal. The skin becomes moist. These symptoms are most marked on the second day and the height of the metabolic curve is reached between the third and the tenth day. There is also a change in the appearance of the patient, the face becoming more expressive and the speech faster and more distinct. The period of discomfort may last one or two weeks, or in old cases, even longer. If the dose of dried thyroid has been smaller or if repeated small doses have been given the symptoms of discomfort are less marked but they are likely to last for a longer time. In any case, by the end of the second week the patient should have a normal metabolic rate and this is now maintained by the use of a standardized thyroid preparation given daily.

In normal animals thyroid extract injected intravenously in large quantities accelerates the heart and lowers the blood-pressure slightly, and when given by the mouth repeatedly for several days, it may also cause some acceleration. This quickening of the heart has been attributed by some investigators to stimulation of the sympathetic nervous mechanism, by others to direct action on the heart; it does not seem to be due to any changes in the inhibitory apparatus. Hearts of animals

which have been treated with thyroid so as to induce tachycardia, and are then removed from the body and perfused with Locke's solution will retain their rapid rate for a considerable period of time, even for hours.

Loss of flesh and thirst have been observed, even when the appetite is good and sufficient food and water are supplied. The urine is uniformly increased in amount. A number of observers have found that the continued administration to animals of thyroid preparations in large amounts leads to diarrhœa, muscular weakness, especially in the hind extremities, emaciation, gastro-enteritis, nephritis, and fatty degeneration of various organs. In other instances no such symptoms have been elicited, the animals remaining perfectly normal after prolonged treatment. Different species of animals vary greatly in their susceptibility to thyroid treatment, and this may explain some of the anomalous results recorded.

The **Metabolism** is changed by thyroid medication more uniformly than any other function, and this is its essential effect. All the nutritive processes seem to be accelerated. This may be observed in many individuals in the rapid loss of weight, which often amounts to several pounds per week. Again, the amount of nitrogen in the urine is increased both in goitre and myxœdema, and very often in apparently normal persons. More nitrogen is excreted in the urine frequently than is taken in the food, that is to say, the treatment leads to the destruction of the proteins of the tissues. If more nitrogenous food be given, however, this may be arrested, and in fact if large quantities of meat be taken, less nitrogen may be excreted than is taken in the food, so that although the patient is losing in weight, he may be actually increasing in nitrogenous tissue. The increase in the nitrogenous excretion is not stayed by the administration of carbohydrates and fats on the other hand, because the glycogenic function of the liver is disorganized by thyroid treatment. The increase in the nitrogen of the urine is accounted for almost entirely by the increase in the urea; the ammonia shows a very slight rise, while the uric acid and the creatinin remain almost unchanged; some creatin appears in the urine.

The calcium metabolism has also been shown to be modified, as the administration of thyroid preparations in addition to raising the general metabolism also increases the calcium output. In exophthalmic goitre there is a high calcium excretion while in myxœdema the reverse is true.

The other constituents of the tissues also are consumed more rapidly, and in fact the accelerated protein waste only accounts for about one-sixth of the loss in weight. The fats are reduced throughout the body, and the sugar metabolism undergoes modifications, which are shown in the disappearance of glycogen from the liver and not infrequently by the occurrence of glycosuria, either spontaneously or after the ingestion of quantities of sugar which would be oxidized completely in normal persons.

The acceleration of the metabolism is also shown by the increased amount of oxygen absorbed and of carbon dioxide exhaled under

thyroid treatment. This has been noted in myxœdema, goitre and obesity treated with thyroid, and has recently been shown to be the most regular effect of thyroxin; 1 mg. is sufficient to increase the basal metabolism by 2–3 per cent, while regular treatment with 2 mgs. per day may raise it 20–30 per cent.

The removal of fluid from the body, perhaps the most potent factor in reducing the weight in these cases, is shown by diuresis, which occurs in myxœdema especially, but also in obesity. This diuresis has been ascribed to some specific action on the kidney, or to the changes in the circulation, but may perhaps be due to the increased excretion of urea and other urinary substances. Recently it has been shown that the administration of thyroxin is followed by a marked mobilization of water and sodium chloride which, entering the blood stream, produces a high degree of hydræmia and that the increase in urine is due to the response of the kidney to this condition. The excretion of sodium chloride may even become excessive and is apparently not due to the ordinary changes in metabolism as the diuresis occurs early while the metabolism changes do not reach their maximum for some time. That the kidney is acted on in some cases is shown by the occasional appearance of albumin in the urine of patients treated with thyroid preparations. The phosphates excreted are increased in the same ratio as the nitrogen, and the increase is obviously due to the same cause, augmented protein waste.

A difference of opinion exists as to the site of action of thyroxin. According to Mansfield and his co-workers, the increase in metabolism is exerted on the periphery inasmuch as section of the cord has no effect on the metabolic changes and the inhibitory action of phenobarbital is probably a peripheral one. On the other hand, Issekutz and Dirner claim that mere section of the cord does not exclude a central action and that phenobarbital in the small amounts present in the blood in ordinary narcosis is not inhibitory to the action of thyroxin and they, therefore, believe the point of attack is on the central nervous system.

It is believed that about 0.5–1 mg. of thyroxin undergoes destruction in the body normally each day and it has been calculated that on an average the normal human body contains 15 mgs.; this amount of thyroxin given to a thyroidless patient will continue to act for one or two months, after which the previous condition recurs.

Kendall states that when injected into the blood about 40 per cent is excreted in the bile and 13 per cent in the urine within two days; there is thus little response to a single dose, but if the same total amount is given in repeated small doses, marked effects may be elicited. After thyroid preparations have been administered, iodine is found in the urine in the form of iodides, so that the thyroxin is evidently decomposed, at least in part, in the body.

The absence or atrophy of the thyroid gland in young animals or children arrests the growth both physical and mental, and treatment with thyroid extract accelerates the growth in many of these cases. In normal growing mammals, treatment with thyroid does not alter the general increase in size and weight greatly, but some organs, such as

the heart, liver, suprarenals, kidney and pancreas grow more rapidly. In tadpoles fed with thyroid the increase in size is slowed or arrested, but the metamorphosis is much accelerated (Gudernatch), so that there results a number of small frogs, while the untreated controls are still large tadpoles; this accelerated development has been used to estimate the quantity of active principle in preparations of the gland. In other amphibia in which the metamorphosis is slower and less regular than in tadpoles, the results of thyroid treatment are even more striking.

When thyroid preparations are fed to fowls in fairly large doses the birds moult, losing their feathers very quickly, possibly inside of ten days, so that they may be almost featherless. The new feathers which come in are frequently different in color from the original in that many which were black or colored are replaced by white feathers, indicating a marked interference with pigment formation.

In regard to their reaction to thyroid medication, individuals vary considerably, for many are scarcely affected by it in any way, and this is particularly true of children, while others lose weight rapidly, and under larger doses show symptoms of poisoning (thyroidism). These seem to be more easily elicited in goitre and myxœdema than in ordinary cases.

The fact that "thyroidism" occurs more frequently in myxœdematous than in normal persons seems difficult of explanation, and it has been suggested that the symptoms are due, not to the extract itself, but to the products of its action. It may be supposed that in myxœdema a large amount of some substance accumulates in the tissues, because the secretion is not present in sufficient quantity to decompose it, and that when the thyroid treatment is commenced, the body is flooded with the products of decomposition and these give rise to symptoms. In normal persons, on the other hand, there is no such accumulation, and the extract therefore induces no symptoms until it is given in such quantity as to induce intoxication itself. For some years the view has prevailed that exophthalmic goitre, or Graves' (Basedow's) disease, arises from an excess of the specific secretion of the gland being poured into the general circulation, and a good deal of ingenuity has been employed in showing that the symptoms of Graves' disease may be induced by the administration of thyroid extracts. Unbiased examination indicates, however, that thyroidism is only one symptom of an unknown underlying anomaly present in Graves' disease, and that the hyperthyroidism induced by thyroid treatment is not accompanied by the other characteristic features of exophthalmic goitre.

Iodine, as has been stated, increases the iodine of the gland, and this explains the beneficial effects formerly seen in goitre from the application of iodine internally and locally. When iodine was efficient in those cases, and any considerable diminution of the gland occurred, it was often accompanied by symptoms exactly resembling those produced by large doses of the extract. Those symptoms were caused by small quantities in some patients, while much larger doses had no such effect in others—a fact which gave rise to some discussion and several erroneous theories. Sometimes the acute symptoms passed into a cachexia of very long standing. The quantity of iodine required to act in goitre is much greater than the iodine of the thyroxin necessary, and this shows that the latter acts not merely as an iodine compound, but as the specific substance of the gland. If the thyroid gland tissue is intact and capable of functioning, iodine or iodides are useful in these cases of thyroid inefficiency because they lead to the formation of thyroxin. Various iodine compounds, such as *iodalbumin* and *iodospongin* (the iodine compound of the sponge) have been shown to be practically inert in goitre.

In recent years much study has been given to the relationships which exist in the body between the various endocrine glands and although much confusion still exists certain facts have seemed to be established. Naturally on account

of its well known importance in the body the thyroid has been studied very extensively.

One of the early relationships which was found was that existing between the thyroid and the anterior lobe of the pituitary. It has been known for a long time that persons with large goitres had enlarged anterior pituitary lobes and that removal of the thyroid caused hypertrophy of the lobe. It was also found that hypophysectomy produced involution of the thyroid and that extracts of the anterior lobe restored the thyroid to normal. Still later it was shown by several workers that fresh extracts of the anterior lobe produced in young susceptible animals a marked hypertrophy and hyperplasia of the thyroid beginning within a few hours after injection. This change in the thyroid results in a loss of iodine in the gland, an increase in metabolic rate and in exophthalmos.

This thyreotropic factor of the anterior pituitary will stimulate thyroid transplants in any part of the body, indicating that the action is a direct one on the cells and not through any nervous mechanism.

The repeated injection of iodothyroglobulin solution into rabbits does not produce any signs of tolerance such as are seen following the repeated administration of extracts of the anterior pituitary gland and of the parathyroid. The administration of iodothyroglobulin is always followed by an increased heat production suggesting that thyroxin is not a part immunologically of the iodoglobulin molecule and further that the hormonal activities of the anterior pituitary and possibly of the parathyroid are more closely associated with the protein molecule (Rosen and Marine).

In a study of the effects of varying amounts of sodium or potassium upon unilaterally adrenalectomized rats it was found that the addition of such salts to the diet had no effects upon the remaining adrenal gland, but that if the animals were subjected to the extra strain of fatiguing work or were given thyroxin the remaining gland in each animal showed marked hyperplasia (Ingle and Kendall).

Therapeutic Uses.—Thyroid when employed in myxœdema, should be used with care, especially if the heart is seriously affected, as the cardiac muscle may be unable to meet the requirements of the accelerated rhythm; several serious cases and one or two fatalities have been recorded in these conditions.

Thyroid extract is useful as a substitute for the normal gland secretion in cases where the latter is wanting or deficient; thus in atrophy of the thyroid in adults (myxœdema), after its extirpation (cachexia thyreopriva), and in its congenital absence or atrophy (sporadic cretinism) the most remarkable improvement follows its use, the patients from a condition of idiocy regaining practically normal intelligence. It is of the first importance to commence the treatment as soon as the condition is recognized because unless the treatment is begun early no complete return to the normal is obtained, although improvement is observed even in neglected cases. The exact dose necessary to maintain a normal rate of metabolism must be determined for each case, but the average amount needed is from 1 to 2 grains of a standardized thyroid preparation daily. Changes in the size of the doses should not be made frequently as the results of such changes are not manifest for about a week. After the correct dose is ascertained it is rarely necessary to change it and it must be maintained in myxœdema or cretinism throughout life.

The use of thyroid preparations in these conditions, in which the gland is atrophied, is readily understood. On the other hand it seems

anomalous to employ it in cases of enlargement of the gland (goitre). Yet great improvement is seen from thyroid treatment in many of these cases. In colloid goitre the gland is enlarged (hyperplasia), but this does not indicate an excessive formation of secretion, but the reverse; the gland hypertrophies in an effort to compensate for the poverty of its secretion in thyroxin, and when the condition is treated with thyroid the hyperplasia lessens and the gland assumes its normal condition as far as the secretory epithelium is concerned, though it may be enlarged through the presence of large colloid masses. The treatment of goitre

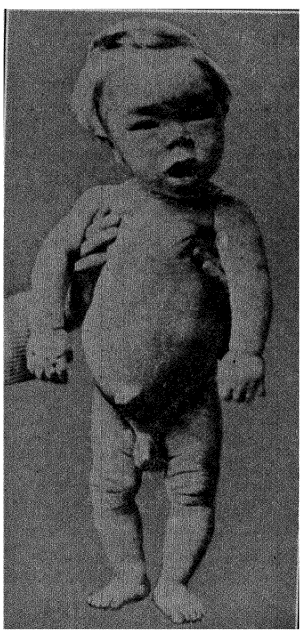


FIG. 46

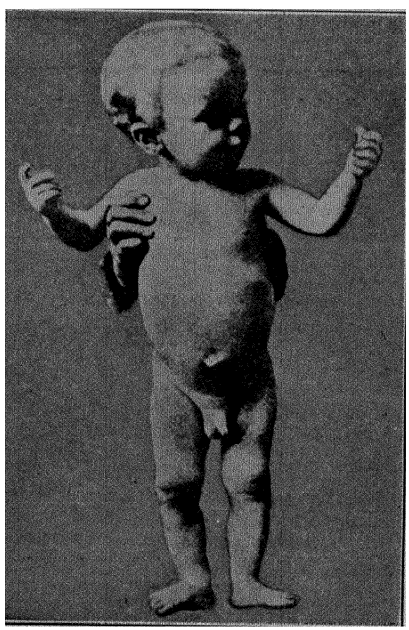


FIG. 47

FIGS. 46 and 47.—A case of sporadic cretinism. Fig. 46, before treatment, age twenty-three months, height 28 inches, circumference of the abdomen 19 inches. Fig. 47, after treatment with thyroid extract for five and a half months, height 30 inches, circumference of abdomen 15 inches. (Osler.)

with thyroid preparations is thus of the same nature as the treatment of thyroid atrophy, for though the gland is enlarged it is unable to fulfill its function. Goitre does not require the permanent use of thyroid as a general rule; the treatment is carried on only until the gland is reduced in size.

The decrease in weight occurring in thyroid medication suggested its use in obesity, and it has been followed by some loss of weight in a certain number of cases, especially when accompanied by proper dietetic treatment. In many instances it has had little or no effect, however, and the initial encouraging action is seldom maintained when the treatment

is continued, the daily loss of weight gradually becoming smaller until it ceases altogether. The amount of fat actually destroyed seems to be trifling, Magnus-Levy estimating that about one pound disappears in ten days, which is much less than can be got rid of by judicious exercise and an appropriate dietary. Besides, the continued use of thyroid in these cases is not altogether devoid of danger. Several authorities state that in some cases the dietetic treatment fails unless it is accompanied at first by thyroid medication; they therefore give a few doses of thyroid to initiate the treatment and continue it by dietetic measures. Many of the antifat remedies put on the market contain thyroid extract and their continued use has led to serious symptoms in a number of cases.

In some skin diseases, especially in psoriasis, it has been of benefit, though not by any means invariably.

The improvement seen in the brain symptoms in myxœdema and cretinism suggested its use in other mental diseases, but the action in the former is due to its substitution for the normal secretion, and little or no effect has followed in ordinary cases of mental disease.

Preparations.

U. S. P.

Thyroideum, 0.065 G. (1 gr.).
Thyroxinum, 0.0005 G. ($\frac{1}{120}$ gr.).

B. P.

Thyroideum, 0.03–0.3 G. ($\frac{1}{2}$–5 grs.).
Thyroxinsodium, $C_{15}H_{10}O_4NI_4Na$. 0.0001–0.001 G. ($\frac{1}{600}$–$\frac{1}{60}$ gr.).

Thyroideum, a powder prepared from the fresh and healthy thyroid gland of the sheep. It forms a light, dull-brown powder with a faint, meat-like odor and taste, free from any odor of putrescence. It must contain, according to the U. S. P., 0.2 per cent of iodine in thyroid combination or, as in the B. P., 0.1 per cent of iodine in combination as thyroxine. One part of dried gland corresponds to about 5 parts of fresh gland.

Thyroxin ($C_{15}H_{11}O_4NI_4$) forms white crystalline needles insoluble in water, but soluble in the presence of strong alkalies; its melting point is 228° C. and it contains 65 per cent of iodine. It may be obtained from the gland or prepared synthetically. In the B. P. it is given as the monosodium salt of thyroxine.

Dried thyroid is usually given in pills or tablets; care must be taken that it is kept dry to prevent putrefaction, and satisfactory results can be expected only when the preparation has been assayed for iodine. The dose should be small at first (*e. g.*, 1 gr. of the dried gland every evening for the first week of treatment), and should be gradually increased, until improvement sets in or unpleasant symptoms arise. Thyroxin has not been largely used as yet as the supply has been limited and the price high and in general the dried standardized gland seems to be absorbed better and to give better results when it is given by mouth.

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V. PARATHYROID.

Recently there has been prepared from the parathyroid glands of animals a very potent extract containing an active principle or hormone which will relieve the symptoms of parathyroid tetany and in addition raise the blood calcium in a characteristic manner. The glands contain two types of cells: the principal cells, which are large and have a vesicular nucleus, and the oxyphile cells, which possess a small, deeply staining nucleus. It would therefore appear that the glands would possess two functions, but which cells furnish the hormone controlling the calcium-phosphorus metabolism is unknown.

In the tetany due to parathyroidectomy or to impaired function of these glands, animals have invariably a low blood calcium and an injection of the hormone will cause an increase in the calcium and at the same time relieve the symptoms. Animals which have had their parathyroids removed may be kept in perfect health by the use of the extract but will exhibit tetany in a short time if its administration be stopped. If now a new injection be given the animal will be restored to normal health in a very few hours.

Administered intravenously to normal dogs or to those having under-

gone parathyroidectomy, the curve of blood calcium rises, to reach its maximum between the fifth and the ninth hour, to return to normal in about twelve hours. When the hormone is given subcutaneously or intramuscularly the increase in the calcium appears somewhat later, beginning about the fourth hour. It reaches its maximum in from twelve to eighteen hours and returns to the previous level in from twenty to twenty-four hours. Associated with the rise in plasma calcium is an increased urinary excretion of calcium and inorganic phosphate and a decrease in the plasma content of the latter substance. If successive effective doses are given at fairly short intervals the effect is cumulative, resulting in a pyramiding of the effect of each dose upon the previous until a condition of hypercalcæmia is produced with values even higher than 20 mg. per 100 cc. of blood. Such animals show signs of a profound intoxication which may end in coma and death. An early symptom of the hypercalcæmia is vomiting, followed by diarrhœa, weakness and some dyspnœa. In fatal cases there are usually hæmorrhages into the gastro-intestinal tract with vomiting of a bloody fluid, the passage of blood from the bowel, and complete anuria. Marked changes are produced in the blood in addition to the calcium alteration, there being an increase in its viscosity associated with a decrease in plasma volume; an increase in phosphates and in urea and non-protein nitrogen and a diminution in alkali reserve. At death the intestinal mucosa is found to be congested and the calcium content of certain tissues, especially of the heart and kidneys, is found to be greatly increased. In the case of the kidney the excess is doubtless due to the organ becoming clogged with it during its efforts to eliminate the surplus. The excess in the heart is probably responsible for the irregularities of that organ which are seen during the course of the intoxication.

It is still an unsettled question as to where the increased calcium in the blood comes from. It has been definitely shown that the hormone does not affect its absorption from the intestine nor does it inhibit its excretion and indeed the excretion of calcium is definitely increased. It is evident, therefore, that the calcium must come from the bones or from the soft tissues with the probability that it is the soft tissues which form the primary source and that they replenish themselves from the bones. Dogs may be maintained in a condition of mild hypercalcæmia for weeks without any marked ill effects, although during this time they must have suffered a considerable loss of calcium from their bones due to the excessive excretion of calcium salts.

Parathyroid extracts administered to young animals retard their growth and, given in excess, they lead to hypoplasia of these glands and finally atrophy. The extracts produce marked changes in the bones where there is primarily a decrease in the trabeculæ followed by an increase of the lamellæ. The early injections produce a resorption of bone, a decrease in osteoblasts and their change to fibrous tissue. These changes are followed by an increase in osteoclasts resulting in osteitis fibrosa. Continuous administration may result in a reversal of the process leading to the so-called "marble" bone (Burrows). It is probable that the hormone leads to resorption of bone and inhibits osteoblastic activity, the osteoblasts disappearing with the appearance of the osteo-

clasts, at which time the serum calcium reaches its maximum, after which it begins to decline.

In addition to the changes in calcium in the body, there is a marked increase in urinary excretion of phosphates due to a lowering of the renal threshold for phosphates.

In connection with this action of the hormone upon the kidney it has been shown that in persons with acute nephritis receiving the parathyroid hormone there is a much decreased phosphate diuresis. At the same time the serum calcium may be increased, demonstrating the two-fold action of the hormone. These two actions may be independent of each other, as it is possible to get a rise in serum calcium in nephrectomized dogs, and in persons with impaired kidney function to get the calcium increase without phosphate excretion diuresis.

It seems therefore that the glands are not only concerned with the increase in the calcium in the blood serum and in its application to the needs of the body, but also in maintaining the normal relationship between the calcium and phosphorus. The normal amount of calcium in the blood serum of man is about 10 mg. per 100 cc., while the average upper limit of inorganic phosphorus is about 5 mg. per 100 cc.

In cases of hypoparathyroidism associated with a lowered calcium content of the blood there is hyperexcitability of the nervous and muscular tissues which may even extend to tetany, while in hyperparathyroidism there is depletion of the calcium content of the bones and an increased viscosity of the blood. It would seem then that the functions of these glands are to preserve a normal nervous system, normal muscular contractility, and a proper calcification of the bones. Tumors of the parathyroids have been described in which there was excessive fragility of the bones resulting in multiple fractures.

That there is an immunity or tolerance to the hormone induced by its repeated administration has been proved both experimentally in animals and clinically in man.

Therapeutic Uses.—The therapeutic use of the parathyroid hormone is still in the experimental stage. It is a potent agent capable of producing dangerous symptoms so that when administered to patients its effect should be carefully controlled by frequent determinations of the blood serum calcium. A serum content higher than 12 mg. is not desirable while higher than 15 mg. may be dangerous.

The only clear indications for its use today are in those conditions associated with low serum calcium content; in tetany parathyreopriva and in infantile tetany.

In conditions of tetany the use of parathyroid extract may be supplemented by the intravenous and intramuscular injection of calcium salts, the gluconate being perhaps most suitable for this purpose. The immediate effects of the calcium are followed by the slower results of the extract which, when given intramuscularly, produces no apparent change in calcium content for four hours, the duration of action being about twenty hours.

It has been suggested that it be used in lead poisoning as both lead and calcium are stored in the bones and both may be mobilized by the hormone. In some cases of lead poisoning treated there has been a marked increase in lead excreted, but the use of an acid-producing salt

such as ammonium chloride is probably just as efficient and much safer. Parathyroid extract has been tried as an aid in the healing of fractures, but it apparently has little or no influence here.

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VI. INSULIN.

In 1889, v. Mering and Minkowski showed that the removal of the pancreas in animals gave rise to symptoms identical with those of diabetes mellitus in man, and many attempts have been made since to obtain an extract of pancreas which might be of benefit in this disease. Success was attained only in 1922 at the hands of Banting and Best, who obtained a preparation which has been named insulin, since it is derived from the islands of Langerhans in the pancreas, and not from the general parenchyma of the gland; in fact the pancreatic ferments proper destroy the insulin, and the recent advance is due to a method of extraction by which insulin is preserved from their deleterious action.

The chemistry of insulin has not been completely worked out as yet. Various workers have succeeded in purifying the extracts to a certain degree, some of these extracts being exceedingly active. Abel and his co-workers obtained a crystalline product for which they suggested as a probable formula $C_{45}H_{69}O_{14}N_{11}S_3.H_2O$. In an early paper they had pointed out the importance of the sulphur content of the molecule and stated their belief that the content of labile sulphur appeared to be in direct relation to the hypoglycæmic activity of the product. This view, however, was not confirmed by later work. Crystalline insulin is a typical protein. Cystine, tyrosine, leucine and glutamic acid are present in amounts from 10 to 30 per cent each, while arginine, histidine, lysine, phenylalanine and proline have been found in smaller amounts. The total amount of sulphur (3.2 per cent) in the molecule probably exists in the cystine. Prepared from various sources and by different methods, crystalline insulin has a constant potency of 24 units per mg., indicating that the active principle is the whole product rather than a smaller chemical group adsorbed on a protein-like molecule.

Following the successful attempts made in 1926 by Abel to crystallize insulin, other workers made repeated efforts to simplify the process of securing crystals and of establishing the special conditions under which crystallization takes place. As a result of the work of Harrington and Scott (1929), in which a new method was discovered, Scott continuing

the work established the fact that crystals of insulin contain zinc and that the addition of a zinc salt to amorphous solutions of insulin aid greatly in the formation of insulin crystals. In the same manner it was found that salts of cobalt, cadmium and nickel had a similar effect, although the zinc salt was most effective. In this connection it is important to note that zinc is found normally in the pancreas. It is probable that the various metals form salts of insulin and the microscopic appearance of the crystals is the same no matter which metallic salt is used to aid crystallization. Zinc insulin crystals contain 0.45 to 0.9 per cent of zinc and have a potency of 22 insulin units per milligram. The crystals contain from 0.2 to 0.4 mg. of zinc per 1000 units.

Studies carried out to determine the effect of the presence of the metal upon the action of the insulin showed that when measured by the effect upon mice, zinc insulin solutions showed only 40 per cent of their original activity when they contained 0.02 per cent of zinc chloride. With such solutions the onset of convulsions in the mice was much delayed, suggesting that the action of the insulin was perhaps not actually lessened but was only delayed. Experiments upon rabbits confirmed this view, as it was found that the level of the blood sugar was lowered very gradually and was still well below normal at the end of ten hours, as contrasted with the original insulin where the blood sugar was practically normal in ten hours. The symptoms of hypoglycemia, such as convulsions, were also less marked, but the total glucose metabolized was approximately the same with the two solutions. Insulin is destroyed by pepsin as well as by trypsin and it is very readily precipitated in a state of adsorption when any of the protein precipitants are used, and is soluble in 80 per cent but not in 95 per cent alcohol. It is rapidly destroyed by alkali, but is more stable in acid solution. Insulin proper is found only in the islands in vertebrates and the claim that a similar substance (glucokinin) exists in plants is probably not correct.[1]

Insulin has no apparent effects when given by the mouth, since it is destroyed by the digestive ferments. Injected subcutaneously in the rabbit, it causes a remarkable fall in the sugar of the blood from the normal of 0.12 per cent to 0.05 or 0.03 or less. When only 0.04–0.05 per cent of glucose is present, the animal becomes restless, and soon clonic convulsions with rotation of the body set in, resembling the convulsions under cocaine. The respiratory quotient rises, indicating an increase in the consumption of sugar. The convulsions can be arrested at once by the injection of glucose, so that they are obviously due to its deficiency in the blood and not to any direct action of insulin on the nervous centres.

Not only the sugar of the blood and tissues is destroyed, but the glycogen of the liver and muscles is drawn upon and may disappear when the convulsive stage is reached.

In diabetic animals and patients, the injection of insulin is followed by a rapid fall in the sugar of the blood, the disappearance of glucose

[1] Insulin has been isolated from the islets of many varieties of fish such as the angler or devil fish, sculpin, cod, pollock and halibut.

and of acetone bodies from the urine, and general improvement in the symptoms of the disease. There is an increase in weight and in strength, a lessened polyuria and a diminished thirst. The dryness of the hair disappears and skin infections clear up. In man a healthy appetite returns and the mental attitude of the patient improves wonderfully. Most patients can return to work and in place of depression and despair there is mental alertness and a feeling of cheerfulness and of hope. As the insulin is consumed in the tissues, the symptoms return, and in order to maintain the normal condition a new injection is necessary every few hours. After a large injection symptoms due to hypoglycæmia are seen in man as in the rabbit, the severity of the symptoms in man depending upon the extent to which the blood sugar has been lowered. With a sugar content of about 0.08 per cent the patient experiences a vague sense of uneasiness and nervousness with a feeling of impending danger. There is an increase in pulse-rate, dilatation of the pupil, and a mask-like appearance of the face. With a blood sugar of 0.055 to 0.07 per cent there is a feeling of anxiety and faintness, profuse sweating and incoördination. If the sugar is reduced still more (0.04 to 0.055 per cent) there is aphasia, disorientation, delusions and mental confusion and possibly coma and death. The symptoms due to hypoglycæmia are rapidly relieved by the administration of glucose given by mouth or if necessary by intravenous injection. Epinephrine is often effective in an emergency but its action is not so certain as it depends for its effects upon the supply of glycogen in the liver and as this may be present in only small amounts, it is well to give glucose at the same time the epinephrine is administered. In the less severe symptoms due to hypoglycæmia milder measures are usually sufficient. Frequently one-half an orange will be found effective, but if the condition has progressed so as to produce sweating, the orange is not sufficient and one or more tablespoonfuls of corn syrup may be indicated.

The essential action of insulin is to restore to the tissues the power of utilizing sugar, which is lost in whole or in part in diabetes. With moderate amounts, this may render the metabolism normal, while under large doses of insulin, the sugar combustion is so much facilitated that the whole energy is supplied by sugar, which practically disappears from the blood; the glycogen is drawn upon and finally disappears and symptoms of low blood sugar appear. The glycogenic function probably is not directly changed, but merely responds to the needs of the organism for carbohydrate. Recent work indicates that insulin promotes the deposition of glycogen in the muscles and under certain conditions in the liver. The normal secretion of insulin is believed to be controlled by the blood sugar concentration, although secretion has been produced experimentally by stimulation of the right vagus.

Several views have been advanced to explain the way in which the sugar combustion is accelerated by insulin, but they are at present scarcely beyond the speculative stage. There is every reason to believe that the action is in the general tissues and not in any special organ, that the normal pancreas secretes insulin into the blood and that its presence in the muscles and other organs enables them to utilize glucose;

in diabetes the supply of insulin fails to a greater or less degree and the tissues cannot adequately make use of sugar as a source of energy.

The use of insulin in diabetes has had brilliant results; replacing as it does the internal secretion of the pancreas as long as it is supplied. Unfortunately this necessitates subcutaneous injections, which must in the majority of cases be continued indefinitely. In a certain, probably small, number of cases under treatment with exercise, diet and insulin, the nutritional state may be so much improved that finally exercise and diet will suffice and insulin may be given up.

Insulin is injected into the subcutaneous tissue, the injections being usually given about one-half hour before breakfast and then repeated if necessary before the noon and evening meals and, in case of need, a further small dose may be given at bedtime. The maximum effect from an injection is usually obtained in about an hour after the insulin has been given. The site of injection should be varied from time to time so as not to inject into any single area more often than once a month. If the injections are repeatedly given in one place tumefactions may result which predispose to infection and necrosis and, in any case, they interfere with proper absorption of the insulin. Also if the injections are scattered less insulin will be required.

The *solution of zinc insulin crystals* rarely needs to be given more than twice daily and in some cases one injection will suffice. It is usually best given about one-half hour before a meal. It is recommended that of two doses which are to be given in a day, three-quarters of the total daily dose should be given from one-half to one hour before breakfast and the remainder some ten or twelve hours later, near the time of the evening meal. The dosage and other details of its administration, however, have to be determined for each patient and will depend upon the blood and urinary sugar findings. On account of the relatively slow action of the crystalline insulin, the original insulin is to be preferred in cases of diabetic coma.

A difficulty which is occasionally met with in the use of insulin and which is more serious than the occurrence of the localized tumefactions is the production of areas of so-called "insulin atrophies." These may appear at the sites of injection or quite frequently at some distance from the spots where the injections have been made. These areas are characterized by depressions of the skin with the disappearance of the subcutaneous fat and even of the muscular tissue also. Sometimes local recovery may take place in a year but again it may take a longer time and they may form a very annoying and disfiguring complication. The cause of these atrophies has not been explained nor is there any treatment known for them at the present time.

In the use of insulin as it is ordinarily given by injections repeated two or three times daily, there are rather large fluctuations in the amount of the blood sugar due to the rapid absorption of the insulin after it is administered and its subsequent disappearance from the blood. To avoid these pronounced oscillations in the blood sugar, efforts have been made to introduce the insulin into the body in some form in which its absorption would be retarded and in this way supply it to the body in a more gradual manner, thus tending to smooth out the large deflections in the sugar curve. One such product which has been introduced

for clinical trial is known as Protamine Insulinate. This is formed by a union between insulin hydrochloride and a protamine derived from a species of trout, Salmo iridius. It has its minimum solubility at about the reaction of blood serum. In this form it is injected as a turbid suspension which is slowly broken down and the active insulin released over a longer period of time. The use of this product is still in the experimental stage, but experience with it thus far is favorable, indicating that it or some analogous compound may be made which will simplify the use of insulin in the treatment of diabetes.

It is still somewhat early to pass final judgment as to the position of *protamine insulin* in the treatment of diabetes. In many ways, however, it represents a distinct advantage over the original product. The effectiveness of the new compound depends upon the fact that it is very slowly assimilated so that it forms a depot of insulin which is slowly drawn upon during the ensuing ten to twenty-four hours. The number of units of protamine insulin which will be required by a diabetic is not very different from the older type, but its effects not becoming fully evident perhaps for four or five days, it is possible that danger may ensue due to overdosage produced by a lack of appreciation of the gradually developing action of the product. On this account the employment of the protamine insulin should proceed gradually.

The duration of the effect of protamine insulin is much greater than that of the older product, as it is clearly demonstrable even twenty-four hours after the preparation has been given. It is due to this prolongation of action that it possesses one of its advantages, as it is possible to give insulin in many cases only once a day, administering, if desired, both the regular product and the new preparation some time before breakfast and making the two injections at different points. As will be seen, the advantages of protamine insulin are largely due to its prolonged action, making it possible for patients to begin the day with a blood sugar at or very close to the normal level. The fewer number of injections necessary and the lessened frequency of reactions due to sensitiveness to insulin are distinctly advantageous, as well as the avoidance of hypoglycemia in cardiac cases or in persons exposed to industrial hazards. Local tissue changes, such as abscesses or fatty atrophy, are rare.

Zinc added to protamine insulin greatly prolongs the hypoglycemic action. This was true especially if the zinc has been added to insulin of low ash content or if the suspension has been allowed to stand for some hours.

Also the addition of spermine to insulin solutions prolongs the hypoglycemic effect provided zinc has been added to the solution.

The use of small doses of insulin has been suggested to improve the appetite in undernourished individuals and thus increase their food intake. However, it is possible that whatever improvement is made is due in part, at least, to psychic effects rather than to the insulin, and in any case it must be understood that insulin is merely an adjunct in the treatment. Final judgment on this use of insulin must wait for more definite clinical studies, although a certain number of favorable reports upon its effect in cases of malnutrition have appeared.

Insulin is supplied in solution suitable for injection. The potency of the solution varies from 10 to 100 units per cc., the unit being the activity contained in 0.125 mg. of an international standard powder (8 units per mg.). No definite dosage can be given for insulin as each case must be treated individually, but the average daily dose for diabetic patients is probably about 30 units (Joslin). In cases of diabetic coma or severe acidosis larger doses of insulin are indicated, accompanied by definite amounts of dextrose, so that the patient will not become hypoglycæmic. Insulin is assayed by comparison with the standard

either by the convulsive dose in mice or by the average blood sugar decrease in rabbits over a five-hour period following injection.

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VII. LIVER AND LIVER PREPARATIONS.

One of the most interesting and important therapeutic discoveries of the past decade has been the demonstration by Minot and Murphy of the remarkable effects following the administration of liver to cases of primary (pernicious) anæmia. A direct outgrowth of the careful work carried on by Whipple and his associates upon the effects of various preparations of iron and of articles of food upon secondary anæmias, the Boston workers were able in 1926 to present the records of 45 cases of primary anæmia which had responded favorably to a diet containing a considerable amount of liver. The results obtained by these workers have been confirmed from all quarters and indeed the action of liver in primary anæmia is now so well established that in a suspected case of the disease if an adequate amount of liver is given and none of the expected changes in the blood picture follow it is probable that the diagnosis of primary anæmia is incorrect.

Following the administration of a sufficient dose of liver, which as experience has shown is about half a pound a day, there will be definite changes in the blood picture, the extent of such changes being dependent upon the degree of anæmia present when the diet of liver is initiated. Usually about the fourth day the reticulocytes, which normally exist in human blood to the extent of about 1 per cent, begin to increase in number. This increase continues for four or five days, usually reaching its maximum between the seventh and the ninth day after which time the curve of increase begins to decline, reaching the normal again about the twenty-first day. The extent of increase in the number of reticulated red cells will depend upon the number of red blood cells in the patient's blood when the treatment is begun. The lower the red cell count the greater is the increase in the number of reticulocytes which will be present in the blood. For example, a patient with a red cell count of 600,000 would be expected to have an increase in reticulocytes to about

50 per cent of his total number of red cells after taking an adequate amount of liver or liver extract by mouth. With an initial count of 1,000,000 a reticulocyte count of 35 per cent would be expected, while with a count of 2,000,000 there would be about 14 per cent reticulocytes and with 3,000,000 red cells about 4 per cent reticulocytes. The percentages are somewhat higher with desiccated stomach and much higher with liver extract administered parenterally. Following this outpouring of young red cells the total red cell count begins to rise. This increase is a gradual one so that in the course of a few weeks a normal count of 4,500,000 or 5,000,000 may be reached. It is interesting that with adequate amounts of liver the red blood cell count in patients will reach normal in eight weeks no matter what was the initial red cell count. A patient with a count of 3,000,000 or 2,000,000 reaches the 5,000,000 level no earlier than one with a count of 1,000,000 or even 500,000. The lines of increase all converge to meet at the common point at the eighth week. At the same time as the red cells increase in number certain abnormalities of the blood disappear. The cells become more normal in size, shape and color. The abnormally large cells which are distorted in shape and the red cells which are nucleated disappear, and cells having a normal size and shape gradually replace them.

In addition to the changes in the blood there are signs of clinical improvement which appear soon after the liver diet has been instituted. After two or three days the patient begins to feel better, his appetite improves and he feels stronger. His color improves. The pads of the fingers and the palms of the hands, the cheeks and the tip of the nose all begin to show a pink flush even before there is any marked change in the blood count. The feeling of nausea disappears and the intestinal condition is better. The condition of the tongue usually improves although in certain cases not to the same extent that there is improvement in the general health. A similar statement applies to the neurological changes which are sometimes present in this disease. Definite degenerative changes which the nervous system may have undergone are usually not appreciably altered by the liver diet. In this connection the maintenance of a normal blood condition seems to be of great importance and frequently symptoms resulting from changes in the nervous system, such as tingling or numbness, may be benefited or entirely disappear with the improvement in the condition of the blood. The condition of achlorhydria which is practically always present in primary anæmia is apparently not benefited by a liver diet.

So far as is known in such cases of primary anæmia liver in some form (or one of the other specific products used in this disease) will have to be continued throughout the patient's life, the dose necessary for maintenance of good health differing with different individuals but averaging about ½ pound of liver five times a week or an equivalent amount of one of the extracts which have been introduced to replace the liver itself.

The existence of an infectious process in a patient, such as a common cold, tonsillitis, bronchitis, cystitis, etc., may interfere with the effects of liver and delay the reticulocyte increase but with recovery from the infection the beneficial effects from the diet will become manifest again. Also

during a therapeutic remission in the disease when the patient is on a uniform maintenance diet, the occurrence of some acute infection with fever will usually be followed by a lowering of the blood count unless the dose of liver is augmented to compensate. Inadequate responses are also noted in older patients, those with arteriosclerosis, and in those in whom absorption or storage is deficient. In spite of the brilliant results which follow the treatment of cases of primary anæmia with a diet containing liver it cannot be denied that the use of such a diet has certain disadvantages. One very practical difficulty with it is that patients get very tired of taking liver every day and again others are unable to tolerate the necessary quantity on account of gastro-intestinal symptoms. These objections to the liver have been overcome in various ways, especially by the preparation of certain partially purified preparations and extracts which can be taken by mouth or in other cases can be injected intramuscularly or intravenously. Each of these modes of administration has advantages which are apparent. For the average patient the use of an extract by mouth is doubtless the most simple, provided the patient does not get careless and neglect his treatment. By injection into the muscles, the dose of liver which it is necessary to administer in order to insure satisfactory results is much less than when extracts are given by mouth. For instance, the daily intramuscular injection of material prepared from 10 to 15 G. of liver is approximately equivalent in efficiency to an extract prepared from 300 G. when given in daily doses by mouth. Still more highly purified extracts of liver have been prepared for intravenous administration, but the objection to such concentrated solutions is that in their preparation a considerable loss of potency occurs, making the use of a larger amount of liver necessary. However, such solutions prepared for intravenous use have proved to be safe and efficient, although those which were used in the earlier days were frequently followed by severe reactions; but more recently, by improved methods, extracts have been prepared which only in very rare instances cause discomfort. Hundreds of cases have been so treated, being given the injections at weekly or monthly intervals and apparently with satisfactory results. Experience in the individual case only will show the most favorable time interval between injections and also the dose necessary in each case to maintain a normal blood picture and the other signs of remission of the disease.

The advantages of giving the material parenterally are manifest. There is not only economy of liver and relief from what becomes a tiresome article of food, but also avoidance of carelessness on the part of the patient due to neglect to take the diet. As between the intramuscular and the intravenous route it is largely a question of choice. Due to the possibility of unpleasant reactions when the preparation is given intravenously and equally good results being obtained by injection into the muscles, the weight of opinion seems to be in that direction at the present time. By most clinicians it is believed that the parenteral method of administering the liver is more efficient than the oral method in bringing about improvement in symptoms due to neurological changes which may have appeared during the course of the disease. Further

experience with these preparations is necessary in order to answer this question.

The mode of action by which preparations of liver bring about a remission of the symptoms of primary anæmia is not known. In this disease, probably due to deranged gastric function, a certain active substance is not formed which should act upon the bone-marrow to bring about proper maturation of the red blood cells. This substance is probably formed by the interaction of the so-called intrinsic factor of Castle which exists in the gastric juice with the extrinsic factor existing in certain foods such as meats. In Addisonian anæmia it is the intrinsic factor which is lacking. This is probably an enzyme, as it is destroyed by heating to 70° C. Under normal conditions the substance formed by the interaction of these two factors is probably stored in the liver and is called upon as needed to act upon the bone-marrow. In the absence of this principle the bone-marrow undergoes the megaloblastic hyperplasia which is characteristic of this disease. It has been shown that when the liver diet is administered and the condition of the blood is improving, the megaloblasts in the marrow decrease and the appearance of the marrow approaches normal. The rapid increase in the very young red cells following the administration of liver in some form is very suggestive that the diet furnishes the necessary stimulant for the proper maturing of the red blood cells.

The chemical nature of the material in liver which is active in pernicious anæmia is unknown. It is non-protein, freely soluble in water and in slightly acid alcohol; and preparations containing it contain carbon, hydrogen, oxygen and nitrogen but no phosphorus or sulphur.

Therapeutic Uses.—Liver and its derivatives are of use only in the anæmias in which a defective formation, absorption or storage of the active material results in failure of proper maturation of red blood cells. These are the macrocytic anæmias. Included in this group of anæmias, in addition to pernicious anæmia, is the anæmia due to tropical sprue where there may be lack of the extrinsic factor in the diet and impaired absorption in the intestine. Liver therapy is very effective in this condition. In pellagra there is apparently a similar disturbance of the factors concerned in proper blood maturation and here, too, liver therapy has been found useful. In cases of cirrhosis of the liver which are associated with a macrocytic anæmia, liver therapy has been found to be efficient. Some have reported improvement in secondary (microcytic) anæmias following the use of liver preparations, but certainly their main value is to be found in the anæmias of the macrocytic type.

Preparations.

U. S. P.

Extractum Hepatis, dry liver extract.
Liquor Hepatis. Solution of liver.
Liquor Hepatis Purificatus. Parenteral solution of liver.

B. P.

Extractum Hepatis Liquidum.
Extractum Hepatis Siccum.

The U. S. P. contains three preparations of liver: a dry extract and a solution of liver for oral administration, and a purified solution to be given by intramuscular injection. All of these liver preparations have to be tested for potency according to methods approved by the Pharmacopœial "Anti-anemia Preparations Advisory Board," and have to meet its standards.

The B. P. dry extract of liver is prepared from ox or sheep liver by means of acid alcohol, in which the active principle is soluble. After careful concentration and purification it is finally reduced to a powder which is placed in hermetically sealed tubes. The powder is of a light brown color with a meaty odor and taste. It is freely soluble in water. The dose of the extract, according to the B. P., is the equivalent of about 225 G. of fresh liver.

The liquid extract of liver is prepared by much the same process as the dry extract with the exception that the extract obtained in the process is dissolved in water and alcohol and glycerin are added so that 1 cc. of the final liquid contains the equivalent of 8 G. of the original liver. The dose of the liquid extract B. P. is 1 fluidounce or 30 cc., the equivalent of 8 ounces or 240 G. of fresh liver.

Aside from the two official extracts described above there are many other extracts available not only for use by mouth but also such as can be given by the intramuscular as well as by the intravenous route. It is hardly necessary to say that no preparation should be employed which has not been tested so as to insure its potency. At present no satisfactory method of testing is available other than in the clinic, where it is administered to patients who have primary anæmia and who are in a state of relapse and to whom no liver or other preparation having a specific action in the disease has been given recently. In such a case a preparation, if it is potent, will bring about the typical increase in reticulocytes and in numbers of red blood cells.

Livers from animals other than oxen and sheep also yield the specific substance which is active in bringing about proper maturation of the red blood cells, and extracts prepared from the livers of horses as well as from the codfish (Gadus) are in use.

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VIII. STOMACH PREPARATIONS.

Following the demonstration of the effect of feeding liver, kidney and other organs to animals in which a secondary anæmia had been produced by bleeding, and the spectacular results obtained in pernicious anæmia by the use of a liver diet, it was shown by Castle that something was

secreted by a normal stomach which would act upon meat, producing in the process of digestion some substance which was absorbed and acted upon the bone-marrow, bringing about maturation of the red blood cells. It is possible that this substance is under normal conditions stored in the liver and kidney, imparting to these organs, as well as to others, their specific effects upon the bone-marrow.

Following the discovery of this action of normal gastric juice in the production of the anti-anæmic substance, equally good results were obtained by feeding to patients with primary anæmia the gastric wall of animals after it had been chopped fine, dried and defatted by the use of petroleum ether. The administration of such material is followed by the same improvement in the blood and in clinical symptoms as results from the giving of liver preparations. A dose of about 15 G. of this desiccated, defatted material, which would correspond to about 100 G. of the fresh material, given daily, is usually sufficient to bring about a complete remission in the condition, although larger amounts are often given, especially in the early treatment of the case. One rule is to give 10 G. of the dried material daily for each 1,000,000 deficit in the red cell count. The maintenance dose is from 10 to 15 G. daily, depending upon the condition of the patient and his reaction to the substance.

The mode of action of the gastric material has not been explained. It appears probable that an enzyme-like material is present in the mucosal cells, and this reacts with the proteins or other substances present in the stomach wall during postmortem autolysis, producing the precursor of the hemopoietically active principle of liver. As the material from the stomach is thermolabile and cannot be extracted by the physico-chemical means used in extracting the thermostabile material from liver, it must undergo further changes during absorption.

The changes in the blood and in the general condition of the patient are much the same after the taking of gastric material as after taking liver extract. On the third or fourth day the reticulocytes increase in number, reach their maximum and decline to their normal in about two weeks. The red blood cells gradually increase in number as after liver, and the appetite of the patient improves and he feels stronger.

Preparations.

U. S. P.

Stomachus; dried stomach. This is the dried and powdered defatted wall of the stomach of the hog.

Desiccated stomach wall is also available under the name "Ventriculin." The product must be tested for potency in essentially the same manner as liver preparations are tested. It is given in doses of from 20 to 40 G. daily for the initial treatment and from 10 to 15 G. daily for maintenance. One gram of the dried material is equivalent to about 7 G. of fresh tissue.

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J. SEX HORMONES.

FEMALE SEX HORMONES.

Knowledge of the complicated processes which govern the manifestations peculiar to sex, whether these agents be nervous or chemical, has been much broadened by researches of the past few years. It will be most logical to consider the chemical products involved under their two natural divisions of the male and female hormones.

Since the early years of this century it has been known that crude extracts of the ovary and placenta would induce uterine growth. Somewhat later Frank (1922) discovered that liquor folliculi also contained an active substance which produced similar effects. Discovery of a method of determining the activity of the extracts through changes they produce in the vaginal mucous membrane of rodents furnished an important aid in the study of the problem. In 1929 the first crystalline estrogenic compound was isolated from urine by Doisy and his co-workers, and was shown to be identical with the active principle of liquor folliculi. In the years immediately following this important discovery other crystalline bodies were isolated from the urine of pregnancy or from ovarian tissue until a number of crystalline substances possessing estrogenic properties have been prepared.

These substances were given different names, such as œstrin, menformon, thelykinine, and folliculin, but a generic name based upon the estrogenic properties of the products was later adopted. Some of the most important members of the series have been thus named Estrone ($C_{18}H_{22}O_2$, ketohydroxy-estratriene), with a synonym "Theelin,"[1] the latter name having been given to this substance by the discoverers of the first crystalline estrogenic compound; Estriol ($C_{18}H_{24}O_3$, trihydroxy-estratriene); Estradiol ($C_{18}H_{24}O_2$, dihydrotheelin); Equilin ($C_{18}H_{20}O_2$), etc.

According to Doisy the primary ovarian hormone is Estradiol, the dihydrotheelin, and it is converted into estrone (Theelin) and estriol (Theelol), the two urinary estrogenic substances. The conversion of estrone into estriol depends upon progesterone, and in conditions of deficiency of this latter hormone the amount of estrone accumulates in the blood and may be associated with the onset of menstruation or labor. On the other hand, due to the increasing amount of progesterone formed by the placenta during pregnancy, the ratio of estriol increases constantly during the period of gestation. The ovarian hormone, estradiol, exists in two forms- the *alpha* form, which is very potent, and the *beta*, which is almost inert. There is also a great difference in the relative activity of estrone and estriol, the former being much the more potent.

The estrogenic hormones, estrone, etc., act as stimulants to the accessory reproductive organs, producing hypertrophy of the uterus and cervix, and increased growth of the ducts of the mammary glands. They are responsible for the contractility of the uterus and for its sensitivity to oxytocics.

[1] Derived from the Greek, "Theely," indicating femaleness.

In castrate animals estrone produces a definite increase in weight of the secondary sex organs.

The estrogenic hormones are responsible for certain secondary sex characteristics in the female, such as the plumage markings of some birds and the sexual swellings of baboons and changes in the sexual skin of some of the monkeys. They will also produce certain female characteristics in the development of the gonads in male chick embryos while it has not been possible to influence female sex of chicken embryos by the male hormone. On the other hand, in mammals (guinea-pigs and mice) it is possible to detect masculinization of the female.

In the pocket gopher and mice the estrogenic hormone causes a resorption of the symphysis pubis, thus enlarging the birth canal. In the guinea-pig the same hormone acting with a second hormone, relaxin (formed in the corpus luteum), produces an enlargement of the birth canal by causing relaxation of the pelvic ligaments.

The anterior lobe of the pituitary gland has a very important relation to the reproductive organs through the action of its gonad stimulating factor which promotes the growth and maturation of the ovarian follicles, which in turn secrete the estrogenic hormone. This hormone is probably produced by the cells of the theca interna, and through its action brings about the changes in the accessory reproductive organs which have been described. As the follicular hormone increases in quantity in the blood it in turn acts upon the anterior lobe of the pituitary, inhibiting the production of the gonad stimulating hormone and thereby lessening the stimulation of the follicles. There is thus produced a regular cycle of alternate activity and quiescence on the part of the pituitary and of the ovarian follicles. In addition, the luteinizing hormone of the anterior lobe of the pituitary causes luteinization of the ovarian follicles with formation of the corpus luteum. This structure in addition to an estrogenic hormone secretes a hormone progestin (later named progesterone) which acts upon the endometrium, inducing secretory changes preparatory to nidation. This hormone is essential to nidation and also for the maintenance of pregnancy. It also stimulates the growth of the alveolar tissue of the mammary glands developed under the influence of the estrogenic hormones. Only in guinea-pigs has it been possible to induce growth of both ducts and alveolar tissue by the estrogenic hormone alone.

The progesterone is produced by the ovary only through the third month of gestation, after which time the placenta assumes responsibility for its production. Progesterone is found in the urine of pregnancy or during the corpus luteum phase of the cycle in the form of pregnandiol.

The excretion of estrogen in normal menstruating women is irregular, varying from day to day, although the curve of excretion shows two peaks during the normal menstrual cycle. The first of these is in the mid-interval, between the tenth and nineteenth day corresponding to to the period of greatest follicular growth, ovulation and corpus luteum formation. The second period is often inconsistent in its appearance but usually occurs in the week prior to menstruation, and probably corresponds to some phase of corpus luteum activity. Following this peak there is a sharp fall in the curve of excretion followed under normal conditions by the onset of menstruation. During pregnancy there is a

gradual rise in the level of excretion starting in the second half of the second month and continuing until the time of labor, after which the curve of excretion falls to normal in a few days.

Injected estrogen is almost entirely destroyed in the liver, only a very small amount, 3 to 12 per cent, can be recovered from the urine. Injected intravenously into dogs, 90 per cent of the amount disappears within a very few minutes.

Therapeutic Uses.—The employment of estrogenic substances in therapeutics is still in the experimental stage and their value in the clinic has by no means been clearly established. It would appear that their main value would be in cases where there was evidence of a deficiency of this substance, as in cases where the ovaries have been removed or possibly at the time of the normal menopause. In some of these cases with vasomotor disturbances the results of the administration of estrogenic products have been favorable, but it must be recognized that in many such patients the psychic factor involved has not been ruled out and equally good results could have been and often are obtained by non-specific medication alone. These substances have also been used in certain forms of amenorrhœa and dysmenorrhœa, but here, too, the results obtained are by no means convincing as proving their value in these conditions. Insofar as the first-mentioned condition is concerned, it may be said that from the physiological standpoint it would not be logical to expect them to be of value, for while estrogenic substances produce estrus in animals, the factors responsible for estrus and those producing menstruation are quite different, and the action of estrogen is quite distinct from that of progesterone. It is sometimes said that the giving of estrogen may stimulate the ovaries, which then may produce more progesterone. Here the difficulty is that the estrogen does not stimulate the ovary itself, but acts merely as a substitutional product which would be active only so long as it is administered and therefore would not be expected to establish a normal menstrual cycle.

In gonorrheal vaginitis of children the results of the administration of estrogenic substances have been more favorable. The improvement often seen is ascribed to changes produced in the vagina, the mucosa of which changes temporarily to the adult type with partial cornification. The secretions instead of being alkaline become acid and under these conditions the gonococci disappear. For this purpose estrogen is usually given in vaginal glycerin-gelatin suppositories. Some changes in the secondary sex organs may follow this treatment if it is too prolonged, but they usually subside when the treatment is stopped.

Senile vaginitis is frequently benefited by the estrogenic hormone. The mucosa returns to the normal type seen during normal sex activity, and there is relief from the burning and pruritus common to the condition. This hormone has also been used in the treatment of hemophilia in the belief that the hormone is absent in the urine of hemophiliacs but present in the urine of normal males. These findings have been shown to be incorrect and the hormone has not been found to lessen the coagulation time of hemophiliac blood so that the use of estrogen in this disease is without value.

PREPARATIONS.

NON-OFFICIAL.

ESTRONE. Theelin, $C_{18}H_{22}O_2$. A crystalline estrogenic steroid obtained from the urine of pregnancy. Dose, 0.2 to 1 mg. by intramuscular injection at weekly intervals or more often if necessary.

ESTRIOL. Theelol, $C_{18}H_{24}O_3$. A crystalline steroid obtained from the urine of pregnancy. Dose, 0.06 to 0.12 mg. given orally one to four times daily as necessary

In addition to these preparations commercial preparations are available which contain estrogenic substances prepared from the urine of pregnancy or from the placenta. These are available under special names such as Amniotin, from the urine of pregnant mares; Emmenin, from the placenta; Folliculin Menformon, from the urine of pregnancy; and Progynon, from the urine of pregnancy or from the placenta.

Corpus Luteum Therapy.—Progestin, or as later named, Progesterone. The value of progesterone in medicine has not been established as yet, largely owing to the difficulty of securing a satisfactory inexpensive preparation. Commercial preparations available are either obtained from ovaries or are the pure hormone prepared synthetically. Experimental experience would seem to indicate that progesterone might be useful in cases of sterility or of habitual abortion which are due to lack of this hormone. It might act either by quieting the contractions of the uterus or by acting on the mucosa of the uterus so as to make it favorable for nidation. It has also been tried in menorrhagia and in metorrhagia, inasmuch as in certain forms of uterine hemorrhage produced experimentally it has lessened the bleeding. Such use in the clinic would for the present be of an experimental character. It is claimed also to lessen the pain in threatened abortion and also in dysmenorrhœa, and any such action would probably be due to its causing relaxation of the uterus.

MALE SEX HORMONES.

For almost a hundred years it has been known that the testes exert an action upon the growth of cockerel combs by a humoral mechanism, but it is only in comparatively recent years that the presence of a male hormone was positively demonstrated by McGee (1927) who showed that the lipid fraction of extracts of bulls' testes will induce such comb growth. This work was speedily confirmed and extended to show that these extracts could also prevent or repair changes in the accessory reproductive organs of mammals which were the result of castration. These extracts were crude mixtures and were referred to under various names such as "bull testis extract," testicular hormone, male hormone, etc.

Shortly after the demonstration of the hormonal activity of extracts of the testes, Funk and Harrow (1929) obtained extracts from the urine of males possessing very similar physiological effects. This product of

the male urine was designated also as the "male hormone" and to distinguish it from the testicular product it was referred to as the "male hormone from urine."

Two years later Butenandt (1931) obtained the hormone from human male urine in crystalline form and showed that it acted upon the capon comb and upon the male accessory reproductive organs. This crystalline substance was named "androsterone" and its formula shown to be $C_{19}H_{30}O_2$. Soon afterwards it was prepared synthetically from cholesterol. Butenandt and his co-workers also prepared a second crystalline hormone from human male urine which was found to be dehydroandrosterone ($C_{19}H_{28}O_2$). This, too, exerted similar effects to androsterone itself, but it required considerably larger doses to produce like effects.

In 1935 a crystalline body was prepared from the testicular tissue and was shown to be very much more active on mammalian tissues than was androsterone. This crystalline body which possessed the formula $C_{19}H_{28}O_2$ was named "Testosterone." Shortly afterwards it too was prepared synthetically from cholesterol. In fact, it is possible that cholesterol is the precursor of all the sex hormones. There are thus three crystalline male hormones known– testosterone from testicular tissue and androsterone and dehydroandrosterone obtained from male urine. The term "Androgen" has been adopted to designate substances possessing masculinizing activity.

Not only is androsterone found in male urine, but also in the urine of women in amounts comparable to those obtained from male urine. The action on the capon's comb of the substances obtained from these two sources is practically identical. Androsterone is found also in the urine of the aged and in the urine of castrated women, although the amount present in each case is less than that obtained from the young adult. The action of the male hormones is essentially one of a replacement nature, restoring the normal structure and function of the accessory genital organs in eunuchs and in castrated apes and rats. The male hormones do not stimulate the hormonal activity of the testes, even though they are said to aid to a certain extent in the maintenance of spermatogenesis.[1] In large doses they may be injurious to the interstitial tissue, since they act upon the anterior lobe of the pituitary, suppressing the gonadotropic hormone in the same manner as do the estrogenic substances.

Therapeutic Uses.—Preparations of the male hormones have not been shown to act as stimulants to hypofunctioning testes. They may prove of value in the treatment of prepuberal castrates where they could stimulate the growth of the accessory reproductive organs. Conversely, gonadectomy in either sex leads to hypertrophy of the pituitary anterior lobe with an alteration of its physiological activity giving an increased secretion of the gonadotropic hormone. In fact the combined action of the androgenic and estrogenic substances is sufficient to account for the humoral control of the anterior pituitary lobe.

[1] See Cutuly and McCullagh for androsterone and testosterone; also Nelson and Gallagher.

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K. VITAMINS, OR ACCESSORY FOOD SUBSTANCES.

Vitamins are substances which must be supplied in small quantities to maintain normal health; if one of them is inadequate, the deficiency leads to the development of disease and death or permanent impairment of health; but if the lacking constituent of the dietary is given before irretrievable damage has occurred in the tissues, complete recovery generally follows. The amount of these substances necessary to maintain health is so small that they cannot be regarded as sources of energy like the ordinary foods, but must resemble drugs in their method of action, exactly as adrenal or thyroid preparations, which form the nearest analogy to them.

The fact that small quantities of apparently indifferent substances are necessary to health was first appreciated a century and a half ago, when it was noted that scurvy could be cured by fresh vegetables or by the juice of lemons and other similar fruits. More recently it was discovered that beri-beri, a disease which is seen chiefly in rice-eating countries, and which became very prevalent when polished rice was introduced, could be remedied by treating the patients with less completely prepared rice or with the germ which had been removed in the process of polishing. But the subject only received the attention it deserved when it could be accurately examined by means of animal experiments. At the same time it became clear that in modern urban populations and with the present methods of preserving and storing foods there is a possibility that these and other "deficiency diseases" may become more prevalent than has hitherto been the case; many people consuming food adequate as far as the provision of energy is concerned live on the borderline below which the vitamins are deficient and ill-health results. It is also true that persons on a badly balanced diet or patients on a highly restricted regimen do at times exhibit signs of vitamin deficiency.

Recognition of the fact that in the preservation of foods under commercial conditions certain of the vitamins are likely to be destroyed in

whole or in part has led some of the manufacturing establishments to adopt procedures adapted to lessen exposure of the food to the action of oxygen when it is being canned and the cans themselves before being sealed have the oxygen exhausted or replaced by nitrogen. For man, like the other animals, cannot manufacture those essential substances, but derives his supply from vegetables either directly or through the flesh of animals which have absorbed them in their food. Nursing infants draw their supply of vitamins from the mother's milk, and a deficiency in her food often gives rise to symptoms in the child; these disappear at once on supplementing the mother's diet where necessary.

Several vitamins are recognized at present and it is not unlikely that there may be others or perhaps that some of those now recognized may prove to contain two or more different principles. Several of the vitamins have been isolated in pure chemical form and their chemical composition established and some have been synthetized.

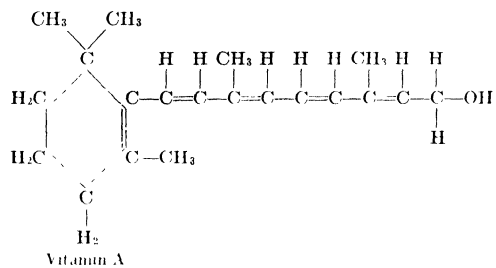
Vitamin A has been known as the anti-ophthalmic vitamin due to the fact that its absence from the food will result in a condition in which there is a characteristic eye disturbance which is known commonly as xerophthalmia. However, the symptoms in this disorder are much more widespread, not being limited by any means to the eye, so that this vitamin is not infrequently referred to also as the "growth promoting" factor A.

Vitamin A, being soluble in fats and oils, was in the earlier work upon these substances confounded with other fat-soluble principles or rather these vitamins, so far as they were known, were all grouped together. Now, however, three distinct fat-soluble vitamins have been recognized and the two which have been differentiated from A are now classified separately as Vitamin D, or the antirachitic principle, and E, or the antisterility factor.

The presence of a large amount of a yellow pigment in plants which contain an abundance of vitamin A led to a further study of such carotenoid pigments and of their relation to the activity of this vitamin. Many of these yellow pigments are designated by special names such as zeaxanthin, from yellow corn; capxanthin, from the red peppers; flavoxanthin, from the buttercup; and toxaxanthin, from dandelions. Many of the green foods which contain the vitamin are rich in this yellow pigment, the presence of which is concealed by the green color. In fact, there seems to be a relationship between the green coloration of various food products and their vitamin A potency. The green leaves of lettuce are richer in this vitamin than are the white leaves of head lettuce and green asparagus tips are more potent than the white. However, cod-liver oil, which is rich in this vitamin, contains none of this pigment.

The pigment, which is known as carotene, has been isolated in pure form and has the formula $C_{40}H_{56}$. The molecule of carotene is capable of being split in half with the formation of an alcoholic group at the end of each split product forming the vitamin A. Carotene differs from the vitamin in certain important respects. For instance, the latter is almost colorless and in addition it has spectrographic properties differ-

ing from those possessed by carotene. Carotene itself is exceedingly active, a daily dose of 0.003 mg. being sufficient to prevent the symptoms of avitaminosis in the rat. It is a hydrocarbon and occurs in three forms, which have been designated as alpha, beta, and gamma carotene. The beta carotene is apparently twice as active as either the alpha or gamma, but in nature they usually appear as a mixture of the three. The vitamin A activity of yellow maize is not due to carotene but rather to a closely related pigment, cryptoxanthin. The changes in the body which are ascribed to vitamin A activity are believed therefore to be due to five substances—vitamin A itself; alpha, beta, and gamma carotene; and cryptoxanthin. The last four are precursors of the vitamin and are found in the plant kingdom. In the animal body they are changed into a compound with the formula $C_{20}H_{29}OH$, which is known



Vitamin A

as vitamin A. The transformation from precursor to vitamin probably occurs in the liver through the action of an enzyme, carotenase, and storage of the substance is also largely in that organ.

Vitamin A has been called the "anti-infective" vitamin but there is not sufficient evidence today to justify such a name. Any such effect is, in the light of present-day knowledge, only indirect in that the vitamin assists in preserving the health and vigor of the body.

Vitamin A is a fairly stable body and resists heating for some time, being only slowly destroyed. It is found primarily in plants, the green leaves being especially rich, but it is found also in the actively growing parts of the plants such as the young shoots, while the storage parts of the plant such as fleshy roots and tubers have much smaller amounts. Green and yellow are color indicators of potential vitamin A in plants—the green because carotenes always accompany the green chlorophylls. Natural yellow color is a rough guide for the selection of vitamin A in animal products as it indicates the consumption of the vitamin precursors by the animals. However some vitamin-rich products are poor in pigment, as for example halibut- and burbot-liver oils. Yellow maize is richer than is white maize and sweet potatoes contain more than white potatoes. Animals receive their supply of this factor from plants and store it up in the various tissues and organs, especially in the liver, kidney and lungs. The liver, for instance, has been shown to contain from 200 to 400 times as much as muscle tissue and the lungs and kidney are 40 times as rich as muscle. Inasmuch as this vitamin is so important for growth it is interesting to find it in large quantities

in milk and in the yolk of eggs. In fact, milk, eggs and green vegetables are perhaps the chief sources of this vitamin for man. Cold-liver oil has long held a position of importance in medicine and this has been partially explained by the fact that the oil contains large amounts of this vitamin in addition to the antirachitic factor (vitamin D). Recently it has been shown that the livers of other fish than the cod contain much larger quantities of this vitamin than does the liver of that species. For example, the liver of the halibut is said to contain 100 times as much; in fact 1 per cent by weight of halibut-liver oil may be vitamin A. The cod, like other fish, gets its supply of vitamin indirectly from the algæ upon which the smaller fish and lower forms of marine life feed, and these small fish serving as food for the cod furnish it with the vitamin, which in turn is stored in the fat of the liver.

On account of its solubility in fats vitamin A is stored in the animal body in larger amounts than are some of the other vitamins, so that no symptoms of deprivation are seen until this store has become exhausted. Young adult rats apparently can store sufficient to keep them alive for about six months. Probably 95 per cent of the vitamin is stored in the liver with small amounts in the lungs and kidneys. The accumulation in the liver is lowest at birth and tends to increase with age and is dependent upon the diet. On this account the vitamin content of milk is very important. As the vitamin formation from carotene is not always complete, milk, eggs and other biological foods contain a mixture of vitamin and carotene, the proportions of each varying often according to species. For example, about two-thirds of Guernsey milk vitamin activity is due to carotene while Ayrshire milk owes about one-third of its activity to carotene and in Jersey milk there are about equal quantities of vitamin and provitamin.

Vitamin A is absorbed well, reaching its maximum in from three to five hours after administration. Carotene absorption is more variable and is slower reaching its maximum in from seven to eight hours. Carotene dissolved in oils or given with a fat diet is utilized well but when given with a low fat diet its absorption is less satisfactory. It should not be given with liquid petrolatum as it is soluble in this vehicle and therefore will not be absorbed. Excess of vitamin is stored as stated and the remainder probably destroyed as very little is found in the excretions.

Probably the earliest sign of chronic hypovitaminosis in which vitamin A is involved is seen in a change in the skin. There appears a dryness of the skin, with a papular eruption which affects all parts of the body except the face. These changes, which are due to involvement of the sebaceous glands, lower the resistance of the skin and predispose to infection. It was the occurrence of these local infections, not only in the skin but also in the eye and elsewhere in the body, which gave rise to the idea that vitamin A was an anti-infective vitamin. This, however, is not true in the strict sense of the term. It acts rather to prevent the keratinization of the superficial cells, which change lowers the resistance of the epidermis. The dermatosis which results is rapidly relieved by the administration of cod-liver oil.

Also one of the early manifestations of lack of vitamin A, and usually following the skin changes and seen in adults, is night blindness (nyctalopia), a condition where there is more or less difficulty in adapting vision where there is faint illumination. This disturbance of vision is apparently connected with failure of the visual purple of the retinal rod cells to regenerate after its exhaustion by exposure to bright light. Normally the vitamin brought to the retina unites with protein to form the visual purple. In the avitaminotic state the vitamin component is lacking, hence regeneration of the visual purple cannot take place. Xerosis or dryness of the conjunctiva is considered to be the second stage of eye disturbance and this is succeeded closely by xerosis of the cornea and inactivity of the para-ocular glands with lessened secretion of tears.

In addition to the eye changes in the absence of this vitamin, animals cease to grow and become susceptible to the eye affection which is known as xerophthalmia or keratomalacia. The eye becomes sensitive to light, there is conjunctivitis with a purulent discharge. The lids are swollen and stick together and the cornea may become involved and blindness result. While the eye condition is one of the most striking signs of this deficiency disease it is by no means the only one. The resistance of the body is apparently lowered and disease of the lungs is quite common, especially in the adult animal. Other signs of increased susceptibility to infection have been described, especially in the ears, in the sinuses, and in the glands at the base of the tongue. Doubtless some of these changes described are due to malnutrition and in others infection plays a part; for instance, in the production of the ophthalmia infection doubtless is important, but that the lack of vitamin is the essential feature is shown by the rapid recovery when the same is supplied.

The main pathological features of deficiency of vitamin A in man are therefore due to the accumulation of keratinized epithelial cells in glands and their ducts where they form cysts filled with yellowish cheesy masses. These keratinized cell masses may lead to occlusion of bronchi and atelectasis and the plugs being exposed to infection serve as a culture medium for bacterial growth.

Vitamin A then appears to act on the general nutrition of all the cells of the body and the importance of an adequate supply for adults as well as for children should be generally recognized. It is best supplied in the form of milk, eggs and green vegetables and, in case of need, cod-liver oil or halibut-liver oil may be given in addition.

Vitamin A_2.—Freshwater fish contain a substance which is closely related to vitamin A which, on account of its distribution, chemical, physical, and biological properties, has been called vitamin A_2. It differs from A_1 in spectrum and color tests. Probably some of the functions of A_1 in saltwater fish are served by A_2 in freshwater fish, and there is no evidence that A_2 can be made from provitamins except by fish. If carotene is fed to fish, the stores of A_1 and A_2 are greatly increased so that carotene serves as a provitamin for A_2 and without doubt the constitution of A_2 cannot be very different from that of A_1.

The carotene which was originally designated as an international standard of reference for vitamin A, 0.001 mg. being designated as a

vitamin A unit, has been replaced by a pure specimen of beta-carotene, $C_{40}H_{56}$, which is dissolved in cocoanut oil. One international unit of vitamin A is defined as the activity equivalent to 0.6 microgram of the International Standard preparation, which itself is equivalent in activity to 1 microgram of the carotene originally chosen as a standard.

Therapeutic Uses.—The therapeutic value of vitamin A rests upon its action in those conditions resulting from its deficiency. Among those conditions are xerophthalmia, certain cases of night blindness, and certain skin infections. As an aid to the development of bodily resistance to infection, it would be of value only when the stores of the vitamin in the body are exhausted or the intake inadequate. There is not sufficient evidence to show that its administration in excessive amounts has any value in the prevention of colds or of other infections. Also as in aid to growth, it has not been shown to be of any greater value to the body than the other vitamins or the essential food constituents.

Inasmuch as carotene is liable to deteriorate unless very carefully protected, a selected specimen of cod-liver oil is usually standardized against carotene and this oil is then used in the evaluation of vitamin A products.

PREPARATIONS.

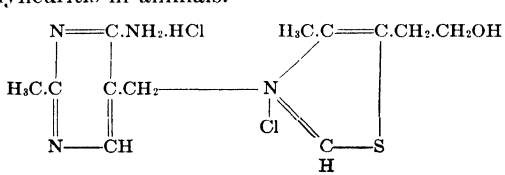
The U S P requires that cod-liver oil shall contain at least 850 U. S. P. units of vitamin A as well as 85 U. S. P. units of vitamin D per gram.

VITAMINA A NATURALIS IN OLEO (Natural Vitamin A in Oil), U. S. P. Vitamin A obtained from animal sources, either fish-liver oil alone, or fish-liver oil diluted with an edible vegetable oil, or a solution of vitamin A concentrate in fish-liver oil or in an edible vegetable oil. Natural vitamin A in oil contains in each gram not less than 50,000 and not more than 65,000 U. S. P. units of vitamin A, and not more than 1000 U. S. P. units of vitamin D. Average daily dose: 0.3 cc. (5 minims).

VITAMINÆ A ET D NATURALES IN OLEO (Natural Vitamins A and D in Oil). Vitamins A and D obtained from animal sources, either fish-liver oil alone, or fish-liver oil diluted with an edible vegetable oil, or a solution of vitamin A and D concentrates in fish-liver oil or in an edible vegetable oil. Natural vitamins A and D in oil contain in each gram not less than 50,000 and not more than 65,000 U. S. P. units of vitamin A, and not less than 10,000 and not more than 13,000 U. S. P. units of vitamin D. Average daily dose, 0.3 cc. (5 minims).

Vitamin B which was originally known as the antineuritic vitamin, is soluble in water and alcohol, but is insoluble in fats and oils. Although it was believed at first to be a single entity, subsequent study has shown that it consists of several components. The mixture itself as it is found in foods has been frequently referred to as the vitamin B complex.

The first of its constituents formerly known as vitamin B_1 has been named Thiamin. It has been isolated in pure crystalline form and shown to be the antineuritic vitamin which prevents beriberi in man and polyneuritis in animals.



Thiamin chloride.

The second component, riboflavin, is a compound which is necessary for growth in chicks and rats and for the prevention of cataract in rats.

Nicotinic acid (P–P factor), the third constituent, is the substance which is effective in human pellagra and in black tongue of dogs. Several other components have been described, one of which prevents the nutritional dermatitis of chicken; the B_3 factor necessary for rapid gains in weight and normal nutrition in pigeons; B_4 for the prevention of specific paralysis of rats and chickens; and B_5 which is necessary for maintenance of weight of pigeons. B_6 prevents the nutritional dermatosis in rats and factor W is necessary for their growth.

The evidence for the presence of the first three components is conclusive and their chemical nature is well known. Only two of them, however, have been shown to be necessary for human nutrition or to be of value in the treatment of human disease inasmuch as the value of riboflavin for the human patient has not been demonstrated. The evidence for the presence of the other factors named is satisfactory in the case of some, but not so convincing for others.

The vitamin B complex is less stable than vitamin A, but it withstands boiling for a short time and in acid or neutral solution is destroyed only slowly even when subjected to a high temperature; in the dry state it is even more stable. It is found in most forms of plant life, but is concentrated in the seeds and in yeast. Its distribution in seeds of different kinds is apparently not uniform, as it has been found throughout the entire wheat kernel while in yellow maize it is confined almost entirely to the embryo, the endosperm containing practically none. Asparagus, celery, dandelion and lettuce contain considerable amounts of this vitamin, while animal foods in general contain only small quantities. Its presence in seeds provides an abundant source, but the ultra-refinement of modern foods tends to remove the vitamin along with the germ, and white bread and polished rice contain little or none.

Fruits, meat, milk and eggs constitute good sources of vitamin B, but as they are among the more expensive foods they are naturally the substances eliminated from a diet in case of financial necessity. Vegetables, including potatoes, are important sources of this vitamin, however, as they are usually boiled, a very considerable portion of the vitamin is extracted from the vegetable and lost unless the water is utilized in some manner. Milk is a valuable source, especially as it is usually not subjected to any treatment which would reduce its vitamin potency. Canned foods are believed to retain their potency well, as do also the foods which are preserved by freezing, although the vitamin is extracted quite easily in the case of frozen products so that expressed juices should be utilized.

Vitamin B, being water soluble, is stored in the tissues to a limited extent only, and a deficiency in the food elicits symptoms rapidly.

In pigeons and the smaller animals a deficiency of this vitamin in the food may become noticeable in about two weeks, while in dogs symptoms may not appear for four weeks. Such of the vitamin as is stored is to be found in the liver which may contain ten times as much per gram as is found in voluntary muscles. The heart contains about

the same amount in proportion to its weight as does the liver, while the kidneys and brain contain very little. If an excess of the vitamin is administered it is quite rapidly excreted in the urine and if diuresis is present the amount of vitamin thus lost will be correspondingly increased. Ordinarily the vitamin is absorbed readily from the intestinal tract, but a serious disturbance of this organ, such as a severe diarrhœa, may result in a considerable loss of vitamin. From a pharmacological standpoint this vitamin has very little effect upon the organs of the body, such as the heart, gastro-intestinal tract or even on isolated tissues. Its action therefore is important up to the point of the needs of the body but not beyond.

A diet providing insufficient vitamin B_1 leads to malnutrition and retarded growth, but the most characteristic effect is the occurrence of polyneuritis, with the usual histological appearances in the nerve trunks. These symptoms (beri-beri) have been observed repeatedly in epidemics in man from the use of polished rice or white bread as the chief constituent of the dietary.

In addition to the polyneuritis of beriberi, deficiency of B_1 has been shown to occur in conditions associated with diets which are improperly balanced, as for example in those of alcoholics. As is well known, in such individuals polyneuritis is a not infrequent complication of the condition and recent work has indicated that the neuritis is essentially a deficiency disease and not due directly to the toxic action of the alcohol. Improvement in such persons rapidly follows the administration of large doses of vitamin B_1 which is usually given as thiamin hydrochloride. Fifty milligrams have been given daily by intravenous injection without any signs of intolerance and with rapid improvement in the condition. In the neuritis of pregnancy and of pellagra vitamin B_1 deficiency has been shown to be important.

The effects of a deficiency of vitamin B_1 are perhaps most satisfactorily studied by feeding pigeons on the deficient diet. Polyneuritis sets in in the course of about three weeks and soon proves fatal. The early symptoms consist of loss of appetite, weakness, lack of vigor, and constipation. Signs of impairment of nutrition of the nervous system appear later but it is still a question as to whether many of the symptoms observed from this form of food deficiency are due to the lack of this vitamin or whether some of them are not due to malnutrition brought about by the lack of desire for the deficient food. The lack of appetite is perhaps the most characteristic of the early specific symptoms as practically all the other early symptoms can be explained by the malnutrition. Later on in the course of the poisoning, the nervous symptoms are prominent and consist of convulsive seizures with opisthotonus and leg weakness. Marked temperature disturbances accompany the acute nervous symptoms in pigeons, there being a profound fall of perhaps 10° or 12° F. in body temperature in a few hours. The normal temperature is regained quickly if the vitamin is furnished. Examination of the gastro-intestinal tract in pigeons and in dogs shows no marked deviation from the normal except that in severe cases in dogs there is atony of the stomach and in pigeons late in poisoning, there is retention

of food in the crop. Study of the blood shows there is an increase in blood sugar and in lactic acid, indicating a marked disturbance in carbohydrate metabolism. Recent work seems to indicate that this disturbance in carbohydrate metabolism may be one of the most important features of B_1 hypovitaminosis especially as it refers to the accumulation of lactic acid in the body. Vitamin B_1 has been described as a coenzyme which is necessary in the chain of carbohydrate oxidation reactions of which lactic acid is the starting point.

Lactic acid loses hydrogen under the influence of a dehydrogenase with the formation of peruvic acid and, according to one view, vitamin B_1 acts as a coenzyme in the oxidative breakdown of this acid. An increase in peruvic acid has been found in the blood, urine and cerebrospinal fluid of cases of beriberi and in blood of B_1 deficient pigeons and rats and these amounts sink to normal in the cured case. If this view of the function of B_1 is correct it ascribes to the vitamin a more or less generalized action in the body in place of one on a given organ or group of cells and places it in the category of substances involved in biological oxidations and reductions (Cowgill).

The actual food taken by animals suffering from a lack of vitamin B_1 is doubtless less than in the normal condition due to the lack of appetite, but such food as is taken appears to be metabolized in a perfectly normal manner with the exception of the carbohydrates. It therefore seems that, in pigeons at least, most of the symptoms can be explained by the failure in nutrition, but there are two striking differences between this disorder due to food deficiency and starvation: one being the lack of desire to take the food and the other the marked nervous symptoms. When polyneuritis has been induced in pigeons or man, the supply of a food rich in vitamin, such as whole-wheat bread or rice polishings is followed by rapid recovery.

Therapeutic Uses.—The administration of the B_1 component of this vitamin is the logical agent for the prevention and treatment of beriberi. It may also be of value in certain cases of anorexia which are due to some dietary disturbance. It may also be given to young children in whom growth is below normal due to a deficiency of the vitamin in the food. In cases of interference with proper absorption of the vitamin-containing food, the administration of so-called concentrates may be advisable. Such conditions may arise from pernicious vomiting, from diarrhœa, or from tube feeding through an intestinal fistula.

Where there is increased excretion, as in marked diuresis, larger amounts may be desirable. In cases with an increased metabolism as, for example, in fevers or in exophthalmic goitre increased amounts of vitamin B_1 are necessary. In such cases 60 micrograms of thiamin hydrochloride (20 U. S. P. units) per 100 calories should be given daily (Cowgill).

Thiamin hydrochloride, $C_{12}H_{18}ON_4SCl_2$, vitamin B_1 (Aneurin), is a white crystalline salt, soluble in water. It may be obtained from natural sources such as yeast or rice polishings or may be made synthetically. For purposes of standardization, 3 micrograms of Thiamin hydrochloride is considered to be one U. S. P. unit—the equivalent of 1 International unit.

It is probable that an average adult needs from 1 to 2 mg. of thiamin daily for the preservation of health. The average adult excretes from 30 to 90 micrograms of the vitamin daily or about 5 to 8 per cent of the total intake of vitamin. If the urinary output of vitamin B_1 is below 12 International units (36 micrograms of thiamin) the individual is probably not receiving an adequate amount in his food (Harris and Leong).

For a very young baby 80 units (240 micrograms) is probably the minimum daily requirement of thiamin, increasing the amount with growth.

Riboflavin (Vitamin B_2 or G).—Originally classed with the antiberiberi or antineuritic vitamin (both being designated "vitamin B"), it has been shown more recently that the B complex in reality consists of several components; the antineuritic component known as B_1, or Thiamin, and a second member, Riboflavin.

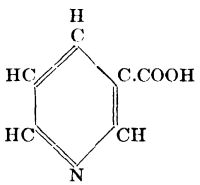
Riboflavin, $C_{17}H_{20}N_4O_6$, a member of the vitamin B complex, was formerly known as vitamin B_2, vitamin G or as lactoflavin. It is obtained as clusters of fine orange-yellow crystals which are only slightly soluble in water, giving the water a strong yellowish-green fluorescence. This greenish fluorescent pigment occurs widely distributed in nature in both the plant and animal kingdoms. It is also made synthetically. It has been obtained from egg white, milk, liver, kidney, egg yolk and from such vegetable sources as dandelion blossoms, grasses, etc. The fact that the substance was obtained from these different sources was responsible for the various names which were applied to it, such as ovoflavin, lactoflavin, hepaflavin, renoflavin, etc., but when it was shown that these products were all chemically identical the designation riboflavin was adopted to cover the group—the first syllable indicating that it is a ribose derivative (dimethyl-ribityl-iso-alloxazin). Riboflavin is apparently formed primarily in the green leaves of actively growing plants and is concentrated there in larger amounts than in other parts of the plant. Carrot tops contain about four times as much of this vitamin as do the roots. The milk content of this vitamin is fairly uniform throughout the year in spite of the difference in feed available for the cows in winter as compared with summer, so that milk forms a dependable source of riboflavin. Liver furnishes at least ten times as much vitamin as does an equal weight of muscle.

Various estimates have been made of the amounts of riboflavin necessary for normal human nutrition and while they differ somewhat, it appears that children up to ten years of age require about 400 units per day and adults 500 to 600 units—1 unit (Bourquin-Sherman) representing the potency of from 3 to 5 micrograms of riboflavin.

It has been shown that riboflavin is required for growth and maintenance of health in rats and presumably in all mammals, including man. Riboflavin is also believed to exert some function in the oxidation processes of the cell. It forms an ester with phosphoric acid which combines with a protein to yield a yellow oxidation enzyme which is presumably present in every living cell and is concerned with the chemical changes involved in cell respiration (Booher).

The part which *riboflavin* may play in the diet of man was shown by Vilter and Spies who treated cases of pellagra with thiamin and nicotinic acid alone, securing some improvement. However, in the course of time the patients, in spite of the thiamin and nicotinic acid, lost their appetites and developed a dermatitis. Riboflavin in 50 mg. doses was given on each of two days and was followed by great improvement in the general condition and in the cutaneous lesions.

Nicotinic acid, a third component of vitamin B, occurs as white crystals which are freely soluble in water. Originally used successfully



Nicotinic acid.

in the treatment of "black tongue" of dogs, it was very soon employed in the treatment of pellagra, a disease of man which is considered to be analogous to the canine disorder.

In pellagra the administration of nicotinic acid is followed by rapid improvement in the glossitis, stomatitis and dermatitis. When the drug is given intravenously signs of healing may begin to appear in a few hours and the mouth lesions may be completely healed in three days. There is also a distinct improvement in the mental state of the patient within two or three days of the commencement of the treatment. Nicotinic acid has no effect upon the polyneuritis of pellagra and it is necessary to give vitamin B_1 (thiamin) for this condition.

The drug is not very toxic but mild symptoms of intolerance may follow its administration. These symptoms which consist of severe flushing, itching and tingling, particularly of the face and extremities, come on within a few minutes when the drug is given by mouth but they last only from ten to twenty minutes. There is no effect on blood-pressure, temperature or respiration. Ten milligrams given intravenously may be followed at once by these symptoms while oral doses of 50 mg. may have no unpleasant effects, although these too will sometimes be followed by symptoms.

Pharmacological studies of the vitamin confirm the views as to its relatively low toxicity. Injected daily in moderate doses (rabbits 20 to 60 mg. per kilogram of body weight) it had no effect on growth nor were there any other evidences of toxicity. Injected into anæsthetized cats and dogs the only effect was a slightly increased blood-pressure (McCrea).

In rats deficiency in the pellagra-preventive component of vitamin B is shown by failure of growth, loss of appetite and a fall in temperature. Later, lesions of the skin appear, and of the mucous membrane of the mouth and tongue, death usually occurring in from two to three weeks. Although in both rats and dogs symptoms resembling those of human

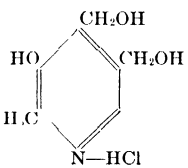
pellagra have been produced, in no case can the experimental condition be considered as identical with that of the human patient.

The dose necessary for the treatment of pellagra has not been definitely established. However, the maximum daily dose recommended is 500 mg. divided into ten doses of 50 mg. each. For intravenous administration a daily dose of from 50 to 80 mg. dissolved in sterile salt solution is effective. One hundred milligrams dissolved in 1 litre of sterile salt solution and given subcutaneously has also proved efficient.

Preparation.

Acidum nicotinicum, U. S. P.

Vitamin B_6 has been isolated in crystalline form and has also been prepared synthetically, the formula for its hydrochloride being $C_8H_{11}O_3N$. HCl (methyl-hydroxy(dihydromethyl)pyridine). Its value was attrib-

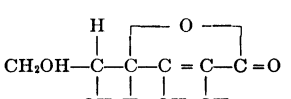


Vitamin B_6

uted at first to its ability to prevent nutritional dermatitis in rats in addition to permitting normal growth. More recently its importance to man has been shown in cases of pellagra where certain of the symptoms of the disease were relieved by the administration of thiamin, riboflavin and nicotinic acid but certain other symptoms such as insomnia, irritability, weakness and difficulty in walking occasionally remained. The administration of 50 mg. of the synthetic vitamin B_6 to such cases was followed by prompt relief of symptoms with rapid increase of strength and ability to walk (Spies, Bean and Ashe).

The synthetic product possesses a potency equivalent to the natural product and is capable of curing the deficiency disease of rats and inducing growth when given in a single dose of 0.1 mg.

Vitamin C, or the anti-scorbutic vitamin, is soluble in water and alcohol, diffuses through parchment and is not readily absorbed. Vitamin C



Ascorbic acid. Vitamin C.

has been isolated in crystalline form and the name "ascorbic acid"[1] assigned to it by its discoverer, Szent-Györgyi. The presence of this acid, which is a powerful reducing agent, was demonstrated in various plant tissues and in the adrenal cortex, from which organ it was first

[1] Ascorbic acid was for a time known as cevitamic acid and is also on the market under the name of "Cebione."

isolated. Vitamin C is quite unstable and is destroyed by prolonged boiling, especially if the reaction of the material is neutral or alkaline. In acid media (such as tomatoes) the destruction is slower but about 50 per cent is said to be destroyed by boiling for one hour. In the form of preserved foods it undergoes slow destruction, but many factors, such as the reaction and presence of oxygen, etc., enter in and may greatly modify the rate at which it disappears. It is found in growing plants but is mainly supplied in the form of potatoes, fruits, and fresh green vegetables. Potatoes do not contain large amounts but on account of the large quantities of this vegetable which are eaten they furnish an important source of this vitamin. It is most abundant in the juice of oranges, lemons and tomatoes. Some of the vitamin is destroyed by the ordinary methods of cookery and preservation and a diet apparently containing a fair amount of vegetable food may be rendered insufficient through the methods of preparation and storage. Dried grains and seeds contain only traces, but if they are allowed to germinate the vitamin is developed and in case of necessity growing malt or peas may be used to supply it. The most convenient method of transporting it is in the form of lemon juice, which retains its virtues for a long time, even when dried. Orange juice powder or the juice itself if it is saturated with carbon dioxide gas, will retain its vitamin potency for long periods. Canned tomatoes are also a very important source of this vitamin. Like vitamin B, it is not stored in the tissues and a more regular supply is necessary than of A.

Deficiency in vitamin C leads to malnutrition with loss of weight and culminates in the symptoms of scurvy, which was formerly prevalent in long sea voyages when fresh vegetables were unobtainable, and which still occurs occasionally in urban populations from neglect and ignorance of the value of fresh vegetable food. In scurvy the chief lesions begin along the alimentary canal, and apparently arise from injury to the capillaries and arterial walls which leads to exudations and hæmorrhages. There is soreness and stiffness of the joints. The gums are painful and hyperæmic and the teeth become loose. These changes appear in the guinea-pig readily and this animal is most suitable for the investigation of deficiency of vitamin C.

There is some evidence that vitamin C deficiency is responsible for certain forms of dermatoses, especially those occasionally seen following the use of the organic arsenicals. In some of these individuals in which there was a dermatitis following the administration of neoarsphenamine the content of ascorbic acid in the blood was found to be exceedingly low. Also the administration of ascorbic acid to persons known to be sensitive to the arsenicals has seemed to lessen the incidence of dermatoses. However, the matter is still in an unsettled state and no positive statement concerning the relationship of vitamin C to the arsenical skin eruptions can be made at the present time.

The vitamin is excreted in the urine in amounts which under ordinary circumstances are remarkably constant, but if excessively large amounts are taken, the curve of excretion rises sharply to a maximum which is

reached in about three hours, after which the amount excreted decreases rapidly to reach the normal level in a day or two.

Ascorbic acid is optically active, the lævo compound constituting vitamin C; the dextro body being practically inactive. It is probable that the average adult requires at least 50 to 60 mg. of vitamin C daily and that a child requires about 40 mg. and an infant 20 mg. daily.

The average vitamin content of orange juice is 0.6 to 0.7 mg. per cc. and of lemon juice 0.47 mg. per cc. For a time lemon juice was used as an international standard for vitamin C, 0.1 cc. of fresh juice being designated as one International unit. Later, when it was found that lemon juice varied in potency and especially upon the discovery of ascorbic acid, the latter substance was substituted for the lemon juice and the activity of 0.05 mg. of l-ascorbic acid was adopted as the International unit. This is the quantity of ascorbic acid usually found in 0.1 cc. of lemon juice.

Therapeutic Uses.—According to present views vitamin C is indicated only for the prevention and cure of scurvy. It is probable that a condition of early or latent scurvy may occur due to inadequate diet or to improper absorption of the vitamin, in which case the administration of the vitamin in some form may be indicated.

It has been claimed that various other conditions may result from lack of an adequate amount of vitamin C, but convincing evidence in favor of such views is lacking, and the prescription of vitamin C in such states is not indicated unless they can be definitely shown to result from such a deficiency. Among the conditions for which such claims have been made are dental caries, anemia, malnutrition, anorexia, and various forms of infections. Vitamin C, like A, has been designated by some as an "anti-infective" vitamin, but while infections may occur in any condition of avitaminosis or malnutrition it has not been shown that these vitamins can directly affect infective processes such as cold, etc., or act as an aid in preventing such infections.

PREPARATION.
U. S. P.

ACIDUM ASCORBICUM (Ascorbic Acid, Vitamin C, Cevitamic Acid).
White or slightly yellow crystals or powder. Odorless and soluble in water. Stable in dry state but deteriorates in watery solutions. Dose, 0.050 G. ($\frac{3}{4}$ gr.).

Vitamin D, often spoken of as the anti-rachitic vitamin, is found in abundance in cod-liver oil, halibut-liver oil, other fish liver oils, in egg yolk, milk, and butter. Being fat-soluble, it was for a time classified with the other vitamins having similar characteristics in this respect, but a more accurate knowledge has permitted it to be given a separate designation.

Its importance lies in its use as a prophylactic and cure for rickets. In this disease, which is classed as a deficiency disease, there is a disturbance of the mineral metabolism so that calcification of the bones does not take place normally. The rachitic infant stores less calcium

and inorganic phosphorus than does a normal child. An early sign of the disease is a low concentration of inorganic phosphorus in the blood, there being only 2 or 3 mg. per 100 cc. of blood serum instead of a normal amount of 5 or 6 mg. When vitamin D is administered there is a prompt increase to normal, the vitamin apparently controlling the concentration of both calcium and phosphorus in the blood and their deposition in the bones. It is impossible to say positively whether this increase in calcium and phosphorus in the blood is due to increased absorption from the intestine or to delayed re-excretion into the intestine but it is most probable that the vitamin acts to delay the excretion. It has been shown that calcium and phosphorus absorbed in the upper part of the intestine are re-excreted lower down the bowel and this latter process is definitely influenced by vitamin D.

Not alone in rachitic infants but also in normal children this vitamin exerts its effects in that its administration to them is likewise followed by an increased retention of both calcium and phosphorus. How vitamin D brings about an improvement in rickets is not definitely known, but the improvement in bone calcification noted has been ascribed to the increased amounts of calcium and phosphate present in the blood. A similar improvement follows exposure to the action of direct sunlight or to the ultra-violet rays from a quartz lamp. It is believed that the effect of the light is to be explained by an action upon cholesterol or an allied substance in the skin by which the anti-rachitic vitamin is formed and taken up by the blood.

Excessive amounts of vitamin D lead to a condition of hypervitaminosis. With moderate overdosage there is a fall in the amount of calcium and phosphate in the intestinal contents and an overcalcification at the growing ends of bone. The latter condition is ascribed to the excessive calcium and phosphorus in the blood and the action of the phosphatase or calcifying enzyme.

In severe poisoning with this vitamin the calcium and phosphate may be drawn from the bones in spite of the overcalcified epiphyses, and there may be a net loss of mineral salts in the bones. Absorption from the intestinal tract is also disturbed, but it is possible that this is not a specific effect but is due to the poor physical condition of the animal.

The knowledge of the relation of this vitamin to cholesterol has been gradually evolved. It was early shown that it was the non-saponifiable portion of the oil which was active and this portion included the sterol, cholesterol, or, in the case of vegetable oils, the similar body phytosterol. It was found, however, that specially prepared and highly purified cholesterol could not be activated and that its apparent activity must be due to some associated body. This was identified as ergosterol, a sterol which may contaminate cholesterol. Ergosterol is found also in bakers' and brewers' yeast, which becomes highly anti-rachitic when irradiated. Ergosterol is also rendered highly active when irradiated, being 500 times as potent as is irradiated cholesterol.

According to present views ergosterol is transformed by photochemical means into vitamin D, the vitamin being an isomer of the parent substance. From ergosterol a crystalline compound, with the formula

$C_{28}H_{43}OH$, has been isolated and named calciferol. Calciferol possesses anti-rachitic properties and has been designated as vitamin D (or D_2) but it should be noted that the crystalline substance was isolated from irradiated ergosterol and up to the present time it has not been obtained from natural sources, such as the fish oils. Until this is done it will be impossible to determine the relationship of the synthetic calciferol to the naturally occurring form.

Vitamin D, without any doubt, exists in several chemically distinct forms, although it is usually as a matter of convenience still referred to in the singular. The term refers to antirachitic sterol derivatives and to certain components of fish oils and other foods having a similar action. Of the various forms of the vitamin only two are of importance in medicine—activated ergosterol and activated 7-dehydro-cholesterol. It is to either one or both of these substances that all antirachitic medicines and foods owe their peculiar property (Bills). Different species apparently react to the vitamin in different degrees. For instance, infants respond to the vitamin when it is in the form of irradiated milk or viosterol better than when it is given in cod-liver oil, while chickens respond to it better when it is administered in cod-liver oil than when given as irradiated ergosterol.

The vitamin itself is quite a stable body, retaining its activity for years. It is quite widely distributed in the animal kingdom, cod-liver oil being perhaps its most important natural source although it has been shown that halibut liver contains much more of this vitamin as well as of A. Fish which contain much body oil such as salmon, sardines and herring are the richest natural sources of the vitamin. The yolk of eggs is also an excellent source and it is not destroyed by boiling or by storage. Milk and butter do not contain much vitamin D, although they are rich in vitamin A. Living plant tissues such as leafy vegetables probably contain no vitamin D.

An interesting and important fact in connection with vitamin D was discovered some time ago. It was shown that the antirachitic activity of various foods as well as other substances may be greatly augmented by certain physico-chemical processes. This was shown also for ergosterol itself, the activity of which can be greatly increased by exposure to ultra-violet light or by low velocity electrons. Such an irradiated ergosterol was designated *Viosterol* and this substance, dissolved in an oil, is used as a curative agent in rickets or as a prophylactic against that disease. It is also added to cod-liver or other oils to increase their antirachitic potency.

Other oils which have been subjected to irradiation are olive oil and cottonseed oil as well as many others. Foods so treated include butter and oleomargarine, flour and various cereals and breakfast foods. The anti-rachitic potency of eggs and butter can be considerably heightened by this treatment and when thus increased it seems to be of quite permanent character, as it has been shown in many instances that there is little if any decrease in potency even if the foods are kept for months. Of how much value this artificially induced anti-rachitic property in the various foods in the diet of children is, it is impossible to tell at the

present time. On the other hand there would not seem to be any danger of hypervitaminosis in administering these foods, as it is probable that the limits of tolerance for this vitamin are quite wide. With viosterol, however, the case is different, as harm may result from the use of excessive dosage as was pointed out earlier.

The value of certain foods such as cream and butter in nutrition has been long recognized and for a time it was thought that cod-liver oil owed its unique position as a therapeutic agent simply to its food value and to the fact that it is easily emulsified and digested, forming a valuable food in cases of malnutrition. The discovery that it is rich in the vitamins A and D, however, changed this point of view and gave a new explanation for the position which it has held for so long in the esteem of the laity as well as of the medical profession. *Oleum Morrhuæ*, cod-liver oil (U. S. P.), contains at least 850 U. S. P. units[1] of vitamin A (B. P., 600 units of vitamin A) and at least 85 units of vitamin D per gram. Both U. S. P. and B. P provide for an assay of the product. It is given in doses of a teaspoonful to a tablespoonful three times a day after meals.

Viosterol (irradiated ergosterol) (U. S. P., Ergosterol Activatus in Oleo) is dissolved in a vegetable oil and standardized so as to contain the equivalent of 10,000 U. S. P. vitamin D units[1] in each gram. Viosterol in oil is given to children as a prophylactic against rickets in daily doses of 2 to 3 minims; and as a curative in doses of 5 to 7 minims. The U. S. P. also recognizes a non-destearinated cod-liver oil. This oil which is of the same potency as the medicinal oil is the raw material from which that preparation is derived through removal of the stearins, a process which is carried out after the oil has been imported. Halibut Liver oil, Oleum Hippoglossi (non-official), has a potency of 50,000 units of vitamin A per gram and not less than 540 units of vitamin D per gram.

"Halibut Liver oil with Viosterol" (non-official) has had sufficient viosterol added to the oil to assure a potency of not less than 10,000 vitamin D units per gram and is further adjusted to have the potency of not less than 44,800 units of vitamin A.

Burbot Liver oil (non-official) has a potency equal to 4480 U. S. P. units of vitamin A and 640 units vitamin D per gram.

In addition to Cod Liver oil the U. S. P. contains: Vitaminæ A et D Naturales in Oil which has a potency equal to about 60,000 units of A and about 12,000 units of vitamin D. Its dose is 0.3 cc. (5 minims).

The B. P. describes Calciferol ($C_{28}H_{43}OH$) with a potency equal to 40,000 units of antirachitic activity (vitamin D) per milligram. Also

[1] The U. S. P. units for A and D correspond in potency to the International units as defined by the Conference on Vitamin Standards held under the auspices of the League of Nations in 1934. The International unit for D is defined as being equal to the vitamin activity of 1 mg. of the International standard solution of irradiated ergosterol which is equivalent to 0.025 micrograms of crystalline vitamin D. In order to conserve the supply of the International standard the committee in charge of the U. S P. has adopted as a standard for vitamins A and D a specimen of cod-liver oil which has been assayed against the International standards for those vitamins, and a U. S. P. unit of vitamin D is defined as being equal in antirachitic potency for the rat to 1 International unit. The unit of vitamin A is the equivalent in activity of 0 6 micrograms of the International standard carotene. (See page 608.)

Liquor Calciforalis—a solution of Calciferol in oil with a potency of 3000 units vitamin D per gram. Dose, 0.3–0.6 cc. (5–10 minims).

Vitamin E is the anti-sterility principle discovered by Evans and his co-workers. They found that when rats were fed on synthetic food mixtures with the proper mineral constituents added and vitamins A and B the animals would grow and appear to be perfectly normal but they sooner or later showed complete sterility. The sterility is due to a deficiency in the diet of certain natural foods containing the vitamin E and it can be cured by giving these foods or by giving concentrated extracts of the foods.

The cause of the sterility, according to Evans, is not the same in the two sexes. In the male there are changes in the germ cells passing on in severe cases to loss of the seminiferous epithelium, while in the female there is death and resorption of the developing embryos. The growth of the embryos seems to be normal for a time but about the eighth day there is retardation in development and fœtal deaths occur about the twelfth day, although there is considerable variation in this respect. If to such a female vitamin E be given, either in the form of the proper food or as an extract, the next generation may result in a normal vigorous litter.

The vitamin is found to a certain extent in animal tissues such as the muscles, fat and the viscera, but it is not present in large amounts. Milk fat also contains little and cod-liver oil is almost lacking in it. On the other hand, it is found in some concentration in plants, especially in seeds and green leaves. Considerable amounts have been found in lettuce leaves. It is also found, in oats and corn and large amounts are found in wheat germ.

The administration to normal females of excessive quantities of this principle, either as food or as extracts, does not act in any way to increase the litter size or number above normal limits. This agrees with the general rule for vitamins in which a certain minimum quantity is necessary but an excess is of no advantage.

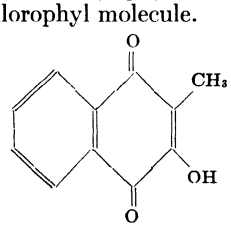
Evans and co-workers have isolated several oily substances (tocopherols) which yield individual crystalline compounds and retain the vitamin activity through several chemical transformations. Assay tests reveal unequal potencies and suggest a synergism between the various fractions of the E "complex." The principle is one of the fat-soluble group of vitamins. It is almost insoluble in water, is stable to heat, light and air and at normal temperature is resistant to acids and alkalies. Preparations containing the vitamin have been prepared from wheat-germ oil and these are very active, 5 mg. administered to sterile females at the beginning of a new gestation have resulted in a perfectly healthy litter being born. Isolated reports have appeared of the administration of extracts containing vitamin E to animals which habitually abort and some of these report an improvement in the condition as a result of the treatment. Similar trials have been made in the case of the human subject but much more extensive experience with the treatment will be needed before definite conclusions as to its value can be reached.

Vitamin K.—In 1935 it was observed that chickens which were fed upon a diet deficient in certain fat-soluble substances, but adequate in other respects, suffered from a fatal hemorrhagic condition in which bleeding occurred not only from the pinfeathers but also into the subcutaneous tissues and muscles. This condition, which was due to a decrease in prothrombin in the blood, could be controlled by the administration of the non-saponifiable fraction of hog-liver fat, by putrefied fish meal or by feeding alfalfa, cabbage, etc. The protective factor concerned was named the "Koagulation vitamin," or vitamin K.

This vitamin, or substances allied to it, is found widely distributed in Nature, especially in the vegetable kingdom. It is present in alfalfa, spinach, kale, carrot tops, tomatoes, and in certain vegetable oils such as soy-bean oil. It is also formed from fish meal under the action of bacteria which are capable of synthesizing the vitamin. Of great importance is the synthesis of this vitamin by the bacteria in the lower portion of the intestinal tract as shown by Almquist and Stokstad. Absorption from this portion of the intestine is minimal in the chicken but is usually adequate in mammals so that they are not likely to suffer from this form of avitaminosis unless there is faulty absorption from the intestine or some forms of liver impairment which may interfere with the synthesis of the prothrombin. The existence of biliary fistulæ or of obstructive jaundice leading to a similar hemorrhagic condition with lowered prothrombin in the blood suggested that bile might be important in aiding absorption of the vitamin. This view has been shown to be correct as in the absence of bile even massive doses of vitamin K are frequently inadequate to restore the blood coagulation time to normal.

Not only experimentally but also clinically has it been shown that the hemorrhagic tendency in biliary fistulæ and in obstructive jaundice is due to a deficiency of prothrombin in the blood. The feature common to these two conditions is lack of bile in the intestine, suggesting that the low prothrombin in the blood is due to failure of vitamin K absorption from the intestine.

Following the discovery of the part played by bacteria in the synthesis of the vitamin, Almquist and Klose showed that phthiocol, the pigment produced by Mycobacterium tuberculosis was capable of replacing the vitamin in vitamin K deficient diets, and the conclusion was reached that phthiocol was the simplest member of an homologous series of antihemorrhagic substances. In harmony with this view it has been shown that while phthiocol is the methylhydroxy derivative of naphthoquinone, vitamin K_1 is the methyl-phytyl derivative, phytol being the alcohol present in the chlorophyl molecule.



Phthiocol (2-methyl-3-hydroxy-1, 4-naphthoquinone).

In vitamin K_1 the phytol is attached in the place of the hydroxyl. The constitution of the second member of the series, vitamin K_2, is not positively known, but it is probably closely related to K_1.

The clinical use of vitamin K naturally is in somewhat of an experimental state at the present time. It has been used in cases of obstructive jaundice and in patients with biliary fistulæ and in disease of the liver parenchyma where there is a tendency to hemorrhage due to a deficiency of prothrombin in the blood. This deficiency may, as stated, be due to improper absorption of the vitamin from the intestine or to the inability of the liver to utilize the vitamin in the formation of the prothrombin.

In its use in the treatment of the hemorrhagic tendency in obstructive jaundice and also in the bleeding of the newborn it has been shown that as a result of the administration of vitamin K preparations there is an increase in prothrombin, a shortening of prothrombin time, together with an improvement in the hemorrhagic state. The administration of bile salts at the same time as the vitamin is beneficial. The vitamin is recommended for preoperative as well as postoperative treatment, but in the latter case larger doses are advised.

Vitamin K has been administered to patients by mouth and also intravenously. Phthiocol is soluble to 0.2 per cent and apparently is of low toxicity so that it has been given intravenously with success. Extracts made from alfalfa meal and from fish meal have also been employed. In patients with obstructive jaundice, and therefore lacking bile in the intestine, the oral administration of the vitamin should be accompanied by the use of bile itself or of bile salts.

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L. THE DIGITALIS SERIES.

The digitalis series embraces a considerable number of substances which are characterized by their action on the heart. They are widely distributed in the vegetable kingdom in very different botanical families, and have long been in use for various purposes in civilized and uncivilized countries. Some of them were employed as remedies by the laity long before their virtues were recognized by the medical profession, while others have been used as arrow poisons and ordeal poisons by the natives of different parts of Africa and the Eastern Archipelago.

The most important plants which contain bodies belonging to this group are *Digitalis purpurea* (purple foxglove) and *Digitalis lanata*,

Strophanthus hispidus, or *Kombe*, and *Scilla maritima* (squills). Others which are less frequently used are *Helleborus niger* (Christmas rose), *Convallaria majalis* (lily of the valley), *Apocynum cannabinum* (Canadian hemp), and *Adonis vernalis* (pheasant's eye). Similar effects are obtained from bodies contained in other species of these genera and in a large and ever-growing list of other plants, such as *Antiaris* (Upas tree), *Nerium* (oleander), *Acocanthera* (ouabaio), *Erythrophlæum* (sassy bark or Casca bark), *Thevetia*, *Cheiranthus* and *Coronilla*. Numbers of other plants[1] are said to resemble digitalis in their effects, and moreover these bodies are not confined to the vegetable kingdom, for Faust, Abel and Chen and his co-workers have isolated from various species of toads substances which induce the same changes in the heart. Salts of barium also induce many of the changes characteristic of this series.

Chemistry of Digitalis.—In the study of the chemistry of the digitalis bodies the main difficulties have arisen from the fact that in many cases more than one active principle is present; that they are present in only very small quantities, and that all have a very complex structure.

Almost all are glucosides which on treatment with acids are hydrolyzed, breaking up into non-carbohydrate constituents, the so-called "aglucones" or "genins" and sugars which in some cases possess unusual character. Many of the aglucones are chemically very closely related and possess the same number (23) of carbon atoms. Their differences in the main are due to the number, arrangement and function of the oxygen atoms present in the molecule.

Research has been especially active with Digitalis purpurea on account of the outstanding importance of this drug as a remedy in certain cardiac disorders. Both seeds and leaves furnish active glucosides which possess the cardiotonic activity of the plant; in addition to which there are present saponin bodies which do not show the typical digitalis effect on the heart but which are extracted along with the glucosides which possess the cardiac actions.

The glucosides from the seeds may be obtained by water extraction, the most important active member of the mixed glucosides being the digitalin of Schmiedeberg. Kiliani obtained it in almost pure form and named it Digitalinum verum. When pure this glucoside is only very sparingly soluble in water, but in watery extracts the saponins, mainly digitonin and gitonin, hold it in colloidal solution. Other active glucosides are also present in the seeds, but their chemistry is still unknown.

Windaus and his co-workers have shown that the formula for Digitalinum verum is $C_{36}H_{56}O_{14}$ and that of its "genin," digitaligenin, is $C_{23}H_{30}O_3$. This, however, is probably a dehydration product of the original genin (gitoxigenin, $C_{23}H_{34}O_5$), two molecules of water being broken off during the hydrolytic cleavage of the original glucoside.

The leaves of digitalis have been the source of even more difficulty than have the seeds on account of the very complicated chemical picture they present. Two crystalline glucosides have been isolated in pure

[1] Periplocin, a glucoside from Periploca græca, a plant indigenous to Black Sea districts, apparently belongs to the digitalis group. MacKeith. Jour. Pharm. and Exp. Therap., **27**, 449, 1926.

form, digitoxin and gitoxin. The former, which was first isolated by Nativelle but named by Schmiedeberg, is characterized by its solubility in chloroform and in alcohol and by its relative insolubility in water. It is perhaps present also in watery extracts of the leaves. It is one of the main active constituents of infusions of the drug. Digitoxin undergoes hydrolysis, breaking up into digitoxigenin and a sugar, digitoxose: $C_{41}H_{64}O_{13} + 3H_2O = C_{23}H_{34}O_4 + 3C_6H_{12}O_4$.

A water soluble glucoside which was extracted from the leaves by chloroform and named "gitalin" has been shown to be a mixture.

The second glucoside, gitoxin, which is characterized by its insolubility when pure, can in like manner be broken up into its gitoxigenin and sugar (digitoxose) as follows: $C_{41}H_{64}O_{14} + 3H_2O = C_{23}H_{34}O_5 + 3C_6H_{12}O_4$. By further treatment gitoxigenin loses two more molecules of water, yielding a product which is identical with the digitaligenin of Digitalinum verum.

Recently Stoll and Kreis, employing a special technique which avoided enzymatic cleavage, succeeded in isolating two new glucosides from digitalis. These correspond to digitoxin and gitoxin but both contain an additional glucose molecule and are designated Purpurea glucoside A and B. If these glucosides are subjected to the action of an enzyme obtained from the leaves they undergo hydrolysis, forming in the case of A, digitoxin and glucose while B forms gitoxin and glucose.

Purpurea glucoside A		Digitoxin		Glucose
$C_{47}H_{74}O_{18} + H_2O$	=	$C_{41}H_{64}O_{13}$	+	$C_6H_{12}O_6$

Purpurea glucoside B		Gitoxin		Glucose
$C_{47}H_{74}O_{19} + H_2O$	=	$C_{41}H_{64}O_{14}$	+	$C_6H_{12}O_6$

Another species of digitalis, Digitalis lanata, has been studied recently and has been said to be three or four times more active than Digitalis purpurea. From Digitalis lanata a number of crystalline glucosides have been obtained which as a group have been designated "digilanid." This, however, consists of a mixture of three isomorphous closely related substances, the digilanids A, B, and C in the approximate proportions of 47 per cent digilanid A, 16 per cent B and 37 per cent C. The formula assigned to digilanid A is $C_{49}H_{76}O_{19}$; digilanid B is $C_{49}H_{76}O_{20}$; and digilanid C is $C_{49}H_{76}O_{20}$. These glucosides yield in addition to the aglucone and the carbohydrate, a molecule of acetic acid, a substance which had not previously been encountered as a constituent of digitalis glucosides. The close relationship of these glucosides to the glucosides of digitalis purpurea is shown by the fact that by means of the enzymes present in the leaves digitoxin is obtained from digilanid A; gitoxin from digilanid B; and digoxin from digilanid C. Purpurea glucoside A of the official digitalis is said to be identical with deacetyldigilanid A and purpurea glucoside B with deacetyldigilanid B, the purpurea glucosides being obtained by the removal of the acetyl group from the corresponding digilanids (Stoll).

The active principles of the different species of Strophanthus have been studied by Jacobs and his co-workers. These principles also have been shown to be glucosides which break up in the same manner into aglucones and sugars. In Strophanthus kombé there are several active glucosides; all being derivatives of one aglucone, strophanthidin ($C_{23}H_{32}O_6$). One of these substances, cymarin, $C_{30}H_{44}O_9$, has been shown to be a glucoside of strophanthidin and a sugar, cymarose. The other

glucosides are further combinations of cymarin with one or more molecules of glucose which can be enzymatically cleaved to cymarin and glucose. K-Strophanthin-B is a compound of cymarin and one molecule of glucose. Amorphous K-Strophanthin, which is the main specific constituent of kombé seeds, is a mixture of water soluble glucosides in which cymarin is combined with two or more molecules of glucose.

Strophanthus hispidus also contains cymarin as a constituent of a mixture of glucosides, in which it occurs free and mostly in combination with glucose. In the latter case these complex glucosides exist as a water soluble amorphous mixture of glucosides from which cymarin has been obtained by enzymatic cleavage.

From *Strophanthus gratus* a crystalline glucoside, ouabain, has been obtained. It was so named as it was first isolated from the root and bark of the Ouabaio tree which is used as a source of an arrow poison by the Somalis of East Africa. *Ouabain*, $C_{29}H_{44}O_{12}$, is one of the most important glucosides of this group. Because of its well-defined physical characteristics and crystalline structure it has served as a standard in the United States for the assay of the digitalis group of drugs.

From Periploca græca, a plant indigenous to the Black Sea districts, a crystallin glucoside ($C_{36}H_{56}O_{13}$), periplocin, has been isolated. This glucoside is a combination of glucose with a simpler glucoside, periplocymarin ($C_{30}H_{46}O_8$). This in turn yields, on hydrolysis, an aglucone, periplogenin, and the sugar cymarose.

Antiaris toxicaria, the upas tree of the Malayan Archipelago, yields two glucosides, α and β-antiarin, which, on hydrolysis, yield the same aglucone, antiarigenin, but different sugars.

From Scilla maritima or Squills a crystalline glucoside, scillaren A ($C_{36}H_{52}O_{13}$), has been isolated as well as an amorphous glucoside, scillaren B, which may be a mixture. Scillaren A yields an aglucone, scillaridine, and a sugar. In certain of its chemical reactions the aglucone scillaridine differs from the aglucones of the digitalis-strophanthus group.

From Thevetia neriifolia a cardiac glucoside thevetin, $C_{29}H_{46}O_{13} \cdot 2H_2O$, has been obtained. The sugar component has not been determined and the aglucone has been obtained only in the amorphous form.

As mentioned earlier, in addition to the active principles possessing the characteristic cardiac effects and which are obtained from various plants, there are also the toad-venoms obtained from the secretions of certain glands of these animals. In the case of Bufo agua, Abel and his co-workers obtained a non-nitrogenous crystalline principle, bufagin. From Bufo vulgaris Wieland and his collaborators obtained bufotalin, which was related to bufagin, and a more complex non-glucosidal substance, bufotoxin, which consists of bufotalin in combination with arginine and suberic acid.

More recently Chen, Jensen and Chen have studied the poisonous secretions of a large number of toads and have demonstrated in the secretion of the parotid glands and also in the skins the presence of bodies having a digitalis-like action.

The close relationship of the various glucosides of the digitalis series to each other is especially well shown when the aglucones into which they are hydrolyzed are arranged in a series, as follows:

Strophanthidin	$C_{23}H_{32}O_6$	Digoxigenin	$C_{23}H_{34}O_5$
Digitoxigenin	$C_{23}H_{34}O_4$	Periplogenin	$C_{23}H_{34}O_5$
Gitoxigenin	$C_{23}H_{34}O_6$	Ouabagenin	$C_{23}H_{34}O_8$

The interest and importance of these aglucones consist in the fact that it is in this portion of the glucosidal molecule that the characteristic cardiac action resides. The sugar portion, while itself inert, apparently through its union with the aglucone gives the special character to the molecule which affects its absorption and transport in the organism, and so influences its specific affinity for cardiac muscle.

Symptoms.—Digitalis taken in even large medicinal doses in health provokes no symptoms unless the dose is frequently repeated. Poisonous quantities induce nausea and vomiting with abdominal pain, and often diarrhœa. The patient complains of general depression, headache, giddiness, and precordial discomfort, and often passes into a stage of great muscular weakness and collapse. At times there are also confusion and hallucinations. The pulse first becomes intermittent and then beats regularly at about 40 per minute. Later, it may become rapid and irregular, and fatal coma follows. The symptoms sometimes do not appear until several hours after the poison has been taken and they may last for several days in cases which survive.

A much more common form of poisoning arises from the prolonged use of therapeutic doses. Here the chief symptoms are headache, giddiness, anorexia, nausea and vomiting, and, in some cases, marked slowing of the pulse. These symptoms disappear within forty-eight hours if the treatment is stopped or the dose reduced.

Action.—The digitalis series possesses a local and a general action. The **Local Effects** consist in primary irritation, followed frequently by paralysis, of the sensory nerve-endings. Thus in the eye a small quantity of a solution, or a minute particle of the dry poison causes the most intense pain, redness, and congestion of the conjunctiva, and all the symptoms of acute inflammation. On the tongue the bitter taste is frequently followed by burning pain, and if the powder be drawn into the nostrils and larynx, marked swelling of the mucous membrane, sneezing, coughing, and hoarseness are produced in many persons. They have little action on the skin, although here too smarting is occasionally produced; but when injected subcutaneously many of them cause marked inflammation, which not infrequently ends in the formation of abscesses, even although the injection has been absolutely aseptic. This irritant action is not equally marked throughout the series, however, for digitoxin is much the most powerful in this respect, while digitalin may be injected subcutaneously without danger and almost without pain. The local anæsthetic property is likewise not equally developed in all the members of the series; several of them have been suggested as local anæsthetics for the eye, but their primary irritant effect precludes their use for this purpose.

After absorption, the chief symptoms are due to their action on the central nervous system and the heart. The action on the **Central Nervous System** consists in stimulation of some of the nerve centres, which is independent of the action on the heart and is limited to the medulla oblongata in many cases. In the frog the excitability of the reflexes is often lowered by members of this series, probably because of the intense stimulation of the medulla oblongata; but sometimes a

distinctly increased irritability is observed. More marked symptoms are produced in mammals, however, by this central nervous stimulation, for in these vomiting is elicited very soon after the injection of large quantities, long before the heart is very seriously affected, and this is undoubtedly due, at least in part, to action on the medulla oblongata.[1] To the same cause is to be attributed the rapid, deep respiratory movements and convulsions, which are often observed in the later stages of poisoning and which are evidently not due to cerebral anæmia, as has been supposed, for the brain at this stage receives quite as much or more blood than it normally does. Even small quantities, such as are used therapeutically, excite the inhibitory cardiac centre in the medulla and slow the heart both in therapeutics and in experiments on mammals. The extent to which the members of this series act as stimulants to the nervous centres varies, but as yet little comparative work has been done in this direction.

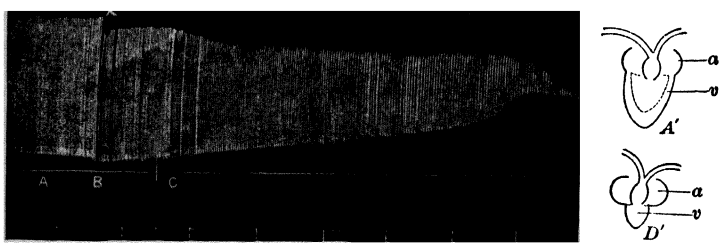

FIG. 48.—Tracing of the movements of the frog's ventricle under one of the digitalis series. *A*, normal; *B*, digitalis applied; *C*, half rhythm begins, and the diastole rapidly becomes less complete until the ventricle ceases in a position of semicontraction. *A'*, diagram of the heart in normal condition; *a*, auricle; *v*, ventricle; the dotted line represents the outline in full systole; the continuous, the outline in diastole. *D'*, outline of the heart in standstill after digitalis; the ventricle, *v*, is fully contracted, while the auricles are dilated. (After Sluytermann.)

The action on the **Heart** is the most important of all, and is what distinguishes digitalis and its allies from all other substances. This action has been studied most carefully in the frog, and is here found to consist of changes in the generation and conduction of impulses and in the contractility. The power of conducting impulses is distinctly reduced, and this makes itself evident in the frequent failure of an impulse to pass from the auricle to the ventricle, which thus remains at rest during a full cycle; very often each alternate impulse of the auricle thus fails to reach the ventricle, giving rise to half rhythm; or the ventricle may remain in diastole during a series of auricular contractions, or may cease altogether in this position, if very small quantities have been injected. This depressant action on conduction is accompanied by a less marked reduction of the rate of the auricle and sinus arising from fewer impulses being emitted by the pacemaker.

Along with this depression of conduction, there is a progressive

[1] *Hatcher and Weiss* believe that the action upon the vomiting centre is reflex, due to irritation of the heart or its appendages.

increase in the strength of contraction of both auricle and ventricle. Soon the relaxation becomes imperfect and the output falls accordingly; though the ventricle continues to empty itself more completely, it no longer contains as much blood at the beginning of systole as before. Later the apex of the ventricle remains contracted during the diastole and remains motionless and white, and this state of contraction slowly spreads over the rest of the chamber, until the ventricle receives no more blood from the auricular systole, and the auricles, unable to empty themselves, come to a standstill in the dilated position.

As a general rule both these actions may be observed intermingled in the frog's heart under digitalis; the effects of the depressed conductivity generally precede those of the changed contractility and are elicited especially by very small doses. Thus when the minimal lethal dose is given, the ventricle is very often found in diastolic standstill from its failure to receive impulses from the auricle; but if it is now stimulated mechanically or electrically, it passes into complete and permanent systole. When larger quantities are given the effects on contractility are elicited in greater measure, and there may be little tendency to ventricular intermission until the chamber is in almost complete systolic arrest.

The excitability of the frog's heart muscle is augmented by digitalis; thus if salt solution is led through the excised heart for some time, it ceases to beat, but if digitalis is now added to the perfusing solution rhythmical contractions often return. This increased excitability may account for a temporary acceleration of the heart-rate which is sometimes seen in the frog under digitalis.

The action on the frog's heart is a direct one on the muscle; the inhibitory mechanism has nothing to do with the change in the conduction or with that in the contractility, for the application of atropine has no effect upon either feature. The muscle of the frog's heart is thus reduced in conductivity and augmented in contractility and excitability by members of this series; the effect on the conductivity is elicited by smaller quantities than are necessary to change the contractility.

The hearts of some invertebrates are said to undergo changes similar to those described in the frog's heart, while the crustacean's seems to be entirely unaffected by digitalis.

Mammalian Heart.—In the mammalian heart digitalis and its allies also affect the muscle directly, but this is complicated by inhibitory action, which is absent in the frog. The direct action on the heart muscle in the healthy mammal is shown in increased strength of contraction and greater excitability, while there is less evidence of the depressed conduction which has been described in the frog's heart. Symptoms of reduced conduction occur in the mammal, it is true, but here they arise for the most part from inhibitory stimulation and not from direct muscular effects.

The action of digitalis on the healthy mammalian heart may be divided into three stages, of which the first and third are always developed when sufficient quantities are administered. The second stage

may be absent in certain circumstances, but is also generally present in poisoning.

In the *first or therapeutic stage* of the action of this series (Fig. 49), the rhythm of the heart is distinctly slower than before the drug, for the inhibitory apparatus is set in activity, and the slowing is accordingly due to a prolongation of the pause in diastole. The ventricles contract to a smaller size, that is, they empty themselves more completely than they normally do. This increased contraction is, like that in the frog's heart, due to action on the cardiac muscle. The papillary muscles undergo the same changes as the rest of the ventricular wall, contracting more strongly and more completely than before the administration of the drug.

The relaxation of the ventricle is found to vary in different conditions. If the heart is weak and dilated, digitalis and its allies tend to lessen this dilatation, that is, the relaxation of the ventricle during diastole is less than before the administration of the drug. If, however, the heart is normal, or does not dilate much during diastole, digitalis increases the relaxation (Fig. 49). The variation in the degree of dilatation of the ventricle depends upon the opposing factors—the inhibition and the muscular action. If the inhibition be the stronger, the ventricle relaxes more completely than before, for vagus stimulation always tends to increase the relaxation of the heart. If, on the other hand, the muscular action predominates the relaxation is lessened, for here, as in the frog's heart, this series tends to lessen the extent of relaxation. In the normal heart the application of one of this series causes, as a general rule, an increase in the extent of relaxation.

It must be added that the inhibition is due to the stimulation of the vagus centre in the medulla only; the peripheral mechanism is little involved, for digitalis hardly slows the heart after section of the vagi, as it would do if it acted on the intracardiac inhibitory ganglia or nerve ends.

Each beat of the ventricle thus expels more blood under digitalis than before, and if the number of beats per minute remained the same, the amount of blood expelled (or the output) would be much increased; but the rhythm is slower than normal, and this may more than compensate for the larger amount of blood expelled by each individual beat. In the therapeutic stage the slowing is not great enough to counterbalance the increased output per beat, and a larger amount of blood is therefore driven into the aorta and pulmonary artery.

The changes in the ventricle, then, are due to inhibitory activity and to direct cardiac action, the first tending to lessen the number of beats and to increase the relaxation of the fibres, the second tending to strengthen the systole and to limit the relaxation while not affecting the rhythm.

In the auricles the inhibitory stimulation causes more or less increase in the dilatation, while it lessens the contraction. The muscular action is the same here as in the ventricle, causing a tendency toward more complete systole and less complete relaxation. After small quantities, the rhythm of the auricle is slow, like that of the ventricle, owing to

the inhibition; the relaxation is little changed, but, owing to the muscular action, the contraction is more complete. In but slightly larger quantities, however, the inhibitory action causes a less complete contraction, so that the work done by the auricle is actually less than before the injection.

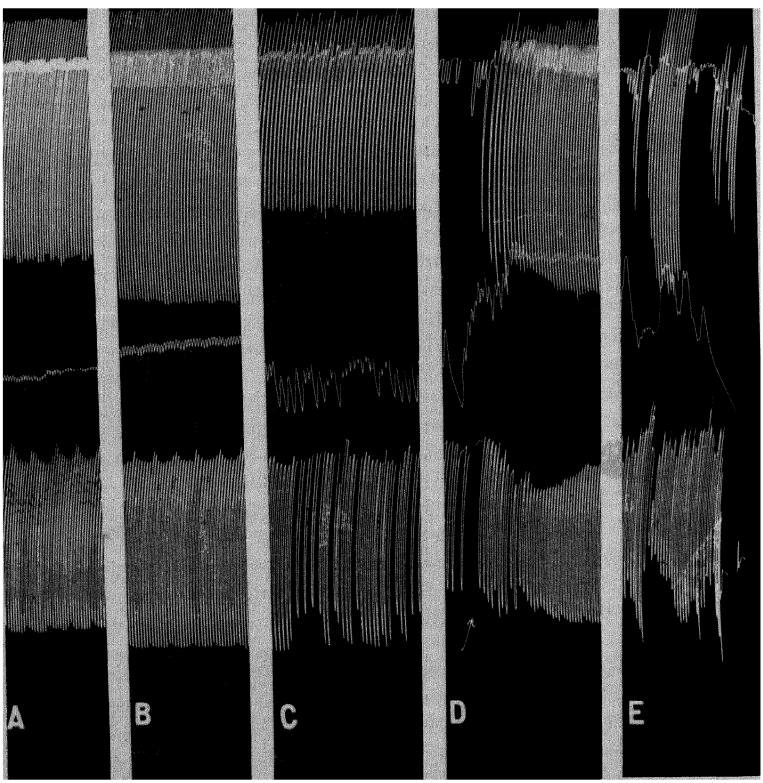

FIG. 49.—Digitalis on the dog's heart. Levers attached to auricle (top tracing); ventricle (lower tracing); middle tracing is blood-pressure. Myocardial levers move down in systole. Time in seconds. *A*, Normal tracing. *B*, Small dose of digitalis giving increase in systole of both chambers and some rise in blood-pressure (therapeutic stage). *C*, Toxic dose. Marked slowing with partial heart block; irregular pulse with low blood-pressure. *D*, Vagi cut with removal of slowing; high (toxic) blood-pressure. *E*, Final toxic stage with great irregularity—both chambers finally passing into delirium with fall of blood-pressure to zero.

The rhythm of the different parts of the heart is exactly the same during this stage, and the changes seen in the right auricle and ventricle correspond to those in the left. The conduction of impulses from the auricle to the ventricle may be slower owing to the connecting fibers being depressed by the inhibitory activity.

An interesting change in the electrocardiogram under digitalis has been described in that the *T*-wave undergoes a characteristic alteration. For the most part the change consists in a diminution in the height of the wave and finally in its inversion. The injection of atropine does not modify this digitalis phenomenon, demonstrating that it is due to an action of digitalis upon the heart muscle. (See Fig. 50, p. 638.)

This change in the electrocardiogram is of considerable importance as it is perhaps the earliest sign that digitalis is acting upon the heart, appearing as it does before nausea and vomiting disturb the patient or even before changes in rhythm or alterations in conduction time have occurred.

If larger quantities of digitalis be administered, either the inhibitory or the muscular action may become increased, and the appearance of the heart will vary according to which of these predominates. It must be distinctly understood that the following symptoms betoken a grave condition of poisoning.

In this, the *second stage* of digitalis action (Fig. 49, *C*, p. 632) the symptoms are due to excessive inhibitory activity, while the direct cardiac action is less developed. The rhythm of the ventricle, and consequently of the pulse, is very slow and irregular, as is always the case when the inhibitory apparatus is strongly stimulated. During diastole the ventricle dilates more completely than usual, while its systole continues powerful, since the inhibitory stimulation increases the relaxation but has less power to diminish the contraction. Each beat expels more blood than normally, but the rhythm is so slow that the output per minute and the efficiency of the heart as a pump are less than usual. This is the feature which differentiates the first from the second stage, in which the same factors are present; in the first stage the efficiency of the heart, *i. e.*, the amount of blood expelled per minute, is greater, in the second stage it is less than before the administration of the drug.

Very often the impulses have difficulty in passing from the auricle to the ventricle (heart-block) owing to the inhibition of the conducting fibres. The ventricle then beats at a slower rate than the auricle, but if the irritability of the ventricle is increased at the same time as the conduction falls, there may arise a spontaneous rhythm in the ventricle, which is independent of, and different from, that in the auricle.

The auricular contractions are much weaker than in the first stage, and even than in the normal heart, and may cease altogether for some time, while the chambers do not tend to dilate further as a general rule.

This stage of excessive inhibition is not observed in every case of poisoning in animals, nor probably in man, although in the recorded instances of poisoning with the members of this series, it seems to have been present, as the pulse is said to have been very slow and irregular. If the inhibitory mechanism is weak, or is paralyzed by the preliminary injection of such drugs as atropine, the second stage is entirely absent.

When still larger quantities of any of this series are injected, the *third stage* may set in. It is preceded by the first for a short time, generally by both first and second. In this stage the ventricular rhythm becomes very much accelerated, usually much beyond the normal, and

even beyond that seen after paralysis of the inhibitory nerves. This acceleration is not produced by paralysis of the vagus, for stimulation of this nerve sometimes still slows the heart and always causes dilatation. It is really due to the drug increasing the irritability of the heart muscle to such an extent that the inhibitory apparatus is no longer able to hold it in check.

The auricles also undergo the same changes. They begin to accelerate their rhythm, which may diverge from that of the ventricle, and the difference in rhythm of the two divisions may lead to a very characteristic periodic variation in the strength of the contractions of both auricle and ventricle. This auriculo-ventricular arrhythmia may continue for some time, but further irregularities soon present themselves. At intervals extrasystoles of either ventricle or auricle appear, that is, two contractions follow so rapidly on each other that the chamber has no time to dilate fully between them and no blood is expelled by the second one. These extrasystoles become more numerous, and soon form groups of two or three, separated by other groups of ordinary contractions. The rhythm becomes more rapid and more irregular and this culminates finally in fibrillation of the auricle and ventricle (Fig. 49, *E*, p. 632).

All the features of the third stage are due to the poison increasing the spontaneous excitability of the heart muscle. This increased excitability in the pacemaker leads to acceleration of the beat of the whole heart, but larger amounts arouse the normally dormant areas in the *a–v* node and in the ventricle, and lead to impulses being discharged from them and causing contractions of abnormal origin and irregular rhythm. In the ventricle this increased excitability leads to the development of a rapid spontaneous rhythm, extrasystoles, and finally fibrillation. In the third stage the conduction from auricle to ventricle is reduced or completely destroyed, and this change differs from the impairment of the conduction seen in the earlier stages in being due to the direct action on the muscle and not to the inhibitory mechanism. In fact, in the third stage the latter is not an important factor, the increased excitability and decreased conduction both arising from the direct heart action.

Throughout the whole course of the intoxication the two ventricles beat in unison, and the two auricles also maintain the same rhythm throughout, but the rhythm of the ventricles may, as has been stated, be entirely different from that of the auricles in either the second or third stage.

Almost all the features observed in the frog's heart under digitalis may also be found in the mammal, and in addition the latter shows the effects of inhibitory stimulation which are not seen in the frog. The inhibition is the cause of the slow rhythm and block in the earlier phases of digitalis action in the healthy mammalian heart, and the direct action on the conducting fibres can be made out only in the late stages of poisoning; in the frog, on the other hand, the slowing and block arise from the direct action only. In the mammalian heart in extreme malnutrition the reaction resembles that in the frog; the rhythm

is slowed and the conduction is impaired through direct action on the cardiac muscle, for it is not prevented by atropine, which excludes all inhibitory activity.

Buckner has shown that in cats the administration of large doses of the digitalis group of glucosides is followed by definite pathological changes in the cardiac muscle. These changes, according to Bauer, may lead to death in a few days, or in the event that a second dose of digitalis is given it may lead to death, even though the amount administered is merely a fraction of the normal lethal dose, the drug having its effects accentuated by the pathological changes in the heart wall. The lesions are most severe in those animals which during life showed cardiac acceleration and arrhythmia. Using the heart-lung preparation of cats which had been injected with either small or large doses of digitalis, Weese and Dieckhoff found that such hearts would show evidence of stimulation in that the strength of the organ was improved, exhaustion delayed, and the survival time of the preparation prolonged. After large doses of the glucosides, with the evidences of heart injury appearing, there was still an increased strength of the organ but it disappeared early, although the onset of fatigue was delayed.

Vessels.—Small quantities of digitalis and its allies, such as are used in medicine, have no direct action on the blood-vessels, but larger amounts induce changes in the muscular coat which present some analogy to the changes in the heart muscle. The latter, however, is much more sensitive to the glucosides than the arterial walls, and an amount of digitalis which is capable of acting on the vessels, proves fatal to the heart in the course of a few minutes. The vascular action has thus no therapeutic importance. It may be observed by perfusing the surviving vessels with digitalis in Ringer's solution in the frog or mammal. The glucosides vary considerably in their power of contracting the vessels when thus perfused, as digitoxin is distinctly more powerful than strophanthin in contracting them. The different vessels also vary in their reaction, those of the intestinal area contracting more readily than those of the kidney, which again appear less susceptible than those of the limbs and brain; the coronary arteries of the heart appear to resemble those of the limbs in contracting when digitoxin is perfused through them, while strophanthin has less effect on their calibre; but therapeutic doses probably have no direct action on the coronaries.

The Blood-pressure.—The changes in the heart and vessels are reflected in the blood-pressure, and it is possible that an additional factor may be involved in the action of some of the glucosides on the vasomotor centre.

In man therapeutic doses of digitalis do not cause any very appreciable change in blood-pressure. In a certain number of cases the systolic pressure is raised; in others it may be lowered but in the majority of cases no change takes place. The drug, in general, tends to bring the systolic pressure back toward the normal. The action on the diastolic pressure is more uniform, as in the majority of instances it is reduced, the net result being to increase materially the pulse-pressure. In patients suffering from heart failure there may be an increased pressure associated with cyanosis, dyspnœa, and circulatory stasis, and the administration of drugs of this group is often followed by improvement in the clinical symptoms and a distinct lowering in blood-pressure. In such cases of heart failure the vasomotor centre is in a state of unusual activity because the circulation is deficient, with resulting poor oxygena-

tion of the blood and cyanosis. As digitalis strengthens the heart, thereby improving the circulation of the blood, the vasomotor centre lessens its activity, the vessels relax and the blood-pressure may be lowered.

In animals quantities of digitalis which are sufficient to affect the heart do not increase the blood-pressure appreciably. The increased efficiency of the heart in itself in the first stage would increase the arterial tension, but this appears to be compensated by a slight diminution in the tone of the vasomotor centre, which reduces the resistance in the peripheral vessels and thus permits a freer passage to the blood. In other words, an augmented efficiency of the heart must lead to a rise in blood-pressure if the vessels remain unchanged in calibre, but may lead to an accelerated flow through the tissues if the vessels relax in proportion as the output of the heart increases. Such an acceleration of the circulation has been observed repeatedly under small quantities of digitalis in animals. The reduction in the tone of the vasomotor centre is not due to the glucosides directly, but arises from the increased efficiency of the heart, which supplies a larger amount of blood to the brain and thus reduces the activity of the centre.

As long as this compensatory action persists in the vasomotor centre, the blood-pressure does not rise from the cardiac action; in man this balance between the heart and the vasomotor centre is more perfect than in the lower mammals, owing to the development of the upright posture, and in man changes in the blood-pressure are thus more carefully guarded against and no alteration is usually caused by therapeutic doses of digitalis which increase the cardiac output.

In experiments in animals, a rise in blood-pressure is generally observed under the members of this group (Fig. 49, p 632), partly because in the lower mammals the balance is less developed than in man and in addition is rendered less active by the anæsthesia, but mainly because much larger quantities are injected in order to induce a rapid effect, such as can be observed in the course of an hour. These larger doses introduce a new factor, however, in the direct action on the vessel walls, which precludes the compensatory activity of the vasomotor centre, and thus the blood-pressure rises, partly from the increased efficiency of the heart and partly from the unusual resistance to the passage of the blood out of the arteries. This appears to be the final result when digitoxin is injected. But when strophanthin, digitalin, or convallamarin is used, a further complication arises, for these have a somewhat less marked vascular action, and though the vessels of the abdominal organs are contracted in the same way as by digitoxin, those of the extremities dilate. This dilation is partly owing to the increased pressure in the interior overcoming the contraction of the walls, but is mainly to be ascribed to an imperfect compensatory action of the vasomotor centre. The general result is that the total amount of blood circulating per unit of time is increased but this increase is not uniform in the different organs. Thus both strophanthin and digitalis accelerate the flow through the lungs and through the peripheral muscles, while their effects on the abdominal organs may be to slow the current, to accelerate it, or to leave it unaltered, according to the relative degree of action on the heart and on the vessels.

It follows that in animal experiments the blood tends to accumulate on the arterial side at the expense of the venous, for more blood is pumped into the arteries and it has greater difficulty in escaping. But while under digitoxin the different regions of the body appear to be equally affected, strophanthin, digitalin, and convallamarin not only tend to accumulate the blood on the

arterial side, but divert it from the internal organs to the limbs. In man, there being no increase in the peripheral resistance, the increased efficiency of the heart must lead to an acceleration of the circulation.

When the extreme slowing of the *second stage* appears in animal experiments, the output of the heart is reduced, and the pressure in the aorta and the velocity of the blood may become subnormal (Fig. 49 *C* and *D*, p. 632). When the acceleration of the *third stage* follows, the output is again augmented and the constriction of the vessels is more developed; the blood-pressure rises again but the heart soon becomes irregular in the force of its contractions, the output varies from second to second, and the pressure in the aorta falls slowly. The blood-pressure tracing shows the irregularity of the heart more or less accurately, but must not be taken to indicate at all the real condition of that organ, as the constriction of the arterioles varies at different times. Eventually the pressure falls to zero, when the heart ceases.

In experiments on animals with large doses, the pressure in the pulmonary artery is not increased by strophanthin, but rises under digitalis, from constriction of the vessels similar to that seen in the systemic circulation. The action on the right heart is similar to that on the left in all particulars.

Action on the Renal Secretion.—When digitalis was first introduced to the notice of the medical profession by Withering, its action on the heart was not appreciated. Withering used it only to remove accumulations of fluid from the body, which it accomplished by increasing the secretion of urine. This observation of Withering was soon confirmed by further experience in the use of this drug, but it was long disputed whether this diuretic action occurred in health, or whether it was not confined to cases in which pathological accumulation of fluid were present. Digitalis, however, as is now conceded by almost everyone, causes some increase in the quantity of urine secreted by the normal animal, although this is small compared with that in cases of dropsy. The fluid of the urine is more largely augmented than the solids, though the chlorides and uric acid are both increased in the urine and as a consequence decreased in the blood. The increase in the urine arises not from a direct action on the kidney, such as is met with under caffeine, but only indirectly through the changes in the circulation; the kidney shares in the general improvement in the circulation and functions more vigorously. At the same time the general circulatory changes promote the interchange of blood and lymph, and any accumulation of fluid in the body tends to be reabsorbed into the blood-vessels and then to be got rid of through the kidneys. The diuretic action of digitalis is therefore secondary to the improved blood flow and is a result of the changes in the heart alone.[1]

The Changes in the Circulation in Man have been followed only imperfectly, owing to the manifest difficulties of estimating the strength and efficiency of the heart contractions. Recently the action of digitalis upon the extent of contraction of the human heart has been definitely shown by means of moving roentgen-ray pictures. In patients with

[1] An attempt has been made to explain the diuresis by action on the vessels, it is stated that small doses in animals constrict the vessels of the kidney less than those of the intestine and thus divert more blood to the kidney, while larger ones contract the renal vessels also; but while this may be true in some experiments, diuresis occurs in both animals and man from doses that have no effect on the vessels, and, in fact, quantities sufficient to constrict the vessels are rapidly fatal to the heart.

auricular fibrillation as well as in those with a normal rhythm a distinct increase in the extent of the left ventricular excursion was shown. In many cases no definite alteration in the rhythm follows digitalis treatment even when it is pushed until nausea and vomiting occur. In others, the pulse is distinctly slower, stronger and fuller than before the administration of the drug. It must be added that the strength of the pulse is not to be regarded as a gauge of the changes in the cardiac muscle, for it is due not only to the increased strength of the cardiac contraction, but also to the slow rhythm. When the heart is beating rapidly, the arteries have no time to empty themselves completely and the pulse is small, while on the other hand, when digitalis slows the heart, the arteries have time to empty their contents into the capillaries before the next contraction occurs, the walls therefore become more flaccid, and a new wave of blood causes a more distinct impulse. In some cases the pulse remains unchanged in rate but there may be other evidences of the action of the drug, such as an increase in the secretion

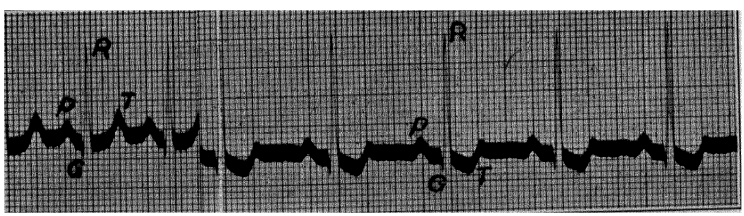

FIG. 50.—Electrocardiograms (Lead II) taken from the same patient before and after digitalis had been given. The first curve is a normal electrocardiogram with a heart rate of 94 per minute and a *P–R* interval of 0.16 second. The second curve shows characteristic digitalis inversion of the *T*-waves. The ventricular rate is 77 per minute and the *P–R* interval is at the upper limit of normal, measuring 0.2 second. The increase in the *P–R* interval is probably due to digitalis. Time lines represent fifths and twenty-fifths of a second.

of urine or relief of dropsy or of dyspnœa. In fever and after hæmorrhage the pulse is especially liable not to show any slowing after digitalis. Electrocardiographic records show that in most cases the pause between the auricular and ventricular contractions is lengthened, indicating that the conduction is impaired, and modification of the *T*-wave has also been described (Fig. 50).

In a series of very carefully controlled investigations Stewart and Cohn have shown that in normal individuals an effective dose of digitalis decreases the output of blood from the heart and at the same time decreases the size of the heart. Changes in the *T*-wave curve were apparent in two and a half hours after the drug had been taken by mouth while the output and area changes began to appear in four hours, reaching their maximum within twenty-four hours. Changes in arterial or venous pressure were not marked. Following the maximum effects of the drug gradual recovery took place but the duration of action varied widely in different individuals, in some cases return to normal

being a matter of a few days while in others normal output and cardiac area were not restored for weeks.

During this period, when the cardiac output is from 65 to 80 per cent of normal, the patient is often conscious that the heart is beating forcefully and there is dyspnœa on exertion and some cardiac pain, probably due to anoxemia of the cardiac muscle from interference with the coronary blood flow.

In patients with cardiac failure, either when the cardiac mechanism is normal or when auricular fibrillation is present, the cardiac output is low, and, as is well known, the cardiac area is increased and the venous pressure is high. In such cases adequate doses of digitalis will increase the output, lessen the cardiac area, and lower the venous pressure. Slowing of the ventricular rate also occurs.

The great point of difference between the effect of digitalis in the normal individual and the one with cardiac failure is that in the former the cardiac output is markedly lessened by digitalis while in the cardiac case it may be greatly increased, the area in either case being decreased. The explanation of this apparent contradiction is doubtless to be found in the fact that under normal conditions the heart size is probably at an optimum for the performance of its work as a pump. Digitalis decreases its size, as shown by a change in the surface area to three-quarters or four-fifths normal, and to that extent lessens its efficiency and therefore its output.

In the enlarged heart of incompensation, however, the cavities are dilated, but the contractile power in the wall of the heart is inadequate and the output is correspondingly low. Under digitalis the size of the cavities is lessened, but not to a degree less than normal, and in this state they are able to eject larger quantities of blood. Whether the decrease in size of the cavities *per se* facilitates the expulsion of blood and is responsible for the improvement in output, or whether a change in the contractile capability of the heart wall is the essential factor, is unknown. Possibly both play a part. The action of strophanthus injected intravenously has been shown to be essentially like that of digitalis except that the action is much more rapid than it is with digitalis given by mouth. In some cases of severe decompensation, a few minutes only were sufficient to increase markedly the cardiac output and the systolic output.

Cattell and Gold demonstrated, by means of the isolated papillary muscle of the cat undergoing stimulation at a uniform rate, that digitalis exerts a direct action upon cardiac muscle, increasing the force of its contractions. This change being produced in the isolated muscle where coronary circulatory changes and alterations in heart rate are absent shows that these latter factors are not necessary to account for the beneficial effects of the drug upon the action of the heart.

The use of digitalis sometimes gives rise to irregularities, and the character of these has received a good deal of attention of late years. The first form arises from the muscular action, which may increase the excitability of the ventricle or auricle so much that spontaneous beats (extrasystoles) arise. When these occur the heart should be carefully

watched and the dose should be reduced (Fig. 51). Other forms arise from the stimulation of the inhibitory mechanism, which, as has been stated, occurs in a certain proportion of patients and which may become very marked. This vagus stimulation merely slows the heart in the milder forms, the beats remaining regular. Or the slowing which occurs in normal people in correspondence with the breathing may be exag-

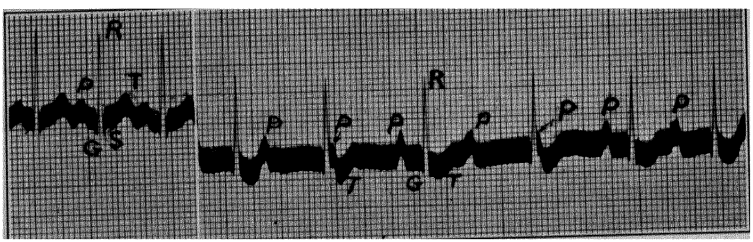

FIG. 51.—Electrocardiograms (Lead II). These tracings are both taken from a boy with rheumatic heart disease. The first curve is not abnormal except for a sinus tachycardia, the heart rate being 136 per minute. The second curve shows the effects of overdigitalization. Partial *A–V* heart block with frequent dropped beats and ventricular escapes is seen, and the *T*-waves show marked inversion. Time lines represent fifths and twenty-fifths of a second.

gerated, and the slow, powerful contractions cause an unpleasant sensation in the chest. This occurs when the vagus is strongly stimulated from any cause and is not peculiar to digitalis. When this form of irregularity sets in, the dose should be reduced or the drug omitted altogether for a few days. Not infrequently, a less obvious vagus effect causes irregularity under digitalis; the passage of impulses from the

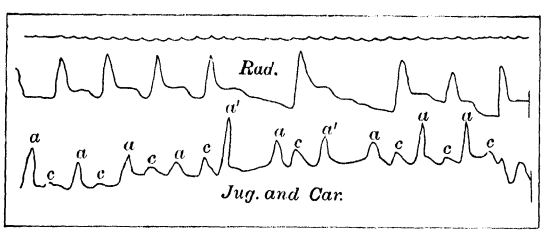

FIG. 52.—Tracings from the radial artery and the jugular vein in a case of heart disease treated with digitalis in large doses. The waves *a*, *a'* on the jugular tracing indicate the auricular contractions and are seen to be perfectly regular in rhythm throughout; the auricle is, therefore, beating regularly. The radial pulse intermits at intervals, showing that the ventricle has not responded to the impulses which in the auricle gave rise to the contractions indicated by *a'*. (Mackenzie.)

auricle to the ventricle is retarded or entirely arrested, from the conduction through the connecting fibres being reduced. Before the treatment the fibres were able to conduct all the impulses from the auricle to the ventricle. But now an occasional impulse fails to pass, or perhaps only one of two impulses passes to the ventricle. When an impulse fails to reach it, the ventricle remains in diastole (dropped beat)

(Fig. 52), and when only one-half of the impulses pass to it, the rhythm of the ventricle is only half that of the auricle (half-rhythm) (Fig. 53). Or the block may be complete, no impulses passing through the fibres at all, and in this case the ventricle takes up its own spontaneous rhythm (heart-block) (Fig. 54). Another form of block may occur between the sinus and the auricle (sino-auricular block), and both

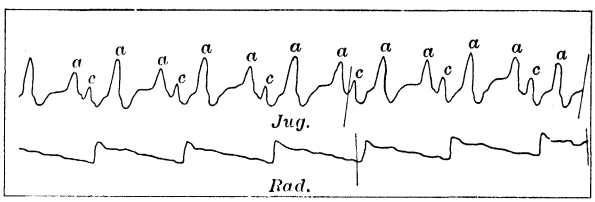

FIG. 53.—Slowing of the pulse due to digitalis depressing conductivity, so that the ventricle fails to respond to every second stimulus from the auricle. While the ventricle contracted forty-eight times per minute, the auricle contracted ninety-six times. (Mackenzie.)

auricle and ventricle now intermit a contraction at variable intervals. In all these forms digitalis interferes with the passage of impulses from the auricle to the ventricle, or from the sinus to the auricle, by stimulating the inhibitory mechanism, which lessens the conductivity of the connecting fibres. The irregularity therefore disappears under atropine, which paralyzes the inhibitory mechanism. In rarer cases, however, the digitalis heart-block does not arise from the inhibitory stimulation,

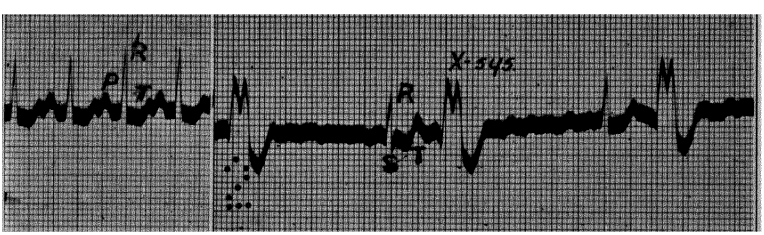

FIG. 54.—Electrocardiograms (Lead II). The first curve was taken from a patient with resolving pneumonia and shows sinus tachycardia, with a rate of approximately 135 per minute, and partial inversion of the *T*-waves. Because of the tachycardia the *P* and *T*-deflections are partially superimposed. The second curve was taken from the same patient after auricular fibrillation had developed and too much digitalis had been given. The ventricular rate is very slow and nearly regular, suggesting complete *A–V* dissociation. Each ventricular beat is followed by a ventricular extrasystole, causing bigeminy. Time lines represent fifths and twenty-fifths of a second.

but from direct action on the conducting fibres, and this form of block, which may be sino-auricular or auriculo-ventricular, is not relieved by atropine. The inhibitory block under digitalis is similar to that seen in experiments on mammals in the second stage, while the rarer block from direct action is the same as that seen in the frog, in the ill-nourished mammalian heart, and in the human heart in auricular fibrillation.

When heart-block occurs under digitalis, the treatment should be abandoned or the dose reduced. Slight slowing in non-fibrillating cases does not indicate a change of treatment (Fig. 50). Another form of irregularity which sometimes appears under digitalis is known as *pulsus alternans*, and is marked by an alternation of strong and weak beats of the radial pulse. This generally indicates impaired contractility of the ventricular wall, and its occurrence under digitalis has not as yet received adequate explanation.

In fever the **Temperature** is not infrequently reduced, although it remains unchanged after the administration of digitalis to the normal animal. This action is said by some to be the result of collapse, while others believe it to be due to the changes in the circulation, but neither of these seems to be a very happy explanation. It has been stated already that the members of this series act as stimulants to some parts of the central nervous system, and a possible explanation of their antipyretic action would be an increased activity of the temperature-controlling centres. It has been shown by Harnack that several central

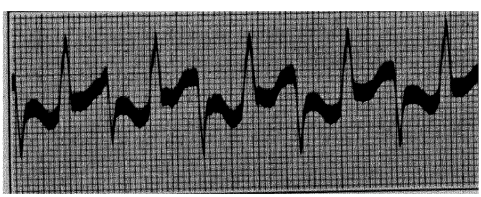

FIG. 55.—Electrocardiogram (Lead II) taken from a patient having auricular fibrillation and high grade digitalis intoxication. The curve shows a ventricular tachycardia with a rate of 168 per minute. The alternation in the type of complexes indicates that the ventricular beats are arising alternately from two different foci in the ventricles. The prognosis is very bad when this type of tachycardia appears. Time lines represent fifths and twenty-fifths of a second.

nervous stimulants, including picrotoxin, cause a fall in the temperature in this way.

Absorption and Distribution.—The glucosides of this series are peculiarly susceptible to destruction in the alimentary tract, and there is no doubt that a part of those taken by the mouth is rendered inert in the stomach and bowel. After a dose of digitalis leaves, the glucosides may be found in the stomach and upper part of small intestine, but none reach the large bowel unchanged. In addition, the absorption is very slow from the alimentary tract for most of the members of the group, and this is especially true for strophanthus. Digitoxin and the tincture of digitalis seem to form an exception to the rule, as they are absorbed quite rapidly. It has been shown that, when full therapeutic doses of the tincture are given by mouth, an effect, demonstrated by a change in the *T*-wave, will be obtained in almost all patients in from three to four hours and a maximum effect in from six to seven hours and the same is maintained for at least twenty-four hours.

Digitalis is slowly destroyed and eliminated, the rate for this destruction having been calculated to be equivalent to about 20 minims of an

average strength tincture in twenty-four hours. This fact is of great clinical interest and importance because, after a patient has been digitalized satisfactorily, it is only necessary to give such an amount of the drug as will replace the amount destroyed or excreted. Naturally there are individual variations, as some patients destroy the drug more slowly, and others more rapidly, than the figure mentioned.

On hypodermic injection, the glucosides cause marked local irritation, and a considerable proportion also seems to undergo decomposition, for much larger quantities are required to induce changes in the heart than are necessary by intravenous injection. After the ingestion of large amounts, some glucoside is said to have been found in the liver, but none is detected in the heart or other organs, and the blood seems to be free from it soon afterward. Some of the principles have been found in the urine and fæces, so both kidney and gut share in the excretion.

Several workers have presented evidence in support of the view that digitalis bodies may be present in the excessive body fluids of œdematous patients. It has been noted that digitalized persons who are given also the organic mercurial diuretics with resulting active diuresis frequently display symptoms suggestive of digitalis poisoning. The explanation given is that the mobilization of the œdematous fluid in its passage to the kidneys subjects the heart to sufficient additional digitalis to produce the symptoms of poisoning (Schnitker and Levine).

After they reach the blood, the action of the bodies of this series is very prolonged, the heart only regaining its ordinary rate several days after the drug has been stopped. If the dose be repeated, the action therefore becomes more and more marked (cumulative action) as the glucoside increases in concentration, and a dose which improves the condition at first may, if continued, lead to poisoning. The different glucosides differ in the duration of their action; thus Hatcher estimates that seven-eighths of the strophanthin in the tissues is eliminated within twenty-four hours, while one-half the principles of digitalis remain active after four days.

Straub has pointed out that the action of strophanthin on the frog's heart is determined by the concentration in which it is applied and not by the total amount of the glucoside supplied; for example, if 10 drops of a solution circulating through the excised heart are insufficient to bring it to a standstill, 100 drops of the same solution will have no more effect, though 10 drops of a solution of double the strength will arrest it. From this he deduces that strophanthin is not taken up by the muscle by any selective action, but only penetrates the cells in the concentration of the solutions; and in confirmation of this, neither Straub nor others have been able to find the glucoside in the heart muscle, while the fluid remaining in the cavity has lost hardly any of its toxic action if applied to a second heart. From the minimal amount of strophanthin which is necessary for action on the heart Straub draws the conclusion that strophanthin acts by changing the membrane of the heart cells, but this cannot be accepted as established. Some others of the series have been found to be taken up in larger quantity by the heart.

By a comparison of the amount of the glucosides which poison the

isolated perfused heart of a cat, as compared with the amount fatal to the intact animal, it was found that sixteen times as much digitoxin, eleven times as much strophanthin and twenty-two times as much scillaren were necessary in the intact animal as in the isolated heart. The question naturally arises as to what organs other than the heart are taking up the glucosides when they are injected into the intact animal. Apparently the lungs cannot take up any of the poison; but the skeletal muscles, while gram for gram they take up only one-fourteenth as much digitoxin as the heart, yet on account of their greater total bulk the amount they will take up is much greater. In the same way, liver was found to take up one-fifth as much glucoside, gram for gram, as the heart; and the kidney, one-half as much. Thus extracardiac tissues consume about fourteen times as much digitoxin as does the heart and twelve times as much ouabain; at the same time, they have no use for it.

Straub has also pointed out that when digitoxin is applied directly to the excised frog's heart it shows no effect for several minutes, there being a long period of incubation. However, after the final effect has once set in, he believed it could not be washed out, as he considered that the reaction of the glucoside and heart muscle was irreversible. More recent investigations by Kingisepp, however, have shown that not only the systolic standstill produced by the other glucosides of the group, but also that produced by digitoxin can be removed by repeated washings with Ringer's solution, and the heart-rate restored to normal. The process, therefore, is not an irreversible one. Straub considers also that the binding of the glucoside to the heart muscle is due to the formation of a cholesteride due to the presence of cholesterol in the muscle and that the essential binding of the glucoside is accomplished in sixty seconds. This is shown by the fact that if the poison is removed at the end of this time and is replaced by Ringer's solution the heart changes continue to the end as if the poison were still present. The other glucosides of this group differ quantitatively from digitoxin in regard to reversibility, as strophanthin, while requiring a longer time for anchorage, may also be washed out, even in the stage of advanced poisoning. Scillaren A from squills is probably most easily reversible.

Tolerance.—Some species of animals tolerate much larger quantities of the digitalis bodies than others. For example, the snake and toad are not poisoned by amounts which would be fatal to the frog. This arises from the tissues of these tolerant animals not being susceptible to the poisons, and not from any difficulty in absorption or rapidity of excretion; for the isolated hearts in these animals show the same refractory behavior as the intact animal. Among the mammals, the rat's heart has been shown to be much less susceptible to the action of these bodies than the rabbit's. Tolerance has not been shown to be acquired for digitalis and its allies through their prolonged use.

The digitalis bodies weaken and eventually paralyze the **Muscles** and the terminations of the peripheral nerves of the frog. For this purpose it has to be applied in quantities which would at once stop the mammalian heart, and this action certainly never even commences in warm-blooded animals. Large quantities of digitalis act on the unstriated muscle of several organs, such as the stomach and uterus, and increase their movements, and this certainly occurs in excised organs exposed to solutions of the glucosides.

Therapeutic Uses.—Digitalis has long been the sheet-anchor in treatment of diseases of the heart, but little was done to elucidate its clinical action until the early part of this century. Much still remains to be investigated, but it has at least been determined that it is much more efficacious in certain forms of cardiac impairment than in others. Its most remarkable therapeutic effects are seen in cases of **Auricular fibrillation,** for which it may be said to be a specific comparable to quinine in malaria. In auricular fibrillation, the auricular muscle is the seat of so-called circus contractions which keep that chamber in continuous incoördinate activity which prevents its emptying its contents into the ventricle. The multitudinous impulses generated in the auricles descend irregularly to the ventricle, which responds with a rapid beat varying not only in rhythm but also in strength; many of the contractions are too weak to expel any blood into the aorta, while others cause large pulses, and these are intermixed in the most confused fashion; the pulse is thus extremely irregular (Fig. 56). This irregular heart is quite compatible with moderate health for long periods, but sooner or later

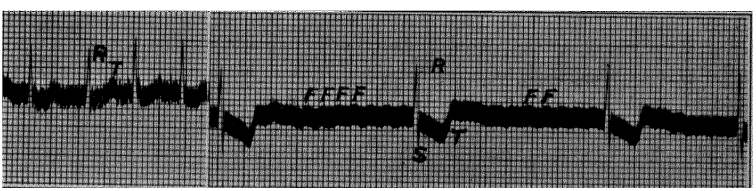

FIG. 56.—Electrocardiogram (Lead II). Both of these tracings are taken from a patient with auricular fibrillation. The first curve taken before digitalis therapy was started shows rapid irregular ventricular responses with an average rate of 165 per minute. The *T*-waves are upright. The second curve taken after the patient was completely digitalized shows the slow regular ventricular responses at an average rate of 56 per minute and marked *T*-wave inversion. The fibrillation waves (marked *f*) are clearly seen. Time lines represent fifths and twenty-fifths of a second.

the signs of failing circulation appear, the pulse becomes alarmingly rapid, and a dangerous condition develops quickly. If digitalis is now exhibited in full doses, these symptoms of heart failure abate rapidly, improvement beginning after six to twenty-four hours, according to the method of administration. If strophanthin ($\frac{1}{130}$ gr.) is injected intravenously, the improvement begins within two hours and is marked in eight to twelve hours. In each case the pulse falls in rate and this slowing proceeds in proportion to the general improvement and may be taken as a measure of it. The heart may be slowed from 130–150 per minute to 50–60 in the course of a few hours, and at the same time the beats become stronger and more equal in size and in time (Fig. 56). The auricles continue to fibrillate after the pulse is slowed, but the ventricle responds to fewer of the impulses emitted by the auricle, because fewer of them reach the ventricle, through digitalis lessening the conductivity through the bundle of His.

The slowing of the pulse in auricular fibrillation does not arise from inhibitory action, for it is not prevented by atropine; in fact, when a patient is under digitalis and the pulse is slowed, the inhibitory mechan-

ism is less active than before treatment when the pulse was rapid; this is shown by the fact that paralysis of the inhibition by atropine does not accelerate the heart so much under digitalis in these cases as it did before treatment was begun. The specific effect of digitalis and its allies in auricular fibrillation must, therefore, arise from the direct action of the drug on the cardiac muscle.[1] Auricular fibrillation can be induced experimentally in animals by electrical stimulation of the auricle, and when this is done in a healthy heart the digitalis action on muscle does not render the ventricular beat slow and regular as it does in auricular fibrillation in man. But if this condition is induced in a perfused, badly nourished heart, digitalis slows the ventricle and makes it regular exactly as in clinical cases. The therapeutic action of digitalis in auricular fibrillation is thus due to the specific muscular action on conduction, which is seen typically in the frog and in the mammalian heart in malnutrition (p. 634). When clinical auricular fibrillation is not attended by grave malnutrition, digitalis does not slow the pulse materially, while in some conditions in which the heart is feeble but no fibrillation is present, slowing is induced. The special action in auricular fibrillation thus arises from the extreme malnutrition of the heart which often occurs in this condition. The blood-pressure cannot be accurately estimated in auricular fibrillation, owing to the irregularity of the pulse, and it is therefore unknown whether it is altered under treatment; Stewart found the rate of the blood flow through the hand distinctly increased in these cases when treated with digitalis, that is, the condition of the heart and its output both improved while the pulse-rate fell.

Not infrequently in this condition the dose has to be very large, and if it be continued the patient suffers from nausea and vomiting. Or the pulse may fall to from 50 to 100 per minute (Fig. 56) and become regular; the ventricle now responds no longer to impulses from the auricle, but has developed its own spontaneous regular rhythm. More frequently the heart develops the bigeminus form shown in Fig. 54, in which each full beat is followed very quickly by a secondary one; here the large contractions arise from auricular impulses, but the excitability of the ventricle has risen to a point at which it also discharges impulses, and this coupled rhythm is the result. These are all indications that the drug has been pushed too far, and they all disappear when the dose is reduced.

In some cases of auricular fibrillation in which the heart is not much accelerated, digitalis has no such striking effect, even though improvement occurs under it. Even when digitalis relieves the symptoms of heart failure in auricular fibrillation, it does not arrest the underlying process and the auricle continues to beat in its previous irregular way. Digitalis prevents the ventricle from being exhausted, by limiting the number of impulses which descend from the auricle. On the other hand, the quinine alkaloids have been shown to arrest the irregular beating of the auricle and to restore it to a condition of sanity (p. 727).

[1] *Wedd* (Johns Hopkins Hosp. Bull., **30**, 131, 1919) says that the cardio-inhibitory centre is also involved in the slowing of the heart which occurs in auricular fibrillation.

Another condition in which digitalis treatment is equally successful is **Auricular flutter,** in which the auricle is again the seat of abnormal excitation and beats at a very high rate, but quite regularly. The ventricle is also regular though very rapid and responds to only half of the impulses descending from the auricle; the rapid rhythm of the ventricle tends to exhaust it and calls for treatment. Digitalis given in full doses changes the regular flutter to fibrillation and at the same time reduces the conductivity of the His bundle, so that the beat of the ventricle becomes very slow, sometimes only 30–40 beats a minute. Upon stopping the treatment, both flutter and fibrillation are found to have ceased and the heart beats in normal rhythm. The explanation seems to be that digitalis, either through its vagus or its muscular action, further excites the auricle and changes the flutter to fibrillation; but fibrillation of recent development tends to revert to normal rhythm and when the digitalis action passes off, the flutter does not return, but the normal pacemaker resumes its sway. The treatment of flutter with digitalis not only abates the symptoms but actually cures the condition from which they arise, thus contrasting with the results obtained from it in fibrillation and resembling those following the use of quinidine (p. 727).

In **Other Forms of Heart Disease** the effects of digitalis are less spectacular and although improvement undoubtedly results from the treatment, there is no such guide as is offered by the slowing of the pulse in fibrillation. It is therefore not always easy to determine how far the improvement is to be attributed to the digitalis and how far to such auxiliaries as rest and general treatment. Such measurable symptoms as dropsy are often presented, however, and the fall in weight from diuresis under digitalis is as significant evidence as the fall in pulse-rate in fibrillation. Few accurate observations are as yet available except in auricular fibrillation, but they suffice to show that the beneficial action of digitalis is not confined to this special form of heart disease. In general terms it may be said that improvement is seen in a large number of conditions in which the efficiency of the heart is impaired and the blood is no longer pumped from the venous reservoirs to the arteries in adequate amount. The deficient circulation no longer suffices to maintain the nutrition of the tissues, including the heart, and dilatation of the heart chambers, congestion of the lungs, œdema and dropsy follow; the kidneys and other organs become overfilled with venous blood and the whole economy is thrown into disorder. The treatment obviously comprises rest to relieve the strained organs, along with some member of this series to increase the strength of the contractions of the heart and thus to compensate for the disorders which are the primary cause of the condition. Under digitalis such improvement occurs; the congestion disappears, the kidneys secrete more rapidly and drain off the accumulations of fluid in the tissues and cavities of the body. The heart itself is better nourished through the acceleration of the blood-stream, and is now able to meet the strain thrown upon it by such damage as destruction of the valves. The only action of the drug which seems to be necessary for this purpose is its power to increase the strength of the contraction; how far the contractions are actually

strengthened in these cases is exceedingly difficult to determine (see page 631).

The beneficial action of digitalis is generally stated to be more obvious in disease of the mitral than in that of the aortic valves. This view may have arisen from the fact that auricular fibrillation is often accompanied by mitral disease. In some cases of aortic valve failure digitalis appears to be of value, but there seems some reason to doubt whether it is as often efficacious as in mitral disease, even when the fibrillation cases are excluded.

In experimental lesions of the aortic valves in animals, digitalis is found to improve the efficiency of the heart and a smaller mortality occurs in animals under treatment than in the controls.

On the right side of the heart the same action occurs as on the left, and in dilatation of the right heart, such as occurs in some pulmonary diseases, digitalis and its allies are beneficial, apparently by increasing the strength of the ventricular contraction.

In the majority of these non-fibrillating cases the pulse is not slowed more than can be accounted for by the rest and general treatment. In a certain proportion, however, distinct slowing is observed as the heart comes under the influence of the drug, or the pause between the contractions of the auricle and ventricle is lengthened; and, as this generally disappears under atropine, it is obviously inhibitory in character in most cases and thus different from the slowing seen under digitalis in auricular fibrillation. The *T*-wave in the electrocardiogram also shows alterations from direct action on the heart muscle.

As regards the irregularities in these non-fibrillating cases, there is no reason to believe that digitalis has any direct action on them, though they may disappear in the course of treatment as the result of the improved nutrition of the heart.

In numerous **Acute Febrile Conditions** the heart becomes affected, possibly in part by the high temperature, but largely from the toxic products circulating in the blood. The chief cardiac symptoms are dilatation with a weak systole and a small "fluttering" pulse. In these cases digitalis and other similar drugs may at times be of service in slowing the accelerated heart and in increasing the extent of systole, and thus improving the general circulation. In *pneumonia* more especially, improvement is sometimes seen after digitalis. In this disease, besides the toxic action on the heart, there may be present more or less obstruction of the pulmonary vessels, resulting in overwork and dilatation of the right heart. The routine treatment of pneumonia with digitalis is often recommended, but is to be deprecated on the general principle that a drug is not to be prescribed until some special indication for it appears; unless distinct evidence of circulatory disturbance is present, digitalis ought to be withheld. As a matter of fact, a study of a large series of cases of pneumonia which had been treated with digitalis, as compared with an equally large group not given this drug, yielded a mortality percentage in favor of the non-digitalized patients. In *diphtheria* the use of digitalis appears to be contraindicated as the drug is unusually toxic in this condition, due apparently to the changes in the

heart muscle produced by the toxin. In any case, if it is to be employed it should be given very carefully.

In acute fevers the inhibitory mechanism is often less irritable than normally, and the activity of the drug must not be estimated by the slowness of the pulse.

In some affections of the heart, such as very extensive fibrous or fatty degeneration, digitalis often is of little or no service, and some authorities deprecate its use, chiefly on the erroneous view that it may raise the blood-pressure and increase the resistance against which the heart has to work. In the light of recent work this argument falls to the ground and the general view may be stated that while digitalis may fail to improve these cases, it has no deleterious effect on them. In other cases, while the condition of the heart is eminently suitable for digitalis treatment, disease of other parts of the body, such as extensive arterial degeneration, is said to preclude its use on account of the danger of rupture of the arterial walls. And many substitute strophanthus for it in these cases in the belief that there is then less risk of the blood-pressure rising to a dangerous height. But as a matter of fact there is no reason to anticipate any extensive rise of blood-pressure under either digitalis or strophanthus, and the apprehension is thus groundless. The same may be said of the supposed danger of digitalis in the high blood-pressure of renal and arterial disease. A high blood-pressure ought not to be regarded as definitely contraindicating the use of digitalis or its allies, for excellent results often follow its exhibition in these cases, provided the special indications for digitalis are presented, in venous stasis, œdema, or deficient urine. In these cases the high pressure presumably arises from excessive activity of the vaso-constrictor centre inducing mesenteric constriction in an attempt to maintain the blood supply to the brain; this involves an abnormal resistance to the circulation and imperfect nutrition of various organs. Digitalis, by increasing the efficiency of the heart, improves the circulation through the lungs and the blood supply of the brain, and the activity of the vaso-constrictor centre is abated, leading to a more normal state of the circulation and often to a lower arterial tension.

Recently there has been a tendency to revert to the use of digitalis in certain cardiac conditions other than those in which signs of decompensation are evident. Such patients are diagnosed as suffering from *chronic myocarditis* or chronic myocardial insufficiency. In these cases with an increased demand upon the heart it is likely to respond by dilatation followed by hypertrophy of the wall. With the hypertrophy the cavities are likely to enlarge still more with stretching of the muscle and still further hypertrophy follows. A limit to the degree of hypertrophy is finally reached and signs of cardiac insufficiency may become evident. The early administration of digitalis in these cases of myocarditis before any signs of insufficiency have developed is believed to delay the progress of such changes by retarding the cardiac enlargement and resulting hypertrophy. Such patients should probably take the drug in small doses for the remainder of their lives.

In the case of experimental cardiac lesions in dogs digitalis apparently exerts an inhibiting influence upon hypertrophy of the heart (Schwab and Herrmann).

Valvular disease is not in itself an indication for digitalis, for the heart tends to undergo compensatory hypertrophy in favorable conditions without the use of any drug whatever, and digitalis is indicated only when no such compensation occurs. At the same time hypertrophy of the heart is not a contraindication, as is often stated, for a special strain may cause excessive dilatation in a hypertrophied heart, and digitalis may be necessary until a second hypertrophy has occurred and restored the equilibrium once more.

The diuretic action of digitalis is not advised except where other indications than a diminution of the renal secretion are present, for in ordinary cases it has much less effect than the caffeine group of diuretics. If the anuria be secondary to disturbances of the circulation, however, digitalis is the diuretic par excellence and cannot be replaced by any of the ordinary means of promoting the urinary secretion, although they may advantageously be combined with it. Digitalis and a diuretic of the caffeine or mercurial group are often prescribed together where large accumulations of fluid have to be removed.

Several of these drugs are of considerable benefit in pulmonary diseases accompanied by cough. Thus in bronchitis, more especially in cases of old standing, the addition of squills to an "expectorant mixture" is often followed by the most satisfactory results. The action here is probably twofold. In the first place, the right heart may be dilated owing to the frequent strain put on it by coughing, and squills remedies this condition by its usual cardiac action. In the second place, all these drugs possess emetic properties to a certain extent, and thus cause an increase in the bronchial secretion, and render the sputum less tenacious and more easily expectorated. The addition of squills has the same effect as the prescription of ipecacuanha, along with the further action on the heart.

Cumulative Action.—Digitalis is often given in insufficient amount from a dread that it may cause serious results through its cumulative action. This apprehension does not seem to exist so much in regard to strophanthus and squills, though these also induce cumulative effects when they are given in sufficient doses. As a general rule no effects are noted for one or two days after the exhibition of drugs of this series in moderate doses. Improvement then begins if the case is suitable and the dose adequate, and steady progress may be made for some time. Then the symptoms of excessive action may set in suddenly—the pulse becomes alarmingly slow and irregular, the patient complains of weakness and faintness, nausea, and occasionally vomiting. This is known as the cumulative action, and is due to the slowness with which the drug is excreted or destroyed. The absorption of the drug given by the mouth is relatively slow, but it is held in the tissues in some form of combination and thus the concentration tends to increase with each successive dose; this slow elimination is shown by the action continuing for several days after the treatment has been discontinued. As the drug accumulates in the tissues the beneficial action is slowly developed, but if the treatment is continued, a higher concentration is reached

and finally becomes equal to that induced by a single poisonous dose and the corresponding symptoms follow. The fear of this condition is much exaggerated, for the symptoms disappear in a day or two if the drug is omitted. And they may generally be avoided altogether if a close watch is kept on the pulse, and the dose is reduced as soon as it becomes slow, or at the first appearance of headache, nausea, or loss of appetite. All of the digitalis series hitherto examined prove to be cumulative in their action, but some of them, notably digitoxin, are more dangerous than others. In fact, according to Fraenkel, digitoxin can only be used safely in doses which induce no changes in the pulse for several days, for if the pulse be slowed by a single dose, its repetition within twenty-four hours induces severe poisoning. Weese showed that it is the digitoxin itself which is bound by the heart muscle that is responsible for the cumulative effects. By estimating the supplemental amounts of digitoxin necessary to poison a cat's heart subsequent to the cat having received fractional doses of the glucoside he showed that the heart can only destroy between 3 and 4 per cent of the glucoside daily. There is thus a certain percentage of the toxic dose bound to the heart for about a month, thus giving the opportunity for symptoms due to the accumulation of the digitoxin in the organ. On the other hand, that portion of the glucoside which is bound in the liver and in the muscles, and which is slowly freed in the form of the genins, is easily destroyed or excreted and plays no part in the cumulative effect of the drug.

As pointed out, the union of glucoside and heart muscle is a remarkably firm one, remnants of digitoxin being still present in the heart after three weeks. Weese also found that in the heart-lung preparation the genin of digitoxin was about as active as the glucoside itself, but in contrast to the glucoside it is entirely reversible, being capable of being completely washed out, with recovery of the heart. Straub believes, therefore, that it is the sugar portion of the molecule which gives the glucoside its special affinity for the heart muscle. At the same time it is the weak point in the molecule and the point which is probably first attacked, leaving the genin, which has now lost its affinity for the heart muscle and can be disposed of and recovery of the heart can take place. The symptoms of cumulative action under digitalis, strophanthus, and squills are very similar. There is perhaps more tendency to diarrhœa under the last two than under digitalis.

Preparations

U. S. P.

Digitalis, Digitalis Pulverata, 0.1 G. (1½ grs.).
Tinctura Digitalis, 1 cc. (15 mins.).
Strophanthinum, glucosides obtained from Kombé strophanthus. 0.0005 G. (1/120 gr.).
Scilla, squills. 0.1 G. (1½ grs.).
Acetum Scillæ, vinegar of squill. 1 cc. (15 mins.).
Syrupus Scillæ, 2 cc. (30 mins.).
Tinctura Scillæ, 1 cc. (15 mins.).

Non-official Preparations.

Infusum Digitalis, 1½ per cent. 6 cc. (1½ fl. drs.).
Strophanthus, 0.06 G. (1 gr.).
Tinctura Strophanthi, 0.5 cc. (8 mins.).
Fluidextractum Scillæ, 0.1 cc. (1½ mins.).
Syrupus Scillæ Compositus, 2 cc. (30 mins.).

B. P.

Digitalis Folium.
Digitalis Pulverata, powdered digitalis leaf. 0.03-0.1 G. (½–1½ grs.).
Infusum Digitalis Recens, infusion of digitalis. 6-20 mils. (90–300 mins.).
Tinctura Digitalis, 10 per cent digitalis in 70 per cent alcohol. 0.3–1 mil. (5–15 mins.).
Strophanthus.
Tinctura Strophanthi, 0.12–0.3 mil. (2–5 mins.).
Strophanthinum, Kombé strophanthin. 0.00025-0.001 G. ($\frac{1}{240}$ - $\frac{1}{60}$ gr.).
Scilla, 0.06–0.2 G. (1–3 grs.).
Acetum Scillæ, vinegar of squill. 0.6–2 mils. (10-30 mins.).
Syrupus Scillæ, 2–4 mils. (30–60 mins.).
Oxymel Scillæ, oxymel of squill. 2–4 mils. (30–60 mins.). Made with acetic acid and purified honey.
Tinctura Scillæ, 0.3–2 mils. (5-30 mins.).

Digitalis, Digitalis Folium, foxglove, the leaves of Digitalis purpurea. The Pharmacopœias allow leaves of first year plants to be used.

Both pharmacopœias include also a standardized powdered leaf prepared for internal administration or suitable for the preparation of the infusion.

Digitaline of commerce varies much in composition and in dose, sometimes proving entirely inert while at other times it has proved poisonous in comparatively small quantities. Crystalline digitaline very often consists largely of digitonin, which is quite devoid of the digitalis action. Other preparations seem to contain much digitoxin. Digitoxin has been prescribed in doses of $\frac{1}{12}$ mg. ($\frac{1}{120}$ gr.), but the forms at present on the market vary greatly in strength. Digalen is a solution of the active principles of digitalis as isolated by Cloetta. It is standardized by the intravenous cat method of assay. Dose, 1 cc. or 15 mins. Digitan, introduced as Digipuratum, is said to contain the cardiac glucosides of the leaves in combination with tannin and freed from most of the inactive constituents. Dose, the same as digitalis.

The powdered leaves and the tincture of digitalis are the most commonly used preparations. The powdered leaves may be given in capsules or in the form of tablets. The preparations ought to be freshly made. The infusion and aqueous solutions of the principles must not be kept, as they soon decompose.

Strophanthus, the seeds of Strophanthus kombé or hispidus. The B. P. requires that Strophanthus, in the form of the tincture, shall be standardized by bioassay.

Strophanthinum, the glucoside or mixture of glucosides of Strophanthus kombé, varies in composition and in power, so the B. P. gives a standard strength for it, requiring that it possess 40 per cent of the activity of anhydrous ouabain. The U. S. P. requires that Strophanthin shall possess a potency equivalent in activity to from 40 to 60 per cent of ouabain. It is given by intravenous injection. Ouabain, or crystalline g-strophanthin from Strophanthus gratus, is also used for intravenous injection in the dose 0.0005 G. ($\frac{1}{120}$ gr.).

Scilla, squills, the bulb of Urginea maritima or Urginea scilla, cut into thin slices. The British Pharmacopœia requires that Squills, in the form of the tincture, shall be standardized by a bioassay.

Syrupus Scillæ Compositus contains senega and tartar emetic.

Squills is sometimes prescribed in pill form as a diuretic; as an expectorant the syrup is more often used. The compound syrup, may be ordered instead of a cough mixture, as it contains the chief constituents of such remedies.

The importance of this group in therapeutics is so great that it is to be regretted that no adequate method of chemically estimating the content of active principles is available. For the crude drugs appear to vary in activity and even when the attempt is made to use the glucosides themselves, the difficulty in their isolation and identification leads to uncertainty in their dosage. The pharmacopœias recognize the advisability of assaying the crude preparations biologically, and the active principles may also be standardized in the same way (see p. 37). Only by using standardized preparations can there be any certainty that the patient is receiving a uniform dose of these drugs.

Methods of Administration.—For ordinary purposes the members of the digitalis group are given by the mouth, and the most suitable preparations are the tincture of digitalis and the powdered digitalis leaf. These are generally given alone in cases of heart disease, and it is of importance to remember that the tincture does not maintain its strength if it is kept diluted with water so that it should be sent out undiluted with directions to take the requisite dose in a wineglass of water. The best results are often obtained from larger doses than the pharmacopœias suggest; thus a dram of tincture of digitalis may be required per day. The tincture of strophanthus is stronger than the tincture of digitalis and has a smaller dose, but its action is uncertain on account of the difficulty of absorption from the intestinal tract, so that it is rarely used today and, in fact, it would be better if it were to be entirely given up. The tincture of squills of both pharmacopœias should be given in larger doses than the pharmacopœias prescribe to elicit the same effects as the tincture of digitalis and certainly for its cardiac effects digitalis is to be preferred to squills. Large doses of these preparations are not always necessary, but there is no question that in many instances the failure of digitalis to relieve symptoms is due to the use of inadequate doses.

The usual treatment has been to prescribe repeated small doses of the tincture of digitalis, such as 1–1.5 cc. (15–20 mins.) thrice daily; in this way the beneficial effects are only attained on the second or third day, when enough has accumulated in the tissues. In order to accelerate the action of the drug it is now advised, in urgent cases which have not received digitalis for ten days previously, to give a large dose at once and to follow this by smaller doses until therapeutic effects are obtained. More or less elaborate rules based upon the weight of the patient have been devised to estimate the dose to be given, but such figures are at best only suggestive, due to individual susceptibility to the drug. If it is desired to get such a patient who has not had the drug recently, under its influence rapidly, 10 cc. of the tincture can be given in one dose and then smaller doses of 2 cc. (30 mins) can be given three times daily. When such large doses are to be given the patient should be confined to bed and under competent supervision. If anorexia, nausea and vomiting, decrease in the heart-rate below 60 per minute, or irregularities of the heart appear, the drug must be stopped at once.

In less urgent cases the initial dose may be smaller or it may be omitted entirely, and the patient given 2 cc. (30 mins.) three times daily.

Ambulatory patients who are seen at intervals of several days may be given doses of 1 cc. (15 mins.) of the tincture three times a day, with instructions to reduce the dose if toxic symptoms appear.

(It should be noted that the above dosage refers to "minims" of the tincture and not "drops." Tinctures dropped from a medicine dropper average 35 to 40 drops to 1 cc.)

The average patient destroys or eliminates the equivalent of from 1 to 2 cc. of the tincture daily, so that to maintain an individual in full digitalization it is necessary to give about this amount of the drug (1.5 cc. of the tincture) daily. This may be given in one dose at night or in divided doses.

The so-called pure principles should not be given by the mouth; strophanthin, the only one of them recognized by the pharmacopœia, undergoes decomposition in the alimentary tract, especially when given in pure form. No preparation can be injected hypodermically in sufficient amount, owing to the local irritant action, and though intramuscular injections of strophanthin have occasionally been made, they also cause much pain and irritation. In emergencies strophanthin may be injected intravenously in sterilized Ringer's solution, but the necessity for such a procedure has become much less common recently, due to the use of the larger doses of the tincture of digitalis. The injection should be made very slowly; not more than 0.5 mg. ($\frac{1}{130}$ gr.) should be given and this is generally dissolved in 2–5 cc. of Ringer's solution. The injection is not repeated within twenty-four hours except in special conditions and after careful examination of the patient; the treatment may be continued with doses of the tincture of digitalis thrice daily, and these may be commenced the day after the injection of strophanthin. The effects of the latter will be passing off when the digitalis begins to act. The lowest dose of digitalis is then found which maintains the improvement and this is continued as long as necessary.

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M. ACONITINE AND VERATRINE.

This series embraces a number of alkaloids, which resemble each other closely in their chemical and pharmacological properties. Some of them which were formerly believed to be distinct are now said to be identical, and it is not improbable that future investigation will still further reduce the number of the group.

These alkaloids are found in a number of species of the Aconitum genus, the best known of which are Aconitum napellus, containing *Aconitine* ($C_{34}H_{45}NO_{11}$) Aconitum ferox, *Pseudaconitine* ($C_{36}H_{51}NO_{12}$), and Aconitum japonicum, *Japaconitine* ($C_{34}H_{49}NO_{11}$).

When aqueous solutions of these alkaloids are heated, they are broken up into one or more acids and simpler bases; aconitine forms acetic and benzoic acids and *Aconine*, so that aconitine is acetyl-benzoyl-aconine. Pseudoaconitine forms *Pseudaconine*, and Japaconitine *Japaconine* in the same way. These decomposition products are found in the plant and in the ordinary preparations, so that their toxicity varies very considerably.

Another alkaloid which resembles aconitine closely in its pharmacological action, but which is less known, is *Delphinine*. It is found in stavesacre (Delphinium staphisagria), along with a number of other bases, which may be the products of its decomposition.

The symptoms caused by aconitine, pseudaconitine, japaconitine, and delphinine are very similar, differing mainly in degree and not in kind. Pseudaconitine is more poisonous than japaconitine which in turn is slightly more active than aconitine. Delphinine is much less poisonous.

Symptoms.—After very large quantities of aconitine death may result instantaneously, apparently from simultaneous failure of the heart and central nervous system.

If smaller quantities be swallowed, there is noted, after the ordinary bitter taste of the alkaloid, a feeling of warmth in the mouth and throat, which agreeable at first, soon becomes prickling and tingling, and extends to the stomach and eventually to the skin. This is accompanied by a profuse flow of saliva and often by vomiting. The pulse is very slow and may be irregular, and later becomes weak and imperceptible when symptoms of collapse appear. The respiration is slow and labored, and great muscular weakness is complained of. After a time the smarting and tingling of the skin are no longer felt, and on examination the cutaneous sensibility is found to be much reduced. The intelligence remains unimpaired to the last in many cases, although unconsciousness sometimes occurs, and death is generally, but not invariably, preceded by convulsions. The pupil is unaffected except when convulsions supervene, when it is dilated. The prickling of the throat and skin is the most characteristic symptom, and is practically diagnostic in cases of poisoning, no other drug excepting veratrine having this effect. Death is sometimes due to paralysis of the respiratory centre from the direct action of the poison, but in other cases the heart fails before the respiration.

In small doses aconitine induces tingling of the lips, tongue and throat, which is followed by some nausea and a feeling of weakness and depression. The heart is generally accelerated from the nausea.

Action.—The prickling, tingling sensation is due to an affection of the **Terminal Organs of the Sensory Nerves,** as is shown by its appearing first at the point of application of the drug. Thus, when aconitine is swallowed, the prickling and warmth is felt in the lips, tongue and throat, and after small doses may be confined to these parts, while if an ointment containing aconitine be rubbed on the skin, the same sensation is induced locally. But no redness or swelling of the skin is induced, nor are blisters formed, so that aconitine differs entirely from the class of skin irritants (page 221). It evidently acts by stimulating the terminations of the sensory nerves, more especially those of common sensation, while the other sensory end organs have not been shown to be involved. Thus, apart from the bitter taste which it possesses in common with all alkaloids, aconitine has no effect upon the taste organs during this stage. The stimulation afterward passes into depression, which induces a sense of numbness at the point of application, and in cases of poisoning, in all the surfaces of the body. The taste nerves seem to be involved in this effect, if Laborde's statement be correct that sweet substances have no taste after aconitine. The irritation of the sensory terminations often causes a number of reflexes, such as sneezing, coughing, increased secretion of saliva, and vomiting, although some of these may be due in part to stimulation of the medullary centres. Evidence of the stimulation of **Other Terminations** is presented in fibrillary twitching of the muscles in the frog and sometimes in mammals. This is prevented by curare, but not by section of the nerves, and is therefore attributed to stimulation of the terminations of the motor nerves in muscles.

Circulation.—The effects of aconitine on the circulation have given rise to some misunderstanding, owing to their complexity. After small quantities, the heart does not seem to be affected in man, while in maximal therapeutic amounts it is very often accelerated through the nausea induced by the irritant effect in the stomach. In cases of poisoning the heart is stated to be very slow and irregular, and this can easily be elicited in anæsthetized animals by the injection of aconitine intravenously. This slowing is due to stimulation of the inhibitory centre in the medulla, and is absent in experiments in which the vagus nerves have been divided previously to the injection or in which atropine has paralyzed the inhibitory terminations in the heart.

In large doses aconitine exerts a further, direct action on the heart, which suddenly accelerates from the slow vagus rhythm to one far above the normal. Soon irregularities of many different forms follow, one of the most common being reversal of the beat, in which the ventricle contracts before the auricle and gives

the rhythm to the heart. Other arrhythmias also are attributable to the same increase in the excitability of the heart muscle, which is manifested in numerous extrasystoles in the auricle and ventricle, or in groups of rapid rhythm arising from one or other chamber and alternating with periods of fairly regular rhythm. The conduction power of the heart muscle is lessened and this leads to intermissions of the ventricle or auricle. And changes occur in the contractility, so that *pulsus alternans* often appears. All of these effects may be elicited at the same time, giving an extremely complicated tracing. Finally the ventricle passes into fibrillation and the circulation ceases. These changes arise from direct action on the heart muscle but there is no reason to suppose that it is affected by therapeutic doses. After section or paralysis of the vagus, a much larger quantity of aconitine is required to produce the acceleration and final delirium than when the nerves are intact. The frog's heart is affected by aconitine in the same way as the mammal's and presents the same diversity in rhythm.

The blood-pressure in mammals falls rapidly from the lessened output of the heart in the stage of vagus stimulation. After the stage of acceleration has set in, the blood-pressure becomes extremely irregular, alternately sinking to zero and remaining at that point for some seconds and again attaining a fair height. The vasomotor centre seems eventually to become paralyzed, while the vasomotor nerves and their terminations in the periphery remain unaffected.

The **Respiration** is early affected in aconitine poisoning; it becomes much slower, the movements are labored, and the animal suffers from marked dyspnœa. In fatal cases the respiration soon becomes interrupted by convulsions, and in the intervals between these becomes weaker and eventually ceases. The action appears to be a direct one on the respiratory centre, which is paralyzed before the heart begins to fibrillate, as a general rule, but sometimes continues to act for a few seconds after.

Central Nervous System.—The higher centres seem to be almost unaffected by the drug, for consciousness has often remained to the end, and when this is not the case, the mental symptoms are to be ascribed to the changes in the heart and respiration. The muscular weakness and depression felt after small quantities appear to arise from the nausea and not from any direct nervous action. Some of the lower centres in the medulla oblongata are directly affected; thus the centres for inhibition of the heart, for vasoconstriction, and for vomiting are all excited by large amounts though therapeutic doses have no effect on them. The respiratory centre, on the other hand, is depressed and finally paralyzed, while the rest of the central nervous system is shown to be still irritable, by the occurrence of convulsions.

The peripheral nerve trunks are paralyzed by the application of aconitine to them and this is said to occur in the frog when aconitine is injected hypodermically. The muscles do not respond to aconitine except in much higher concentration.

The **Secretion** of saliva is greatly increased by aconitine, from the irritation of the sensory terminations in the mouth and from the nausea. The cold perspiration observed in poisoning may be ascribed to the collapse rather than to any direct action on the sweat glands, although Aubert states that aconitine is a powerful diaphoretic in itself.

Aconitine sometimes reduces the **Temperature** both in fever and in normal animals, but the precise way in which this action is elicited is unknown. Brunton and Cash found that after aconite the temperature fell more rapidly than usual if the animal was kept in a cool bath, but rose more readily if it was subjected to external warmth; this observation would seem to indicate that aconite renders the temperature centres less sensitive.

In cases of **Poisoning** in animals, atropine has been found to alleviate the symptoms and not infrequently to lead to recovery after doses which would otherwise have been fatal.

Aconitine is **Excreted** mainly by the urine. Minute quantities have also been found in the saliva and bile.

Benzaconine is much less poisonous than aconitine and, in fact, can scarcely be included among active poisons, though large quantities act on the heart,

slowing it and rendering it irregular, and also depress the respiration. It has no effect on the sensory terminations. **Aconine** itself is almost inactive but large quantities strengthen the heart beat and paralyze the terminations of the motor nerves like curare. It seems unlikely that these alkaloids have any influence on the action of the aconite preparations, although the possibility cannot be excluded at present.

The alkaloids obtained from some other species of Aconitum have been found to differ considerably from aconitine and pseudaconitine in their action. In Aconitum septentrionale three bases, *lappaconitine*, *septentrionaline*, and *cynoctonine*, have been discovered. Lappaconitine causes clonic convulsions, vomiting, dyspnœa and finally paralysis of the respiration and heart, and in the frog lessens the sensibility of the skin. Septentrionaline does not cause poisoning when taken internally, but injected subcutaneously induces local anæsthesia and later paralysis of the motor terminations, like curare. Cynoctonine is also inactive when swallowed and is less poisonous than the others when applied by hypodermic injection, when it causes tonic and clonic convulsions which are not generally followed by paralysis. Two alkaloids, *lycaconitine* and *myoctonine*, have been found in Aconitum lycoctonum, and induce almost identical symptoms. They increase the reflex excitability, and this is followed by convulsions and later by paralysis of the terminations of the motor nerves and by failure of the heart.

Therapeutic Uses.—Aconite has been employed to some extent to slow the pulse and reduce the temperature in fever especially in children. Accurate observations show that it has no effect in slowing the pulse when given in therapeutic doses, and its action on the temperature is very uncertain. It has, therefore, been replaced by the newer and more powerful group of antipyretics for this purpose.

The action of aconitine on the sensory nerve terminations suggested its local use in cases of neuralgia, and there is some evidence that its application relieves this condition, though it cannot be said to be beyond question. Either the tincture, or a 2 per cent solution of the alkaloid in oil may be employed externally. Aconitine has also been injected subcutaneously in neuralgia, but this mode of application is not to be recommended, as it causes very severe pain, which in some cases lasts a long time. Aconitine is the most poisonous of the alkaloids, 0.2 mg. ($\frac{1}{300}$ gr.) taken by the mouth inducing distinct symptoms in man, and its use must be guarded. The internal administration of aconite in neuralgia does not seem to be followed by any improvement. Stavesacre is scarcely used in medicine at present.

Preparations.

U. S. P.

Aconitum, monk's hood.
Tinctura Aconiti, 0.6 cc. (10 mins.).

B. P.

Aconitum.
Linimentum Aconiti.

The tincture of aconite of the U. S. P. is standardized by a biological assay method (page 38).

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Veratrine.

A number of alkaloids have been found in species of Veratrum and allied genera, and resemble aconitine in their pharmacological action. *Veratrine* is found in the seeds of Schœnocaulon officinale or Asagræa officinalis (sabadilla or cevadilla seeds) and also in Veratrum sabadilla and Veratrum viride or Green Hellebore.[1] It is a mixture of two alkaloids, *cevadine* and *veratridine*. The chief alkaloid of Veratrum album, White Hellebore, is *protoveratrine*. Alkaloids of this series have been found in several species of Zygadenus, the Death Camas, which is an important cattle poison in the Western United States.

Each of these alkaloids is accompanied by a number of others, most of which are imperfectly investigated chemically and pharmacologically. In cevadilla, in addition to *Veratrine*, there are found *Cevadilline*, *Sabadine*, *Sabadinine*, and *Sabatrine*. In white hellebore *Protoveratrine* is accompanied by *Jervine*, *Pseudojervine*, *Rubijervine*, *Protoveratridine*, and others. Green hellebore contains *Cevadine*, *Jervine*, *Pseudojervine* and *Veratridine*. Jervine, Sabadine, and Sabadinine are known to possess some action on the organism; Cevadilline has not been examined, while the others are said to be inactive.

Cevadine ($C_{32}H_{49}NO_9$), veratridine ($C_{17}H_{53}NO_{11}$) and protoveratrine ($C_{32}H_{51}NO_{11}$) are powerful alkaloids, the last almost rivaling aconitine in its toxicity. Like aconitine, each of these may be decomposed into a base and an acid, cevadine forming angelic acid and cevine, while protoveratrine forms isobutyric acid and a similar base.

The effects of veratrine resemble those of aconitine very closely in their general character and particularly in regard to the sensory terminations; but the muscles present a curious reaction to veratrine, which is entirely absent in aconitine poisoning.

Symptoms.—The symptoms differ from those of aconitine only in the greater tendency to colic and purging under veratrine, and in the presence of fibrillary twitching of the muscles and convulsions in the later stages of poisoning.

Action.—The prickling of the skin is a striking feature of veratrine poisoning and the same action leads to violent sneezing and coughing when small quantities of veratrine come in contact with the sensitive mucous membranes of the nose and throat. After the irritant action has lasted for some time, the sensory terminations in the skin become less sensitive, and a feeling of numbness and cold is noted. Protoveratrine seems to cause less irritation of the sensory terminations than veratrine, and the subsequent local anæsthesia is more complete.

The most characteristic action of veratrine is that on the **Striated Muscles.** If a small quantity be injected into the lymph-sac of a frog a curious clumsiness and awkwardness in the movements becomes apparent, and after a few minutes it is evident that this is due to inability to relax its muscles. When a muscle is exposed, it is seen to contract as rapidly as usual, but instead of immediately relaxing again, it remains shortened and offers resistance to the contraction of the opposing muscles. The animal can therefore no longer coordinate its movements; for example, it can no longer extend a limb immediately after flexing it, as it does ordinarily in crawling, and locomotion becomes very slow and ungainly.

This characteristic action is most easily seen on exposing an excised frog's muscle to a solution of veratrine; as long as the muscle remains at rest no change is seen, but on stimulating it with a single induction shock, it is found that the height of the contraction is increased and the second part of the curve is extraordinarily prolonged (Fig. 57). Instead of the almost instantaneous return to the base line seen in the normal tracing, the curve shows generally a slight undulation, and then a very slow fall, the period of relaxation generally being 20 to 30

[1] Hellebore is also the popular name of Helleborus niger, which differs entirely from Veratrum in its principles and also its action.

times as long as that in the unpoisoned muscle, and the whole contraction lasting five to ten seconds in favorable circumstances.

Cold and fatigue and high temperature antagonize the veratrine action, and restore the normal tracing; on the other hand, veratrine removes the fatigue effect in the muscle curve. During the prolonged contraction, more heat is formed than in a normal contraction, and the absolute strength of the muscle is also increased, so that it contracts against a greater weight than usual. Larger doses finally paralyze the frog's muscle, the form of the tracing first returning to the normal and the contraction then becoming weaker and disappearing. The irritability of the muscle is not increased by veratrine, but falls in the later stages; the indirect irritability also lessens, owing to weakness and final paralysis of the nerve ends. These muscular phenomena are best seen in the frog, but can also be elicited in warm-blooded animals by very large doses; they are not so obvious in the latter because the quantity necessary to induce them is sufficient to affect the respiratory centre. The contraction is not a tetanus, but a prolonged single twitch, as is shown by the electrical reaction. The muscle

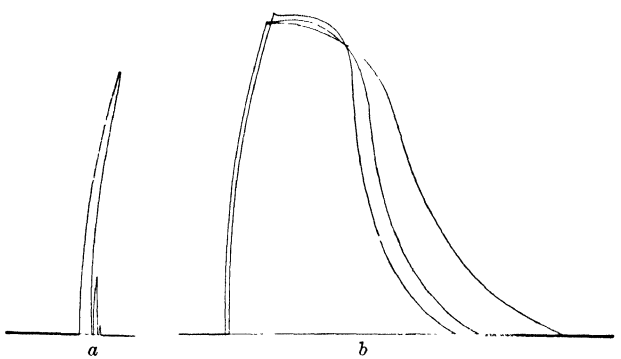

FIG. 57.—Tracings of muscular contractions from the gastrocnemius of the frog. *a* normal, *b*, three successive contractions taken at intervals of one minute, five minutes after the injection of veratrine. The contraction is higher and much more prolonged than in *a*, and the lever returns very slowly to the base line.

fibre is affected directly and not through the nerve-endings. Protoveratrine has less tendency to prolong the muscle contraction, but the frog's sartorius exposed to it often shows the typical effect. It paralyzes muscle more readily than veratrine, but has less effect on the nerve terminations.

Certain phenanthrene derivatives, formed by substituting various chemical groups on the 9-carbon atom produce a veratrine-like action on mammalian skeletal muscle. Sodium phenanthrene-9-carboxylic acid, one of the more soluble compounds of the group, after administration to cats and rabbits produced isotonic and isometric gastrocnemius muscle contraction records which were often double or multiple-peaked and showed a prolonged relaxation phase of from one to six seconds in duration. An increase in the amplitude of contraction was also commonly observed. The action persisted after curarization. No delayed relaxation comparable with that produced in mammalian muscle was observed in frogs (Smith).

The **Nerve** fibres are paralyzed by veratrine directly applied to them, and also by protoveratrine, though less powerfully.

Circulation.—The ventricular systole of the frog's heart is at first stronger and more prolonged, and soon it dilates only half as often as it did at first, while the auricles maintain their original rhythm. This is evidently due to action on the muscle; the contraction is so prolonged as to limit the number of diastoles,

and the ventricle can therefore react only to every alternate contraction of the auricle. After this "half-rhythm" has persisted for some time, the contractions become slower and weaker, and the heart finally comes to a standstill.

In mammals the changes in the circulation resemble those under aconitine except that larger amounts of veratrine are required to produce the same effects and the more obvious symptoms of stimulation of the myocardium are not elicited.

As regards the other alkaloids of this series, jervine, sabadilline, and sabadinine seem to possess the same action as veratrine, but are much less poisonous. Protoveratrine, which has less stimulant effect on the sensory terminations and on the muscle fibers, is more poisonous, its action resembling that of aconitine as much as that of veratrine.

Therapeutic Uses.—Veratrine is used in the form of the oleate or ointment as an external application in cases of neuralgia and is certainly a safer remedy than aconite. Veratrum album has been used to reduce the pulse rate and the blood-pressure.

U. S. P. Preparations.

Veratrum Viride; Green Hellebore. 0.1 G. ($1\frac{1}{2}$ grs.).

Tinctura Veratri Viridis. 10 per cent. 1 cc. (15 min.).

Veratrina (Non-official) a mixture of alkaloids obtained from the seeds of Asagraea officinalis, insoluble in water but soluble in alcohol. Dose, 2 mg. ($\frac{1}{30}$ gr.).

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N. THE NITRITES.

The nitrites have a powerful action on the arteries, in which they cause dilation by depressing the muscle of the walls.

Those which have been examined more carefully are the *Nitrite of Sodium* and the *Nitrous Esters* of the methane series, especially the *Nitrite of Amyl*, which is largely used in therapeutics. In these compounds the radicle —NO is attached to the metal or alkyl, through an atom of oxygen, the formulæ being Na—O—NO, CH_3—O—NO, C_3H_7—O—NO, C_5H_{11}—O—NO, etc., and the chief constituent is the O—NO, the metal or radicle being of less importance. A closely allied series of bodies are the nitrates, in which the nitrogen has five valencies and is connected again to the metal or radicle by oxygen, Na—O—NO_2, CH_3—O—NO_2, C_5H_{11}—O—NO_2, etc. The metallic nitrates differ entirely from the nitrites in their effects and are used as diuretics (p. 51).[1] Some of the *Nitric Esters*, however, undergo reduction when brought into contact with organic matter, and nitrites are thus formed, so that these bodies have effects very similar to those of the true nitrites, and have to be discussed along with them. The

[1] Stieglitz has shown that bismuth subnitrate, even when given by mouth can apparently exert a nitrite action and lower blood-pressure in cases of hypertension

best known of such nitrates is the so-called *Nitroglycerin*, which is really the trinitrate of glycerin, $CH_2(ONO_2)CH(ONO_2)CH_2(ONO_2)$, and is broken up by alkalies into a mixture of nitrates and nitrites. The nitrates have practically no action in the small quantities given, so that almost all the effects of nitroglycerin are due to the nitrite formed. Many other organic nitrates also form nitrites in the tissues, but none of them with such rapidity as nitroglycerin.

Two which have been used to some extent in the last few years are solids—*Erythrol Tetranitrate*, and *Mannitol Hexanitrate*. They act much more slowly and for a longer time than nitroglycerin.

Another series of bodies which may be mentioned as occasionally acting like nitrites, although more feebly, are the nitro-bodies. In these the nitrogen is attached to the alkyl directly, and not through the intervention of an oxygen atom. Examples of these are Nitromethane, $H_3C—NO_2$, and Nitroethane, $CH_3—CH_2—NO_2$. Their action is so feeble as to preclude their use in therapeutics, and seems due to the $—NO_2$ being split off in the tissues.

The best known member of the group is **Amyl Nitrite**, and its action will first be described, while the points in which the effects of the other members diverge from it will be discussed later.

Symptoms.—After the inhalation of a few drops of amyl nitrite, the face becomes flushed, and the patient complains of a feeling of fullness and throbbing in the head. Some headache and confusion is often present, the pulse is accelerated, and the respiration is somewhat quicker and deeper. The flush is often confined to the face and neck, but sometimes spreads over the whole trunk, and passes off in a few minutes, unless the inhalation is continued. If large quantities of the drug be inhaled at once, however, or if the inhalation be continued for some time, a feeling of giddiness, weakness and eventually stupor follow, the pulse becomes slow, while the respiration still remains accelerated but is shallower and often somewhat irregular; convulsive movements may occur, but in general large quantities may be taken without actual danger in the human subject. The blood is said to have assumed a dark color in some cases, but this seems to be rare.

Action: Circulation.—The flushing and dilatation of the arterioles of the head are found to be accompanied and followed by a profound fall in the blood-pressure in man and animals. The heart is accelerated at the same time, and therefore is not responsible for the change. The cause, as has been repeatedly demonstrated, is the dilatation of the peripheral vessels, both arterioles and veins widening very considerably under the influence of the drug; the vessels of the abdominal organs and the face are more affected than those of the extremities. The vasomotor centre is not concerned in the widening of the vessels, for if amyl nitrite is allowed to pass through the medulla without reaching the peripheral vessels, no fall of pressure occurs. And stimulation of a constrictor nerve such as the splanchnic still produces some rise in the blood-pressure, so that the nerve terminations seem to be intact. The seat of action of amyl nitrite is therefore the unstriated muscle of the arteries and veins. No satisfactory explanation has been offered for the fact that in the skin only the vessels of the head and neck should

be dilated, but other facts seem to indicate that these vessels occupy an exceptional position as regards their innervation and their reactions to drugs. Darwin was the first to point out that the blush of amyl nitrite corresponds in extent with the blush produced by emotion. This blush effect seems due to the amyl in part, for other amyl esters induce it, though not to the same extent as the nitrite. The direct action on the vessel walls may be easily shown by passing blood into the artery of the amputated extremity of an animal, and measuring the amount coming from the veins. If a few drops of amyl nitrite are added to the perfused blood, the outflow from the vein is greatly increased, although here no nervous mechanism can be concerned.

FIG. 58.—Tracing of the blood-pressure (B. P.) and intestinal volume (I. V.) in a cat. Amyl nitrite was inhaled at the point marked with an arrow. The blood-pressure falls while the volume rises from the dilation of the splanchnic vessels.

The acceleration of the pulse is more marked in man and the dog than in other animals, and is the result of the fall in blood-pressure which induces anæmia of the brain and thus depresses the tone of the inhibitory cardiac centre and probably excites the accelerator apparatus. The coronary arteries of the heart are dilated along with those of other parts of the body, but the blood supply to the heart is reduced.

Bronk and Ferguson have shown that the inhalation of amyl nitrite increases the discharge of nerve impulses along the sympathetic fibres going to the heart. There is a definite relationship between the number of sympathetic impulses in these fibres and the heart rate and in general with a lowering of blood-pressure, such as follows the use of amyl nitrite, there is found an increased number of impulses and an acceleration of the heart.

Studies have also been carried out upon the action of amyl nitrite in cases of bradycardia due to complete heart block. In this condition, which is dependent upon a diseased condition of the bundle of His, the auricle may be contracting at or near its normal rate while the ventricle is always beating much more

slowly, usually in the neighborhood of 30 per minute. The effect of the inhalation of amyl nitrite in such cases is hard to predict. Although it usually increases the rate of the auricle, its effect upon the ventricular rate is often practically *nil* while in other cases the rate may be greatly increased. In those cases in which the ventricle does not accelerate under amyl nitrite it is evident that this compensating factor to the lowered blood-pressure is absent and any compensation which is brought about through the action of the heart can only be by an increased output of the organ. However it has been shown that in normal individuals inhalation of amyl nitrite lessens very considerably the systolic output and that the compensating factor when amyl nitrite is inhaled is the increase in heart rate. This in itself may increase the output of blood per minute to a very considerable degree. From these findings it would seem likely that in cases of heart block little compensation to the lowered blood-pressure produced by nitrites can be furnished by the heart unless, as occasionally happens, the ventricle itself is quickened.

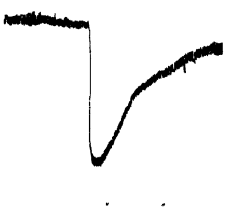

FIG. 59.—Blood-pressure under amyl nitrite taken on a slow drum in order to demonstrate the recovery. The whole tracing occupied some six minutes. The rapid fall of pressure is followed by an almost equally rapid return to normal. (Cash and Dunstan.)

Large quantities of amyl nitrite slow and weaken the contractions of the heart, owing to a direct depressing action on the muscle. In the frog, the heart is usually slowed from the beginning of the application.

The **Respiration** is generally accelerated, and at the same time rendered deeper by amyl nitrite.

Not infrequently the breath is held at first, owing to a reflex from the nasal mucous membrane, but this is not so marked as in the inhalation of more irritant vapors, such as chloroform or ether. The acceleration is the result of the fall in pressure lessening the supply of blood to the

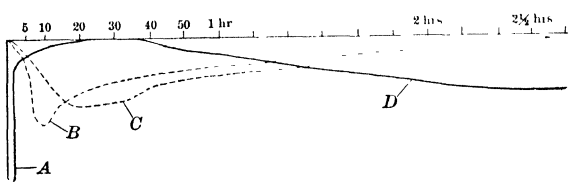

FIG. 60.—Diagram to illustrate the intensity and duration of the action of the members of the nitrite series. The extent of the fall of pressure is measured along the vertical, the duration along the horizontal line. *A*, amyl nitrite, ethyl nitrite, etc.; *B*, nitroglycerin; *C*, sodium nitrite; *D*, erythrol tetranitrate. The greatest fall in pressure occurs in *A*, but it passes off for the most part in five minutes and entirely in twenty. Nitroglycerin acts more rapidly than the last two, and its effects continue almost as long as those of sodium nitrite. Erythrol tetranitrate only exerts its full effect after the action of the others has passed off. (After Bradbury.)

brain and arousing the respiratory centre. After long inhalation the respiration becomes slower and shallower and in animals death occurs from asphyxia. The walls of the pulmonary vessels are less

affected by the nitrites than those of the systemic circulation, and any change which occurs in the pulmonary blood-pressure is probably the indirect result of the acceleration of the heart. The bronchial muscle is apparently relaxed by the inhalation of amyl nitrite or by the administration of other members of the group by the stomach, for relief is given in asthma. An old method of inducing this effect is by burning paper impregnated with saltpeter and inhaling the fumes, which contain nitrite formed by the reduction of the nitrate.

The **Kidneys** are not much affected by this series; occasionally a slight increase in the urine is observed, at other times a decrease, and after large quantities anuria may occur. These effects are evidently due to the changes in the calibre of the renal vessels. A small quantity may widen them when they are too contracted to allow of the maximal secretion, while on the other hand, if the normal calibre is the optimal, a nitrite may lessen the secretion by lowering the general blood-pressure. When large quantities lower the pressure, they inevitably lead to a lessened secretion or anuria.

Small quantities of amyl nitrite seem to have no action whatsoever on the higher parts of the **Central Nervous System**. The throbbing in the head and slight confusion are evidently due to the fall in general blood-pressure. The sight is curiously affected in some people, for when a dark object on a white background is looked at, it seems surrounded by a yellow ring and that again by a blue one. In the beginning the medullary centres may be slightly acted on reflexly from irritation of the nasal sensory terminations, and later the fall in blood-pressure and consequent anæmia of the medulla lowers the activity of the inhibitory centre for the heart and stimulates the respiratory and vasomotor centres. The spinal cord is not acted on in mammals, but is depressed in the frog.

After large quantities convulsions are often observed; these seem to be of cerebral origin, and are probably due to the circulatory changes and the formation of methæmoglobin.

The **Peripheral Nerves** and the **Muscles** are unaffected by the inhalation of amyl nitrite, but when the frog's muscles are exposed to the direct action of the vapor, they undergo a slow, passive shortening and rigor, and on periodical stimulation the contractions become rapidly weaker, until finally no response is made to the electric shock. Involuntary muscle is more easily affected than striated fibres, as has been shown by the behavior of the intestine and ureters, but even these seem less readily paralyzed than the muscle of the vessel walls, the depression and paralysis of which lead to the fall in the arterial tension, as has been already stated. The nerve terminations seem to be unaffected even by very large quantities, so that as long as a contraction of the muscles can be elicited by direct stimulation, it follows also on stimulation of the motor nerve, and the vagus terminations in the heart can transmit impulses so long as the heart continues to beat. The **Temperature** is somewhat lowered by the nitrite series, owing to the dilatation of the skin vessels, but this fall is insignificant.

During the fall in the blood-pressure, the **Blood** is diluted by the lymph

pouring into it from the tissues, while as the pressure rises the concentration returns to the normal. The nitrites change the hæmoglobin to methæmoglobin and nitric-oxide-hæmoglobin, giving a dark chocolate color. This does not entail the destruction of the red corpuscles, and the compounds are eventually reduced by the tissues, although the reduction progresses much more slowly than that of ordinary oxyhæmoglobin. In man, usually very little of the hæmoglobin is thus transformed, and even after large quantities have been inhaled no abnormal coloration of the blood is noticeable, but the alteration of the hæmoglobin is the cause of death in some animals, through the blood becoming incapable of carrying oxygen to the tissues. If, however, asphyxia be prevented by the inhalation of oxygen under pressure, the tissues themselves are eventually acted on. The formation of methæmoglobin does not seem to bear any relation to the action of the nitrites on the vessel walls and is identical with that caused by other reducing bodies, which have no action on the blood-vessels.

Excretion.—After absorption into the blood, amyl nitrite seems to break up with the formation of nitrites of the alkalies. These undergo partial oxidation and appear in the urine in the form of nitrates and nitrites, but the quantity of these excreted is never equal to the nitrite absorbed, so that it seems probable that some part undergoes still further change. The amyl disappears, and is probably oxidized completely, although some may appear in the breath.

Nitrite of amyl given by the stomach is much less active than when inhaled, as the nitrous acid is freed by the gastric juice and immediately decomposed. When injected subcutaneously it acts much more slowly and weakly than when absorbed by the lungs, and generally gives rise to glycosuria and slight diuresis. No satisfactory explanation of this fact has been given, but it is possible that the formation of methæmoglobin may cause partial asphyxiation of the tissues, and thus cause the formation of excess of lactic acid and glycosuria.

The pharmacopœial amyl nitrite is a mixture of the nitrites of amyl, butyl, propyl, and ethyl. The pure nitrites of this series resemble each other closely in general features; the more unstable the compound, the more rapidly does the fall in blood-pressure occur, while the less easily decomposed compounds are somewhat slower in their action, but cause depression of the blood-pressure for a longer time.

Sodium Nitrite resembles the organic nitrites closely in action. It is administered by the stomach, and therefore acts more slowly than amyl nitrite, but its effects last much longer. The gastric juice liberates part of the nitrous acid before absorption can occur, and it is immediately decomposed and often causes some eructation and may also give rise to irritation of the gastro-intestinal mucous membrane. The nitrite absorbed is excreted as nitrate in the urine, although some of it may remain unoxidized. The metallic nitrites do not as a rule cause so much headache and flushing of the face and neck as the alkyl compounds.

Nitroglycerin produces the same effects as the other members of this series, but acts more powerfully than either the metallic or alkyl nitrites. It presents some minor points of difference, as in causing more severe

headache in man. It is not decomposed in the stomach, but on reaching the blood at once breaks up into glycerin, nitrites and nitrates. Its action commences very soon after its administration, and lasts much longer than that of amyl nitrite. The explanation of its greater activity may be that it is absorbed unchanged, but is then broken up at once, while the metallic nitrites are decomposed in the stomach and much of the nitrous acid is lost. Nitroglycerin is not wholly broken up in the human body, however, for it has been found in the urine, and the headache which so frequently follows its administration in man has been ascribed to the undecomposed molecule, and not to the nitrite constituent. Nitroglycerin disappears very rapidly from the blood of dogs following its intravenous administration. Within one minute an average of only from 10 per cent to 15 per cent of the amount given is detectable as remaining in the blood and none can be found at the end of from fifteen to twenty minutes. It is generally supposed to be extremely poisonous, and is prescribed in minute doses, but it has been shown that while very small quantities are sufficient to produce therapeutic effects in man, the toxic dose is enormous in animals.

A certain degree of tolerance to the nitrites is gained by man from their repeated administration. Especially is this true as regards the headache which they often produce, whereas tolerance is not so easily produced against their vascular effects. Also, a fairly complete cross tolerance apparently exists between the different members of the series.

Several other organic nitrates have also been found to reduce the blood-pressure, and to cause the formation of methæmoglobin, but their decomposition proceeds more slowly than that of nitroglycerin and they have not been much used in therapeutics. Erythrol tetranitrate and mannitol hexanitrate act more slowly, and the fall of pressure is more gradual, and lasts longer than under any others of the series.

Therapeutic Uses.—The nitrites were introduced into therapeutics by Brunton, who advised their use in angina pectoris to relieve spasm of the arteries. Some question has arisen as to whether angina pectoris is generally accompanied by high arterial tension, and amyl nitrite often gives relief in cases in which the blood-pressure does not seem abnormal, so that the mechanism of its action is not completely determined. For rapid transient effects nitrite of amyl seems specially indicated, while nitroglycerin and nitrite of sodium are more suited to produce a depression of some duration. Thus during the attack of angina pectoris, amyl nitrite is often found to give instant relief, but if nitrite of sodium or nitroglycerin is administered every four to six hours, no attack may occur. The disadvantage of the metallic nitrites is the frequent eructation they produce, while nitroglycerin often causes severe headache, which, however, disappears in some cases after repeated use. The pulse assumes the dicrotic character under all of the nitrite series, owing to the reduced peripheral resistance (Fig. 61).

Besides in angina pectoris, the nitrite series may be used in any condition in which it is supposed that the arterial tension may be lowered with benefit to the economy. Thus nitroglycerin has been advised in heart disease and has accordingly been placed by some among the

heterogenous group of "Cardiac tonics or stimulants." Its beneficial effects are not due to any direct action on the heart, but to its decreasing the resistance against which the systole is performed. In this way the contraction of the ventricle is rendered more complete and the output of the heart may be increased. In weak hearts struggling against

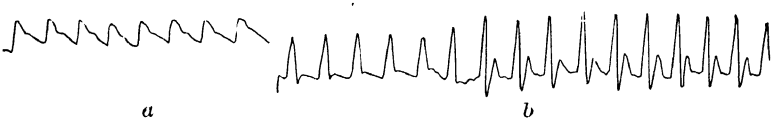

FIG. 61.—Pulse-tracing in a case of angina pectoris *a*, before, *b*, during the inhalation of amyl nitrite.

a high aortic resistance, this relief may be followed by marked benefit, and for this reason nitrite preparations (nitroglycerin) are often prescribed in chronic Bright's disease. Stewart has shown that the flow through the peripheral blood-vessels is accelerated by nitroglycerin. Amyl nitrite has been advised in accidents during chloroform anæsthesia on the theory that it would benefit the circulation; but, as a matter of

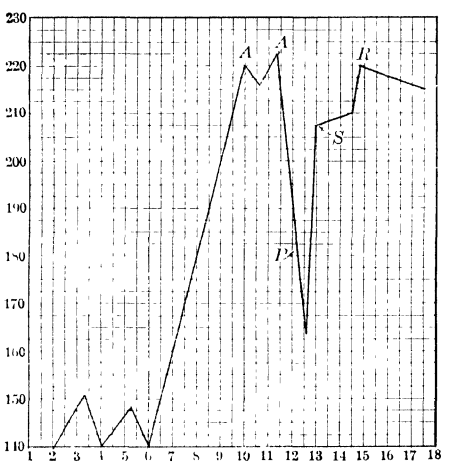

FIG. 62.—Blood-pressure chart during an attack of angina pectoris. The pressure, originally 140 to 150 mm. of mercury, rapidly rose to 220, and intense pain was present over the heart. At *A* and *A*, amyl nitrite was inhaled and the pressure fell to 165 mm. At *P* the pain had disappeared. The pressure rose again rapidly and at *S* the pain recurred slightly and was very severe at *R*. Time in minutes.

fact, it would appear strongly contra-indicated, in these cases, in which it is true that the heart is extremely depressed, but in which the arterial tension is practically zero. Its use is especially irrational if, as has been suggested, the failure of the respiration is partly due to anæmia of the central nervous system. The cases in which recovery has occurred after

this measure may, in fact, be said to have recovered, not owing but to, in spite of the use of amyl nitrite.

Amyl nitrite has been suggested in internal hæmorrhage, on the view that by reducing the pressure in the interior of the vessels it would permit a clot to form at the point of injury. On the other hand, the dilatation of the abdominal vessels may lead to anæmia of the brain and syncope, and this has prevented the use of the drug in practice, except in unusual conditions.

In very advanced degeneration of the cardiac muscle fibre, the administration of amyl nitrite is distinctly contra-indicated, for the blood-pressure is low and any further reduction may lead to syncope from anæmia of the brain, and to still greater weakness of the heart from the low pressure in the coronary arteries lessening its nutrition.

Nitrite of amyl has been used largely in asthma and in cardiac dyspnœa. Its action is often beneficial and has been attributed to its depressing the bronchial muscles, which are believed to be in a condition of spasmodic contraction in asthma. In the cardiac cases its action in removing the dyspnœa may be due to its lowering the pressure in the systemic arteries and thus relieving the heart.

In some cases of headache, nitrite of amyl is of marked benefit, while in others it aggravates the condition. This is perfectly intelligible, as some forms of headache may be due to cerebral congestion and peripheral constriction, while others arise from anæmia of the brain.

The action and employment of nitrites as antidotes in cyanide poisoning is discussed in the section on Cyanide Antidotes (p. 685).

Preparations.

U. S. P.

Amylis Nitris, 0.2 cc. (3 mins.).

Spiritus Glycerylis Trinitratis, spirit of nitroglycerin, 1 per cent glyceryl trinitrate in alcohol. 0.06 cc. (1 min.).

Tabellæ Glycerylis Trinitratis. Tablets of nitroglycerin must contain within 12.5 per cent of the amount of nitroglycerin indicated on the label.

Sodii Nitris, $NaNO_2$. 0.06 G. (1 gr.), in tablets or solution.

Spiritus Æthylis Nitritis, sweet spirit of nitre. 2 cc. (30 mins.).

Erythritylis Tetranitras Dilutus, diluted erythrol tetranitrate, a mixture of erythrol tetranitrate and lactose in equal proportions. Official as a white powder or as tablets. 0.3 G. (5 grs.).

B. P.

Amylis Nitris, 0.12–0.3 mil. (2–5 mins.).

Liquor Glycerylis Trinitratis, 1 per cent of glyceryl trinitrate in 90 per cent alcohol. 0.03–0.12 mil. ($\frac{1}{2}$–2 mins.).

Tabella Glycerylis Trinitratis, each tablet contains 0.0005 G. or $\frac{1}{120}$ gr. of glyceryl trinitrate.

Sodii Nitris, 0.03–0.12 G. ($\frac{1}{2}$–2 grs.).

Spiritus Ætheris Nitrosi, sweet spirit of nitre. 1–4 mils. (15–60 mins.).

Amyl Nitrite is a yellow, very volatile fluid, with a strong, fruity odor, soluble in alcohol and ether but rapidly decomposed by water. It consists of the nitrite of isoamyl for the most part, along with small quantities of the nitrites

of butyl, propyl, etc. 2–5 mins. are poured on a handkerchief and inhaled. A convenient preparation is the amyl nitrite "pearls," which are thin glass capsules, each containing a dose of the remedy, and one of which is broken in the handkerchief when necessary. Amyl nitrite is liable to decompose when kept for long, and ought to be used only when recently prepared.

SPIRITUS ÆTHYLIS NITRITIS, sweet spirits of nitre, contains 4 per cent of ethyl nitrite, along with ether and aldehyde in alcoholic solution. When freshly prepared it acts like the other nitrites, but when prescribed along with water, as is usually the case, the nitrite escapes rapidly, and it has little effect except from the ether and alcohol.

ERYTHROL TETRANITRATE ($CH_2ONO_2(CHONO_2)_2CH_2ONO_2$) is a solid, and is recommended in doses of 0.05 G. (1 gr.), in pills, tablets or alcoholic solution. Like nitroglycerin, it is a dangerous explosive, and one fatality has already occurred in forming it into pharmaceutical preparations.

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O. MINOR DRUGS AND POISONS.

I. MISCELLANEOUS DRUGS.

1. Saponin, Sapotoxin and Solanine.

This group comprises a series of glucosides which are very widely distributed in plants and which resemble each other in certain reactions with living cells. They contain no nitrogen and are typical glucosides, but their chemical structure is otherwise unknown; some have an acid reaction. The most poisonous among them are designated by the general term of *Sapotoxins*, while *Saponin* may be used to include the less active and the wholly innocuous members of the group.

These glucosides reduce the surface tension of water to a very marked degree, and even dilute solutions form froths like soap when shaken up. From this property the plants derive their popular names of soap-root or soap-bark. The reduction of the surface tension also explains their property of holding insoluble bodies in suspension. The saponins have a peculiar affinity for lecithin, which they dissolve, while cholesterol forms an insoluble chemical compound with

many of them; they tend to be deposited on the surface of cells with which they come in contact.

Saponins or sapotoxins are found in about 150 species of plants. The chief of these are: *Quillaja saponaria*, or soap-bark; *Saponaria officinalis*, or soap-wort; *Cyclamen Europeum*, or sowbread; *Polygala senega; Agrostemma githago*, or corn-cockle; *Gypsophila struthium* and other species; *Chamælirium luteum*, or blazing star; *Smilax*, various species, including those known as sarsaparilla.

In addition to the plants which owe their action to the presence of these bodies, a number of drugs contain saponins along with other more important principles. Thus an almost inactive saponin (*digitonin*) is met with in digitalis, and similar saponins occur in several others of the digitalis series; helleborein appears to stand midway between the true digitalis glucosides and the saponins in its action.

The most poisonous sapotoxins are those of quillaja, agrostemma, gypsophila, and cyclamen, and some saponins may be regarded as harmless when taken in ordinary quantity.

Another body closely resembling the saponins in action is *Solanine*, a glucosidal alkaloid found in many species of Solanum, such as S. nigrum (black nightshade), S. dulcamara (bittersweet), S. tuberosum (potato), and probably in some species of Scopola. Solanine breaks up on being heated with acids into sugar and a base, *Solanidine*, which retains the poisonous action. Some interest attaches to solanine from its having been held responsible for some instances of widespread poisoning from the use of potatoes. But it is now known that the symptoms arose from putrefactive bacteria and their products, and that solanine is never present in the tuber of the potato in sufficient quantity to be noxious.

Action.—The sapotoxins have a harsh, acrid, taste, and when swallowed provoke nausea and often vomiting, with pain and colic, and less frequently diarrhœa. They are not absorbed by the normal epithelium of the alimentary canal, and seem to undergo decomposition in the bowel, and therefore fail to produce general symptoms. Thus pigs feed with avidity on cyclamen and are unharmed by it unless some lesion of the intestine is present. The unbroken skin is not affected by a single application as a general rule, but when they are applied repeatedly or rubbed in as ointment they cause irritation and pustules. Absorption is extremely slow from the cutaneous tissues, in which they act as irritants, however, and produce inflammation and suppuration. The sapotoxin derived from agrostemma differs from the others in being absorbed fairly rapidly from the alimentary canal and from the subcutaneous tissues, so that more dangerous symptoms may arise from it than from the other members of the series.

When these bodies are injected directly into the blood-vessels, they induce much more characteristic changes, which very often prove fatal after a longer or shorter interval. Very large quantities thus injected may kill animals within a few minutes from respiratory paralysis, and no characteristic appearances are to be found postmortem. Smaller doses induce depression, loss of appetite, sometimes vomiting and diarrhœa, general weakness and collapse, with some dyspnœa and irregular, feeble pulse. Weak convulsions appear just before the failure of the respiration, while the heart continues to contract for some minutes longer. In these cases ecchymoses are found in the serous membranes, pericardium, pleura and peritoneum, and occasionally in the kidneys. Endocarditis has been observed in some instances, but the most important alterations occur in the stomach and intestines, the mucous membrane of which is swollen and congested and contains numerous blood extravasations. The lymphatic glands of the abdominal cavity are also swollen and congested and often filled with hæmorrhages. Occasionally the kidneys are found to contain numerous blood casts, filling the lumen of the tubules, and in these cases albumin and hæmoglobin appear in the urine before death; these are more often elicited by solanine than by the sapotoxins. In cyclamen poisoning (from intravenous injection) hæmoglobinuria is one of the earliest symptoms.

The property of dissolving lecithin, which is characteristic of this series, renders them poisonous to living tissues when they come in contact with them in sufficient concentration. On the other hand, cholesterol deprives them of toxicity by forming inactive cholesterides, but as a general rule the cholesterol is not in

sufficient amount to neutralize them completely. Their irritant action on the mouth, throat and stomach is the cause of the nausea and vomiting observed when they are administered in this way, and they cause sneezing and coughing from the same action in the nose and throat. On other mucous membranes, such as the conjunctiva, and in wounds, they cause similar irritation and inflammation, which may be followed by suppuration. A form of local anæsthesia often follows this irritation, the termination of the sensory nerves apparently being benumbed, but the preliminary irritation precludes their use for this purpose.

When the individual organs are exposed to the action of saponin bodies by the direct application of solutions to them, a similar poisonous action is elicited. Muscle contracts more weakly even in dilute solutions, is eventually entirely paralyzed, and is altered in structure, the transverse striæ of voluntary muscle and of the heart becoming very indistinct. Nerves exposed to solutions are also paralyzed in the same way, and the movements of cilia cease at once when they are exposed to sapotoxin bodies. The blood undergoes characteristic changes when it is acted on by saponin, either in the vessels or in the test-tube. The red blood cells undergo rapid destruction and the hæmoglobin is freed in the plasma. Even 1 part of cyclamen added to 100,000 parts of diluted blood completely lakes the red blood cells, while hæmoglobin appears in the serum when considerably less poison is added. The other saponin bodies act less powerfully in this direction than cyclamen, but still produce distinct solution of the substance of the red corpuscles. When a saponin is injected into the blood of a living animal this destruction of the red blood cells takes place to some extent, and the plasma contains hæmoglobin, while the blood corpuscles are considerably diminished in number. This hæmolytic action is not the result of changes in the hæmoglobin, but is due to the dissolution of the stroma of the corpuscles, through the solvent action of the saponin on the lecithin. This solvent action occurs more readily when the blood cells are suspended in normal salt solution than in the plasma or serum, because the cholesterol of the serum forms inactive compounds with the saponins. Even when the hæmoglobin in the corpuscles is coagulated and saponin fails to induce laking, the structure of the corpuscle is altered, as is shown by its reaction to salts (Stewart).

Murphy and Howard showed that saponin will hemolyze red blood cells of normal persons to an equal degree as those from cases of pernicious anemia, hemolytic anemia, leukemia and certain other diseases if the cells are washed thoroughly and then suspended in saline solution. On the other hand, the cells in their own plasma are protected against the action of saponin by the presence of cholesterol and not by the plasma protein. The protection afforded the cells by the plasma of patients with hemolytic anemia or of pernicious anemia in relapse is distinctly less than normal, but in the case of pernicious anemia following the use of anti-anemia remedies with the increase in number of red cells resulting therefrom the protection afforded by the serum approaches normal.

The frog's heart perfused with sapotoxin is arrested in systole in the same way as by digitalis, and the mammalian heart is also weakened when saponin is injected intravenously, though it continues to beat after the breathing has ceased. The central nervous system is also susceptible to the changes in the lecithin in the nerve cells, and the failure of the respiratory centre is the cause of death In many experiments the collapse from the irritation of the alimentary canal proves fatal, but in others in which large doses are immediately fatal the poison is believed to act directly on the nerve cells, whose activity is suspended by changes in the distribution of the lipids similar to that under the alcohol-chloroform group. A similar central nervous action may explain experiments in which only small quantities of the poison have been injected, but in which the animal dies after a few days, presenting no distinct symptoms except general weakness and depression.

The sapotoxins are poisonous to invertebrates, unless these are protected by a shell through which the poisons cannot penetrate. Thus the amœba and other simple organisms cease their movements, while intestinal worms are first excited and then paralyzed in the presence of some of the group.

Therapeutic Uses.—The drugs of this group are all quite superfluous. They may be used to increase the bronchial secretion in cough through the nausea caused by their slight irritant action in the stomach, but they have no advantages over such drugs as ipecacuanha; syrup of senega is often prescribed in expectorant mixtures for this purpose. Sarsaparilla has been supposed to have an obscure action on the nutrition, and had some reputation in the treatment of syphilis, but there is no reason to believe that it is of any service here or in any other condition, although it may be used as a vehicle for the administration of mercury and iodide of potassium. Quillaja has been used to some extent as an expectorant and more largely to form emulsions and to suspend insoluble powders. Its irritant action ought, however, to preclude its use for this purpose. It is frequently stated that members of the sapotoxin series are antidotes in digitalis poisoning, but this is incorrect.

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2. Hydrastine and Hydrastinine.

Hydrastine is an alkaloid which occurs in Hydrastis Canadensis (Golden Seal) along with two other alkaloids, *Berberine* and *Canadine*. Hydrastine ($CH_2 \cdot O_2 \cdot C_9H_7NCH_3 \cdot C_{10}H_9O_4$) is readily decomposed into *Hydrastinine* ($CH_2O_2C_9H_7NCH_3$) and opianic acid. Chemically hydrastine is nearly related to *Narcotine* ($C_{22}H_{23}NO_7$), one of the opium alkaloids, which differs from it only in the possession of another methoxyl group; and narcotine can also be decomposed into *Cotarnine* ($C_{12}H_{15}NO_4$) and opianic acid, cotarnine differing from hydrastinine again only by a methoxyl. Another opium alkaloid, *Laudanosine*, undergoes a similar decomposition and the resulting alkaloid has been shown by Laidlaw to resemble hydrastinine in action. The effects of the three original alkaloids, hydrastine, narcotine, and laudanosine, in the body also present many similarities.

Action.—Hydrastine causes in frogs an increase in the reflex irritability and eventually tetanus exactly resembling that produced by strychnine, and like it terminating finally in paralysis.

In mammals the pulse is slowed by comparatively small quantities, while somewhat larger doses cause general feebleness, tremor, dyspnœa, and incoordination in the movements. Very large quantities elicit clonic and then tonic convulsions and tetanus, during which the respiration ceases. The pulse is slowed at first from stimulation of the vagus centre, is afterward quickened from its paralysis, and still later becomes slow again from direct action on the cardiac muscle. The blood-pressure rises from constriction of the arterioles but afterward falls from the weakness of the heart. Hydrastine injected intravenously arouses the uterus to contractions, which are sometimes rhythmic in character, but sometimes assume a prolonged tetanic form; the action is a local one, for it also occurs in the excised organ. Hydrastine is excreted as such in the urine. When it is administered for some time, a cumulative action is said to be developed.

Canadine in small quantities produces depression and drowsiness followed by complete recovery without further symptoms. In larger quantities v. Bunge found that it caused a short stage of excitement, which was followed by depression and paralysis of the central nervous system. It has little or no effects on the mammalian circulation when administered in ordinary doses, but very large quantities cause weakness and arrhythmia of the heart. Its injection is followed by violent peristalsis of the intestine and diarrhœa. Cana-

dine is present in only very small quantity in the Golden Seal and has apparently little importance in therapeutics.

Hydrastinine differs from hydrastine in causing no marked disturbance of the centres of motion and feeling save in enormous doses, which paralyze the nervous system. The heart is slowed and strengthened by small doses, apparently from direct action on the muscle, and the output is increased. This causes a small rise in the blood-pressure, and another factor leading to the same result is a slight constriction of the arterioles through a direct action on the muscular coats; this slight constriction is observed also on perfusing the surviving organs. The action on the blood-pressure is not very marked, however, even when large doses are employed.

The most important action of hydrastinine is that on the uterus, which increases in tone and often contracts rhythmically and powerfully under its influence. This occurs also in the excised organ and is due to a direct action on the uterine muscle. There is apparently another effect due to stimulation of the ganglia on the fibres of the hypogastric nerves supplying the uterus, for in the non-pregnant cat, Laidlaw observed an inhibition of the organ from hydrastinine which could be removed by large doses of nicotine. This nervous action is not of importance, however, in the pregnant uterus in which hydrastinine is used chiefly, and in fact would here reinforce the direct muscular effect. Archangelsky states that a 10 per cent solution of hydrastinine applied locally causes dilatation of the pupil, which reaches its maximum in two to three hours, and lasts for twelve to fifteen hours.

Cotarnine differs from hydrastinine in not constricting the vessels or strengthening the heart, so that the blood-pressure falls under it. The action on the uterus also seems rather weaker. The base obtained from laudanosine resembles hydrastinine exactly in action.

Therapeutic Uses.—Hydrastis has been used as a stomachic bitter and the larger quantity of berberine contained in it would seem to give it a place along with the simple bitters. It has also been credited with some obscure action on the mucous membranes when applied locally, through which it is said to benefit many forms of catarrhal inflammation; for this purpose the glycerite may be used. Besides various conditions in which its use was attended by doubtful success, it has been used in hæmorrhage from the uterus; but for this purpose hydrastinine ought to be preferred, as it acts more strongly on the uterus than hydrastine. The conditions in which it is indicated seem to be moderate hæmorrhage; for example, hydrastinine may be of value in excessive menstrual flow, while in post-partum hæmorrhage it seems to have little effect. In other forms of hæmorrhage, these drugs appear to have no value whatever. Hydrastine and hydrastinine have not attained any assured position in therapeutics, for at best they can only be considered inferior substitutes for ergot, which has a much more decided action on the vessels and the uterus. Cotarnine is inferior to hydrastinine and might be dismissed.

Preparations.

NONOFFICIAL.

Hydrastis, the rhizome and roots of Hydrastis Canadensis, Golden Seal, containing 2.5 per cent of hydrastine.

Cotarninæ Hydrochloridum, Stypticine, Styptol, a yellow crystalline powder. 0.06 G. (1 gr.).

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3. **Aspidosperma or Quebracho.**

The bark of Quebracho blanco (Aspidosperma quebracho) contains a number of alkaloids which are probably very similar in chemical composition and which seem to possess almost the same action. They are *Aspidospermine*, *Aspidospermatine*, *Aspidosamine*, *Hypoquebrachine*, *Quebrachine*, and *Quebrachamine*. Another species of Aspidosperma, Payta, contains two alkaloids, *Paytine* and *Paytanine*, of which Paytine resembles closely the Quebracho alkaloids in its pharmacological action. Quebrachine is also found in the bark of the Yohimbehe tree (Corynanthe yohimbi) and was formerly known as *Yohimbine*.

These alkaloids all produce nausea, but even after large doses vomiting does not occur, except after Aspidosamine. The nausea is accompanied by the usual concomitant symptoms—salivation, increased secretion of mucus in the respiratory tract, depression, and alternately rapid and slow pulse. Large quantities often cause symptoms of central nervous stimulation, tonic contractions and convulsions. The respiration is quicker and deeper after small quantities, but after lethal doses becomes slow and weak, and finally ceases. Periodic respiration often occurs before the final standstill, a series of deep dyspnœic movements alternating with several shallow, insufficient ones. The failure of the respiration is the cause of death in mammals, the heart continuing to contract for some time longer. Quebrachine is the most powerful of these alkaloids, aspidospermine nearly rivaling it, while quebrachamine and aspidosamine are less active.

These symptoms are generally ascribed to a direct action on the central nervous system, which is first stimulated and then depressed. The chief seat of action seems to be the medullary centres and the spinal cord, although the basal ganglia may also be more or less involved. The stimulation of the medullary centres explains the nausea and vomiting and also the changes in the respiration, while the convulsions and increased reflex excitability point to the spinal cord.

The terminations of the motor nerves in voluntary muscles are paralyzed by aspidosamine and quebrachine in the frog, not by the other alkaloids; but all of them lessen the strength of muscular tissue and eventually paralyze it in these animals. Neither of these results has been observed to follow the injection of the alkaloids in mammals. Some anæsthesia has been observed from the local action of quebrachine on mucous membranes and nerve fibres.

The circulation in mammals is affected indirectly through the nausea, and large doses slow and weaken the heart through a direct action in addition; the blood-pressure falls from depression of the vasomotor centre. Under very large quantities the neuromuscular apparatus appears to be paralyzed, for epinephrine causes no rise in pressure. The ganglia on the course of the autonomic nerves are also weakened or paralyzed by these alkaloids in large quantity. Even small quantities of quebrachine dilate the vessels of the skin and genital organs from action on the vessel walls (Muller). This causes erection and promotes sexual desire in both male and female animals, and this has led to the use of quebrachine (under the name of yohimbine) in veterinary medicine and also in man to improve sexual power in cases of neurasthenic impotence and similar conditions.

Some diarrhœa has been observed after the administration of these alkaloids, and this apparently arises from accelerated movements of the intestine (Cow). Diuresis is said to follow their use in some instances.

Some authors have observed a change in the red corpuscles under quebrachine, but its nature is unknown.

Commercial "aspidospermine" is a mixture of all the alkaloids along with other bodies. It is sometimes prescribed in doses of 1–2 mgs. ($\frac{1}{60}$–$\frac{1}{30}$ gr.).

Aspidosperma was advised by Penzoldt in the treatment of dyspnœa from a variety of causes, and his statements have received a certain amount of support from clinicians. The special conditions in which it has been advised are dyspnœa from pulmonary disease, especially emphysema, and from car-

diac weakness and asthma. Its action on the respiratory centre may explain to some extent the benefits derived from it, but the increased secretion of the bronchi produced by the nausea may also be of some importance. The use of quebrachine in impotence has been mentioned already.

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4. Phlorhizin.

Phlorhizin is not used in therapeutics, but has attracted some attention from its effects in animals, and may therefore be mentioned briefly. It is a glucoside ($C_{21}H_{24}O_{10} + 2H_2O$) found in the rootbark of the apple, pear, cherry and plum trees. When given in large quantities by the mouth it sometimes causes some diarrhœa in animals, but apart from this its only effect is glycosuria, which also follows its injection subcutaneously or intravenously. The urine is found to contain 5–15 per cent or even more of sugar, sometimes along with acetone and oxybutyric acid, so that the intoxication seems at first sight to resemble diabetes mellitus in man very closely. Phlorhizin induces the same results in man, and the glycosuria is generally not accompanied by any other symptom. It differs from true diabetes, however, in the fact that the sugar of the blood is not increased in amount. The glycosuria is not due to any change in the general metabolism of the body, therefore, but to some alteration of the renal epithelium, by which the blood sugar escapes into the urine, instead of being retained in the body and used as a source of energy. This has been definitely proven by Zuntz, who showed that when phlorhizin was injected into one renal artery, the urine secreted by the corresponding kidney contained sugar, while that from the other remained normal for some time. As the available sugar is drained off in the urine, the tissues rapidly manufacture more and pour it into the blood. As long as sufficient food is given, the loss of sugar does not seem to entail any increase in the destruction of the tissue protein, but when phlorhizin is given to starving dogs, the waste of sugar has to be made up from the tissues, and the nitrogen of the urine accordingly rises in amount, while at the same time the liver cells become infiltrated with fat globules. The statement that the sugar of the milk is increased by phlorhizin has proved to be incorrect.

Glycosuria may be maintained for an indefinite time if the administration of phlorhizin be continued, and animals recover rapidly when the treatment is stopped. The glucoside is probably excreted unchanged in the urine, although this has not been quite satisfactorily demonstrated as yet. Phlorhizin may be decomposed into a sugar, phlorose, and phloretin, which also induces glycosuria.

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II. POISONS WHICH INCREASE METABOLISM.

1. Dinitrophenol.

Among the nitro derivatives of phenol and naphthol which have been studied in the past few years dinitrophenol, 1-2-4, has attracted the most attention on account of its marked effect as a metabolic stimulant.

In 1885 it was shown that it would increase the metabolism of dogs and that the administration of large doses was followed by vomiting, fever, hyperpnœa and death; rigor mortis setting in very rapidly. During the World War munition workers suffered from poisoning due to this chemical; in many cases the poisoning being severe and even fatal. Experiments upon animals showed that the oxygen consumption was increased many times and that the site of the action of the drug was peripheral rather than central. In 1933 Tainter, Cutting, and their coworkers published the first of their papers upon the subject, confirming the earlier work and suggesting that the drug might prove useful as a stimulant to metabolism and especially as a remedy to be used in obesity.

Since that time many publications have appeared dealing with the different aspects of the drug's action.

Administered to man in doses of from 3 to 5 mgs. per kilogram of body weight, dinitrophenol increases the metabolic rate from 20 to 30 per cent and this increase may last for from two to three days before it has returned to the normal level. Slightly larger doses cause profuse sweating while doses of 10 mgs. per kilogram, in addition to the sweating, cause an increase in body temperature of 3 or more degrees Centigrade. There is a marked increase in respiration and a sensation of great heat.

Doses of 0.1 G. each given three times a day may have little effect upon blood-pressure but there is a marked increase in pulse rate and in venous pressure.

Toxic doses are followed by nausea and gastro-intestinal distress, sensations of heat, flushed skin, marked sweating, restlessness, rapid and deep respirations and fever. As the fever increases the breathing becomes exceedingly rapid and of maximum depth until the patient is using all his accessory muscles of respiration in an effort to secure adequate aëration. There may be pain in the chest or anginal cramps. The respiration finally fails to keep up with the oxygen consumption, the blood becomes cyanotic and anoxemia develops. There is an increase in lactic acid in the muscles associated with the high fever of over 110° F. Heat rigor of the muscles rapidly follows, starting in the extremities and spreading to the respiratory muscles.

The symptoms in animals resemble very closely those seen in man.

In rabbits moderate changes were found in the electrocardiograms following the prolonged use of the drug. These seemed to indicate a prolongation of the recovery time of the heart muscle and a decrease in the voltage initiated by the ventricular contraction, suggesting some alteration in the metabolism of the myocardium. In contradistinction to thyroxin which lowers the cardiac glycogen to a considerable degree, dinitrophenol has no such effect as the hearts of chronically poisoned rats still retain glycogen at a normal level. No evidence could be found for the view that dinitrophenol caused death through an action on the heart.

Numerous cases of idiosyncrasy to the drug have been reported, the most common symptom being a pruritic skin eruption. The rash is usually preceded by itching which may become very intense, forming a very disagreeable complication as it leads to excessive scratching. The rash may be of the maculo-papular or urticarial type. It usually

disappears a few days after the drug has been discontinued but is likely to recur when treatment with it is renewed. In some cases the skin manifestations are more serious, as exfoliative dermatitis, similar to that seen after the use of the arsphenamines, has been described.

The nervous system is affected, as shown by loss of sense of taste, and less frequently, of smell and some disturbance of hearing together with polyneuritis affecting especially the feet and legs. In some cases the blood-forming organs have been affected, as shown by agranulocytosis which has resulted in death.

One of the most important among the toxic effects which have followed the use of dinitrophenol is the appearance of changes in the lens with the formation of cataracts leading to impairment of vision and even to blindness. These changes in the eye have been encountered in a number of young women who have taken the drug in order to reduce their weight. It would seem that the cataract formation is the result of a direct toxic effect of the drug.

Post mortem changes in acute cases have shown marked rigor mortis, acute pulmonary congestion and œdema, hæmorrhages in the endocardium, pericardium and pia and mild necrotic changes in the kidneys.

A study by Tainter and his coworkers of the metabolism in patients upon a restricted diet receiving therapeutic doses of dinitrophenol showed that while the loss of body weight was increased there was a simultaneous increase in metabolic rate. This increase may reach 100 per cent. The extra energy was derived almost exclusively from the fat and practically none from protein or carbohydrate. It would seem, therefore, that the drug causes very little breaking down of body protein. The fat was completely oxidized without producing acidosis or ketone bodies. No significant changes were found in urinary nitrogen, nonprotein nitrogen of the blood, urea, uric acid, creatin or creatinine, indicating practical absence of effect upon total nitrogen metabolism. The ethereal sulfate of the urine was not increased, showing that the drug was not conjugated in the body as an organic sulfate compound. The increased metabolism was accompanied by increased perspiration and lessened urine output.

The increase in metabolism produced by dinitrophenol, as shown by these findings, evidently differs fundamentally from that following the use of thyroid preparations in which there is a very characteristic increase in nitrogen excretion associated with the increase in metabolism.

According to Taussig rats which have been deprived of their glycogen by phlorhizin or by refrigeration do not react to dinitrophenol by an increase in temperature. Inasmuch as protein and fat are still available, it is possible that the presence of carbohydrate in the tissues is essential for the rise in metabolism following administration of the drug.

Newman and Tainter studied the effect that the increased metabolism produced by dinitrophenol might have upon the fate of alcohol in the body. They believe that any change in the blood-alcohol curve following the use of the drug is due entirely to the increased pulmonary ventilation and that the augmented metabolism and heightened temperature play no part whatsoever. On the other hand, Harger and Hulpieu, in an earlier study, had ascribed the acceleration of the disappearance of alcohol under these conditions to an increased consumption by the tissues.

In dogs, doses which were sufficient to cause subacute poisoning and death were not found by Schulte to affect liver function in so far as such could be judged by the galactose and uric acid tolerance tests. The administration of small doses of dinitrophenol to animals has little or no effect upon the growth curve, but with larger amounts there may be a sharp fall in weight and definite shortening of life. In rabbits Molitor ascribes this decrease in weight to a lessened intake of food. Also in these animals he observed the development of cataracts while Tainter found no such eye changes in rats, nor did Schulte see any in dogs.

Therapeutic Uses.—Dinitrophenol has been used extensively recently for the treatment of obesity. Reports are by no means in agreement as to whether the results obtained by its use are superior to those which may be gained through the control of diet alone. There is, however, no doubt that the drug is dangerous as shown by the numerous cases of poisoning reported in the literature and by the deaths which have resulted from its administration.

The drug certainly should not be employed except in selected cases under the care of experienced physicians. The situation at the present time is especially dangerous as, due to widespread publicity, the drug is appearing in remedies of secret composition advertised for the reduction of weight. Many of the cases of poisoning are due to the use of such preparations.

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2. Tetrahydronaphthylamine.

A poison may be mentioned here which has the property of causing fever temperature and even proves fatal from hyperthermia in some cases. Tetrahydro-β-naphthylamine ($C_{10}H_{11}NH_2$) raises the temperature by increasing the heat production through muscular movement and by limiting the heat loss through constriction of the vessels of the skin and superficial tissues. The muscular movement arises from central nervous excitation, and is shown in tremor and convulsions after large doses; the oxygen absorption and the carbon dioxide production are greatly augmented. The constriction of the cutaneous vessels is also mainly due to stimulation of the vasomotor centre, though there may be some slight action on the vessel walls also. The pupil is widely dilated and the eyeball is protruded, from stimulation of the sympathetic mechanism, partly in the periphery but mainly in the central nervous system. Cocaine has a similar but weaker action; the naphthylamine compounds do not cause local anæsthesia.

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III. POISONS WHICH ACT ON THE BLOOD.

1. Nitrobenzol Compounds.

The nitrobenzol bodies are chiefly of interest because they have often given rise to poisoning of late years from their use as explosives, in chemical manufactures, and to flavor alcoholic liquors. They are readily absorbed from the skin and serious symptoms have followed the wearing of clothing dyed with them. In man nitrobenzol causes a grayish-blue, cyanotic color of the skin and visible mucous membranes, often with nausea, vomiting, great muscular weakness, marked dyspnœa, delirium, and some convulsive movements of the face and jaws, less frequently of the whole body. Total unconsciousness and coma are followed by arrest of the respiration.

These effects are due in part to changes in the blood, in part to central nervous action, in which stimulation and paralysis seem to follow one another. The blood is found of a chocolate-brown color, and some of the red cells are either deformed or entirely destroyed. Examined with the spectroscope, methæmoglobin is very often found in it, while in other cases an absorption line is observed between the yellow and the red, which does not seem to correspond to that of any of the ordinary hæmoglobin products, and has therefore been called the nitrobenzol-hæmoglobin line. The blood contains a much smaller amount of oxygen than normally, in some cases only 1 per cent, instead of 17, and artificial respiration or even shaking the blood in air fails to oxidize it further, as the combination of nitrobenzol and hæmoglobin seems to be incapable of absorbing oxygen. Similar changes may be produced in venous blood outside the body by shaking it with nitrobenzol. These changes in the blood are the cause of the cyanosis, and the imperfect oxidation of the tissues leads to the appearance of a number of abnormal products in the urine, such as hæmatoporphyrin. In animals a gastro-intestinal catarrh is almost constantly produced unless the intoxication is very acute, and this occurs even when the poison is inhaled or injected subcutaneously.

Metadinitrobenzol ($C_6H_4(NO_2)_2$) has repeatedly given rise to poisoning in the manufacture of the modern explosives, such as roburite and securite. In action it resembles nitrobenzol, but is more poisonous, and the gastric symptoms are more marked. Amblyopia and jaundice-like coloration of the skin often occur from prolonged exposure to this poison.

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2. Toluylendiamine.

Toluylendiamine ($C_6H_3CH_3(NH_2)_2$) has never been used in therapeutics, but it is of importance from the light which it has thrown on some forms of jaundice. Stadelmann found that its administration in dogs produced the

typical symptoms of icterus, while in cats the icterus was less marked, but very large quantities of hæmoglobin were excreted in the urine. The explanation of this action is the destruction of the red cells in the blood, which leads in the dog to the formation of large amounts of bile pigments in the liver. Some of this pigment is reabsorbed from the bile vessels and leads to typical jaundice. The absorption is promoted by a curious increase in the mucus secretion of the bile ducts, which renders the bile more viscous, and by thus delaying its evacuation into the intestine favors its absorption into the blood. This increased mucus formation is believed to be due to the action of the poison on the secretory cells of the larger bile ducts. The formation of bile pigment from hæmoglobin liberates large quantities of iron, which seem to be stored in the liver, spleen, and bone-marrow. In the cat the hæmoglobin is not so largely formed into bile pigment, but escapes in the urine. In both animals some methæmoglobin is probably formed.[1] According to Joannovics and Pick the hæmolysis is not directly due to the toluylendiamine, but is the result of bodies formed in the liver under the action of the poison.

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3. Benzol.

Benzol, or benzene, is much less poisonous than its hydroxyl compounds, but may give rise to symptoms resembling those of phenol when it is inhaled in large quantities. It was at one time suggested as a general anæsthetic, but the preliminary excitement is much greater than that seen in the use of chloroform or ether, and partakes more of a convulsive character. Even after unconsciousness and anæsthesia are attained, the characteristic muscular tremor of the aromatic compounds continues. In some animals it produces violent and prolonged convulsions, with only partial loss of sensation, and even large quantities do not cause the complete relaxation of the muscles requisite for surgical operation. It seems to have little or no irritant action on the alimentary tract or kidneys in animals, and is excreted in part by the kidneys as phenol double sulfate, in part unchanged by the lungs.

Santesson states that hæmorrhages occur very frequently in fatal poisoning in man, and found the same result in experiments on rabbits; he ascribes it to fatty degeneration of the arterial walls, which was well-marked in most of his experiments. A number of cases of fatal intoxication are on record, some of them arising from the drug being swallowed by suicides, but most of them from the accidental inhalation of large quantities in india-rubber factories. Animals exposed to benzol vapor do not seem to absorb enough to be seriously poisoned, but when it is injected subcutaneously or applied over a large skin area, it proves fatal to them. It has recently been noted that in benzol poisoning a marked fall in the number of the leucocytes of the blood occurs and this has suggested the use of benzol in some forms of leucæmia; a great diminution in the white cells follows and the general symptoms show a corresponding improvement. It is too soon to state how far the treatment leads to permanent relief, or how long it may be continued.

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[1] A somewhat similar action follows the administration of Cephalanthin, the active principle of Cephalanthus occidentalis, Button-bush or Swamp dogwood (Mohrberg), and of the alkaloids of several species of Senecio such as ragwort and groundsel.

P. HYDROCYANIC OR PRUSSIC ACID.

Prussic, or hydrocyanic, acid differs entirely from the other acids in its pharmacological action, and has therefore to be described apart from them.

The pure acid is scarcely ever seen save in the chemical laboratory, and is dangerous to handle, as it is very volatile and when inhaled may produce death within a few seconds. It is generally met with in a very dilute solution, which is formed by the decomposition of one of its salts.

In nature, prussic acid occurs in the secretion of some of the myriapoda, and in the decomposition products of a few glucosides, of which *Amygdalin* is the best known. Amygdalin is in itself practically inactive, but may be decomposed by dilute acids or by a ferment, emulsin, which is generally found associated with it in plants (see p. 33). Prussic acid may be formed from the amygdalin of the bitter almond and the kernels of such fruits as the apple, cherry, plum, etc., and from the bark and leaves of several trees including the laurel (Prunus laurocerasus). A paste formed from bitter almonds has given rise to symptoms from the prussic acid, but a more dangerous substance is the oil of bitter almonds, which consists of benzaldehyde and prussic acid in a loose combination and in very varying proportions. Sweet almonds contain no amygdalin and are therefore harmless. Laurel water and the preparations of Virginian cherry bark contain benzaldehyde and prussic acid in too small quantity to have any poisonous action. Several plants which contain glucosides similar to amygdalin have given rise to poisoning in cattle, probably from prussic acid being freed from the glucosides in the intestine.

Prussic acid and its salts have practically the same action, although none of the latter are so poisonous as the free acid. Cyanogen, $(CN)_2$, also resembles prussic acid in its effects, but is not so active.

The ferrocyanides and other double cyanides are in most cases harmless but other compounds, from which prussic acid is formed in the organism, are poisonous. The organic combinations containing the—CN radical form two series, the *Nitriles*, in which the nitrogen is trivalent (*e. g.*, $CH_3—C{\equiv}N$), and the *Isonitriles*, or *Carbylamines*, in which the alkyl is attached to the nitrogen (*e. g.*, $CH_3—N{\equiv}C$). These compounds are all much less poisonous than prussic acid, and the nitriles are said to differ from it in their effects, inasmuch as the chief symptoms caused by them arise from gastro-intestinal irritation. The isonitriles are more poisonous than the nitriles and resemble the acid more closely in their action. Both nitriles and isonitriles give rise to the formation of prussic acid in the tissues.

Symptoms and Action.—Prussic acid acts upon almost all forms of living matter; in mammals the central nervous system is especially susceptible. The fatal dose in man is believed to be about 0.05–0.08 G. (1–1½ grs.) of the pure acid, so that it is less poisonous than some of the alkaloids and glucosides. It acts so rapidly, however, that it must be regarded as a most dangerous poison. One volume of prussic acid in 2000 of air is generally fatal to animals.

After very large doses in mammals, there may be practically no symptoms; the animal falls to the ground with a slight convulsive movement or a scream, and death follows in a few seconds from simultaneous arrest of the heart and respiration.

In smaller quantities prussic acid has a bitter, acrid, burning taste, which induces salivation, and is followed by numbness in the mouth and throat. A sensation of warmth in the stomach is followed by nausea and vomiting, confusion and headache, dyspnœa, slow pulse and general muscular weakness. The pupils are widely dilated and the eyeballs protrude, as generally occurs in asphyxia. Unconsciousness follows, and then violent convulsions, which pass into paralysis, with involuntary evacuation of the contents of the bladder and bowels; the respiration becomes extremely slow and eventually ceases, while the heart continues to beat for some time afterward.

The **Central Nervous System** is first stimulated and then paralyzed; the convulsions resemble those produced by stimulation of the hind-brain, although the subsequent paralysis seems to include all parts of the central axis.

Striated and unstriated **Muscles** and the **Nerves** are weakened and eventually paralyzed when suspended in an atmosphere of the gas, but they are not affected in poisoning; the nerves are more readily poisoned than the muscles. When prussic acid in solution is applied locally to the **Skin** it produces numbness and partial loss of sensation, but this does not follow in general poisoning.

The **Respiration** is rendered quicker and deeper by the injection or inhalation of small quantities of prussic acid. After larger quantities, the acceleration is often interrupted by a prolonged pause after which the breathing returns spontaneously. In fatal poisoning no such return occurs, and after very large doses the breathing may cease within a few seconds.

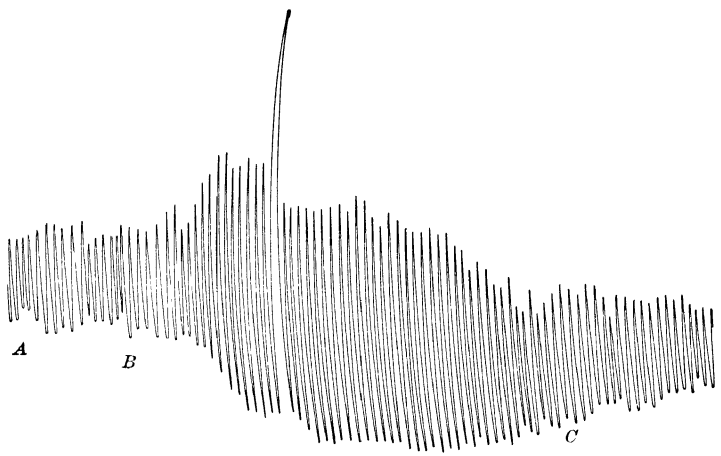

FIG. 63.—Tracing of the movements of the diaphragm (respiration) of the rabbit under a large but not fatal dose of cyanide of potassium injected intravenously. *A–B*, normal respiration. At *B* 1 mg. injected, the respiratory movements are much larger. At *C* recovery. Note the short duration of the stimulation.

The **Circulation** is altered mainly through the action on the central nervous system, although prussic acid also acts directly on the heart. The stimulation of the inhibitory centre generally slows the pulse, but this is accompanied by a very considerable rise in blood-pressure from increased activity of the vaso-constrictor centres. Later, the blood-pressure falls, from the depression of the vasomotor centre; the heart is now directly affected, the chambers being greatly dilated, and block often appearing.

Nutrition.—Prussic acid exercises a depressant action on protoplasm in general. Both plants and animals are retarded in their movements and in their nutritive processes by its presence, although they may recover and show no subsequent deterioration, provided the poison acts only during a short time and in sufficient dilution. For example, the development of seeds is hindered by the presence of prussic acid, but proceeds when it is withdrawn; yeast cells cease their activity, and the insectivorous plant Drosera no longer moves its tentacles in the presence of cyanides or prussic acid (Darwin). This action in plants arises from the poison arresting the respiration of the cells through paralysis of the oxidizing ferments, for no carbon dioxide is given off nor oxygen absorbed. The hydrolytic ferments are less affected or may be unchanged in activity.

The effects of prussic acid on the mammalian tissues were first examined by Geppert in a long and careful research. He found that the oxygen absorbed by the tissues was much lessened by it; even during the most powerful convulsions after prussic acid, the absorption of oxygen is often distinctly lower than in the normal resting animal and the carbon dioxide formed by the tissues falls

correspondingly. The imperfect oxidation is due to the tissues being unable to absorb the oxygen brought to them by the blood cells; in fact, a change occurs in the protoplasm which retards the normal respiration of the cell. In consequence of this, the oxyhæmoglobin of the blood is not reduced in the capillaries, so that the venous blood has the same bright red color as the arterial. Prussic acid is rapidly changed to harmless products in the tissues, however, provided a lethal dose has not been given, and as this process goes on, the protoplasm recovers its oxygen-absorbing power, the expired air becomes less rich in oxygen and richer in carbon dioxide, and the venous blood assumes its ordinary dark color. The usual results of imperfect oxidation in the tissues are seen in an increase in the sugar and lactic acid in the blood, and augmented nitrogen, urea and unoxidized sulfur in the urine, although the last substance may be accounted for by the thiocyanate formed.

This lessened O_2 absorption in the tissues arises from the intracellular ferments being paralyzed in animals in the same way as in plants. In fact the whole action of prussic acid is so like that of asphyxia, that there is every reason to hold that it is limited to this arrest of oxidation.

Prussic acid is changed, in part, to thiocyanate in the tissues and excreted in this form in the urine, while part of it undergoes further and unknown changes. An enzyme "rhodanese," which promotes thiocyanate formation from sulfur and cyanide, has been demonstrated in the various tissues examined except blood and muscle. It appears to be most abundant in liver.

There is no combination with hæmoglobin formed by cyanide in the living tissues, the change in the color being due to the oxyhæmoglobin not being reduced in them. If normal blood is brought in contact with a solution of peroxide of hydrogen, it effervesces, owing to the liberation of oxygen by the peroxidase ferment, and the peroxide being all decomposed in this way, the oxyhæmoglobin remains unchanged; if, however, prussic acid be present, no effervescence occurs, because the peroxidase is rendered inert, and the hæmoglobin is at once changed to methæmoglobin from the oxidizing action of the peroxide, which is no longer dissipated.

Therapeutic Uses.—Prussic acid might be eliminated from therapeutics without loss. It was formerly applied to soothe itching surfaces, and in the vomiting of pregnancy, but is hardly used for these purposes now. It was also a constituent of expectorant mixtures in which it was supposed to relieve cough. Recently it has been injected intravenously in the form of sodium cyanide as a respiratory stimulant; but this heroic treatment is not likely to appeal to many.

Preparations.

Acidum Hydrocyanicum Dilutum (B. P.), a 2 per cent solution formed from potassium ferrocyanide or silver cyanide. It is a colorless fluid with a characteristic smell and taste, and ought not to be kept long, as it is liable to decomposition; much of that actually used in medicine is partially decomposed and therefore under 2 per cent in strength. Dose, 0.12–0.3 mil. (2–5 mins.).

A number of other preparations contain prussic acid in small quantities along with benzaldehyde, and are used as flavors (page 246).

In **Poisoning** with prussic acid or the cyanides, the treatment is thorough evacuation of the stomach, warmth, and general measures against collapse. Artificial respiration should be resorted to when necessary, as cyanide is comparatively quickly rendered inactive, and the recovery is rapid when it once sets in.

Cyanide Antidotes.—Due to the rapidity of development of manifestations and early death in cyanide poisoning, the need of a specific and rapidly effective antidote, as an adjuvant to general measures of treatment, has long been realized. The detoxication in the body of at least a part of the cyanide by thiocyanate formation suggested the use of sulfur compounds to increase the available sulfur supply for this purpose. Sulfur in the oxidized form, such as sodium sulfate, proved to be of no value. Conversely, compounds containing unoxi-

dized sulfur such as sodium thiosulfate, sodium tetrathionate, colloidal sulfur, cystine and cysteine have given positive results in animal experimentation. However, the practical value of such compounds is seriously limited by their slowness of action, rarely being effective unless administered within a few minutes after the cyanide. However, a definite protective action is realized if they are already present in the circulation and tissues when the poison is given. In a few clinical cases the relatively non-toxic sodium thiosulfate has been successfully used intravenously; some aldehydes and ketones have also shown an antidotal action experimentally, presumably by binding the cyanide by cyanhydrin formation. The value of glucose in this regard is questionable but certain compounds such as dihydroxyacetone and glyceric aldehyde have proved effective. Here, again, the beneficial action is lessened if the antidote is administered after the cyanide and even under favorable circumstances there may be a recurrence of symptoms due to the freeing of the cyanide radicle from the cyanhydrin compound. Such treatment may also be limited by the toxicity of effective doses of the antidotes. Methylene blue has recently been suggested as a clinical antidote in cyanide poisoning, since its restorative action on intracellular oxidation processes depressed by cyanide in *in vitro* systems is generally recognized and since its protective action has been proved in animals even when administered after the development of symptoms. Numerous favorable clinical reports are now available in which cyanide poisoning was treated by the intravenous injection of 50 cc. of a 1 per cent solution, repeated in certain cases. The mechanism of the antidotal action of methylene blue is not definitely established. It has been ascribed by Hug and by Wendel to the formation of methemoglobin which in turn binds the cyanide as the stable non-toxic cyanmethemoglobin. From this compound the cyanide is freed so gradually that it can be detoxicated by normal body processes. Methemoglobin on intravenous injection is likewise effective. Brooks on the contrary, believes that methylene blue acts by its intracellular oxidative function, maintaining that it does not form methemoglobin *in vivo* as the presence of reducing substances such as glucose immediately reconverts it to hemoglobin. Hug has further demonstrated that several methemoglobin forming substances have an antidotal action in cyanide poisoning, probably the most effective being sodium nitrite, which has recently been used successfully in a few clinical cases. This type of antagonism is limited, however, by the amount of hemoglobin which can be spared for methemoglobin formation. In animals a maximum of approximately four lethal doses may be tolerated by this mechanism. A curative action definitely beyond the additive effect has been demonstrated by following the administration of a promptly effective methemoglobin-forming substance with a more slowly acting sulfur compound. Presumably the toxic action of the cyanide is lessened by cyanmethemoglobin formation and the increase in available sulfur promotes thiocyanate formation as the cyanide is gradually freed from the non-toxic compound. The greatest potentiation has been observed experimentally with sodium nitrite and sodium thiosulfate. The effectiveness of amyl nitrite as an alternative or as a preliminary adjuvant to sodium nitrite has also been demonstrated. For clinical use it has been suggested that from 6 to 10 mg. of sodium nitrite per kg. be injected intravenously in 3 per cent solution and be followed by 0.5 G. of sodium thiosulfate per kg. intravenously in 50 per cent solution. Amyl nitrite inhalation for from fifteen to thirty seconds every two or three minutes may be used as a temporary measure. However, such combinations have been used in too few cases to establish an optimum dosage.

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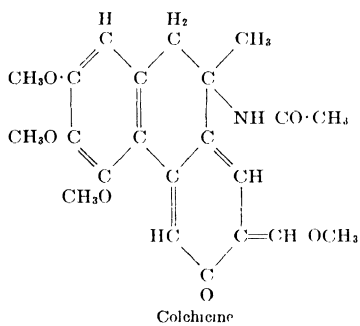
* Antidotes.

Q. COLCHICUM.

Colchicine and *colchiceine* are two nearly related bodies found in the seeds and corm of Colchicum autumnale, which owes its activity to their presence. Colchicine



Colchicine

is the methyl ester of colchiceine, which is much less active pharmacologically. Colchicine is feebly basic, while colchiceine is slightly acid in reaction.

Symptoms.—No symptoms whatever follow the use of colchicum in small quantities. Large doses, corresponding to 4–5 mgs. of colchicine, cause diarrhœa with some griping in susceptible persons, and in the therapeutic use of the drug purging is often observed; symptoms only arise several hours after the drug is administered, and this interval is not shortened by increasing the dose.

In poisoning with colchicine, whether given by the mouth or injected hypodermically, the symptoms arise from the alimentary tract. Pain in the gastric region is followed by salivation, nausea, vomiting, and diarrhœa. At first the evacuations are the ordinary contents of the stomach and intestine, but afterwards a quantity of sticky mucous fluid may be ejected, often streaked with blood. Later, a condition of depression, apathy, and collapse follows, and the movements become slow and difficult, more especially in the posterior extremities, which

eventually become completely motionless; the paralysis then progresses upward until the movements of the fore-limbs and respiratory muscles are involved, when death occurs from asphyxia. In man the intelligence remains until death, though there is generally some giddiness and precordial anxiety and occasionally some confusion or even delirium preceding the collapse.

In mammals poisoned with colchicine the alimentary canal exhibits all the appearances of acute gastro-enteritis, with numerous ecchymoses, especially in the upper part of the bowel. In less acute cases these inflammatory symptoms are less marked, and in man there is seldom more than catarrh of the duodenum.

The **Circulation** is apparently but little affected. In animals, the blood-pressure and heart rhythm remain normal, and though a small, rapid pulse may be one of the features of the poisoning in man, this is due to the collapse rather than to any direct action on the circulatory organs.

The **Respiration** is slow, but is deep and full at first. Later it becomes shallow, and the failure of the centre is the cause of death, the heart continuing to beat for some time afterwards.

The **Movements of the Bowel** are much hastened when the symptoms set in, and Dixon states that colchicine acts on the bowel in the same way as pilocarpine, and that its action is antagonized by atropine; but this is entirely inadequate to explain the acute inflammatory appearances, which are evidently due to an irritant action on the mucous membrane. Increased movement is said to be induced in the plain muscle of the spleen, uterus, and bronchial muscle from a pilocarpine-like action.

When **Locally Applied** to sensitive mucous membranes, or when injected hypodermically, colchicine is intensely irritating, producing redness and prickling in the skin, and a burning sensation in the mouth and throat.

The **Nervous Symptoms** are supposed by some to be due to a direct action on the central nervous system, but are to be ascribed rather to a condition of collapse produced indirectly through the action on the abdominal organs.

The influence of colchicine on the **Kidneys** varies, for in some cases complete anuria is produced for many hours, while in others the urine is slightly increased. The constituents of the urine are not materially altered by ordinary therapeutic doses of colchicum, and, in particular, the uric acid shows no constant change in amount. In animals, bloody urine is sometimes passed after colchicine.

In poisoning with colchicine the leucocytes are at first reduced in the peripheral circulation, but afterwards increased to beyond the normal number.

All of these symptoms are exactly those caused by a large number of poisons, including some of the bacterial toxins and the heavy metals. Many local irritants when injected into the blood or when absorbed from the subcutaneous tissue or the alimentary canal, exercise an immediate, local action, which betrays itself in pain or ecchymosis and swelling

at the point of injection, but these symptoms pass off in a short time and the animal becomes apparently normal for many hours or even days. At the end of this time, however, symptoms begin to develop at two points—in the alimentary canal and in the kidneys. The reason probably is that the poisons are excreted at these points and are either freed from some harmless combination in which they have circulated in the tissues, or perhaps collect in larger quantities in the excretory organs; it is believed that the seat of action is in the walls of the capillaries, which are dilated, rather than in the tissues in which they are embedded, and these poisons are therefore often termed "capillary poisons." At any rate, irritation and later acute inflammation are set up at these points. At first the irritation excites only diarrhœa and diuresis, but as it goes on, gastro-enteritis and anuria or hæmaturia may be produced. The symptoms from the intestine and kidney may not be equally well marked; at one time the one becomes inflamed while the other is only subjected to mild stimulation, while at other times both are the seat of acute inflammation. The inflammation of the bowel produces a condition of collapse, which is seen also in various intestinal diseases, such as cholera. Sometimes the poisons (and also cholera) produce no very marked symptoms of gastro-intestinal disorder, but rather those of collapse; here it may be supposed that there is general paralysis of the capillaries, similar to that in secondary shock from injury.

A number of colchicine derivatives have been examined by Fühner, who finds that colchiceine has little action and that oxycolchicine is equally inactive in mammals, but is very poisonous in frogs, in which it prolongs the muscle curve in the same way as veratrine and also causes strychnine-like convulsions. Colchicine itself only acts in the frog after a latent period extending over some weeks, as a general rule.

It has been shown recently that colchicine exerts a remarkable effect upon the mitosis of cells in both normal and malignant tissues. This action, which was first described by Dustin, consists in a great increase in mitotic figures, a condition which is best seen in tissues where cell division is of frequent occurrence. Large numbers of abnormal mitotic figures appear, and the chromosomes may be scattered and clumped into groups. Inhibition of the normal process of mitosis has taken place in the metaphase in that there is not a vestige of spindle mechanism visible and very few cells showing the later stages are to be seen. The number of mitotic figures in an area may increase from a normal of 2 or 3 up to 10 or 12 in a few hours, with perhaps 50 per cent of the cells showing mitosis in twelve hours. The abnormality has been ascribed to the failure of the mechanism of which the spindle is the visible attribute (Ludford).

On account of this effect of colchicine it has been used as an index of the rate of cell growth. No similar action is shown by colchicine toward the multiplication of yeast cells inasmuch as it is a process of budding in that instance and no mitotic figures are involved.

Therapeutic Uses.—Colchicum has long been used in gout on purely empirical grounds. In acute cases of gout the tincture of colchicum is given in doses of 20 to 30 minims every four hours until there is some evidence of its action, such as nausea or slight purging. Prolonged administration is not advisable. The pathology of gout is so obscure that no rational treatment for it can be looked for at the present day, and the efficacy of colchicum in this disease can, therefore, be argued solely from clinical experience. There is no doubt that the pain and

inflammation around the joint in an acute attack of gout are relieved by colchicum, often without any other obvious effect, but sometimes only after enough has been given to cause some diarrhœa. In the intervals between the acute attacks, colchicum does not appear to have any beneficial effect, and it is not clear that continued treatment wards off the attacks. The uric acid excretion is not altered by colchicum treatment in gout, nor in health. And though some investigators have stated that the excretion of endogenous uric acid is increased by colchicum, while that derived from the food remains unaffected, this has not been established. The failure to explain the action of colchicum in gout, by changes in the uric acid elimination or in any other way, does not diminish the importance of the clinical evidence that it is beneficial in this disease, but merely indicates that further research is necessary before the problem can be solved.

Preparations

U. S. P.

Colchici Semen, 0.2 G. (3 grs.).
Tinctura Colchici Seminis, 2 cc. (30 mins.).
Colchicina, an alkaloid obtained from colchicum. 0.0005 G. ($\frac{1}{120}$ gr.).

B. P.

Colchici Cormus, 0.12–0.3 G. (2–5 grs.).
Extractum Colchici Siccum, 0.015–0.06 G. ($\frac{1}{4}$–1 gr.).
Colchici Semen, 0.12–0.3 G. (2–5 grs.).
Extractum Colchici Liquidum, 0.12–0.3 mil. (2–5 mins.).
Tinctura Colchici, 0.3–1 mil. (5–15 mins.).

Colchici Cormus, the corm or bulb of Colchicum autumnale, containing 0.25 per cent of colchicine according to the B. P.

Colchici Semen, the seed of Colchicum autumnale, containing on an average 0.40 per cent of colchicine U. S. P., or in the B. P., 0.3 per cent of the alkaloid.

Colchicina ($C_{22}H_{25}NO_6$), an alkaloid obtained from colchicum, pale yellow in color, with a bitter taste and characteristic odor; soluble in 22 parts of water and in alcohol.

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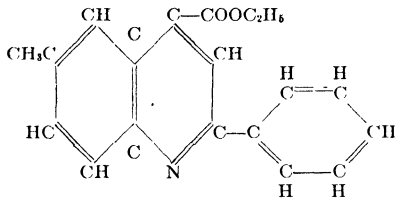
R. CINCHOPHEN. PHENYLQUINOLINE CARBOXYLIC ACID.

A number of compounds of the type of quinoline carboxylic acid have been shown by Nicolaier to increase the amount of uric acid excreted in the urine in a remarkable way; among these the phenylquinoline carboxylic acid is the most efficient and has been introduced into medicine under the name of *cinchophen* or *atophan*.

A nearly related substance, the ethyl ester of a methyl-cinchophen is employed under the name of *Neocinchophen* or *Novatophan*.



Neocinchophen

Cinchophen may be taken in large quantities (100 grs.) without any obvious symptoms, but considerably smaller doses (30 grs) may suffice to increase the uric acid of the urine threefold; in other cases the augmentation is not so great, but it is increased in the majority of instances from 40 to 50 per cent. The urine is little changed in amount but is often turbid when passed, and deposits quantities of urates on standing; this turbidity may appear within forty-five minutes of the administration of cinchophen. No other constituent of the urine is altered appreciably in amount as a general rule. This increased elimination of urates and uric acid occurs in persons on ordinary diet and also on a purine-free diet, in which the uric acid excreted can arise only from the tissues. When cinchophen is given for one day only, the excretion of uric acid rises immediately, and the following day it sinks below the normal amount, and this depression of excretion may continue for even three days as if the first large excretion had exhausted the supply. When it is given continuously for some time, the excretion falls rapidly after the first day and may reach the normal or even below it on subsequent days; very often, however, more uric acid is excreted each day than normally, although the marked excretion attained at first is not repeated.

The more rapid excretion of uric acid is sometimes, but not always, attended by a fall in the uric acid content of the blood. In many cases the blood uric acid has been found to be above normal even when there is an increased excretion through the urine. The action has been ascribed to a direct effect on the kidney, rendering it more readily permeable by the urates, so that those previously retained in the blood through the difficulty attending their elimination by the kidney now escape in the urine. The action of the kidney is usually changed only in relation to the uric acid, but in some cases of retention of urea and chlorides, these are said to be excreted in larger quantities also. The rapid removal of the urates of the blood and tissues appears often to increase the formation of uric acid in the body, for the continued treatment with cinchophen is attended by an abnormally large amount of uric acid in the urine even when it extends to weeks in duration. And it has been found that under cinchophen more uric acid is sometimes eliminated in the urine from a given quantity of nucleinic acid than can be obtained in ordinary circumstances, but this is not invariably the case or the increase may be very small. The formation of uric acid in the organs is thus favored by the cinchophen treatment. The evidence points to cinchophen increas-

ing elimination by the kidney; probably the normal reabsorption of urates in the tubules being hindered by cinchophen. In addition there is doubtless an additional action upon the tissues, as shown by the fact that even with an increased output of uric acid there may still be an abnormally high percentage in the blood. Abl found that calcium and atropine lessen the excretion of uric acid under cinchophen. Cinchophen appears to undergo decomposition in the tissues for the most part, though some appears in the urine unchanged. Like so many other aromatic substances, cinchophen reduces fever temperature and lessens pain (see Antipyretic group).

Grabfield and Gray found that in dogs the administration of cinchophen was followed by an increase in the total nitrogen, sulfur, allantoin and uric acid in the urine, the effect on the nitrogen being brought about through a direct action on the kidney similar to that of the salicylates, where the relationship of the sulfur excretion to the nitrogen excretion remains essentially constant. Denervation of the kidneys in dogs reversed the action of cinchophen upon the uric acid excretion, there being a very marked lessening in the output. However, within a month or six weeks after the operation, a normal increase in uric acid resulted from the exhibition of cinchophen, a change which was ascribed to a regeneration of the renal nerves which had been destroyed. However, the period of time (eighteen to fifty-four days) was so brief that it would seem that another explanation should be sought. Ergotamine also eliminates the increase in uric acid while atropine does not affect it, so that it would appear that the action of cinchophen upon uric acid excretion in the dog is through the adrenergic fibres. As the increase in allantoin is not affected by denervation of the kidney but is eliminated by both atropine and ergotamine, Grabfield and his associates conclude that the cinchophen increase in allantoin is through both adrenergic and cholinergic fibres. Inasmuch as the increased amounts of uric acid which are excreted in the urine under the influence of cinchophen probably come at least in part from stores of uric acid in the tissues, Fürth and Edel studied the effect of cinchophen upon the uric acid content of the liver of rats and they found that very small doses of the drug caused a marked decrease in the uric acid content of the organ, but in no case was there complete disappearance of the product—a residue of 1 to 2 mgs. per cent being retained in every instance. The optimum dose for this effect was found to be about 0.8 mg. of cinchophen daily per kilo of body weight or what could correspond to about 0.05 G. for a man of average weight or, in other words, about one-tenth of the average therapeutic dose of the drug. A sufficient dose of cinchophen or of neocinchophen produced a considerable loss of weight but in the production of this change cinchophen was found to be about three times as toxic as its newer ally. Barbour and Gilman gave neocinchophen to young rats in doses equivalent to 1 G. per kilogram of body weight for a period of one hundred days with no effect on weight and no demonstrable change on the liver. An equal amount of cinchophen given under the same conditions caused death in a very few weeks. The dose of neocinchophen necessary for the production of an effect upon the temperature was found to be two and a half times that of cinchophen.

Recently attention has been called to the not infrequent occurrence of poisoning following the use of cinchophen. In many cases the symptoms are similar to those usually seen in drug idiosyncrasies, such as various cutaneous disturbances, as pruritus, urticaria and different forms of skin eruptions. Anaphylactoid reactions may be present, or gastro-intestinal disturbances, but more serious than these are the cases of toxic hepatitis with jaundice and, in a considerable number of cases, acute yellow atrophy with death. The special factors or conditions which

lead to these cases of serious poisoning are unknown. Long-continued use of the drug has been reported in some instances. In others disturbed kidney function interfering with excretion of the drug may be a factor, but more commonly it is probably due to some previous impairment of the liver rendering it more susceptible to the drug. The hepatic changes are much less common following the use of neocinchophen, but on account of its close relationship to the parent drug it should be used with discretion until its harmlessness is proven.

In a comparative study of the effects of cinchophen, neocinchophen and sodium salicylate upon the livers of dogs and rats, Barbour and Fisk found that all three drugs affected the liver, but that cinchophen was by far the most toxic of the three and that neocinchophen had the least effect upon the organ. Upon the kidneys of dogs, sodium salicylate was the most harmful and neocinchophen had the least effect. Cinchophen-treated dogs also showed in a considerable percentage of instances, duodenal or gastric ulcers. The experimental results confirmed clinical experience indicating that cinchophen should be used with caution on account of the possibility of liver damage.

Gastric ulcers have been produced experimentally in dogs by a number of workers. It is possible with the continued administration of cinchophen to produce ulcers in dogs having all the appearance of those which are found clinically in man. There is first an acute gastritis involving the fundic portion of the stomach and this is followed in a week or two with a perforating type of ulcer located on the lesser curvature near the pylorus. There is an increase in quantity of gastric juice but no heightened degree of acidity. If the drug is stopped the ulcer heals rapidly, recovery being complete in from two to seven weeks (Bollman, Stalker and Mann).

Cinchophen is used in gout, in which condition it is given in doses of about 0.5 G. (8 grs.) four times a day. When large doses are given it is advised to keep the urine alkaline by the use of sodium bicarbonate or potassium acetate or citrate. In gout, cinchophen increases the uric acid elimination in the same way as in health and does not usually induce any other symptoms. This free removal of uric acid appears to be of benefit in the disease and several observers state that the deposits of urates (tophi) are lessened in size and the chronic inflammation of the joints is relieved; others have observed less benefit and deny that uric acid deposits are reabsorbed under cinchophen.

In acute articular rheumatism cinchophen and neocinchophen have proved to be quite efficient. Here they may be given in large doses in much the same manner as are the salicylates, 0.5–1 G. every hour until symptoms of "cinchonism" appear. Such doses of cinchophen may cause pain in the epigastrium, which symptom is absent when neocinchophen is given. Long-continued use of these drugs, especially of cinchophen itself, is to be avoided on account of the danger of poisoning.

Cinchophenum (introduced as *Atophan*) ($C_{16}H_{11}NO_2$) forms small colorless crystals with a bitter taste, almost insoluble in water but soluble in alkalies and acids. Dose, 2–4 G. (30–60 grs.) per day in divided doses, given as powder or tablets.

Neocinchophen (introduced as Tolysin) is an odorless and tasteless

powder. Its action is practically that of cinchophen, over which it possesses the advantage of being devoid of taste and of being non-irritating and, still more important, of probably being less likely to produce the toxic action on the liver; however, the evidence in this respect is not conclusive.

PREPARATIONS.

U. S. P.

NEOCINCHOPHENUM, Neocinchophen, 0.5 G. (8 grs.), introduced as Tolysin or Novatophan.

B. P.

CINCHOPHENUM, Quinophan. 0.3–1 G. (5–15 grs.).

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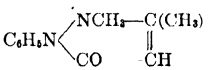
8. THE ANTIPYRETICS. (ACETANILIDE AND ANTIPYRINE SERIES.)

The antipyretics are a relatively recent addition to therapeutics, the oldest of this group now in use dating only from 1884. Up to 1875 the only means of combating high temperature were baths, vegetable alkaloids, such as quinine, or alcoholic preparations, but in that year Buss discovered that salicylic acid produces a fall in the fever temperature, and soon afterward carbolic acid and resorcin and its isomers were employed as antipyretics. A very large number of antipyretics have been introduced since that time, but most of them have had only a temporary vogue, and those in general use at the present time are comparatively few in number.

Quinine is a quinoline derivative, and quinoline itself, as well as some of its simpler compounds, were among the earlier antipyretics suggested. *Quinoline* (C_9H_7N) was soon found to be dangerous from its producing collapse, but its derivatives *Kairine* ($C_9H_9(OH)N—C_2H_5$), *Kairoline* ($C_9H_8(CH_3)(OH)NH$) and *Thalline* ($C_9H_9(OCH_3)NH$) were used extensively, although they have now been entirely abandoned; *Analgen* is a quinoline derivative but it too is very rarely prescribed today.

A new antipyretic was introduced in 1884 under the name of **Antipyrine** or **Phenazone,** which is derived from phenylhydrazine, and has proved superior to all of the earlier drugs. *Phenylhydrazine* (C_6H_5—NH—NH_2) produces a fall in the fever temperature, but this is frequently accompanied by collapse and changes in the blood, which prevent its use in medicine. Several of the simpler compounds have received a more or less extensive trial as antipyretics, but have proved dangerous and inferior to *Antipyrine*, phenyldimethylpyrazolon,



which is still largely used as an antipyretic, either in its original form or as a constituent of numerous combinations which have been introduced of late years. Among these may be mentioned Aminopyrine or *Pyramidon* (dimethylamino-antipyrine), *Hypnal* (chloral and antipyrine), *Salipyrine* (salicylic acid and antipyrine).

Antipyrine early found a rival in **Antifebrine** or **Acetanilide,** which was advised as an antipyretic in 1886 by Cahn and Hepp. *Aniline* ($C_6H_5NH_2$), from which it is derived, has also some action on the temperature, but like phenylhydrazine produces dangerous collapse and destruction of the blood cells. *Acetanilide* ($C_6H_5NHCOCH_3$), the first of its derivatives to be introduced, is not entirely devoid of this poisonous action, and has been supplanted to a considerable extent by more complex and less poisonous bodies. It was soon found that both aniline and acetanilide undergo a partial oxidation in the body, with the formation of aminophenol or its derivatives, and the belief that the antipyretic effects were due not so much to the original substance as to these oxidation products led to the introduction of numerous derivatives of paraminophenol (NH_2—C_6H_4—OH). This body has antipyretic properties but suffers under the same disadvantages as aniline. Among its derivatives the most satisfactory antipyretics are those in which the hydrogen of the hydroxyl is substituted by alkyl, while an acid radicle is added to the amino-radicle. The first of its compounds to be introduced was **Phenacetine** (CH_3CONH—C_6H_4—OC_2H_5) which differs from acetanilide only in the addition of ethoxyl in the para position. It is less dangerous than acetanilide and antipyrine, and has therefore been largely used, and has been followed by other bodies which are identical with it, except for the acid radicle attached to the nitrogen. Among these phenetidines may be mentioned *Lactophenine* (lactyl-phenetidine), *Triphenine* (propionyl-phenetidine), *Malakine* (salicyl-phenetidine), and *Salophen*, which contains similar constituents, *Citrophen* (citryl-phenetidine), *Kryofine* (methylglycolic-phenetidine), and *Phenocoll* (glycocoll-phenetidine), with its compound with salicylic acid, *Salocoll.*

Several urethrane derivatives have also received a trial as antipyretics, among them being *Euphorine* (phenylurethane), which is somewhat poisonous, and *Thermodine* (phenacetine-urethane).

Many of the antipyretics at present in use probably owe their activity to the formation of simple derivatives of paraminophenol in the tissues, and differ chiefly in the rapidity with which this decomposition occurs; when it is quick, it is followed by destructive blood changes and a tendency to collapse, while the antipyretic effects pass off soon. Those drugs are found the most satisfactory antipyretics in which the decomposition proceeds gradually, so that the temperature falls slowly and remains low for a longer time. The simpler antipyretics, such as acetanilide, have given way largely therefore to the phenetidine compounds.[1] Among these it is impossible to determine the most suitable, but none

[1] For a detailed discussion of these principles see *V. Mering*, Therap. Monatsh., p. 577, 1893, and *Hinsberg and Treupel*, Arch. f. exp. Path. u. Pharm., vol. **33**, p. 216.

of them has been proved to be superior to phenacetine. Where the merits seem so equally divided, it is perhaps more important to learn to use one with judgment than to hurry after each new product without sufficient experience with its predecessor.

Symptoms.—The effects of the antipyretics vary not only with the dose but with the individual patient. Many persons can take very large doses without apparent effect, while in others comparatively minute quantities produce symptoms of greater or less importance. The effects are not always the same, even in one individual under the same dose of the antipyretic, and it is impossible to state at present what are the conditions that involve the peculiar train of symptoms. A very large number of disorders have been attributed to the antipyretics in man, but it is impossible to consider any here except those more commonly observed. Among these are *skin eruptions* of various forms, such as red, erythematous, itching patches or more widely diffused hyperæmia resembling the onset of measles or scarlatina; urticaria occurs not uncommonly, while eczema and bullæ are rarer. In some cases an œdematous swelling has been observed. Some *fever* occasionally accompanies the eruption and renders the diagnosis from the infectious exanthemata even more difficult. These skin affections seem to be elicited more frequently by antipyrine[1] than by acetanilide and the phenetidine compounds. They have been attributed to dilatation of the cutaneous vessels, but this in itself is insufficient to explain their appearance, although it may be a favoring condition. Profuse *perspiration* not infrequently follows the use of the antipyretics in fever, and if the fall in temperature is rapid, and the action of the drug passes off soon, the subsequent rise of temperature may be accompanied by *shivering and rigor*, but these symptoms are scarcely to be looked upon as direct effects of the drug, but rather as resulting from the rapid changes in temperature. They are produced much more frequently by the older and simpler antipyretics than by those of more recent introduction.

Sometimes *catarrh*, burning and swelling *of the throat* and *mouth* are observed after antipyrine, and more rarely *nausea* and *vomiting*. *Cerebral symptoms* are rarely elicited beyond slight dullness, confusion, or apathy. Alterations of the hearing similar to those described under quinine, have been observed in some cases. More serious symptoms are those of *collapse*, which are sometimes induced by acetanilide. In the milder cases the skin is cool, the pulse is rather small and rapid, and some anxiety and alarm are felt by the patient, but the condition passes off in a short time. In more severe cases the skin is cold and covered by a clammy perspiration, the heart is weak, irregular and sometimes fluttering, the temperature may be subnormal and the pupils are slightly dilated. The patient may be conscious, fainting may occur, or an apathetic, confused condition may be produced. The weakness of the heart is the chief source of anxiety, and the total failure of the circulation seems to be the cause of death. These cases of collapse occur more frequently when a rapid fall of temperature has been produced than

[1] The skin eruption resulting from the use of antipyrine is frequently clinically identical with that which sometimes follows the use of phenolphthalein (see page 270).

under other circumstances, but may be observed in cases in which no fever has been present.

Marked *cyanosis* occurs sometimes under acetanilide and the earlier members of the series, very rarely under antipyrine and the phenetidine compounds. It arises from the formation of methæmoglobin in the blood, and when this is accompanied by collapse, the cyanosis may be very intense. It is often accompanied by dyspnœa and acceleration of the pulse, and it lasts for a varying length of time, sometimes passing off in a few hours, at other times persisting for several days.

Occasionally a certain *tolerance* is gained, and larger doses of the antipyretics are required to produce effects than were necessary at the beginning of the treatment. Many cases of *chronic poisoning* are recorded from the habitual use of acetanilide. The symptoms consist in disturbance of the digestion, cyanosis, tremor, muscular weakness and general mental debility; the blood is often chocolate-colored from the formation of methæmoglobin, and the urine often contains hæmoglobin or its products, or may be colored by the oxidation products of paraminophenol. The condition is sometimes difficult to recognize, especially as the patient may deny that the drug has been taken. The symptoms disappear rapidly when it is given up.

These drugs are by no means very poisonous, normal animals showing no reaction to doses which are sufficient to cause marked changes in fever. In the frog **Antipyrine** causes an increase in the reflex irritability, which sometimes leads to tetanic convulsions and is followed by depression, loss of the voluntary movements, and eventually by complete paralysis and death. In mammals its injection is followed at first by a period of quiet and sometimes of somnolence, which is said by some authors to occur also in the frog previous to the increase in the reflex irritability. Some rise in the reflex irritability may be made out in the mammal at this stage, and large doses cause convulsions and tremors, and subsequently unconsciousness and collapse, ending in complete paralysis. The pulse is accelerated by small doses, while in the later stages of poisoning it may be slow, and some dilatation of the skin vessels and flushing have been observed. The respiration is at first accelerated, and then becomes slow and irregular, when large doses are injected. In dogs vomiting and dilatation of the pupil generally occur.

Acetanilide is more poisonous than antipyrine in both frogs and mammals, but resembles it in its general effects, producing first a more or less marked stage of lessened activity, followed by convulsive movements. The respiration is not so much accelerated as by antipyrine, and, according to some observers, is slow from the beginning of the action. The heart is first accelerated and then slow and irregular, and cyanosis and collapse are more frequently observed than under antipyrine. In feeding experiments on mice Fantus and his associates found that if alkali were administered either as bicarbonate or indirectly as citrate the animals would consume larger amounts of acetanilide than they would if the acetanilide were given alone. The increased amount consumed was due to the fact that they lived longer, indicating that the simultaneous administration of alkali with acetanilide lessens the toxicity of the latter drug. Smith and Hambourger, in their studies on the toxicity of acetanilide, found that if rats were given from two to three times the minimum therapeutic dose necessary to affect the temperature the drug produced no significant changes in the blood or in body growth. Further, to produce signs of chronic poisoning it was necessary to give daily amounts equal to one-fourth the acute fatal dose. They were not able to demonstrate any mutually protective action between acetanilide and sodium bromide or acetanilide and caffein. Attacking again the effect of bicarbonate on the toxicity of acetanilide, Smith found that

if bicarbonate were added to the acetanilide in the molecular ratio of 2 to 1, the mortality from the M. L. D. (50 per cent mortality) of acetanilide was reduced to 20 per cent. The antipyretic action in rats was not altered. The blood changes seen in chronic poisoning were not prevented by the presence of the alkali. Stanton and Agricola investigated the addictive properties of acetanilide on rats and could find no evidence of addiction even after the drug had been given daily over a period of weeks. There was also no cumulative effect seen—rather was there a distinct development of tolerance which was more marked if the animals were subjected to a rapid increase in dosage. The large doses given were completely absorbed as no residues were found in the feces. **Phenacetine** and its allies are much less poisonous than acetanilide and antipyrine, but in large quantities produce almost identical effects—somnolence followed by convulsions, cyanosis, and collapse symptoms, first rapid, then slow respiration and heart. **Lactophenine** is said to have a more sedative effect than the other antipyretics, and to induce complete narcosis in the rabbit.

Action.—The action of these drugs on the various organs is very imperfectly understood. The **Nerve Centres** are affected, as is shown by very slight somnolence occasionally in animals and also in man, but much more frequently by the relief of pain, as in neuralgia and headache; Martin, Grace and McGuire state that after phenacetine the general sensitiveness of the body may be shown to be lower by measurements of the threshold sensibility of the skin. This is generally attained without any observable depression of mental activity and is, therefore, quite distinct from the analgesia obtained by the use of morphine or anæsthetics. This suggests that the antipyretics relieve pain by affecting not the cerebral cortex, but some lower point, which may be assumed to be a synapse on the path conveying pain sensations; there are two of these, one in the spinal cord and one in the thalamus, and as the antipyretic action of this group is due to changes in the neighborhood of the latter, it seems likely that their action in abating pain may be located here also (Head).

Most of the antipyretics increase the excitability of the spinal cord at first, and this may lead to convulsions in the frog. The origin of the convulsions in mammals is still somewhat doubtful; in general, they seem to be of cerebral origin, but when large quantities are injected they are seen even when the spinal cord is divided from the brain, so that the cord appears to be thrown into a condition resembling that discussed under strychnine poisoning. In considering the cause of these convulsions perhaps too little weight has been laid by some writers on the changes in the blood, respiration and circulation, for it is possible that the convulsions in some cases are asphyxial in character, and not due to the direct action of the poisons on the brain.

In ordinary poisoning the peripheral **Nerves** and nerve-ends do not seem to be seriously involved, and the final paralysis in both frogs and mammals is undoubtedly central. Santesson found that antipyrine tended to increase the power of the frog's **Muscles**, and several observers have noted that the nerves and motor terminations are paralyzed by the direct application of this drug. Antipyrine has some effect as a local anæsthetic when applied to the mucous membranes.

The **Heart** in the frog and mammals is first accelerated and then slowed by the antipyretics in general, these alterations being entirely

independent of the inhibitory mechanism and due to a direct effect on the cardiac muscle. The increased rhythm of the heart leads to a slight rise in the blood-pressure, which sinks again as the pulse becomes slower. There is no satisfactory proof that the vaso-motor centres are involved in the rise of pressure, although it is not unlikely that they undergo a primary stimulation at the same time as the respiratory centre.

Most of this series, except antipyrine and its compounds, tend to cause alterations in the **Red Blood Cells** when they are given in large quantities. This action is manifested especially by the simpler bodies of the series, and is still more marked in poisoning from aniline, phenylhydrazine, paraminophenol or quinoline. On the other hand, most of the phenetidine compounds produce it much more rarely, and antipyrine seems devoid of this action. The alteration consists in the formation of methæmoglobin, which may be readily detected by its characteristic spectroscopic appearance. Small quantities of the antipyretics cause its formation within the blood cells, which remain intact, but larger doses, especially of the more poisonous members, destroy the red blood cells and free the methæmoglobin in the plasma. In the blood various distorted, shrunken red cells may be observed, often entirely devoid of coloring matter, while part of the methæmoglobin escapes through the kidneys, and nephritis occurs in some cases with albumin, hæmoglobin and even blood in the urine. This effect on the blood arises from the decomposition products of the antipyretics, such as an hydroxylamine product ($C_6H_5NOH \cdot COCH_3$) from acetanilide, and perhaps paraminophenol or the corresponding quinoline derivatives from others; this decomposition proceeds more slowly in phenacetine and its allies and is absent after antipyrine, which explains the rarity of the symptoms after these drugs; it only occurs in the tissues and no methæmoglobin is formed when the antipyretics are added to drawn blood.

All of the antipyretics have some **Antiseptic** action, which varies in the different members with their solubility and stability. Antipyrine is found to preserve blood from putrefaction for some days when added to it so as to form a solution of 2–5 per cent. Watery solutions of this strength destroy protozoa and stop the movements of the leucocytes.

The action of the antipyretics on the **Metabolism** of healthy men and animals has been the subject of a number of investigations which have by no means given uniform results, especially in regard to the nitrogen elimination. *Antipyrine* has no influence, or only an insignificant one, on the metabolism of the healthy tissues, whether this is measured by the nitrogenous excretion or by the gaseous exchange in the lungs.

Acetanilide, on the other hand, has a distinct effect on the nitrogen eliminated, although this is elicited only by large doses. After ordinary quantities the urea and total nitrogen of the urine may be slightly augmented, but in large doses acetanilide causes an increase of 30–35 per cent in these, which indicates a large increase in the tissue waste. The *other antipyretics* have not been examined so carefully. The exchange of gases in the lungs is not affected by the antipyretics in healthy

animals, and no definite change has been observed in the excretion of uric acid.

The specific effects of the antipyretics on the **Temperature,** while recognized by all, have been the subject of endless discussion, owing to the complex mechanism through which they are elicited. In the normal animal the temperature is but little altered, except by doses large enough to produce collapse, but when it is abnormally high, as in fever, the antipyretics cause a fall of greater or less extent.[1] This fall in temperature occurs at varying intervals after the ingestion of the drug, but, except in refractory cases, always begins within two to three hours. Its extent varies, the temperature in some cases reaching the normal or even a subnormal point, while in others the change is insignificant. Continuous fever without any natural rise and fall is much less affected, as a general rule, than one with alternate rise and fall of the temperature, and in the latter form the result is greater if the drug is given at the beginning of one of the natural remissions.

The fall in temperature is often accompanied by flushing of the skin and perspiration. The oxygen absorbed and the carbon dioxide excreted are lessened, and the urea and nitrogen of the urine are also diminished after antipyrine, while they are not infrequently increased after acetanilide, especially when administered in large quantities.[2] The heart is often reduced in rate, and the pulse improves in strength, but these changes are due to the fall in the temperature and not to the direct action of the drugs. Some remedies owe their antipyretic properties to their increasing the secretion of the sweat glands, but although perspiration not infrequently occurs during the fall of temperature under the new antipyretics, this is merely a secondary result here, for when the perspiration is checked by atropine, the fall of temperature proceeds uninterruptedly.

The temperature in healthy warm-blooded animals is kept uniform through a balance being established between the heat formation and its dissipation through the lungs, skin, and other organs. If an excessive formation occurs, as during muscular exertion, this is counterbalanced by an increase in the output from the skin through the dilatation of the vessels and by the perspiration. If, on the other hand, more heat is dissipated than usual through exposure to cold, the combustion of the tissues is increased and more heat is formed. The output of heat is thus determined by the degree of dilatation of the cutaneous vessels and the activity of the sweat glands, while the amount of heat formed varies with the voluntary and involuntary contractions of the muscles. In order to preserve a balance between these two factors, there must exist a coördinating mechanism, and this is located in the basal ganglia

[1] This difference in the reaction of normal and fevered animals has aroused much interest. It may be an example of a general law for which some evidence is available, that it is easier to reduce an abnormal organ or function to its normal condition, than to change a normal one to unusual activity or inactivity; a definite rate of function is the habit of each organ and it moves away from this normal with difficulty and returns to it with readiness.

[2] Even when the nitrogenous metabolism is reduced in fever by antipyretics, it is said to be remarkably increased as the temperature rises again, so that no real economy of protein results from their use.

of the cerebrum, in the neighborhood of the tuber cinereum. Lesions in this neighborhood generally cause a rise in the temperature, often without further disturbance, and it is of interest to learn that as long as the cerebrum is intact, shivering is produced by cold, while after section between the optic thalamus and the corpora quadrigemina the animal offers no resistance to a fall of temperature.

Other facts might also be adduced to show that in the normal animal the temperature is kept uniform by this coördinating mechanism, which controls both the output of heat through the skin and its formation by the contractions of the skeletal muscles. In many individuals this coördination is not perfect in health, and in all it may be disorganized by poisons, such as those formed in fever. The more perfect the coördination, the smaller is the divergence from the normal temperature necessary to elicit a protective increase in the production or in the dissipation. The efficiency of the mechanism may, therefore, be measured by observing what fall of the body temperature occurs before shivering sets in, what rise produces dilatation of the cutaneous vessels and perspiration. In this way it has been found that during fever the coördination is quite as perfect as in health, but that the protective reactions are induced at a higher temperature. The same measures are taken to preserve a uniform temperature as in health, but the temperature maintained by these means is higher. If a comparison be made with the thermostat of the laboratory, it may be said that in fever the mechanism is "set" for a higher temperature than in normal life, but that the apparatus acts efficiently for each temperature. The higher temperature is maintained by an increased metabolism or heat formation, and also in most cases by a lessened dissipation. The fever temperature itself seems to increase the metabolism, the tissues undergoing more rapid waste under it than in normal conditions.[1] The coördinating mechanism appears to be more susceptible to various influences in fever, and the consequent variations in its activity cause the large undulations of the temperature curve which are characteristic of pyrexia. Among these influences is the temperature itself, for Barbour has shown that the overheated blood tends to change the activity of the centre so that the heat loss is augmented.

The antipyretics do not lower the temperature by reducing the heat production, for, though the nitrogen eliminated and the oxygen absorbed fall during their action in fever, this lessened tissue waste is the result, not the cause of the fall of temperature, the metabolism proceeding more slowly when the temperature is reduced.

Calorimetric investigations have shown that the dissipation of heat in fever is much increased by the antipyretics, while in health they seem to have little effect. This augmentation in the output is due to dilatation of the cutaneous vessels, which exposes a large amount of blood to the cold air. The dilatation is great enough to be recorded by the plethysmograph in many cases, while in others flushing of the

[1] It must not be supposed from the foregoing statements that fever consists only in an alteration of the normal temperature. This is only one of the symptoms produced by the poisons of fever, but is the only one affected by the antipyretics.

skin may be observed. The increased dissipation of heat is accompanied by a lessened formation which, however, is much less important and which is generally attributed to the metabolism proceeding less actively at the lower temperature. In other words, the antipyretics reduce the temperature by increasing the output of heat, and the cells of the body grow and change less when removed from the hot-house temperature to which they have been exposed previously. It must be added, however, that some observers hold that the fall in heat formation is too great to be explained in this way, and suppose that the antipyretics lessen the combustion through some other action, but not by affecting the tissues directly. And Barbour states that the heat formed may actually increase under antipyretic treatment; this is usually masked by the increased heat loss, but in cases of abnormally low temperature, when the heat loss is not increased by antipyretics, it may actually lead to a rise of temperature under the drug.

It has been stated already that the fevered animal resists any change in its temperature in the same way as the normal, and it might therefore be expected that when the temperature is reduced by antipyretics the organism would at once increase its heat formation. The fact that this does not occur, but that, on the contrary, the metabolism is lessened, indicates that some further change occurs, that the antipyretics not only reduce the temperature by allowing the heat to escape, but also alter the condition of the coördinating mechanism by which the temperature is kept uniform. To return to the comparison with a thermostat, the body temperature is set at a lower point by the antipyretics, while it is set higher by the fever poisons.

The action of the antipyretics on this coördinating centre is therefore of interest, and has been examined both in health and disease. In healthy men the temperature does not undergo any marked change under the antipyretics, for though it may fall a few tenths of a degree in some cases, this is of no significance. The sensitiveness of the coördinating centre is apparently increased, however, for in some individuals in whom hard muscular work causes a rise of temperature normally, this is absent or less marked after the antipyretics. In the same way the rise of temperature which is occasionally caused by very hot baths is absent or diminished when antipyrine has been administered previously. When the basal ganglia are cut off from their connections with the lower part of the body, neither septic infections nor antipyretics have any effect on the temperature, while after section above the basal ganglia, fever is caused, and the antipyretics induce the usual fall of temperature (Sawadowsky). In experiments in which high fever was produced by lesions in the neighborhood of the ganglia, Gottlieb found that the antipyretics reduced the temperature and increased the output of heat to a marked extent, while the formation was increased to a less degree. Further evidence that the antipyretics act on the regulating mechanism in the brain is afforded by experiments in which they were injected directly into the neighborhood of the centres, when much smaller quantities sufficed to reduce fever temperature than were necessary when they were carried to them by the blood.

Finally, the condition of the centre has been examined by Stern and Richter after the temperature had been reduced by antipyretics. They both found that the protective mechanism was called into play when the temperature was slightly raised, and generally when it was depressed. For example, a fevered dog (temperature 40.9° C.) received an antipyretic, and its temperature was reduced to 37.6°. Attempts were now made to raise the temperature by external heat, but the animal resisted this by increasing the output as soon as the temperature rose to 37.8°. The coördination which maintained the temperature at 40.9° before the drug was administered now attempted to keep it at 37.6°.

The results of these researches may be summed up briefly as follows: The antipyretics reduce the temperature in fever through alterations effected in the heat-regulating nervous mechanism, which result in lowering the point at which the temperature is maintained. As a consequence of this action, a great increase in the dissipation of heat must occur in order to free the body from the warmth which it has

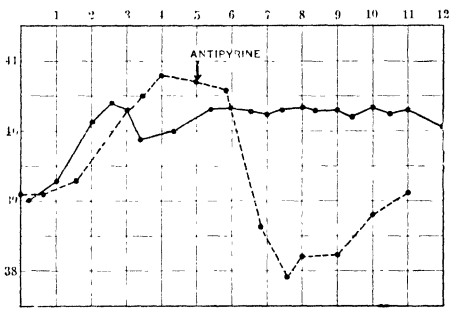


FIG. 64.—Temperature charts of two rabbits under fever toxins. The unbroken line was obtained from an untreated animal, the dotted line from one which received antipyrine at the point indicated by an arrow. The time is given in hours along the horizontal line, the temperature in degrees Centigrade on the vertical. (After Kiliani.)

accumulated, and this increased output is attained by dilatation of the cutaneous vessels. The seat of action of the antipyretics is probably situated in the base of the cerebrum.

Both antipyretics and fever toxins act upon the temperature-regulating mechanism, the one exciting, the other depressing it; the antipyretics may thus be regarded as acting as antagonists to these toxins in the brain in the same way as atropine antagonizes pilocarpine in the heart. The centre poisoned by the toxins is apparently more readily acted on than in the normal condition. The toxins are often regarded as stimulating, the antipyretics as depressing the centre, but there are equally valid grounds for reversing the rôles and holding that the toxins depress and the antipyretics stimulate it (Barbour).

When the temperature is depressed too rapidly by these remedies, a condition of collapse is often produced, while in other cases the loss of heat caused by the dilatation of the skin vessels seems to be excessive, and shivering and rigor follow in order to increase the production.

When the temperature has reached the new point fixed by the coördination under the influence of the antipyretics, the heat dissipation rapidly diminishes and may become less than normal, because the new temperature is maintained at a constant point by the same mechanism as the normal.

The antipyretics are rapidly absorbed, and as rapidly **Excreted** by the kidneys, so that they disappear from the body within twenty-four to thirty hours after their administration.

The fate of antipyrine seems to differ in different animals. In the dog it is found to be partially oxidized to oxyantipyrine which is excreted in the urine in combination with glycuronic and sulfuric acids. In others it is said to be excreted in the urine unchanged. Acetanilide undergoes a partial oxidation, the final product differing in different animals, but none of the original body appears in the urine except after very large doses. In man it appears as paraminophenol and its compounds in combination with sulfuric and glycuronic acids. In the rabbit's urine paraminophenol alone is found, while in the dog this is accompanied by oxycarbanil ($C_6H_4O{\cdot}NH{\cdot}CO$); in each case it forms a double sulfate or glycuronate. The fate of the other antipyretics resembles that of acetanilide, the quinoline derivatives undergoing a partial oxidation resulting in a body analogous to paraminophenol, while the phenetidine compounds are partially decomposed and appear in the urine as glycuronates of phenetidine. The combinations containing salicylic acid break up in the body, and the acid appears in the urine, while the rest of the molecule undergoes the usual partial oxidation.

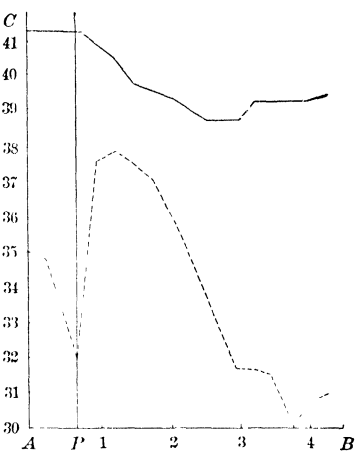


FIG. 65.—Curve of internal temperature (unbroken line) and of the skin temperature (dotted line) in fever treated with antipyrine (Rosenthal). The abscissa AB represents the time in hours, the vertical, AC, the temperature, Centigrade. At P, antipyrine was given, and the skin temperature rose at once (augmented heat output). The internal temperature soon began to fall, and after it had reached a certain point the skin temperature fell again as the vessels contracted.

The presence in the urine of these bodies, or rather of further products of their oxidation, gives it a dark, reddish-brown color, which may be observed when it is passed, or more frequently after it has been exposed to the air for some time.

Therapeutic Uses.—The antipyretics were introduced to **Reduce the Fever Temperature.** The most satisfactory results are obtained from those which act somewhat slowly, but which preserve a low temperature for some time, and the phenetidine compounds are thus preferable to the earlier remedies, which produce a more abrupt fall, after which the temperature soon regains its former height. The best effects are obtained when the antipyretic is given at the commencement of a natural remission, the temperature often falling 2 to 4° F. in the course of the next two to three hours, and only rising slowly afterward. In some fevers the antipyretics have much less tendency to lower the temperature

than in others. Thus in septicæmia larger doses are required than in typhoid and not infrequently no satisfactory reduction of the temperature follows the administration of the maximal quantity. Pneumonia is also said by some writers not to be affected so easily as some other febrile conditions in which the heat-regulating centre appears to be in a less stable condition, as is manifested by the occurrence of large spontaneous variations of temperature. The reduction of the temperature by the antipyretics lasts only as long as the drug is present in sufficient quantity in the body, and accordingly as soon as sufficient has been excreted, the intoxication of the regulating mechanism begins again, and the temperature soon rises to its former height. The antipyretics do not act on the cause of the disease, but only remove one of the symptoms, but this in itself is not an argument against their use, as is apparently believed by some writers, because as long as the physician is unable to treat the cause directly, he is justified in taking such measures as are possible to remove the symptoms, rather than in adopting an expectant treatment, pure and simple. The extensive use of these remedies shows very clearly that the high temperature is merely a symptom of disease, and not the disease itself, and the question has been much debated whether the reduction of fever is in any way beneficial. No one questions that some antipyretic measures should be taken when the temperature rises so high as to form a danger in itself, but their use in ordinary fever cases is more doubtful, and many physicians deprecate it unless in exceptional conditions. The very large doses formerly used undoubtedly induced dangerous symptoms occasionally, but there is little risk of this occurring from the intelligent use of the less violent members of the series. It was shown by Schutze and Beniasch that the use of the antipyretics does not retard the formation of the protective substances (antitoxin) to which the recovery from fever is attributed, for in infected animals treated with enormous quantities of antipyrine the serum displayed the same agglutinating properties toward the bacilli as that of controls which were not subjected to any medication.

A more serious argument against their use in fever is that the course of the disease is less readily followed, because one of the guiding symptoms—the temperature variations—is no longer dependent solely upon the severity of the intoxication with the fever poisons, and both diagnosis and prognosis are thus rendered more difficult. For example, in typhoid fever a sudden fall of temperature often gives the first indication of such a complication as perforation, but if an antipyretic has been given beforehand, the significance of such a fall in temperature may not be properly appreciated. On the other hand, it is urged in favor of the antipyretic treatment that the patient feels more comfortable and easier when the temperature is reduced, and that this alone may favorably influence the course of the disease. Besides, the high temperature in itself increases the tissue waste and causes larger draughts on the resources of the patient than would be made with the same amount of poison in the tissues at a lower temperature; and although the influence of the high temperature on the metabolism was undoubt-

edly exaggerated at one time, this consideration is by no means devoid of weight.

The antipyretic treatment of fever is of value, then, in cases where the temperature is so high as to endanger life, in cases in which the rise of temperature is the chief cause of distress and no complications are to be apprehended, and, in general, in cases in which the increased comfort of the patient is not counterbalanced by its obscuring the diagnosis and prognosis. On the other hand, there is no reason to suppose that the antipyretics lessen the mortality or shorten the course of most fevers, or that they prevent complications of any kind except excessively high temperature, and the routine treatment of fever with antipyretics is to be deprecated.

The chief rival of the antipyretics in the treatment of fever in the present day is the so-called cold-bath treatment, in which the fever patient is placed in a bath of cold water or is sponged frequently with water the temperature of which varies from 70 to 80° F. in different hospitals. The fever temperature generally falls to a considerable extent under this treatment, and very often a general improvement in the symptoms occurs. The effect on the temperature is due mainly to the abstraction of heat from the body, and thus far corresponds to that of the antipyretics. In the cold-bath or cold-sponge treatment, however, the loss of heat is not immediately due to the dilatation of the skin vessels, for baths at 70° F. have the effect of constricting the vessels primarily, whatever may be the subsequent effect. The heat output is increased here from the change in the external medium, and not from any alteration in the skin itself. The fall of temperature is generally not so great as under the antipyretics, and the regulation is not directly affected, for the patient shivers and becomes cyanotic long before the normal temperature is reached. The therapeutic virtue of the cold bath was formerly believed to lie exclusively in the abstraction of heat and the fall of temperature, but many advocates of the treatment now hold that this is of less importance than the effects on the circulation, respiration and the brain, which are elicited reflexly by the cold water applied to the skin. The whole nature of the fall in temperature, however, is different from that produced by the antipyretics, and the metabolism, instead of becoming less active as it does under the latter, rather tends to increase under the cold baths, at least as far as the tissue change can be measured by the nitrogen excreted. Each method of treating fever has its advantages, but however the matter may stand in hospital practice, in which trained assistance is available, the antipyretics have a great advantage in many cases in which treatment has to be carried out without any such facilities, for the administration of these drugs may, of course, be entrusted to ordinary persons, whereas the cold bath can be given only by trained attendants. The sponging with cold water is, of course, much simpler. However, in the milder fevers, where no complicated measures, such as the cold bath, are considered necessary, the antipyretics give relief to the patient by removing the feeling of heat and discomfort.

Although the antipyretics were introduced primarily to lower fever

temperature their great importance today arises from the fact that they are used more extensively to relieve certain forms of **Pain.** The analgesic action of these bodies is apparently quite different from that of morphine but the action, while different, is in its way just as specific as is the morphine action. It is of course true that in many instances in which the morphine is successful they fail to alleviate the condition. On the other hand antipyrine and its allies can often be used where morphine is contraindicated, either from the danger of the habit being formed, or from the somnolence it induces. They were first used in neuralgic pain and headache, but have been found equally efficient in other forms of pain and discomfort, and the relief given in fever appears to arise from this analgesic action as much as from the reduction of the temperature. It is not possible at present to specify the characters of the pains which they relieve or to distinguish them from those in which recourse must be had to morphine; in very severe pain and especially in those forms in which it arises from spasmodic contraction of hollow organs, the antipyretics are of little service, while pain arising from affections of the nerves is more amenable to their action. Acetophenetidine and its allies are frequently used for the purpose, antipyrine less often at present; acetanilide should be employed with care. Acetylsalicylic acid has been largely used instead of the antipyretic group of late years. Caffeine is often prescribed along with the antipyretics in headache and neuralgia and in some cases its action seems to be beneficial.

Several of the antipyretics have been used as **Substitutes for Quinine** in the treatment of malaria, but none of them have the specific action of the latter on the organism of malaria, and, although they may reduce the temperature, they do not prevent the other symptoms and do not remove the cause of the disease. In the same way they do not seem to equal salicylic acid in efficiency in acute rheumatic fever, although here again they reduce the temperature.

In whooping-cough antipyrine often lessens the severity of the attacks and also renders them less frequent, and is said to shorten the course of the disease.

Antipyrine and several others of this series have been advocated as local anæsthetics, and have been used occasionally to lessen the irritability of the throat and larynx and thus to permit of the minor manipulations of laryngology. Holocaine, a body closely related to phenacetine, has been employed to a limited extent as a local anæsthetic in ophthalmology.

The occurrence of collapse and other symptoms has led to a considerable amount of distrust of the antipyretics among many of the medical profession. In justice it has to be remembered that in many cases these symptoms were produced only by very large doses, and that since experience has shown that beneficial results may be obtained by smaller quantities, these cases have notably diminished in medical practice. Unfortunately, this distrust is not entertained by a large class of the laity, and numerous cases of poisoning arise from the impression that the antipyretics are not dangerous drugs. For the most part, poisoning seems to be due to a peculiar sensitiveness or

idiosyncrasy, which cannot be foreseen, but in cases of great exhaustion and asthenia, especially when accompanied with anæmia, these drugs have to be used with care.

In 1922 a new clinical syndrome was described by Schultz and designated as "Agranulocytosis." It was characterized by an ulcerative angina, severe leucopenia, marked prostration and was not infrequently followed by death. On account of the prominence of the anginal symptoms the condition was later designated "Agranulocytic Angina." Schultz suggested that the condition might be due to depression of the bone-marrow either by some microorganism or by some chemical agent. While extensive studies have failed to prove an organism as the causative factor, greater success has followed the search for a chemical agent which will produce the blood changes characteristic of the disease. It is now known that four classes of chemicals will bring about a leucopenia: aminopyrine, dinitrophenol, gold salts and organic arsenical compounds. Of these the first named is by far the most important on account of its widespread use. In the vast majority of cases of agranulocytosis there is a history of aminopyrine administration, taken either alone or in combination with one of the barbiturates.

Various explanations have been advanced as to the mechanism involved in the intoxication. It is well known that it is only in the very occasional individual that the drug will produce these effects. In the present state of knowledge it can only be designated as a case of unusual susceptibility or idiosyncrasy to the offending drug. There is a depression of the myelocytic function of the bone-marrow resulting in a marked decrease in the granulocytes of the peripheral blood. This deprives the body of its major defensive mechanism, resulting in bacterial invasion of the mucous surfaces: mouth, throat, rectum and vagina. It is not known which part of the molecule of aminopyrine is responsible for the blood changes. By some the pyrazolon group has been believed to be implicated especially on account of its similarity to phenylhydrazine. On the other hand, it would seem probable that the benzene ring might be involved and the administration of benzene and some of its derivatives has a marked effect upon the blood. The relation of aminopyrine to certain of the cases has been clearly demonstrated; the administration to convalescent persons of a small dose of aminopyrine being followed by a very rapid reappearance of the granulocytopenia.

The disease is easy to diagnose—the decrease in granulocytes being characteristic. The most important element in the treatment is the avoidance of the offending drug. Blood transfusions have been used, and injections of pentnucleotide have been given into the gluteal muscles. The latter drug has been tried in the treatment of these cases on account of the marked increase in the leucocyte count which follows its administration to normal individuals. Its value in agranulocytosis is still a matter of discussion.

Preparations.

U. S. P.

Antipyrina, 0.3 G. (5 grs.).
Acetophenetidinum, Phenacetin. 0.3 G. (5 grs.).
Acetanilidum, Antifebrin. 0.2 G. (3 grs.).
Aminopyrina, Pyramidon. 0.3 G. (5 grs.).

B. P.

Phenazonum, Antipyrine. 0.3–0.6 G. (5–10 grs.).
Phenacetinum, Acetphenetidin. 0.3–0.6 G. (5–10 grs.).
Amidopyrina, 0.3–0.6 G. (5–10 grs.).

Antipyrine or Phenazonum forms colorless inodorous crystals, with a bitter taste, very soluble in water, alcohol, and chloroform.

PHENACETIN or ACETOPHENETIDIN, colorless, tasteless crystals, insoluble in water, is given in powders, cachets, tablets, or suspended in mucilage.

ACETANILIDUM, acetanilide or antifebrine, colorless crystals insoluble in water, soluble in alcohol, ether, and chloroform. It has no odor when pure, but has a slight burning taste.

AMINOPYRINA, introduced as Pyramidon, is dimethylamino-antipyrine. It is a white crystalline powder fairly soluble in water (1 G. in 18 cc.). It is best given in powder or tablet.

The antipyretics are almost invariably given by the mouth.

Among the members of this group, phenacetine has been widely used and antipyrine has also been popular. Acetanilide is much more dangerous than these but, at the same time, for a single dose or two it is the most effective member of the group.

Aminopyrine has been popular; while its action is rather slower to appear it is more lasting. It is also claimed to be relatively free from harmful effects on the heart or kidneys. However, its possible toxic effect upon the bone-marrow with resulting leucopenia, which has been discussed above (p. 707), has led to a very sharp curtailment in its use. If it is to be given over a prolonged period its use should be accompanied by frequent examinations of the blood. It probably should not be used for the treatment of dysmenorrhœa, or at or near the menstrual period.

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T. SALICYLATES.

Salicylic Acid, $C_6H_4OHCOOH$, was introduced into medical use as a substitute for carbolic acid, but its chief interest now lies in the use of its sodium salt in acute rheumatic fever. Some of the esters have also been employed; *methyl salicylate*, $C_6H_4OHCOOCH_3$, which is found in the volatile oil obtained from the *wintergreen* (Gaultheria procumbens) and from *birch bark* (Betula lenta) and which is also formed synthetically; *phenylsalicylate* or *salol*, $C_6H_4OHCOOC_6H_5$, formed synthetically; the numerous other salicylic esters which have been introduced by enterprising manufacturers have not attained a wide use. A recently introduced compound which has been largely employed is *acetyl-salicylic acid*, $C_6H_4OCOCH_3 \cdot COOH$, or *aspirin*. *Salicin*, $C_{13}H_{18}O_7$, is a glucoside found in the poplars and willows, which forms salicylate in the body and has had a limited use.

Local Action.—Salicylic acid has some value as an antiseptic, largely from its acidity, and the neutral salts are almost devoid of this property; thus protein solutions do not putrefy and the alcoholic and acetic acid fermentations are retarded by comparatively small quantities of salicylic acid, while the salicylates are almost inert. The salicylic preparations are generally less efficient than phenol in the presence of proteins, probably because the latter is more volatile and forms less stable combinations and therefore penetrates more readily. Salicylic acid, on the other hand, does not evaporate and therefore preserves objects which are exposed to the air for a longer time than does carbolic acid, which is soon dissipated. The movements of plant protoplasm, protozoa and leucocytes are prevented by salicylic acid, which also retards the digestion of proteins by the gastric and pancreatic juices, and the decomposition of glucosides by ferments, but this is probably due to its acidity and not to the salicylate ion.

Irritant Action.—When salicylic acid is applied for some time as a powder to wounds, mucous membranes, or even the skin, it may induce corrosion and necrosis. It sometimes causes soreness and irritation of the mouth and throat when swallowed in powder, and congestion and even erosion of the mucous membrane of the stomach have been observed; even dilute solutions often cause pain and discomfort in the stomach. Sodium salicylate is only very slightly irritant, but when it is swallowed, some of the acid is liberated by the hydrochloric acid of the stomach and may be deposited on the mucous membrane and give rise to acute dyspepsia.

Symptoms.—Salicylic acid and its salts are rapidly absorbed from the intestine and as a general rule produce no symptoms, unless when given in large doses. Some individuals, however, are peculiarly sensitive to the action of the salicylates, and in these comparatively small doses are followed by symptoms which are generally of only slight importance, but which are sometimes sufficiently grave to cause anxiety, and in very rare cases have been followed by death.

The ordinary symptoms are nausea, vomiting, and sometimes diarrhœa; a feeling of heaviness and fullness in the head, with hissing or

roaring sounds in the ears exactly resembling those produced by quinine. These may be followed by some confusion and dullness and by indistinct sight and hearing. Very often the patient complains of excessive perspiration and a sense of warmth all over the body. Dyspnœa, marked by exceedingly deep and labored respiration, has been noted in more serious cases of poisoning, and a condition of collapse with slow, weak pulse, subnormal temperature, and partial or complete unconsciousness may follow. In others, delirium and hallucinations of sight and hearing have occurred, these being more frequently seen in chronic alcoholic patients and in cases of diabetes than under other conditions. Albumin, casts and even hæmoglobin and blood in the urine are often noted as sequelæ. Various forms of skin eruptions have been described as occurring under the use of salicylic acid, sometimes after a single dose, but more frequently after prolonged treatment. They resemble those seen under the antipyretics, but seem to be less frequently elicited by salicylic acid. Hæmorrhages from the nose, mouth, intestine and uterus have also been credited to the action of this drug, and the last may explain the occasional occurrence of miscarriages under it; it has no influence on the uterine movements in the concentrations found in the blood in man, though stronger solutions increase the contractions in animals. Numerous other symptoms have been noted after it, but so rarely that a doubt may be entertained as to whether they were not due to some special condition, or perhaps to some impurity in the drug.

In animals salicylates injected intravenously cause some acceleration of the pulse and respiration, followed by slowness and weakness of the heart, and often by marked dyspnœa. Depression of the central nervous system is shown by slowness, weakness, and incoördination of the spontaneous movements, and eventually by stupor and arrest of the respiration, which is generally preceded by convulsions. Photophobia and clonic spasms have been observed in some dogs. Hyperæmia of the kidney, liver, brain and tympanum are sometimes found at the autopsy on dogs poisoned with salicylates, and, when the drug has been given in powder, congestion, irritation, and necrosis of the gastric mucous membrane. This irritation of the stomach often causes vomiting in dogs, and the poison being thus eliminated, no further symptoms appear. Vomiting occurs in cats when salicylate is injected hypodermically, which indicates some action on the medullary centres; increased reflexes, tremors and restlessness are also described in these animals in which a more distinct stimulation of the central nervous system seems to be elicited than in man.

In the frog salicylic acid produces quickened respiration and increased reflexes, followed by depression of the spontaneous movements, tremor, and clonic contractions. The heart is slow, dilated, and weak.

The symptoms elicited by salicylic acid and its salts are therefore very indefinite, and with few exceptions occur so seldom in man that they may be discussed shortly.

The **Disorders of Hearing** have been ascribed to congestion of the tympanum, but may perhaps indicate some changes in the nerve cells of the ear analogous to those observed under quinine. As a general

rule they pass off in the course of a few hours or days, but they sometimes leave a more or less permanent impairment of the sense of hearing. The **Dimness of Sight,** sometimes amounting to complete blindness, is due to vascular or retinal changes in the eye (see Quinine), and some disturbance of the circulation of the brain and head may be the cause of the dullness and fullness of the head complained of, and of the not infrequent epistaxis. Maragliano showed by plethysmographic measurements that the **Vessels of the Skin** are dilated by salicylates in the same way as by the antipyretics.

With small therapeutic doses of the salicylates the **Circulation** is little altered unless in a suceptible individual, when the heart may be somewhat accelerated. Full therapeutic doses may cause some depression of the circulation, but usually this is not important. The general **Blood-pressure** may be found to be increased by small quantities of the salicylates from stimulation of the vaso-constrictor centre, while after very large injections into the blood-vessels, the pressure is lowered, partly perhaps from depression of the centre, but mainly from the cardiac action of the drug.

Small quantities may accelerate the **Heart** in animals in the same way as small doses of the other aromatic bodies, apparently from direct action on the cardiac muscle. Very large doses produce a slow, weak, and dilated heart, and a corresponding fall in the blood-pressure. Friderichsen found that 0.12 per cent of salicylate in the blood causes no symptoms from the heart, but any higher content is injurious.

The acceleration and deepening of the **Respiration** and the dyspnœa which have been noted in man, seem to be due to central action, either from a direct stimulation of the centre by the salicylate or from an indirect effect due to some products resulting from the activity of the drug. In animals, too, the respiration is first accelerated to some extent, and then slowed, apparently from the respiratory centre being first excited, then depressed, and eventually paralyzed, by very large quantities of the drug. In the early stages of respiratory acceleration there is a marked increase in pulmonary ventilation but this increase may not keep pace with the increase in respiratory rate. In certain cases the tidal air is below normal. Death seems to be due to respiratory paralysis, the heart continuing to beat for some time afterward.

The effects of salicylates on the **Central Nervous System** seem to be comparatively slight, except in cases in which a special idiosyncrasy exists. No such convulsive action as occurs under others of the aromatic series has been observed under it, and in animals there seems no marked depression save in the medulla oblongata. The convulsions which are observed before death are probably not due to the direct action of the drug, but to the asphyxia. In the medulla oblongata the respiratory and vaso-constrictor centres, and probably the vaso-dilator, seem to be first stimulated and then depressed.

The **Perspiration** which so often follows the administration of salicylic preparations may be due in part to the dilatation of the skin vessels, but is probably to be ascribed rather to increased activity of the sweat centres. Some of the **Skin Rashes** may also be caused by the dilatation

of the cutaneous vessels, and perhaps in all cases this may be looked upon as a favorable condition, which leads to eruption in individuals who are predisposed to them.

Salicylic acid and its salts may increase to some extent the **Secretion of the Urine**, probably through a direct action on the renal epithelium, although the increased formation of urea may also play a part in the slight diuresis. Very frequently the effect of the administration of full therapeutic doses of the salicylates is to lessen the quantity of urine. This action is probably due partially to the diaphoresis and partly to a direct action on the kidney. The latter action is shown not only by albuminuria but also by an increase in the urea in the blood and by a diminished excretion of phenolsulphonphthalein. Nephritis has been observed in some cases, with not only albumin but also blood in the urine. The administration of bicarbonate of soda with the salicylate does not appear to lessen the tendency to renal irritation in any way.

Recent experimental studies have again demonstrated the nephrotoxic action of salicylates, especially for the kidneys of dogs. It is apparently more toxic for the kidneys of these animals than are the cinchophen compounds, although this relationship does not hold for all species, the rat apparently forming an exception (Barbour and Fisk).

The salicylic preparations produce a slightly augmented flow of **Bile**, apparently from some specific action on the liver cells. The bile is generally more dilute than normal, the fluid increasing more than the solids, though the total solids excreted are augmented.

Salicylate has been said to lower the normal **Temperature**, but this seems to be erroneous, except when very large quantities produce a condition akin to collapse. In fever patients, however, it often causes a marked fall of temperature, and it was formerly used as an antipyretic for this reason. The action is probably explained by the dilatation of the cutaneous vessels, and the increase in the output of heat. (See Antipyretics.) Dilatation of the skin vessels also occurs in normal persons after salicylates, but this is counterbalanced in them by increased heat formation. The fall in temperature after salicylic acid is generally less in extent and of shorter duration than that following the members of the antipyrine series.

An interesting fact, pointed out by Barbour, is that persons with unstable temperature centres, such as those persons who are only temporarily afebrile or who are convalescent, react to acetylsalicylic acid in the same manner as do febrile patients; that is, their heat elimination is greatly increased, perhaps 40 per cent, while in normal persons the elimination of heat may not be altered.

In its passage through the tissues, salicylic acid modifies the **Metabolism**, as is shown by an increase of 10–12 per cent in the nitrogen and sulfur of the urine. This indicates a considerably augmented decomposition of the proteins of the body, but whether it is accompanied by increased oxidation is unknown. A still more notable augmentation of the uric acid excretion has been observed, different authors estimating it at 30–45 and even 100 per cent. This occurs also in ani-

mals and persons on a purine-free diet; the uric acid escapes through the kidney more easily, and the percentage in the blood falls as that of the urine rises. (See Cinchophen, p. 689.)

It has been shown that the salicylates bring about a moderate lowering of the alkali reserve, producing an acidosis due probably to an increase in fixed acid. This increase in acid is possibly due to the presence of lactic and phosphoric acids resulting either from altered metabolism or possibly from impaired excretion due to disturbance of kidney function.

Salicylate circulates in the blood as the sodium salt; most of it is carried in the plasma, but some passes into the corpuscles; it does not accumulate in the joints more than elsewhere, as was asserted. It is found in practically all secretions and organs of the body; the brain is said to contain less than most of the other organs, averaging perhaps a third as much as is found in the muscles, blood or spleen. About three-fourths of that ingested is **Excreted** by the kidneys, for the most part unchanged. Part of the drug is oxidized further to dioxybenzoic acid and to hydroquinone and part is excreted in combination with sulfuric and glycuronic acid. It appears in the urine within an hour of its administration by the mouth and is all eliminated in forty-eight hours. It has been found also in the milk, perspiration and bile, but does not appear to be excreted into the stomach, nor is any found in the fæces. About 20 per cent or more is completely destroyed in the tissues, and this fraction is higher in rheumatic fever than in normal persons; the actual concentration in the blood and urine may thus be lower in rheumatic fever.

Van Leeuwen and Drzimal have shown that the blood of asthmatics who are sensitive to salicylates binds salicylic acid less intensively than does normal blood. They ascribe the cause to the action of the colloids. More salicylic acid can be extracted by ether from the blood of such persons than can be obtained from the blood of normal persons. They think sensitivity of the individual in such cases may rest upon the failure of the colloids to adsorb the acid.

Methyl Salicylate (oil of wintergreen) has a hot, burning taste, and like other volatile oils produces a feeling of warmth in the stomach. In many cases it is well borne, but some patients complain of pain in the stomach, loss of appetite, and even nausea and vomiting. Much of it is decomposed to salicylate in the intestine and this is rapidly absorbed and produces the characteristic symptoms in large doses. Much less salicylate is excreted in the urine than after the corresponding sodium salt, and some of the oil reappears unchanged.

Mesotan is a methyloxymethyl ester of salicylic acid. It resembles methyl salicylate but it is more irritant. It is absorbed from the skin but is used mainly for its local action as a counterirritant in rheumatic conditions. It is a clear yellowish oily fluid which is diluted with from 1 to 4 parts of olive or cotton-seed oil before being applied to the skin. Care must be taken not to use friction in applying it and not to repeat the application too often in the same place.

Salicin, a glucoside found in many species of willow and poplar, is decomposed into salicyl alcohol, which is oxidized to salicylates in the body. It is probable that the decomposition, like that of the ordinary esters, takes place chiefly in the intestine, for when it is injected intravenously it is excreted unchanged. It is very bitter, but does not irritate the mucous membranes, and is not so certain in its action as salicylate. When administered by the mouth it is excreted in the urine partly as salicin, partly as saligenin or salicyl alcohol, and partly as salicylic and salicyluric acids. It is little used in therapeutics today.

Acetylsalicylic Acid, or **Aspirin,** passes through the stomach unchanged and is free from the gastric effects of salicylic acid and the salicylates. It is partially decomposed into salicylic acid in the bowel, but some of it is absorbed in its original form. The salicylate formed from it exercises its usual action in the tissues, but there is a further action resembling that of the antipyretics in headache and neuralgia, and this is attributed to the action of the acetylsalicylate which has escaped decomposition and has been absorbed.

Symptoms of idiosyncrasy to acetylsalicylic acid are more common than to the other salicyl compounds. They are largely characterized by exudative features suggesting increased capillary permeability. Congestion of the nose with localized œdemas are most commonly encountered. These latter œdemas may involve the eyelids, pharynx, lips, or the extremities. Urticarial eruptions are not infrequent.

To investigate further the relative safety of acetylsalicylic acid, feeding experiments were carried out on white rats employing large doses over a prolonged period of time. The results were negative in so far as growth curve and the general physical condition were concerned. The animals went through normal pregnancies and produced normal litters in spite of daily doses of acetylsalicylic acid corresponding to 39 G. for a 70 kg. man. Climenko found that 100 mg. of a mixture of acetylsalicylic acid and magnesium oxide was as effective in lowering temperature of fevered rabbits as was a dose of 100 mg. of acetylsalicylic acid given alone. The adding of the magnesium oxide had no effect upon the toxicity of the acetylsalicylic acid.

Salysal is the salicylic ester of salicylic acid. It resembles the other salicylates quite closely in its general effects, but being insoluble in water it is practically tasteless and is relatively free from local irritating effects. Its average dose is from 0.3 to 0.6 G.

Salicylic acid is ortho-oxybenzoic acid, and there are two isomers, *metaoxybenzoic* and *paraoxybenzoic* acid, which differ from it structurally only in the relative position of the hydroxyl and carboxyl side chains. Yet their salts are devoid of action in acute rheumatism and are not employed in therapeutics.[1]

The three isomeric *cresotinic acids* ($C_6H_3 \cdot CH_3 \cdot OH \cdot COOH$) that correspond to salicylic acid in the position of their hydroxyl and carboxyl groups, resemble it in action and are effective in acute rheumatism; they are approximately equal to salicylic acid in toxicity, but ortho-cresotinic acid has a more depressant action on the heart, and as they offer no advantages over salicylates, they have only been used experimentally in therapeutics.

Therapeutic Uses.—The chief sphere of usefulness of salicylate at the present time is in the treatment of acute rheumatic fever, in which it seems to have a specific action similar to that of colchicum in gout. Some other members of the aromatic series are useful in this condition, but none is superior to the salicylic preparations in efficacy. Under this treatment the pain, swelling, and redness in the joints rapidly lessen, the temperature often falls, and the disease makes less demands on the strength and courage of the patient. It is a question whether it acts on the unknown cause of the disease, and some hold that it is a purely symptomatic treatment and that salicylate may be replaced

[1] This difference in activity between the isomers of the benzene series is very frequently met, and the relative toxicity differs in the different compounds, thus the ortho-compound is most active in the oxybenzoic acids (salicylic acid), while among the cresols the metacresol is said to be the most poisonous, and parachlorphenol is more antiseptic than either of its isomers.

by a mixture of other antipyretic and analgesic remedies, although experience seems to indicate that none of the members of the antipyrine group is as efficient in relieving the pain and discomfort in this condition as are the salicylates. It is still debated whether the salicylate treatment reduces the liability to involvement of the heart, which is a common complication of acute rheumatic fever. It is generally believed now that the incidence, extent, and prognosis of cardiac damage do not appear to be affected by the use of the salicylates, although some clinicians still believe that the cardiac affections are less often met with and are less severe under salicylate treatment. Levy and Turner believe that the salicylates definitely influence favorably the conduction mechanism in the heart in acute rheumatic fever. They say that in this disease the auriculo-ventricular conduction time may be considerably prolonged, but under the salicylates it is brought back to normal and they suggest that the salicylates probably lessen œdematous

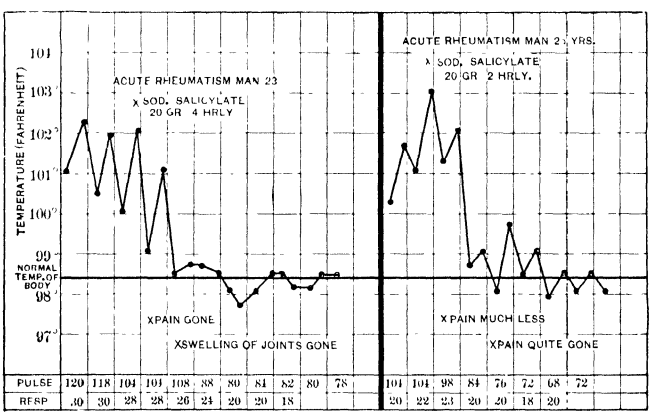

FIG. 66.—Clinical charts of cases of acute rheumatic fever treated with salicylate of sodium. Case 1, 20 grs. every four hours, Case 2, 20 grs. every two hours. (Stockman.)

infiltration in the region of the bundle with a resulting shortening of conduction time. Other clinicians have failed to confirm these findings. The remedy sometimes fails in rheumatism, as quinine does in malaria, and it sometimes acts more satisfactorily in one joint than in another. Relapses occur even during the continuous treatment with ordinarily adequate quantities of salicylate, and it has been found advisable to keep the patient under observation as long as was necessary before the salicylate treatment was introduced (Miller). Large doses of sodium salicylate (1–2 G. or 15–30 grs.), repeated every two or three hours are necessary in most cases at first, the quantity being reduced as the symptoms abate. A convenient rule for sodium salicylate dosage in this condition is to give a grain per day per pound of body weight—this dose is to be reduced greatly if toxic symptoms arise. If the use of the large doses produces gastric distress and vomiting the drug may be given by rectum. The important point in the treatment is to secure

through one avenue or the other the absorption of a sufficient amount of the drug. After the acute symptoms have subsided the drug should be continued in smaller doses, 10 grs., three times daily, for several weeks or months. This continued administration is believed to lessen the likelihood of relapses. Children in general seem to tolerate the salicylates well and to take relatively larger doses than could ordinarily be given when calculated according to their age. The effective dose of acetylsalicylic acid in rheumatic fever is about two-thirds that of sodium salicylate, but the latter drug is to be preferred in this disease. Salicylic acid should not be given, as it is more irritant to the stomach. Sodium bicarbonate is frequently recommended along with the salicylate on the ground that it lessens the gastric irritation by preventing the formation of the irritant salicylic acid. The use of the bicarbonate also seems to be justified by the condition of acidosis with resulting hyperpnœa which, as stated, not infrequently results from the use of large doses of salicylates. Cinchophen (p. 689) has been found efficient as a substitute for salicylate in rheumatic fever but seems to have no definite advantage over it, and its possible toxic action on the liver would seem to contraindicate its use, especially in large doses and for a long time.

In other acute constitutional diseases accompanied by fever, salicylate has no such specific action as in acute rheumatic fever; even when the joints are involved, as in gonorrhœal arthritis, salicylate is of little or no service, so that some special relation appears to exist between the salicylate and the cause of rheumatic fever.

Salicylates have also been used in the various forms of disease which are roughly classified as rheumatic—chronic rheumatism, arthritis, neuralgia, myalgia—but the effects are less satisfactory than in acute rheumatism.

Salicylate in some cases promotes the absorption of effusions into the serous membranes, such as the pleura, and also subretinal effusion. It is unknown how this is effected.

The cholagogue action of the salicylates is quite inconsiderable in comparison with that of the bile itself, and in any case in which an increase of the bile secretion is desirable, recourse should be had to the latter. It has recently been suggested by Kuhn that the salicylic salts excreted in the bile may retard the growth of microbes and thus prove of value in the treatment of liver and gall-bladder infections.

Salicylic acid is occasionally applied locally in excessive sweating (2–4 per cent in talc) and has also been used in various skin affections in which it is desirable to soften or partially dissolve the epidermis; it is the chief constituent of many "corn-salves." For this purpose it is best used 20 per cent in collodion. Both acid and salts are absorbed too rapidly to act as intestinal disinfectants.[1]

Salicylate is hardly used as an antipyretic at the present time, and

[1] Salicylic acid has been used very largely as a preservative in wine and beer. No evil effects have been shown definitely to follow the prolonged use of liquors thus treated, but they may tend to disturb the digestion, and several governments have found it advisable to prohibit its use for this purpose.

it has no value as a substitute for quinine in malaria, for which it was suggested.

Salicin has been used as a substitute for salicylic acid in rheumatic fever but it is very rarely prescribed today.

Acetylsalicylic acid is used chiefly to relieve headache and neuralgia in the same way as the antipyretic group, and for this purpose may be given in doses of 0.3–0.6 G. (5–10 grs.) in tablets.

Salicylic preparations have to be used with care where any symptoms of renal irritation are present and large doses should be used with care in cases of pregnancy, as they may lead to miscarriage. In cases of poisoning, the treatment is determined entirely by the symptoms, and no antidote is known.

Methyl salicylate, or oil of wintergreen, is often applied locally in muscular and articular rheumatism. Absorption certainly occurs through the skin, as is proved by the appearance of salicylates in the urine. Several other synthetic compounds have been suggested in place of wintergreen oil in external treatment, but they have no advantage over the older drug.

Salol is used most extensively as an intestinal disinfectant. (See p. 810.)

PREPARATIONS.

U. S. P.

SODII SALICYLAS, 1 G. (15 grs.).
ACIDUM SALICYLICUM, 0.75 G. (12 grs.).
PHENYLIS SALICYLAS, Salol. 0.3 G. (5 grs.).
METHYLIS SALICYLAS, oil of wintergreen. 0.75 cc. (12 mins.).
ACIDUM ACETYLSALICYLICUM, Aspirin. 0.3 G. (5 grs.).

B. P.

SODII SALICYLAS, 0.6–2 G. (10–30 grs.).
ACIDUM SALICYLICUM, 0.3–0.6 G. (5–10 grs.).
ACIDUM ACETYLSALICYLICUM, Aspirin. 0.3–1 G. (5–15 grs.).
METHYLIS SALICYLAS, 0.3–1 mil. (5–15 mins.).
SALICINUM, 0.3–1 G. (5–15 grs.).
UNGUENTUM ACIDI SALICYLICI, 2 per cent salicylic acid in ointment.

SODII SALICYLAS, sodium salicylate ($C_6H_4OHCOONa$), a white, odorless powder with a sweetish taste, very soluble in water, less so in alcohol.[1] It is given in capsules or tablets, or still better dissolved in water.

ACIDUM SALICYLICUM, salicylic acid ($C_6H_4OHCOOH$), small, white, needle-like crystals, or a light crystalline powder, odorless with a sweetish, afterward acrid, burning taste, slightly soluble in water, very soluble in alcohol or ether. A reddish tinge indicates the presence of carbolic acid or other impurities.

PHENYLIS SALICYLAS, Salol, a white powder, with an aromatic odor, almost insoluble in water. Given as a powder.

OLEUM GAULTHERIÆ, oil of wintergreen, a colorless or yellowish fluid with a characteristic, pleasant odor and a sweetish, aromatic taste, insoluble in water, soluble in alcohol. Contains 90 per cent of methyl salicylate.

METHYLIS SALICYLAS ($C_6H_4OHCOOCH_3$), is practically identical with the oil of wintergreen.

[1] Salicylate formed synthetically from phenol is often said to be more poisonous than that obtained from the oil of wintergreen (methyl salicylate), but this is not correct.

SALICINUM, salicin ($C_6H_{11}O_5OC_6H_4CH_2OH$), a glucoside obtained from several species of willow and poplar, consists of white, silky, crystalline needles, with a very bitter taste, soluble in 28 parts of water. Given in powder, capsules or in solution, which, however, is very bitter. It is very rarely used in therapeutics today.

ACIDUM ACETYLSALICYLICUM, Aspirin ($CH_3CO—OC_6H_4COOH$), is composed of small colorless crystals, without odor, and is slightly soluble in water with a more pleasant acid taste than salicylic acid. Given in powder or tablets.

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I. Benzoic Acid and Benzoates.

Benzoic acid and its salts resemble the salicylic preparations closely in their action in most points, the acid being antiseptic and irritant, while the salts are less active in this respect. Benzoates have less action on the central nervous system, and the disorders of hearing which are characteristic of the salicylates, have not been observed. Nausea and vomiting occur from very large quantities in man, and it is believed that the expectoration is increased by the use of small doses of benzoates in bronchial catarrh.

Benzoic acid (C_6H_5COOH) combines with glycine in the kidney and in other organs to form hippuric acid ($C_6H_5CO—NHCH_2COOH$), which is excreted in the urine; some of the benzoic acid escapes in the urine unchanged, the proportion of hippuric acid formed apparently varying with the dose administered and other conditions; and some appears to be excreted in combination with glycuronic acid when very large doses are administered. The amount which is transformed to hippuric acid does not increase significantly when glycine is administered along

with benzoic acid, yet the glycine seems to lessen the tendency to convulsions in animals. In birds benzoic acid is excreted by the kidneys as ornithuric acid ($C_{19}H_{20}N_2O_4$), from which benzoic acid can be split off, leaving ornithin. Benzoic acid often increases the nitrogen eliminated in the urine, so that in these cases it augments the decomposition of the proteins like salicylic acid; in other investigations no material change has been observed, probably because the benzoic acid was changed to hippuric acid too rapidly to admit of its action on the metabolism being developed. It differs from salicylic acid in reducing the uric acid excretion. Some diuresis occurs after benzoic acid, and the acidity of the urine increases in the same way as after other acids which do not undergo combustion in the tissues.

Benzoic acid has sometimes been employed as an antiseptic, and sodium benzoate has been credited with some virtues as an intestinal and genito-urinary disinfectant. The treatment of gout and other diseases with benzoates on the theory that they lessened the uric acid excretion is obsolete. Ammonium benzoate has been given to increase the acidity of the urine, but is not so useful as the acid sodium phosphate. Benzoic acid is still an ingredient in many expectorant mixtures, generally in the form of benzoin or balsam of Tolu.

PREPARATIONS.

U. S. P.

ACIDUM BENZOICUM, 1 G. (15 grs.).
SODII BENZOAS, 1 G. (15 grs.).
AMMONII BENZOAS, 1 G. (15 grs.).

B. P.

ACIDUM BENZOICUM, 0.3-1 G. (5-15 grs.).
SODII BENZOAS, 0.3-2 G. (5-30 grs.).

ACIDUM BENZOICUM (C_6H_5COOH), benzoic acid, or flowers of benzoin, form white crystals, almost odorless, with a warm acid taste, very insoluble in water, soluble in alcohol, ether, fixed and volatile oils and in alkaline solutions.

SODII BENZOAS, easily soluble in water. 1 G. (15 grs.).

Cinnamic acid (C_6H_5—CH=CH—COOH) seems to resemble benzoic acid in its pharmacological characters, but has not been so carefully examined. It increases the leucocytes of the blood and the uric acid of the urine to a marked degree.

II. Iodoxybenzoic Acid.

o-Iodoxybenzoic acid in the form of its salts has recently been introduced into therapeutics as a remedy against infectious arthritis. It is usually given in this disease by the intravenous injection of the ammonium salt, although it has been given in capsules or in the form of an enema. When the drug is injected intravenously, more or less severe reactions are not uncommonly met with although many patients can take it without any disturbance. Thrombosis of the vein is not infrequent but this is not so common with the ammonium salt as when the sodium compound is used. The patient may complain of a stinging sensation in the nose and mouth; there may be lacrimation and sneezing and nausea and vomiting are not uncommon, especially in children. Not infrequently the injection is followed by a sharp reaction with a chill and fever. This is most likely to occur when acute cases are treated.

The result of the treatment is said to be a lessening of pain in the joints, a decrease in the swelling and an increase in range of motion with loss of stiffness. There is often an improvement in the general health, with a gain in weight, strength, and in general well being. Not all patients are benefited by the treatment—an important factor influencing the results being the degree of anatomical deformity with loss of function which is present in the individual case. The drug is still in the experimental stage and time alone can determine its therapeutic value.

Iodoxybenzoic acid when injected into animals acts on the blood, producing a mild polymorphonuclear leucocytosis. Following its injection it also acts upon the respiration, producing apnœa which has been ascribed to the oxygen which is attached to the iodine. This explanation has not been generally accepted. In the isolated perfused heart it produces an increase in amplitude followed by weakening.

The compound is actively germicidal to staphylococci, and when injected into dogs it stimulates the production of antibodies and in rabbits it stimulates the production of hemolysin and agglutinin, when injected soon after immunization.

Therapeutic Uses.—In infectious arthritis the drug is given by intravenous injection in 1 G. (15 grs.) doses, usually biweekly. The acid is added to 50 cc. of sterile freshly distilled water and enough ammonium hydroxide is added to make it just alkaline to litmus. Sufficient sterile distilled water is added to make 100 cc. and the solution is injected slowly at body temperature so that the injection will take at least seven minutes. The ammonium salt may be used in place of the acid by merely adding it to the required amount of water, thus avoiding the use of the ammonia. The drug is given twice weekly for four or five weeks and then a period of rest of several weeks is allowed, followed by a new course of injections. These courses may have to be repeated according to the requirements of the case.

Preparation.

o-Iodoxybenzoic acid (non-official), a white powder, insoluble in cold water and slightly soluble in hot water. Its sodium and ammonium salts are freely soluble in water. Dose 1 G. (15 grs.), usually by intravenous injection.

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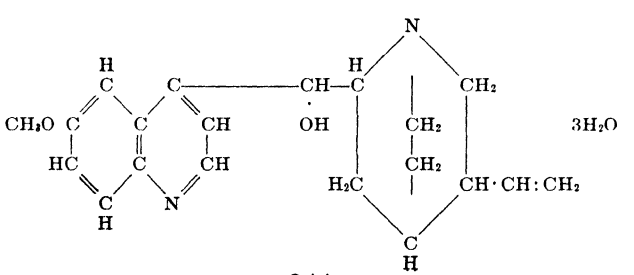
U. QUININE.

The barks of various species of Cinchona and Remijia (Cuprea) contain numerous alkaloids which resemble each other in their chemical and pharmacological properties. The best known of these are *quinine, quinidine, cinchonine* and *cinchonidine;* the others, amounting to some twenty in number, are believed to resemble these in their effects on the organism, but very little has been done to determine this, and little is known regarding their relative activity.



Quinine

The cinchona alkaloids are derivatives of quinoline. Cinchonine and cinchonidine are isomeric ($C_{19}H_{22}N_2O$), while quinine and quinidine, another pair of isomers ($C_{20}H_{24}N_2O_2$), are methoxyl compounds of cinchonine. These isomers differ in their optical activity, quinine and cinchonidine being lævorotary, while quinidine and cinchonine are dextrorotary; they are not complete mirror images of each other, however, as there are four asymmetric carbon atoms in each, and two of these appear to have the same sign of rotation in all these alkaloids.

Besides these alkaloids cinchona bark contains several acids, including tannins, and some neutral substances.

The cinchonas are natives of Western South America, but are now cultivated in India and Java. It seems questionable whether the virtues of the bark were known by the native Indians before the invasion of the Spanish, and its introduction into medicine dates from about 1630–1640; its name bears testimony to its efficacy in the case of the Countess of Chinchon in 1638.

Action.—Quinine differs from most of the other important alkaloids in acting, not on some specialized form of living matter, but on the general nutrition of almost all forms of protoplasm. Other alkaloids, such as strychnine, are also possessed of similar effects as regards nutrition, but their strong affinity for, and intense action on, some special tissue prevent their effects on the fundamental properties of living matter from being elicited in the higher animals. Quinine is therefore often termed a protoplasm poison because its action extends with but little variation throughout most forms of living matter. The effects of quinine on protoplasm generally consist in transitory augmentation of its activity, followed by depression and death.

The action of quinine on **Undifferentiated Protoplasm,** such as is found in the unicellular organisms and in the ovum, is therefore of greater interest than that of most alkaloids. Binz found that while very minute quantities sometimes increase the movements of the amœba and infusoria at first, large amounts paralyze them immediately, and the protoplasm assumes a darker granular appearance. The rhythmic movements of ciliated organisms are rendered slow and finally arrested by very dilute solutions, and the microbes of putrefaction are also acted upon by quinine, although they are more resistant than the protozoa; still, quinine solutions, 1:2000, delay the growth of bacteria. The alcoholic, lactic and butyric fermentations are similarly retarded, but it is apparently devoid of action on some of the lower forms, for moulds (Penicillium) grow freely in solutions of the salts, perhaps because the quinine fails to penetrate through the cell membrane. Another example of its action on the vegetable cell is that discovered by Darwin in some insectivorous plants (Drosera), in which the movements seem to be first excited and later paralyzed by the quinine salts.

The influence of quinine on the reproductive cells of animals has been carefully studied by O. and R. Hertwig, who found that both the spermatozoön and the ovum of the sea-urchin are injured by the addition of quinine to the sea-water, the movements of the former being paralyzed, and the stages preceding impregnation in the latter

progressing more slowly, or actually retroceding. When quinine is applied after the male nucleus has entered the ovum, the complete conjugation is delayed and the whole process is rendered abnormal by the admission of several spermatozoa. Quinine applied still later prevents or delays the division of the ovum through its effects both on the nucleus and on the general protoplasm of the cell.

The individual cells of more complex organisms are affected in the same way as these more simple ones. This was first demonstrated in the leucocytes by Binz, who showed that when quinine is added to a drop of blood under the microscope, the amœboid movements of the leucocytes are arrested, and they assume a spherical form, become darker in color and granular, and soon break up into débris. In the blood-vessels similar changes occur when quinine is applied locally, as to the frog's mesentery; the leucocytes again become darkly granular, and ceasing their creeping movements, are carried along by the current much more rapidly than usual. They are no longer observed to push their way through the vessel walls, and if they have already penetrated into the tissues their movements are arrested. If irritation be applied to the part, no such accumulation of leucocytes occurs in the tissues as in the unpoisoned animal, and if an irritant has been applied first and the leucocytes have poured out of the vessels before the quinine is applied, the process is arrested at once on its application This poisonous effect on the leucocytes has received much attention, but only occurs when the alkaloid is present in a concentration of 1:3000, which is higher than can obtain in the blood of a living animal. More recent studies (Macnaughten) have shown that lower concentrations affect some other functions of the leucocytes, whose phagocytic powers are lessened by concentrations of 1:24,000; the bactericidal action of the plasma is also reduced by this concentration. There is no reason to suppose that this action on the white blood cells occurs when quinine is administered in therapeutic doses, which would not give rise to this concentration. All of these effects are greatly influenced by the reaction of the medium, since any increase in its alkalinity increases the toxicity; this may probably be ascribed to the alkaloid penetrating more easily into cells than its salts.

Some enzymes seem to be rendered inactive by quinine; for example, Binz states that the blood no longer forms the blue oxidation product of guaiac in the presence of quinine, but only if the alkaloid be present in a concentration of 1 per cent. A number of other ferments act more vigorously in very dilute solutions of quinine, while they are retarded by larger quantities; for example, the autolytic ferment of the liver, pepsin, and rennet. And some appear to be much less susceptible to its action than others, for they are augmented in activity by quantities that retard or destroy those more readily affected.

The action on striated **Muscle** is similar to that on the lower organisms. There is sometimes a transient increase in its power but very soon the muscle contraction is weaker and fatigue follows more quickly than normally. Injections of large amounts of quinine salts into muscle kill the fibres and lead to sloughing.

The **Nerve Trunks** are said to be remarkably tolerant to solutions of quinine, which do not lessen their irritability when applied locally in sufficient quantity to cause marked abnormalities in the muscular contraction. In the frog, the terminations of the motor nerves in striated muscle are paralyzed by large doses, but not in mammals.

Unstriated Muscle in the mammals tends to contract under quinine, this action being especially marked in the **Uterus**, which is thrown into strong rhythmical contraction when it is suspended in Ringer's solution containing quinine. Contractions are also initiated in the resting uterus when quinine is carried to it by the blood in the intact animal and this has led to its use in obstetrics to arouse the relaxed organ. Similarly the excised intestine suspended in Ringer's solution is aroused to increased movement by quinine, but there is no evidence that this occurs when quinine is carried to it by the blood. The spleen contracts, however, in the intact animal and in man, apparently from its acting on the muscle fibres, and quinine perfused through the arteries of an excised organ often narrows their calibre from contraction of the muscle of the walls; this contraction is often followed by relaxation. In each of these cases the action seems to be exerted directly on the muscle, which is first contracted and then relaxed if the dose is large.

The **Heart** is said to be sometimes accelerated in mammals, but is generally slowed and weakened when quinine is injected intravenously; this is due to direct action on the heart muscle, but large amounts may depress the vagus terminations. The heart continues to beat after the respiration has ceased in fatal poisoning. The weakness of the heart leads to a fall in blood-pressure, but the main cause of the fall is dilatation of the peripheral vessels due in part to an action upon the vasomotor endings and in part to a direct action on the muscle fibres themselves. Both quinine and quinidine antagonize the pressor effects of epinephrine as the latter drug fails to cause an increase in blood-pressure following the intravenous administration of the two cinchona alkaloids. The cardiac effects are not observed except in a very slight degree when quinine is absorbed from the stomach even in large therapeutic doses. In the frog also the heart is slowed and weakened from depression of the muscle.

The **Central Nervous System** is found to undergo a slight and transient excitation, when large doses are injected in mammals, but the chief effects are of the nature of depression. Thus in the frog a short stage of slightly exaggerated reflex movement is followed by the loss of spontaneous movements, the arrest of the respiration, and paralysis of the spinal cord and ends of the motor nerves. In mammals, the spinal cord is stimulated by small quantities and then depressed. The respiration is sometimes quickened at first and later becomes weak and slow and its cessation is the cause of death. General depression and muscular weakness are usually the only cerebral effects observed in mammals and the tremor and convulsions which sometimes occur are perhaps due to the failure of the respiration.

The **Secretions** are not affected by quinine unless very large quantities are injected when they are arrested

In **Man**, quinine taken by the mouth has the same action on appetite

as the simple bitters. Ordinary therapeutic doses often produce no very obvious symptoms, the most frequently observed effect consisting in derangement of the **Sense of Hearing,** less frequently of that of **Sight.** Ringing or roaring sounds in the ears, accompanied by slight deafness, are produced by moderate quantities, and large doses are not infrequently followed by complete loss of hearing for a time. Contraction of the field of vision is observed less often, but in some cases total blindness has been produced and has lasted for several days or even weeks. Color-vision is especially liable to be rendered imperfect or temporarily paralyzed by quinine; these disorders of sight are accompanied by a very marked contraction and even obliteration of the retinal vessels and sometimes by degenerative changes in the retinal nerve cells and even by atrophy of the optic nerve. It is still undecided whether the vascular change or the nervous degeneration is the primary lesion, but the majority of investigators at present favor the view that the constriction of the vessels is merely an accompaniment of the graver effects on the ganglionic structures.

In an experimental study carried out upon dogs it was found that quinine and several of the synthetic compounds of the series exerted a deleterious action upon the eyes of the animals. There were few signs to be observed by inspection except that the pupils were dilated and reacted sluggishly and there was some pallor of the disc but no marked change in the retinal vessels. The striking change was in the cells of the ganglionic layer of the retina, many of which had been destroyed. There was also some œdema of the retina. These changes were produced by quinine and by the synthetic drugs, ethylhydrocupreine, ethylapocupreine and isopropylapocupreine. On the other hand, the closely related hydroxyethylapocupreine given in comparable doses was not found to have any such effect upon the retinas of any of the animals. In a study of the value of these compounds on the pneumococcus the latter compound was the least active of the group but it was still present in the serum of the animals in amounts which were pneumococcocidal.

The symptoms in the ear have generally been regarded as the result of congestion and hæmorrhages in the tympanum and labyrinth, but Wittmaack has shown that this view is founded on erroneous observations, and states that degenerative changes occur in the spiral ganglion in the cochlea exactly analogous to those described in the retina. When quinine is taken continuously as a prophylactic, it is said to impair the hearing and sight permanently in some cases.

Quinine possesses some irritant action which betrays itself in discomfort in the stomach and eructation after large and repeated doses by mouth, and by pain and tenderness when it is injected subcutaneously.

Large doses of quinine produce some confusion and depression with a sense of fullness and heaviness in the head from their action on the **Cerebrum,** and this is sometimes accompanied by uncertain gait and slow pulse. Very few cases of fatal poisoning have been satisfactorily determined to be due to quinine, although a considerably larger number have been attributed to it. In these cases marked weakness of the heart and collapse accompanied by loss of sight and hearing, muscular weakness, apathy, slow gasping respiration and finally unconsciousness and total failure of the respiration were observed. In some cases delirium

and convulsions have been noted. Enormous doses of quinine sulfate have been swallowed without any serious results. Thus in one case 30 G. (1 ounce) produced only some confusion and noises in the ears.

The extensive use of quinine in therapeutics has demonstrated that many persons have curious **Idiosyncrasies** in regard to it. This is betrayed in many cases by the development of ear symptoms after comparatively small doses, but in others symptoms arise which do not appear in the great majority of people even after large doses. The commonest of these are skin eruptions, of which a large variety have been described, and which can be distinguished from ordinary diseases of the skin only by the history, or by the detection of quinine in the urine, or by a positive reaction to a quinine solution when it is applied to a scratch in the skin. These exanthemata are often accompanied by some rise in temperature, which has received more attention than it appears to deserve, for it is rare and, even when present, is of insignificant extent. Other less important effects, which have been noted, are dyspnœa, gastric discomfort, vomiting and diarrhœa. Patients with an idiosyncrasy to quinine sometimes exhibit abnormal reactions to other alkaloids of this group. This is not always the case, as malarial patients who have been unable to take quinine on account of its unpleasant effects upon them have been successfully treated with quinidine. In some cases the administration of quinine is followed by fever and hæmoglobinuria (black water) or albuminuria. The exact relation between quinine and this condition is a matter of dispute; blackwater fever occurs occasionally in sufferers from old malarial infection when no quinine has been given, but in many cases the symptom is provoked only by quinine; on the other hand it often passes off when the treatment is continued. Quinine has no hæmolytic action except in quantities which would prove immediately fatal, and the blood of these blackwater patients is not more readily laked by it than normal blood.

The **Uterus** is aroused to contraction by quinine, and abortion occurs occasionally after its use in malaria, while in other cases labor pains may be induced.

The **Blood** often contains fewer leucocytes after quinine in man and in animals. According to Roth, a single dose generally causes leucocytosis at first, perhaps arising from contraction of the spleen. This is followed by a fall in the number of white corpuscles, especially of the lymphocytes, though the polynuclear cells are also reduced. The polynuclears then increase in number until a distinct leucocytosis is again present, but the lymphocytes remain reduced in number, while in the preliminary leucocytosis they predominate. Hæmolysis occurs only when quinine is present to the amount of 0.5 per cent, which is more than sufficient to arrest the heart.

The **Spleen** undergoes a marked diminution in size (Roth), presumably from active contraction of its muscular fibres. A similar constriction has been observed in the bronchi in animals.

The **Metabolism** is often said to be reduced by quinine, more especially that of the proteins, while the excretion of carbon dioxide and the absorption of oxygen are universally stated to be unchanged. Careful experi-

ments by Hardikar have failed to show any alteration in the protein metabolism either in man or animals under treatment with large doses of quinine. Under the older view quinine was believed to conserve the stores of protein in the body and to have a special value in wasting diseases and fevers from this "roborant" action.

Hardikar also found that in normal rabbits 15–20 mg. per kg. caused little change in the respiratory exchange, but that with large doses (60 mg. per kg.) there was a definite fall in both respiratory exchange and in heat production. In animals with B. coli fever the reaction was the same.

Temperature.—Quinine has no significant effect on the normal temperature in man or in animals; it may reduce it by 0.1–0.2 degrees in some cases, while in others its use is followed by a rise of similar dimensions. Its specific effects in preventing the rise of temperature in malaria are due to its destroying the parasite and not to any direct action on the mechanism which controls the temperature; until the parasite is destroyed, quinine is unable to reduce the body heat or even to prevent its rising. In other forms of fever, quinine not infrequently fails to reduce the temperature in man, though it is sometimes successful in doing so. In animals large doses are found to lower fever temperature, but this is often accompanied by such symptoms as depression and muscular weakness, which in themselves would reduce the amount of heat formed and thus lower the unstable fever temperature.

This antipyretic action of quinine has been the subject of a number of investigations, which have given varying results. The general view which was held previously was that in fever quinine reduced the temperature by lessening the heat formed, and this effect was ascribed to its depressing the nitrogenous metabolism. But this view, which has always been vulnerable, has been rendered impossible by recent observations that quinine in quantities which reduce fever temperature in man and animals has no measurable action on the metabolism.

The only alternative explanation of the reduction of fever temperature by quinine is that the amount of heat lost by the body is increased by it in the same way as by the antipyretic series (see p. 699). This change in the output of heat involves an action on the temperature-regulating centre in the brain. However several early investigators found that quinine reduced the temperature when this centre was put out of action by section of the spinal cord. But in many of these experiments it appears that the possible action of large doses of quinine on the central nervous system and circulation was not taken into account sufficiently, and that some of the results which have been attributed to metabolic changes may have arisen from changes in these systems.

Further work is required to determine under what conditions and in what forms of fever the temperature falls under treatment with quinine, and it may then emerge that the action on the temperature is indirect as in the case of malaria.

Excretion.—Quinine appears in the urine within a short time (15 minutes) after its exhibition by the mouth, and it continues to be excreted by the kidney in some quantity during the next twenty-four

hours, and in smaller amounts up to about seventy-two hours. Only about one-third of that absorbed appears in the urine, however, and only traces have been found in the other excretions, so that two-thirds or more undergoes complete destruction in the tissues. When quinine is injected into the subcutaneous tissues, some of it is deposited locally and only slowly redissolved, so that traces may be found in the urine for a week or more. When it is injected into the blood, it leaves the plasma within a few minutes, becoming attached to the corpuscles either by a process of adsorption or by forming some firm combination from which it is difficult to liberate it. It does not accumulate in any of the organs to any significant extent although small quantities have been found in the lungs, liver, heart, kidneys, and brain during the first two hours after the drug has been given intravenously.

It is sometimes stated that a tolerance to quinine may be acquired by prolonged treatment, but this seems to be incorrect, the same symptoms occurring and the same amount appearing in the urine after prolonged administration.

Of the other cinchona alkaloids, *quinidine* resembles quinine closely in most respects. It has recently been employed for its effects on the heart, which appear to be similar in character to those of quinine, but are five to ten times more powerful. The action is essentially a depression of the heart muscle, more marked in the auricle than in the ventricle, and manifesting itself in a reduction in the conductivity, and in a lower excitability in response to the natural impulses and to electric shocks; the refractory period is thus longer than before the quinidine. The strength of the contraction is sometimes increased to some extent, but this does not seem to be constant. In addition the ganglia on the course of the inhibitory impulses are weakened and this may lead to acceleration of the beat sometimes; on the other hand this may be counteracted by the depression of the pacemaker in the sinus; the accelerator nerve is unaffected. In consequence of the reduced excitability, such irregularities as extrasystoles disappear under quinidine treatment, and paroxysmal tachycardias from repeated extrasystoles in the auricle and ventricle also give place to the normal rhythm. Most important of all is its effect on auricular fibrillation, which can be elicited only with difficulty or not at all by electrical stimulation of the auricle under quinidine. Similarly in man, auricular fibrillation may be arrested by the use of quinidine. The depression of the heart is attended by a marked fall in the blood-pressure in animals; possibly there may also be dilation of the arterioles, but this is still uncertain. The fate of quinidine in the body and its manner of excretion are practically the same as of quinine. (For method of administration see page 736) Hydroquinidine acts on the heart in the same way and in about the same strength as quinidine.

Cinchonine, while very similar to quinine in most points, has some tendency to produce convulsions, but this effect is much more liable to occur under **Cinchonidine,** which, save for its resemblance in other features to quinine, would be entitled to be classed among the convulsive poisons. These convulsions are of an epileptiform character, and are only produced by very large doses, but

even small quantities administered to epileptics have been said to increase the number of the attacks. These epileptiform seizures are not prevented by the removal of the cerebral cortex in dogs, and the irritability of the motor areas is not altered by cinchonidine, so that some lower division of the central nervous axis appears to be the seat of action in these animals; but in man the more highly developed cerebral cortex is also involved. Different species of animals apparently differ in respect to their susceptibility to the convulsive action of the cinchona alkaloids, rats and mice rarely or never showing convulsions. Even in other species which are susceptible in this respect the doses of the more common cinchona alkaloids necessary to produce convulsions approach very nearly amounts which would prove lethal. **Cinchonamine** possesses an even more marked convulsant action than cinchonidine.

The effects of the other alkaloids have not been the subject of much investigation, but they seem to differ from quinine chiefly in their effects on the central nervous system. These are not entirely absent in quinine itself, for, as has been stated already, the reflex irritability is at first increased and then diminished in both frogs and mammals, and in some cases even convulsions are stated to have occurred in quinine poisoning.

Many synthetic derivatives have been formed from the cinchona alkaloids, but few of them have been examined pharmacologically. *Optochin* or *ethylhydrocupreine*, one of these derivatives which has been used in therapeutics, appears to differ from quinine only in slight measure in its general action, but is more liable to induce blindness. *Cupreine*, obtained from Remijia, has been used experimentally, but has not proved of therapeutic value, while the ethyl derivative of cupreine seems to possess distinct antimalarial properties, but it is possible that it may be toxic for the eye also (see page 724.)

Therapeutic Uses.—The introduction of cinchona into therapeutics was due to the discovery of its efficacy in ague or **Malaria,** and with growing experience in the disease and its treatment, the confidence in the drug, or rather in its chief alkaloid, has constantly increased, until the action of quinine in malaria is now quoted as the best example of a specific in therapeutics. The explanation of its action was only reached when Laveran discovered the parasites of malaria, although in 1868 Binz suggested that the then unknown malarial poison was probably rendered inert by quinine. Malaria is now known to be due to three distinct parasites. These enter the red-blood corpuscles and multiply there, and then, issuing from the cells in immense numbers, invade new corpuscles. When the spores break out of the red cells, there is a sharp attack of fever, which passes off when they have reached the interior of new corpuscles, but returns when a new swarm of spores is liberated. The fever thus recurs at regular intervals in the simpler forms of malaria, but may be rendered irregular by double or multiple infections. The parasites of malaria belong to the group of the protozoa and are thus nearly related to the amœba on which Binz made his observations, and also to the organisms of amœbic dysentery and of syphilis.

The organisms of malaria are most susceptible to quinine when they are in the free state in the plasma, though the less dangerous forms are also destroyed after they have reached the shelter of the corpuscles. In the more malignant form of infection, the parasites in the corpuscles are apparently not affected by quinine and can only be got rid of by preventing them from being reinforced by new broods. It is therefore of the first importance to supply quinine to the blood at the period at which the spores are liberated. When quinine is given at the appropriate

time, the organism breaks up and disappears, but a few more resistant forms may escape and multiply until they are numerous enough to provoke another paroxysm of fever; the treatment should therefore be continued until all the parasites have succumbed.

In a drop of malarial blood the plasmodia may be seen in active movement, but a minute drop of quinine solution paralyzes and kills them, exactly as it kills the common protozoa found in water, the only difference being that the malarial organism is infinitely more susceptible to its action; this greater susceptibility does not arise from the presence of the blood plasma, for other organisms in the human blood do not succumb to quinine, and one which occurs in bird's blood and resembles the malaria plasmodium closely, is not materially injured. The malarial organism appears to be acted on specifically by quinine, that is more strongly than other living cells, and the alkaloid can consequently be introduced into the human body with impunity in doses which are destructive to the simpler organisms which have invaded it. Experience has shown that quinine is most effective when it can act during and immediately after the paroxysms, and this is now explained by the fact that the organisms are in their least resistant form—the amœboid—at this time. If quinine is given three or four hours before an attack, sufficient will remain in the blood when the temperature begins to fall to destroy the unprotected spores of the parasite, or the same result may be obtained by a dose given as the temperature begins to fall, provided the drug is rapidly absorbed, as is ordinarily the case. It may be ordered in one dose of about 1 G. (15 grs.), or in divided doses given at intervals during the fall of the temperature. This frequently prevents the next attack, but some of the organisms survive and the treatment should be continued for a considerable time in order to destroy all the organisms. The U. S. National Malarial Committee recommended that in acute malaria 10 grs. of quinine sulfate should be given by mouth three times a day for three or four days in order to relieve the clinical symptoms. This dosage should be followed by 10 grs. given every day for eight weeks to cure the infection. Such a course of treatment will cure from 90–95 per cent of the cases. Some 5–10 per cent of cases are probably not cured under twelve weeks treatment, but it would not seem wise to subject all patients to the prolonged course in order to cure the last few refractory cases. These cases would have to be treated for a longer time. If a relapse occurs the course of quinine is begun again with the daily dosage of 30 grs. and continued with the 10-gr. dosage just the same as a new case. More recently the so-called "short quinine treatment" has been introduced in which the quinine is only given for about a week. It is said to be quite as effective as the longer period of treatment and is certainly more economical and less disturbing to the patient. Bass says no quinine salt is superior to the sulfate and no method of administration is better than that by mouth, except in certain urgent cases.

The general impression is that benign tertian malaria is more amenable than the other forms, but Acton holds that quinine is more successful in malignant tertian in which the treatment is seldom followed by

relapses, while quinidine is more efficient in the benign form; there is need for further comparison of the different alkaloids of cinchona, although several studies upon this problem have been carried out recently. Quinidine is probably as efficient as quinine in malaria but its tendency to depress the heart has prevented its more extensive use in cases of malarial infection.

A mixture of cinchona alkaloids has been introduced for the treatment of malaria under the name of *Totaquine* (Totaquina). It is prepared from suitable species of Cinchona and contains not less than 70 per cent of crystallizable alkaloids of which not less than one-fifth is quinine. Amorphous alkaloids should not exceed 20 per cent. This preparation has been recommended by the Health Committee of the League of Nations for the treatment of malaria where the high cost of quinine makes the wide use of the pure alkaloids impracticable. A second preparation of the mixed alkaloids of cinchona is *Quinetum*. This consists of equal parts of quinine, cinchonidine and cinchonine, that being approximately the normal proportion of these alkaloids in Cinchona succirubra.

In children quinine tannate or euquinine may be employed, and in severe vomiting or other emergencies a soluble preparation is injected into the veins, but this procedure is not considered to be entirely safe, as in a certain number of cases death has resulted therefrom. A great deal of weight was formerly laid on the use of purgatives and emetics as preliminaries to the treatment of malaria with quinine, and the former are undoubtedly of service sometimes, although it is unnecessary to delay the quinine treatment by waiting for the intestines to be evacuated. Special sensitiveness to quinine may render the treatment of malaria difficult but at times the trouble may be avoided by substituting one of the other cinchona alkaloids such as quinidine. In some cases small doses may be followed by severe effects on the hearing; in these cases bromide often relieves the symptoms when given in adequate doses. Again, the digestion may be much disturbed and it may be necessary to commence the treatment by an intravenous injection of the hydrochloride. Hæmoglobinuria following quinine indicates that the dose should be reduced. Pregnancy is not a contra-indication but suggests that small doses should be used.

Quinine is used not only as a remedy, but also as a prophylactic against malaria. Its value for this purpose has been attested by long experience, but there is still no unanimity of opinion as to the best method of administration and the dose required. Thus Koch advised 15 grs. to be taken on two consecutive days every week or ten days. The Malarial Commission of the Health Organization of the League of Nations recommends a daily dose of 0.4 G. of quinine be taken during the malarial transmission season or longer. They also suggest as an alternative 0.2–0.4 G. doses of atebrin given biweekly, but prefer quinine as being safer. As a prophylactic quinine still ranks first among the antimalarial drugs on account of its lack of toxicity, its effectiveness, lack of side effects and the wide knowledge of its use and dosage (League of Nations Committee). Quinine is best taken after meals, when it disturbs the digestion least. The malarial organisms do not acquire

tolerance to quinine, and the prophylactic use of the drug thus does not impair its value in the treatment of an infection.

One of the results of quinine medication in early cases of malaria is the reduction of the enlarged spleen, and this has led to its use in other **Diseases of the Spleen** with enlargement. In malaria the effect on the spleen is only secondary to the removal of the cause of the disease, but the action of quinine in contracting the muscle fibres of the spleen may explain its being of benefit in other splenic disorders. Some of the newer synthetic substitutes for quinine such as atebrin (p. 735) will also reduce the size of the spleen but they produce their effect more slowly. In some cases of leucæmic enlargement encouraging results have been obtained from the continued use of quinine.

Various other **Febrile Conditions** have been treated with quinine, partly for the sake of its antipyretic effects and partly in the belief that it acts as an antiseptic in the blood. As regards its effect on the temperature in non-malarial fever, it does not reduce it so rapidly nor to the same extent as its rivals of the antipyrine group, but may maintain it at a low point for a longer time; the unpleasant effects on the brain and hearing further limit its use. The use of quinine in non-malarial cases has been based in part on the belief that it lessened the tissue waste, which has now been proved to be erroneous. So that it is now being confined more and more closely to combating malaria, and in other forms of fever antipyrine and its allies have succeeded in ousting quinine from its former position as the best of the antipyretics. The use of quinine has been recommended in septicæmia, largely from a belief in its antiseptic action in the blood. In this connection it is to be remarked that the microbes of septic fever are much more resistant to the action of quinine outside the body than are the protozoa, and the question therefore arises whether the blood and tissues are not liable to be seriously injured by the quantity of quinine required to act on the parasites they contain. In many cases of septicæmia in which beneficial results are said to have been obtained by the use of quinine, the quantity administered was obviously too small to have any effect on either the temperature or on the microbes [1]

Quinine has been used in various forms of **Neuralgia and Headache,** but has been replaced by the antipyrine series and especially by acetylsalicylic acid for these conditions.

The tinctures of cinchona are often prescribed as **Stomachic Bitters,** and for this purpose may be fortified by preparations of nux vomica or of the simple bitters.

Quinine has been advised as an **ecbolic** to increase the contractions of the uterus during labor. This was suggested by the observation

[1] Morgenroth found that ethylhydrocupreine, a derivative of cupreine differing from quinine in the presence of ethoxyl instead of methoxyl, had a well-marked beneficial action on mice infected with pneumococcus and that its previous injection protected these animals from infection. It does not appear to have any such remedial action in pneumonia in man and has not been shown to improve the prognosis. Moore and Chesney found, however, that the serum of patients treated with this drug has definite bactericidal powers. Severe and even fatal poisoning has occurred from the intravenous injection of less than a gram of ethylhydrocupreine (Optochin) in man. Ethylhydrocupreine hydrochloride is used in a 1 or 2 per cent solution in the treatment of pneumococcus infections of the eye.

that in malarial regions, abortion occasionally occurred after quinine, and satisfactory results are reported from the treatment of uterine inertia with 1-G. doses of quinine; the action is the same as that under pituitary preparations, which are more commonly employed for this purpose at the present time.

Quinine has been advocated as a **local anæsthetic**; the quinine and urea hydrochloride has been used chiefly, but is strongly acid in reaction and the neutral hydrochloride of quinine in 0.5–1 per cent solution is preferable for injection, while stronger solutions may be applied to the throat and some other mucous membranes. It differs from cocaine in inducing anæsthesia more slowly and still more in maintaining it for many hours or even days. It has been advised to wash painful wounds after operation, to relieve after-pains, to spray the throat and for many other purposes. Its toxicity after absorption is very low, but it injures the tissues locally and delays healing.

A 5 per cent solution of quinine and urea hydrochloride has been recommended as a sclerosing agent in internal hemorrhoids. However, the relief afforded is usually only temporary and the treatment not without its drawbacks as complications such as hemorrhage, ulceration and stricture of the rectum may follow.

Preparations.

U. S. P.

Cinchona, the bark of Cinchona succirubra, Cinchona ledgeriana and C. calisaya and of hybrids of these and other species of Cinchona, yielding not less than 5 per cent of total alkaloids. Dose, 1 G. (15 grs.).

Tinctura Cinchonæ Composita is the only preparation of red cinchona, and contains in addition serpentaria and bitter orange peel. 4 cc. (1 fl. dr.).

Quinina,
Quininæ Sulfas,
Quininæ Bisulfas,
} 0.1 G. (1½ grs.) as tonic. 1 G. (15 grs.) or more daily in malaria.

Quinidinæ Sulfas, the sulfate of an alkaloid obtained from cinchona. Dose, 0.3 G. (5 grs.).

Quininæ Æthylcarbonas, Euquinine, quinine ethylcarbonate, is only slightly soluble in water and is practically tasteless. Dose as of Quinine.

Quininæ Hydrobromidum. Dose as of Quinine.

Quininæ et Ureæ Hydrochloridum, quinine and urea hydrochloride, contains about 58 per cent of quinine. It is very soluble in water. Dose, hypodermic, 1 G. (15 grs.).

Quininæ Tannas, quinine tannate (non-official), corresponds to 30–35 per cent of quinine. It is only slightly soluble in water and is practically tasteless. Dose, 0.2 G. (3 grs.).

B. P.

Cinchona, the bark of various species of Cinchona trees containing at least 6 per cent of the alkaloids of cinchona. 0.3–1 G. (5–15 grs.).

Extractum Cinchonæ, 0.12–0.5 G. (2–8 grs.).

Extractum Cinchonæ Liquidum contains 5 per cent of the alkaloids of cinchona, 0.3–1 mil. (5–15 mins.).

Tinctura Cinchonæ contains 1 per cent of the alkaloids of cinchona. 2–4 mils. (30–60 mins.).

Tinctura Cinchonæ Composita contains 0.5 per cent of the alkaloids of cinchona, also orange peel, serpentary and cochineal. 2–4 mils. (30–60 mins.).

Quininæ Bisulphas, 0.06–0.6 G. (1–10 grs.).

QUININÆ DIHYDROCHLORIDUM, 0.06–0.6 G. (1–10 grs.).
QUININÆ ET ÆTHYLIS CARBONAS, Euquinine. 0.1–1 G. (1½–15 grs.).
QUININÆ HYDROCHLORIDUM, 0.06–0.6 G. (1–10 grs.).
QUININÆ SULPHAS, 0.06–0.6 G. (1–10 grs.).
QUININÆ TANNAS contains about 33 per cent of quinine. 0.1–1 G. (1½–15 grs.).
TOTAQUINA, a mixture of alkaloids from various species of cinchona, containing not less than 70 per cent of crystallizable alkaloids with not less than one-fifth of quinine. 0.06–0.6 G. (1–10 grs.).
LIQUOR QUININÆ AMMONIATUS, ammoniated solution of quinine, contains 2 per cent of quinine sulphate. 2–4 mils. (30–60 mins.).
SYRUPUS FERRI PHOSPHATIS CUM QUININA ET STRYCHNINA, Easton's Syrup. 2–4 mils. (30–60 mins.).
QUINIDINÆ SULPHAS, 0.2–0.6 G. (3–10 grs.).

Quinine is practically insoluble in water and several of its salts are only dissolved sparingly. Thus, the sulfate requires 800 times its own weight of water, the hydrochloride 35, and the hydrobromide 40. The presence of acid in excess renders them much more soluble, and the acid hydrochloride or dihydrochloride is dissolved in less than its own weight of water, the bisulfate in 10 parts. They all form crystalline powders with a very bitter taste, and their solutions in water have a blue fluorescence when sulfuric acid is present. The acid hydrochloride and the bisulfate have an acid reaction, the others are neutral.

The hydrochloride of quinine is the most soluble of the salts and is therefore preferable to the others; the sulfate is frequently prescribed, the hydrobromide and salicylate seldom. Instead of the acid salts being prescribed, some sulfuric acid or hydrochloric acid may be ordered to be added to the neutral salts in order to facilitate their solution.

The salts of quinine are usually given in the form of capsules, pills, cachets, or tablets, which have the advantage of avoiding the bitter taste, but from which the alkaloid is more slowly absorbed than from solutions. Care must be taken that the pills are soft and freshly prepared, as when kept for any length of time they become hard, and in this condition frequently pass through the bowel unabsorbed. The salts or the pure alkaloid may also be given as powders, or the former in solution, but these are objected to by patients on account of the bitter taste. When rapid absorption is desired, solutions may be used, flavored, if necessary, with syrup and volatile oils; however, it is rarely necessary to give the drug in solution, as the absorption from the stomach when the quinine is given in capsules is quite rapid. Solutions of the salts are occasionally injected as enemata, but are liable to set up irritation and to be rapidly evacuated. Intramuscular injection has also been advised in cases of emergency, or where the salt cannot be retained or absorbed from the stomach; this form of mediatione is painful and the action of the drug is slower and is far less dependable than when it is given by mouth. Damage to the tissues is also not uncommon and necrosis and abscesses may follow. There is therefore no place for quinine given by intramuscular injection in the treatment of malaria (Bass). Subcutaneous injection of quinine salts, especially the acid ones, is also very painful and has sometimes been followed by sloughing. The intravenous injection of quinine has been practised with success in cases of pernicious malaria; the dihydrochloride dissolved in 20 cc. or more of water is slowly injected into one of the veins of the arm; a marked fall of blood-pressure may follow too rapid injection of quinine from its poisonous action on the heart. The dose may be repeated in two or three hours if necessary, but this method should not take the place of quinine by mouth if it can be given that way.

Many other salts of quinine have been proposed and have enjoyed a certain reputation for some time. Among the better known of these is the *tannate*, which is exceedingly insoluble, has little taste, contains 30 per cent of quinine and is prescribed in powder in doses of 0.2 G. (3 grs.). Other salts which have been recommended are the *tartrate* and the *lactate*. Quinine ethylcarbonate,

(*Euquinine*), is the very insoluble ethyl-ester of quinine-carbonic acid ($CO(OC_2H_5)(OC_{20}H_{23}N_2O)$) and possesses the therapeutic virtues of quinine with a less bitter taste. It may be given in powder or suspended in syrup. *Aristochine* ($CO(C_{20}H_{23}N_2O)_2$) and *Chinaphenine* ($CO(NH{\cdot}C_6H_4{\cdot}OC_2H_5)(OC_{20}H_{23}N_2O)$) are less satisfactory compounds of quinine of a similar nature. All three preparations are prescribed in powder or tablets, in the same dose as quinine. Eukupine, iso-amyl hydrocupreine, and Vuzine, iso-octyl hydrocupreine, have been introduced as wound antiseptics.

A famous preparation of quinine is *Warburg's tincture*, which has been extensively used in India in the treatment of malaria. It contained a very large number of ingredients, many of which were certainly entirely superfluous. Among the more important constituents were aloes, rhubarb, gentian, camphor, and various volatile oils; it is possible that some of these may have aided the quinine through their effects on the stomach. Various drugs, such as capsicum and piperine, have long had some reputation as adjuvants in quinine treatment for a similar reason.

The other alkaloids have been used occasionally as substitutes for quinine, and MacGilchrist has carefully compared their efficiency in malaria. He finds that hydroquinine is rather more effective than quinine, cinchonine and quinidine while cinchonidine is the least useful of the cinchona alkaloids; optochin was also of little value.

Plasmoquin.—Among the compounds which have been introduced in the past few years as substitutes for quinine is a synthetic product known as Plasmoquin. It is believed to be N-diethyl-amino-isopentyl-8-amino-6-methoxy-quinoline. It is not a derivative of quinine but is somewhat distantly related to it. It was found to be quite effective against bird malaria and on that account was introduced into the treatment of malaria in man. Here it has been found to be quite active against the gametocytes and removes the crescents from the peripheral blood in a very short time. It thus renders the blood non-infective to mosquitoes and on this account may prove quite important in preventing the transmission of malaria from one person to another. On the other hand, Plasmoquin has much less effect on the asexual form of parasites which are the cause of the clinical symptoms and which are very susceptible to quinine. On this account it has been recommended that the two drugs, plasmoquin and quinine, should be combined, thus reducing the dosage of plasmoquin and lessening the likelihood of poisoning. By this method plasmoquin is given in 0.01 G. doses with 0.125 to 0.3 G. of quinine.

The Malarial Commission of the Health Committee of the League of Nations says that this combination of drugs is one of the most efficacious methods of treating benign tertian and quartan malaria and given twice a week it lessens greatly the number of relapses. The combination of Plasmoquin and Atebrin is not desirable as each drug seems to aggravate the toxicity of the other.

Plasmoquin is a fairly toxic drug. In cats doses of 2 to 3 mgs. per kilo will produce methemoglobin formation. Injected intravenously into dogs and cats it is quite toxic to the heart, causing marked irregularities and heart-block together with depression of the heart and a fall in blood-pressure. Injected into normal cats and dogs, doses of from 5 to 7 mgs. per kilo prove lethal; the symptoms consisting of dyspnœa, cardiac irregularity, methemoglobinæmia and asphyxia. Methemoglobin formation is one of the chief effects of the drug and is produced *in vitro* as well as *in vivo*.

The drug is disposed of rather slowly in the body; some is probably destroyed, while some is excreted in the urine.

In man the administration of plasmoquin is frequently followed by epigastric pain and by a certain degree of cyanosis. The appearance of cyanosis should be taken as a warning to discontinue the use of the drug. In mild cases this symptom is seen only in the fingers and lips but in severe poisoning the whole body may be discolored. The gastric distress is less if the drug is given after a meal.

In severe intoxication in man there is headache, dizziness, marked sweating and abdominal pain, which may be quite marked over the liver. Diarrhœa and

cyanosis may be present together with methemoglobinæmia and methemoglobinuria. There may be jaundice and marked anemia and the patient may become drowsy and comatose. Anemia seems to predispose to the formation of methemoglobin, so that in cases of marked anemia the drug should be used very cautiously. In fact, on account of its toxicity the drug should never be given except under strict medical supervision. A safe dose is said to be 0.06 G. per day and it is practically always given in connection with quinine and, indeed, it is said it should never be given in malaria without quinine.

Atebrin.—During the past few years a number of drugs prepared synthetically have been introduced as substitutes for quinine in the treatment of malaria. One of these is Atebrin, the dihydrochloride of an alkylamino-acridine derivative. It is a yellow powder soluble in water, forming a neutral fluorescent solution.

When administered by mouth it is absorbed quickly and is well tolerated when given in small doses, while large doses may produce nausea, vomiting and diarrhœa. The minimum lethal dose for cats is about 0.1 G. per kilo, while rabbits will tolerate such amounts apparently without injury. Large doses in cats will produce fatty degeneration of the liver and kidneys.

The drug is excreted in an unchanged form by the kidneys, its presence in the urine being detected by the formation of a yellow color upon the addition of an acid. The excretion of atebrin is very slow, from 50 to 70 per cent of the administered drug appearing in the urine. It appears about the second day but it may persist in the urine for two or three weeks, or even longer, after its administration has been stopped The rate of excretion is determined somewhat by the quantity of urine passed. The drug, therefore, has a marked tendency to accumulate in the body and in a considerable number of cases it may produce a distinct yellowish tinge in the skin.

The action of the drug against malaria has been studied experimentally in both birds and man. In the malaria of monkeys it has been found to be very effective, 2 or 3 doses of 0.025 G. causing the parasites to disappear from the peripheral blood. While several injections of quinine are needed to produce this effect, a single dose of atebrin will often suffice; the difference in results being apparently largely influenced by the relative rates of excretion of the two drugs. Relapses are prone to occur but are easily controlled by renewed administration of the drug.

Its mode of action resembles that of quinine in destroying the asexual forms of the parasites. A dose of 0.1 G. three times daily has been found sufficient to control the symptoms and cause the disappearance of the parasites. Such a dosage is usually necessary for five days. In the human patient, as in monkeys, relapses are not infrequent (5 to 8 per cent of cases), requiring a renewal of the treatment. In the repetition of courses of atebrin great care should be exercised to give a sufficient interval of time between them on account of the slow excretion of the drug with resulting tendency to accumulation. While the administration of the drug by mouth seems to be relatively safe, it is much more toxic when it is given intravenously, so that this method should never be used except in an emergency and then it should be given very slowly.

In man the toxicity of atebrin is low and there seems to be a fairly wide margin of safety, but symptoms of intolerance have been reported, such as gastric uneasiness and even acute pain, loss of appetite and headache. The drug can be safely given during pregnancy, whereas quinine may exert an oxytocic effect. In some patients there has been a feeling of profound depression which has lasted for several days after the drug has been stopped and in certain cases the mental symptoms have approached those of a definite psychosis.

As a prophylactic measure against malaria atebrin appears to resemble quinine. It can apparently be given in doses 0.1 G. daily for a long time without injury, such doses being at least as effective as 0.3 G. of quinine given daily. Atebrin has also proved very effective as a prophylactic when given in doses of 0.2 to 0.4 G. twice a week. Atebrin in doses of 0.1 G. has been combined with Plasmoquin 0.01 G. and given daily as a prophylactic. Such a combination is not unlikely to produce toxic symptoms so that it should be

employed only under the supervision of a physician. It is probably safer to use a combination of quinine-plasmoquin rather than atebrin-plasmoquin.

Atebrin appears to be quite an effective remedy against the different types of malaria but at the present time it is in the experimental stage, especially on account of its possible toxic qualities due to its slow excretion.

The League of Nations Malarial Commission recommends that for ordinary cases of tertian malaria either quinine or atebrin may be used with plasmoquin to reduce relapses. In treating large numbers of cases atebrin in daily doses of 0.3 G. or quinine in daily doses of 1 to 1.3 G. may be given in either case for a period of five to seven days. The Commission says there is no preference except one of expense.

Quinidine Sulfate has been used recently as a cardiac depressant to combat the exaggerated excitability seen in **Auricular Fibrillation and Flutter, Extrasystoles** and other forms of heterotopic rhythm; in about 50 per cent of the cases of auricular fibrillation thus treated, the normal rhythm is restored for a longer or shorter time. When the effect of the treatment is watched by means of the electrocardiograph, the oscillations of the auricle are seen to become progressively slower and coarser, while the rhythm of the ventricle generally quickens; then the fibrillation is suddenly replaced by normal movements of a rapid rhythm and this in favorable cases passes into regular beating of auricle and ventricle at 70 to 80 beats per minute. The effects are quite different from those under treatment with digitalis, which does not arrest the fibrillation but protects the ventricle from the auricular impulses; under quinidine, the abnormal activity of the auricle ceases from the depressant action of the alkaloid. Quinidine sulfate is generally given by the mouth in a preliminary dose of 0.2 G. (3 grs.) which may be repeated after two hours in order to determine the patient's susceptibility to the drug. If no unpleasant symptoms arise the treatment is begun on the following day by giving doses of 0.2–0.4 G. (3–6 grs.) from three to five times daily for from one to three days. If the normal rhythm is restored smaller doses of quinidine given for a few weeks may help to maintain it; otherwise many cases may relapse into fibrillation again. The treatment must be controlled, and at present this is best done by the electrocardiograph. The pulse accelerates as the auricle is slowed and this may become alarming; if digitalis is given for a few days before the quinidine, the quickening of the pulse is smaller. The restoration of the normal rhythm is not free from danger, for during fibrillation the auricle forms a backwater in which clotting may occur; and when it resumes its normal beat under treatment, the expulsion of the clot may lead to fatal embolism. Nausea, headache, palpitation and discomfort from the roaring in the ears may be complained of under the treatment. (See also page 727.)

Emstene and Lowis believe that quinidine produces vomiting by a peripheral action which is exerted somewhere below the diaphragm and which is carried to the vomiting centre over sympathetic pathways. They showed that vomiting was not produced by application of quinidine solutions to the vomiting centre nor was it prevented by denervating the heart nor even by eviscerating the animal. It was prevented, however, by the previous use of nicotine and usually by ergotoxine, indicating the involvement of the sympathetic fibres in the process.

Preparation.

Quinidinæ Sulfas. Dose, U. S. P., 0.3 G. (5 grs.); Quinidinæ Sulphas. B. P., 0.2–6 G. (3–10 grs.). Given in capsules.

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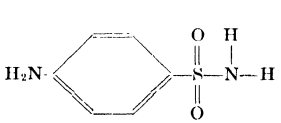
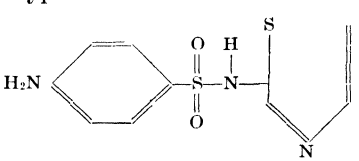
V. SULFANILAMIDE, SULFAPYRIDINE AND ALLIED COMPOUNDS.

SULFANILAMIDE.

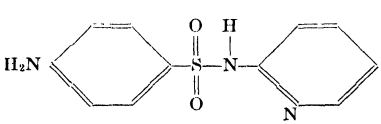
Sulfanilamide (p-aminobenzenesulfonamide; also known as Prontylin, Prontosil Album, Streptocide, etc.) was introduced into the practice of medicine for the treatment of certain bacterial infections, primarily those of the hemolytic streptococcic type.



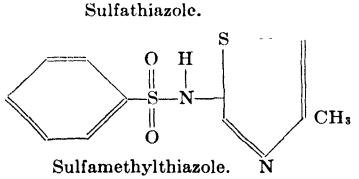
Sulfanilamide.



Sulfathiazole.



Sulfapyridine.



Sulfamethylthiazole.

The introduction of this compound was the direct outgrowth of work which appeared in 1935 regarding the therapeutic effects of a closely related but more complex compound, Prontosil (4-Sulfonamido-2, 4-diamino-azobenzene) which had been used by Domagk in the treatment of mice infected with virulent hemolytic streptococci. Subsequent studies carried out in the Pasteur Institute showed that equally favorable results could be obtained by the use of the portion of the Prontosil molecule containing the sulfonamide group. This finding was very important as it showed that the more complex azo structure was unnecessary.

It seems probable that the activity of the prontosil molecule in the body is due to the fact that the azo bond is broken and the active component of the molecule released. This simpler compound, p-amino-benzenesulfonamide (sulfanilamide), was not new as it had been made by Gelmo, of Vienna, in 1908 and had been used for making azo dyes which were found to possess certain valuable commercial properties. In the succeeding years efforts were made to utilize it in the search for new effective therapeutic agents, but the actual synthesis of prontosil by Mietsch and Klarer apparently was not accomplished until 1932.

Following the observation that sulfanilamide was an effective chemotherapeutic agent in the control of hemolytic streptococcal infections, numerous experimental and clinical investigations were carried out which showed that the drug possessed a wider valency of action than was originally suspected and that it was effective in the treatment of meningococcal, gonococcal and various other types of infections.

Inasmuch as the sulfanilamide molecule readily lends itself to chemical manipulations, numerous modifications of the drug have been prepared and tested for their effects as chemotherapeutic agents. However, despite the thousands of new compounds that have been made, none, with the exception of 2-sulfanilamido-pyridine (sulfapyridine), have shown themselves to possess superior degrees of chemotherapeutic activity. This latter compound was found by Whitby to possess a definite margin of superiority over sulfanilamide in the control of pneumococcal infections- an observation which has been widely confirmed.

It has also been shown that the amide (SO_2NH_2) group is not necessary for activity and that the sulfides, sulfoxides and sulfones possess in the order named increasing degrees of chemotherapeutic activity in the control of experimental streptococcal infections. However, the toxicity of these compounds has been, in general, of such an order as to preclude their use in clinical medicine.

Mode of Action.—Although several years have passed since the chemotherapeutic effects of sulfanilamide were first observed, its exact mode of action is as yet unknown. Practically all investigators are in agreement that the drug does not act by stimulating defense mechanisms of the body, but believe that the drug acts directly upon the susceptible bacteria.

It was first noted by Fourneau and his associates that the addition of sulfanilamide to the medium delayed the growth of Aspergillus niger *in vitro*. Subsequently, other workers observed that sulfanilamide in low concentrations had a bacteriostatic effect upon the growth of small inocula of hemolytic streptococci and certain other susceptible microörganisms *in vitro*. It was noted that these bacteriostatic effects could be increased by impoverishing the medium in which the organisms were grown or by raising the concentration of sulfanilamide in the medium, and that bacteriostasis was frequently associated with alterations in the morphology of the microörganisms. In certain instances either one or both of these factors could be so adjusted that the drug would exercise *in vitro* even a bactericidal effect upon certain susceptible bacteria. It was also observed that low concentrations of sulfanilamide added to defibrinated whole-blood cultures of hemolytic streptococci often brought about a rapid steriliza-

tion of such cultures, although if the blood were free of leukocytes sterilization did not take place.

In addition to the bacteriostatic effect of sulfanilamide some evidence has been adduced that the drug has the power of neutralizing the toxic products of bacteria. Levaditi noted that the endotoxins of various bacteria, notably the gonococcus, are rendered inactive by sulfanilamide. Carpenter confirmed this finding. Nevertheless there is general agreement that the drug has little or no effect upon the soluble toxins of the hemolytic streptococcus. However, there can be little doubt that the observations of Levaditi and Carpenter indicate that the action of sulfanilamide may not be limited to an inhibitory effect upon the growth of susceptible bacteria.

It was observed that while a fair degree of parallelism existed between the *in vitro* and *in vivo* effects of the drug upon susceptible bacteria, it was not absolute and in certain instances, namely, in hemolytic streptococcal infections, the *in vivo* effects of the drug were more marked than those *in vitro*, while with the pneumococcus the reverse was notably apparent. It is probable that the variations noted between *in vitro* and *in vivo* effects are in a measure dependent upon the response of the host to the particular infection. Thus, it has been repeatedly shown that in experimental Group A hemolytic streptococcal infections, the bacteriostasis of the streptococci brought about by sulfanilamide therapy is accompanied by an active phagocytosis which helps dispose of the microörganisms and that in experimental pneumococcal infections, while bacteriostasis occurs, it is not accompanied by an increased rate of phagocytosis and the infected host is slowly overwhelmed by the infection unless life be sufficiently prolonged for natural antipneumococcal antibodies to develop.

The exact way, therefore, by which sulfanilamide acts to decrease the rate of multiplication or actually kills susceptible microörganisms is as yet unknown, although several hypotheses have been advanced. It was suggested in 1937 by Mayer that sulfanilamide itself was not the active substance and that the drug had to be oxidized to para-hydroxylaminobenzenesulfonamide before it became truly active. However, the observations of Bliss and Long, that sulfanilamide and sulfapyridine are almost as active, or as active, under conditions of strict anaërobiosis, tend to cast doubt upon the thesis that sulfanilamide and sulfapyridine are oxidized by molecular oxygen to an active form, although these experiments do not rule out the possibility that other types of oxidation reduction reactions may play an important rôle in the mode of action of sulfanilamide.

Another hypothesis advanced independently by Lockwood and by Levaditi and Vaisman postulates an interference on the part of sulfanilamide with the availability of nitrogen to the susceptible microörganism. Whether the drug prevents streptococci from assimilating complex proteins or whether it makes protein unfit for bacterial consumption has not been adequately explained, although partial confirmation of the experimental data supporting the hypothesis has been recorded. The correct interpretation of the data is, however, still a subject of speculation.

All available evidence, therefore, points to the fact that sulfanilamide acts directly upon microörganisms and that by its action it may alter the morphological appearance of the organism, seriously hamper its rate of growth and, under certain conditions, actually kill susceptible bacteria. It is also apparent that a second factor, namely that of the reaction of the host to the organisms which have been acted upon by sulfanilamide, must be taken into account in any complete explanation of the mode

of action of sulfanilamide in a given infection. However, the manner in which sulfanilamide affects susceptible organisms is as yet not clear and is still in the realm of speculation.

Toxic Symptoms.—In human beings, sulfanilamide and its derivatives may produce unpleasant reactions either through their direct toxic actions or because of a special idiosyncrasy of the host to these drugs. Central nervous system disturbances, changes in the acid-base equilibrium and cyanosis are commonly seen as the result of the toxic action of the drug. Fever, dermatitis, hepatitis, neutropenia, agranulocytosis, acute hemolytic anemia and neuritis may occur in the course of treatment with these drugs, and are generally supposed to be due to a special sensitivity of the host tissues to sulfanilamide and its derivatives. A patient who has suffered from a reaction due to a special sensitivity to these drugs is quite liable to have a more severe reaction if one of these compounds is prescribed a second time. Hence, great care must be taken when either of these drugs is prescribed for a patient who previously has had a reaction.

The toxic effects of sulfanilamide and sulfapyridine upon the central nervous system are varied. Anorexia, nausea and vomiting are common (especially in the course of sulfapyridine therapy), as are also headache, dizziness and lassitude. Neuritis is rare. It is evident from the frequent occurrence of these symptoms that machine workers and those individuals who are engaged in heavy labor should be warned against carrying on their work while taking sulfanilamide. The driving of automobiles and the piloting of airplanes should be forbidden in the course of sulfanilamide therapy.

The effect of sulfanilamide upon the acid base equilibrium in the body is still a moot question. Certain observers believe that the fall in the carbon dioxide combining power of the blood often noted in the course of sulfanilamide therapy represents the effects of a hyperventilation alkalosis, while other investigators ascribe it to a primary alkali deficit type of acidosis. It seems at the present time that the available evidence favors the latter view and because of this, it is customary to administer bicarbonate of soda in conjunction with sulfanilamide. Sulfapyridine does not produce a fall in the carbon dioxide combining power of the blood.

The origin of the cyanosis which is so commonly noted in the course of sulfanilamide therapy and not infrequently when sulfapyridine is administered, is also in dispute. Current evidence shows that at times it may be associated with the formation of methemoglobin, but this does not always seem to be the case, and it has been postulated that the discoloration of the red blood cells results from their being stained by an unknown pigment formed possibly from sulfanilamide in the body. Clinically, however, in most instances the cyanosis is of little importance.

Idiosyncrasies in the form of fever or dermatitis usually appear in from the fifth to tenth days of therapy, although these manifestations may appear at any stage in the course of treatment. Morbiliform types of rashes are most common, but the dermatitis may assume a scarlatiniform, urticarial, erysipeloid, or purpuric character. In extreme in-

stances an exfoliating dermatitis may occur. The mechanism of the production of these idiosyncrasies is not understood.

Toxic manifestations resulting from untoward effects of these drugs upon the hematopoietic system are not uncommon. A slowly developing hemolytic anemia is commonly seen in patients who have received the drug over a considerable period of time. Acute hemolytic anemia, often severe, and generally occurring within the first five days of treatment have not infrequently been reported. Abrupt neutropenias after one or several doses of sulfanilamide have been reported. Agranulocytosis, generally occurring between the seventeenth and thirtieth days of therapy, and frequently terminating in death, is not uncommon. The mechanism of the production of these dyscrasias is also unknown.

The drug has produced acute hepatitis and at times this may be so severe that acute yellow atrophy of the liver may occur.

Renal injury has not been reported in the course of sulfanilamide therapy, but hematuria, pain in the flank, azotemia and even anuria have been reported in the course of sulfapyridine therapy. This toxic manifestation apparently results from the precipitation of acetylsulfapyridine in the renal tubules and pelves. In the latter, masses of acetylsulfapyridine crystals large enough to be classed as renal calculi have been noted on several occasions. The injury sustained by the kidney when acetylsulfapyridine stones are formed is primarily mechanical in that it results in the blocking of the tubules or ureters with concretions. If the drug is stopped in time no permanent damage is done.

Regardless of the type of toxic manifestation resulting from treatment with sulfanilamide or sulfapyridine, the therapy is the same, *i. e.*, the drug must be stopped and fluids forced in order that the drug may be eliminated as quickly as possible.

Pharmacology.—It should be borne in mind that the acute toxic effects of sulfanilamide which have been noted in animals cannot, in general, be compared with many of the acute toxic effects noted in human beings, because these latter frequently represent idiosyncrasies to the drug that are not reproducible in animals.

In mice, the peroral L.D. 50 of sulfanilamide (*i. e.*, the dose of sulfanilamide that will kill 50 per cent of the animals) is between 3 and 4 G. per kilogram of body weight. However, before lethal effects are obtained, ataxia, purposeless movements, rigidity, convulsions and coma may be noted. Rabbits and guinea-pigs are more susceptible to the lethal effects of sulfanilamide than are mice. Dogs are quite susceptible. The growth rates of young rats are not appreciably disturbed by the daily administration of from 0.25 to 1 G. of sulfanilamide per kilogram of body weight so that sulfanilamide is, in so far as animals are concerned, a drug possessing a relatively low degree of toxicity.

The administration of large doses of sulfanilamide to animals gives rise to toxic effects such as ataxic movements, convulsions, and at times coma. The urinary excretion of porphyrins is increased in rats by daily doses of the drug, and Molitor and Robinson reported that rats which received sulfanilamide daily developed cyanosis in from seven to ten days. These latter observers reported that no changes in liver function (as determined by the bromsulphthalein test) could be detected in dogs receiving moderate doses of sulfanilamide over a two months' period. The drug appears to be without effect upon the cardiac output, the blood-pressure, respiration, smooth muscle or the basal metabolism of experimental animals. Hence, it may be said that, in general, it is remarkably inert in so far as its physiological effects in the animal body are concerned.

Outstanding among the investigations upon the effects of sulfanilamide are those of Marshall and his associates concerning the absorption, distribution and excretion of this drug in animals and human beings. They noted that in both man and animals the absorption of the drug is practically complete four hours after the oral administration of a single dose of sulfanilamide in capsules or tablet form. If, however, the drug is given in solution, the absorption is much more rapid, taking place within thirty minutes to one hour. Following its absorption, a certain percentage of the sulfanilamide is changed to acetylsulfanilamide. It was noted that guinea-pigs and rabbits conjugated relatively large amounts of the drug, mice and human beings relatively small amounts, while in dogs none of the sulfanilamide is changed to the acetyl form. It has been shown that sulfanilamide is changed to acetylsulfanilamide in the liver and it is probable that this phenomenon represents a detoxifying mechanism. Inasmuch as acetylsulfanilamide is almost completely inactive from the chemotherapeutic point of view, its presence in the body fluids is rarely determined as a routine measure; hence, most reports upon the concentration of sulfanilamide in body fluids represent estimations of sulfanilamide itself, while total determinations represent the sum of sulfanilamide and acetylsulfanilamide.

In the body sulfanilamide is quite freely diffusible and is present in practically all of the tissues (with the exception of bone, fat and brain tissue) in about the same concentration as exists in the blood. It passes readily into the spinal fluid and is found in fair concentrations in all body secretions; hence, it is present in the milk, saliva, gastric juice, bile, intestinal secretions, pancreatic juice, sweat and tears. It is present in exudates and transudates in concentrations of two-thirds to four-fifths of those noted in the blood, and it passes the placental barrier with ease.

The drug is excreted almost entirely (90 to 95 per cent) in the urine, and excretion begins almost as soon as any of the drug appears in the blood. It is excreted as sulfanilamide and acetylsulfanilamide in proportions of one-third to two-thirds of sulfanilamide. The ratio between sulfanilamide and acetylsulfanilamide in the urine may vary markedly from day to day, the factor controlling these variations being unknown. The fact that the drug is excreted almost entirely by the kidneys makes it possible to obtain high concentrations of the drug in the urine, thus accounting for its therapeutic effects in certain urinary infections. If, however, kidney function is impaired, the excretion of sulfanilamide will be decreased, resulting in a greater or less accumulation of the drug in the body. Hence, care must be exercised when sulfanilamide is prescribed to individuals whose kidney function is impaired.

When therapeutic doses of sulfanilamide are given, the concentration of the drug in the blood is roughly proportional to the dose. A single dose of 0.1 G. per kilo will give a concentration of ± 10 mg. per cent in the blood. Also, because absorption is generally complete in four hours, the maintenance of an even concentration of the drug in the blood requires the administration of maintenance doses of sulfanilamide at four-hourly intervals. It is obvious that factors such as hypermotility, constipation or vomiting which interfere appreciably with the normal function of the gastro-intestinal tract, may also disturb the normal rate of absorption of sulfanilamide. Further, as sulfanilamide is excreted almost entirely in the urine, marked variations in the urinary output may be reflected by varying concentrations of the drug in the blood of patients who are on a constant dosage schedule of sulfanilamide.

Therapeutic Uses.—Sulfanilamide is a highly effective chemotherapeutic agent in the control of Lancefield Group A hemolytic streptococcal infections. It is not very effective in Group B hemolytic streptococcal infections and is about two-thirds as effective in Group C as it is in those infections produced by hemolytic streptococci belonging to Group A. The drug has no effect against enterococcal infections regardless of whether the enterococci are non-hemolytic, or of the hemolytic

group. It is effective in the control of infections produced by alpha hemolytic streptococci (Streptococcus viridans) providing the organisms are not members of the enterococcal group. It is ineffective in the case of alpha hemolytic streptococcal subacute bacterial endocarditis, as in this disease the nature of the pathological lesion renders sulfanilamide therapy as a rule unavailing. There is little information available regarding the value of the drug in non-hemolytic streptococcal infections. Moreover it is ineffective in anaërobic streptococcal infections.

The drug is very effective in the control of infections caused by pathogenic Gram-negative cocci such as the meningococcus and the gonococcus. While it has some therapeutic value in pneumococcal infections, this effect is definitely less marked than is that of sulfapyridine. Sulfanilamide therapy is highly effective in gas gangrene caused by the Welch bacillus, in chancroidal infections (Ducrey's bacillus infection), trachoma, certain types of urinary tract infections (those caused by the colon bacillus, Aërobacter aërogenes, B. proteus, typhoid bacillus and staphylococcus) and is moderately effective in brucella infections.

It has little, if any, effect in typhoid fever, staphylococcal infection, influenza bacillus infections, colon bacillary infection or in common colds and influenza. With the exception of lymphopathia venereum, no diseases due to filterable viruses have shown themselves susceptible to therapy with sulfanilamide.

It should be noted that in every instance (with the exception of trachoma and the urinary tract infections) the clinical effectiveness of sulfanilamide has been suggested or corroborated by the therapeutic effects noted in the treatment of experimental infections in animals.

Dosage.—The dose of sulfanilamide in adults in cases of serious infection is about 1 G. (15 grs.) every four hours for forty-eight hours and then from 0.4 G. (7½ grs.) to 0.66 G. (10 grs.) every four hours thereafter. It is usually advisable to continue therapy for a few days after clinical recovery in order to avoid relapse (and in a case of gonorrhea for a minimum of two weeks). Infants will tolerate from one-third to one-half the adult dose and children from one-half to three-fourths of the adult dose. Patients who cannot take the drug by mouth may be given subcutaneous injections of a 0.8 per cent solution of sulfanilamide made by adding 8 G. of pure sulfanilamide crystals to 1 litre of warm physiological solution of sodium chloride or 1 per cent sodium chloride solution or, better still, ⅙ molar sodium lactate solution. The same total dosage may be employed for parenteral as for oral administration, but the injections should be given at six- to eight-hour intervals. In less serious infections, where no threat to life exists, a lower dosage of from 3-4 G. daily (in adults) is to be recommended, without the larger initial dosage.

SULFAPYRIDINE.

Sulfapyridine [2(sulfanilamido)pyridine; M. & B. 693; Dagenan] is a slightly bitter white crystalline compound, soluble at 37° to about 1 part in 1000 of water. It was first described by Whitby. While

both experimental and clinical data tend to show that it is a fairly effective chemotherapeutic agent in a variety of bacterial infections, the superiority of sulfapyridine over sulfanilamide has been established only in the treatment of pneumococcal and staphylococcal infections in man.

Studies upon the absorption, distribution and excretion of sulfapyridine in human beings show that, in general, it follows the pattern of sulfanilamide. However, in contrast to sulfanilamide, sulfapyridine is absorbed somewhat more slowly and is excreted less rapidly, thus making the curve of its concentration in the blood less steep and more sustained than is that of sulfanilamide. The ability of individuals to absorb sulfapyridine when the drug is given by mouth varies markedly. Hence, therapy with the drug is more difficult because one cannot count upon it being uniformly absorbed by all patients. Another factor that also makes treatment with this drug more difficult is the tendency of many individuals to conjugate a large proportion of the absorbed drug to the inactive acetyl form. Thus, when the absorption of the drug is excellent, it may be so rapidly conjugated that satisfactory therapeutic effects are not obtained. These variations in absorption and conjugation make frequent determinations of the concentrations of the "free" and conjugated fractions of sulfapyridine a necessary adjunct to rational therapy with this drug.

The unabsorbed portion of the drug is excreted in the stools, while that which is absorbed is excreted almost wholly in the urine in the form of sulfapyridine and acetylsulfapyridine. As a rule, more of the drug is excreted in the urine in the conjugated form than is noted when sulfanilamide is prescribed. Inasmuch as acetylsulfapyridine is poorly soluble, it tends to precipitate out in the urine, forming crystals and at times calculi, which may give rise to marked signs of renal irritation. As a rule, it requires from three to four days after the drug is stopped before the urine is free of sulfapyridine.

It is likely that the mode of action of sulfapyridine is quite similar to that of sulfanilamide in that it appears to exert a bacteriostatic effect upon pneumococci and hemolytic streptococci both *in vitro* and *in vivo*. However, in pneumococcal infections it seems quite clear that the main action of the drug is to hold the infection in check until the body develops an immunity sufficient to overcome the infection. Hence, if the drug is discontinued before a sufficient degree of immunity develops, a recrudescence of the infection is liable to occur.

It has been shown by Marshall *et al.* that sulfapyridine when absorbed is about twice as toxic as sulfanilamide in so far as acute toxicity experiments in mice are concerned. In human beings it has produced essentially the same toxic manifestations as have been noted in the case of sulfanilamide, the exception being that renal calculi composed of acetylsulfapyridine which have produced signs and symptoms of renal irritation have been noted in the course of therapy with sulfapyridine.

Dosage.—Adequate standards of dosage have not as yet been agreed on by investigators who have used this drug in the treatment of pneumococcic infections. However, the evidence points to the fact that it

is important to establish adequate blood levels of the drug within the first day of treatment. Hence in adults suffering from lobar pneumonia large initial doses are given, such as 4 G. in a single dose followed by 1 G. of the drug every four hours by mouth, this to be continued until the temperature has been normal for at least forty-eight hours; then the dose may be cut to 1 G. every six hours and continued until the resolution of the pneumonic process is well under way. At this point the dose of the drug should be reduced to 0.5 G. four times a day and should be continued until the lungs are clear. It has been noted that if treatment with the drug is stopped too soon, recurrence of the pneumonic process may occur. Concentrations of 4 mg. per 100 cc. or more of free sulfapyridine in the blood seem to be necessary for prompt therapeutic responses to the drug. In children, the initial dose should be from 1–2 G., depending on the weight of the child, and then from 0.5–1 G. every four to six hours until the temperature has been normal for forty-eight hours. Following this, the dose of the drug may be gradually reduced until the lungs are clear. Adequate standards of dosage have not been worked out for the drug in other types of infections.

SULFATHIAZOLE AND SULFAMETHYLTHIAZOLE.

Among the many compounds closely related to sulfanilamide and sulfapyridine which have been synthesized, two deserve special mention at this time, although it is quite possible that in the near future many others will demand recognition. The two which have been introduced into clinical practice to a limited extent are thiazole derivatives of sulfanilamide. Their chemical relationship to the parent compound can be seen in the formulæ given above (page 737).

Of the various compounds synthesized sulfathiazole [2(para-aminobenzene-sulfonamido) thiazole] and sulfamethylthiazole, the methyl derivative, have been most thoroughly studied as to their toxicity and therapeutic efficiency in relation to the two older compounds. Sulfathiazole in acute toxicity experiments in mice seems to be definitely less toxic than either its methyl derivative or sulfapyridine. However, in chronic toxicity experiments on mice, when it is placed in their diet, sulfathiazole is more toxic than sulfapyridine. In growing rats sulfapyridine seems the more toxic and in monkeys this compound seems to cause kidney lesions more commonly than does the thiazole compound. Thus these experiments indicate that repeated doses of sulfathiazole are more toxic for mice but less toxic for rats and monkeys than sulfapyridine. Sulfathiazole disappears from the blood more rapidly and is excreted more quickly than is sulfapyridine, but the compound is conjugated in the body to a smaller extent than is sulfanilamide.

In experimental pneumococcic infections in mice both drugs are about equally effective. In man sulfathiazole is absorbed more readily from the intestinal tract than is sulfapyridine, resembling in that respect sulfanilamide, and it also resembles it in the ratio of the free to the conjugated form in the blood. It is excreted more rapidly than is sulfapyridine.

In man the symptoms of intolerance, such as nausea and vomiting, are definitely less with sulfathiazole and symptoms on part of the central nervous system, such as headache, dizziness, etc., are rarely met with. Fever, skin rashes and conjunctivitis are fairly common and hematuria, which at times is followed by anuria, is occasionally encountered. A number of cases of peripheral neuritis have also been reported.

The position of sulfathiazole in therapeutics is not established as yet, the reports being somewhat contradictory. It is probably not so effective in pneumococcal pneumonia as is sulfapyridine, but seems to be more effective in staphylococcal and coli infections.

In its clinical use it is more difficult to maintain a uniform level of drug in the blood than is the case with sulfapyridine due to its relatively rapid absorption and excretion.

As regards dosage of sulfathiazole no very definite statement can be made at present due to lack of experience with the compound, but for adults an initial dose of 4 G. has been advised, to be followed by 1 G. doses at four-hour intervals.

Information concerning the toxicity and clinical value of sulfamethylthiazole is still more fragmentary, but it has been reported as being effective against staphylococcal organisms.

The reports of the occurrence of peripheral neuritis following the use of the thiazole compounds indicate that care should be exercised in their administration until more has been learned about toxic side actions that may follow their employment.

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W. EMETINE AND OTHER ANTIAMŒBIC DRUGS.

I. EMETINE (IPECACUANHA).

Ipecacuanha (Cephaelis or Psychotria Ipecacuanha) has long been used for its emetic and expectorant virtues, and was believed to contain only one alkaloid, *Emetine*, but it has been shown, that this so-called principle is really made up of several distinct alkaloids, *Cephaeline* ($C_{28}H_{38}N_2O_4$), *Emetine* ($C_{28}H_{37}CH_3N_2O_4$), and *Psychotrine* and others of less importance; emetine is methylcephaeline, and cephaeline is obtained from psychotrine by reduction; they are all three derivatives of isoquinoline, and emetine and cephaeline resemble each other in their action, while psychotrine is said to be almost inert.

Symptoms and Action.—When administered internally emetine has a bitter, acrid taste, and produces a copious salivary secretion, followed later by nausea and vomiting. The drug is generally largely eliminated by vomiting, so that no further effects are observed.

The nausea and vomiting are accompanied by the usual symptoms —muscular weakness and depression, increased secretion of saliva and of mucus by the glands of the throat and respiratory passages, often perspiration, and generally temporary acceleration of the pulse.

Quantities which are too small to provoke vomiting, induce prolonged nausea with increased mucous secretion along the respiratory passages, and some perspiration.

Emetine possesses a powerful **Local Irritant Action,** which is, however, much more marked in certain individuals than in others. The smallest quantity of the powdered root of ipecacuanha is sufficient to induce in the subjects of this idiosyncrasy considerable swelling and injection of the conjunctival and nasal mucous membranes, with salivation, tears, sneezing, coughing, and bronchial catarrh. When applied to the skin as a liniment, it produces redness, itching and occasionally a pustular eruption, but when injected hypodermically the alkaloids do not irritate the subcutaneous tissues.

The emetic action is mainly due to ipecacuanha irritating the stomach, and is thus a further example of its specific action on the mucous membranes. It is probable that there may be a further action on the medullary centre when large quantities are injected intravenously in animals, but this is not involved in the ordinary methods of administration. If the action were due to the effects of the drug after absorption, vomiting would be caused by a smaller dose injected hypodermically or intravenously than is necessary by the mouth; but it is found that a dose of emetine sufficient to cause vomiting when swallowed, may be injected

without any effects whatever. In the case of apomorphine, on the other hand, in which the action is central, the hypodermic emetic dose is smaller than that necessary when it is given by the mouth. The increased bronchial secretion, the perspiration, the acceleration of the pulse, and other attendant symptoms are similarly reflex in origin from the gastric irritation and do not indicate any direct action on the bronchi and other organs.

When large doses are injected hypodermically, emetine induces nausea, vomiting, and purging, and blood is frequently voided in the stools, a condition of collapse follows, and the animal generally dies of exhaustion in the course of a few hours after the onset of the symptoms. Very large quantities injected subcutaneously or intravenously may fail to elicit vomiting, but the collapse symptoms appear, and after some weak convulsive movements, the animal dies of cardiac failure. In those cases in which death follows rapidly on the injection, no pathological lesions may be found after death, but in experiments where smaller quantities are injected, and the animal survives for eighteen to twenty-four hours, the stomach and intestine often exhibit the appearances of acute gastro-enteritis. The mucous membrane is swollen, congested, and often covered with a muco-purulent secretion or studded with ecchymoses, and in dogs ulceration is often present. A lesion which is not by any means constant, but which occurs in a considerable number of animals and especially in rabbits, is œdema of the lungs. The heart changes are usually quite severe, animals surviving three or more days, showing necrosis of some fibres and degenerative swellings of the remaining muscle cells. These cardiac changes are apparently severe enough to be a cause of death.

The gastric and intestinal symptoms which follow from these large hypodermic doses suggest that emetine is excreted by the mucous membranes of the alimentary canal, and that it induces irritation and inflammation in the course of its excretion. In man, vomiting has followed the hypodermic injection of four grains of emetine, but one grain administered in this way has no such effect.

Emetine injected into a vein weakens the heart's action, and induces a fall of blood-pressure, but when it is injected subcutaneously or given by the mouth, the heart is not affected directly, but pathological changes in the muscle become apparent later.

In the frog emetine does not cause vomiting, but a slowly advancing central paralysis follows its injection, the spontaneous movements ceasing early, and later the reflex excitability disappearing. The contractions of the heart are rendered weak and irregular, and eventually cease from paralysis of the cardiac muscle.

Ipecacuanha has long enjoyed a reputation in one form of tropical dysentery, and the discovery that the cause of this form of dysentery was an amœba (Entamœba histolytica) was soon followed by Roger's statement that emetine has a specifically poisonous action on this parasite. This specific toxicity cannot be demonstrated in ordinary forms of amœba, nor in other protozoa, and even the entamœba of dysentery is not strikingly susceptible to emetine when exposed to it in the test-tube; sometimes 1 per mille or even 1 per cent of emetine has not killed the amœba in the test-tube within an hour. On the other hand the effects in cases of dysentery treated with emetine are very satisfactory and the entamœba disappears from the stools and tissues. The quantity of emetine that comes in contact with the parasite must be even smaller than that of quinine in cases of malaria, and the equivalent concentration is harmless to entamœba outside the body. There is thus some difficulty in assigning the success of the treatment to a directly poisonous

action on the parasite. Experimental work upon the treatment of cats infected with amœbæ obtained from human sources have demonstrated that emetine will exert a beneficial action in such infections; apparently in such experiments the drug will act in the same way as in the natural disease in man.

Emetine and cephaeline, the two chief alkaloids of ipecacuanha, resemble each other closely in their effects, cephaeline being somewhat more irritant than emetine. Ipecacuanha owes its action to the alkaloids, and differs from them only in acting more slowly and in having less tendency to cause purging, owing to its containing a large amount of tannin. The relative action of the two alkaloids in dysentery has not been accurately determined, but emetine is superior to cephaeline.

Therapeutic Uses.—Ipecacuanha has been largely employed as an emetic, and although it has been replaced for some purposes, notably in cases of poisoning, by apomorphine, it still has a certain field of usefulness in cases in which an emetic is indicated, but in which the hypodermic method is objectionable, as in children. In cases of obstruction of the respiratory passage, as in croup in children, the syrup of ipecac is often employed in emetic doses. The increase in secretions and the movements attending vomiting will frequently relieve the condition. At present ipecacuanha is used chiefly as an expectorant in the treatment of inflammatory conditions of the respiratory passages. For this purpose it is prescribed in smaller quantities than those necessary to produce emesis. It acts indirectly through its nauseating properties, and has the advantage that its action is much more prolonged than that of apomorphine, and at the same time is not so unpleasant as that of several metallic substances, such as tartar emetic, which are used for the same purpose. It increases the secretion of the bronchial mucous membrane, and further tends to render it more fluid, so that the mucus can be coughed up more easily. The increased secretion may also be of service by protecting the inflamed and irritable membrane from the cold air and thereby lessening the cough; opium is often added in order to further allay coughing by depressing the centre, the well-known Dover's powder being a favorite prescription for this purpose. When the secretion of the bronchi is already excessive, and the cough is rather to be encouraged than repressed, these preparations are of course contra-indicated.

Ipecacuanha is also employed as a diaphoretic, either alone or more commonly as Dover's powder. The perspiration is not so copious as that following pilocarpine and other sudorifics, but resembles rather that produced by warmth applied to the skin. Dover's powder is therefore a common remedy in chills and in commencing catarrh of the respiratory passages.

Ipecacuanha root was formerly used in amœbic dysentery, but very large quantities were required, and it was difficult to avoid nausea and vomiting. Opium and morphine were added for this purpose, and in addition the powder, made into pills, was enclosed in keratin or salol, which prevented it acting on the stomach, the pills being dissolved in the intestine, freeing the ipecac to exert its influence in that structure. But all these cumbrous methods have been rendered obsolete by the

introduction of emetine into therapeutics. Rogers showed that the hypodermic injection of the alkaloid is more efficient than the ipecacuanha treatment in amœbic dysentery and in its sequelæ, hepatitis and hepatic abscess. After the hypodermic injection of 1–2 grs. in divided doses of ½ gr. each, the amœbæ disappear from the stools and from the liver in a considerable proportion of cases, and an immediate improvement in the symptoms follows. The treatment should be continued (1 gr. each day) until 10 grs. in all have been given. It should then be discontinued, as the prolonged use of emetine is liable to set up irritation of the bowel. Its main value therefore is in the acute stages of dysentery where the improvement in symptoms is likely to be rapid. For the continued treatment in subacute or chronic cases some other drug should be employed, as emetine is eliminated slowly and cumulative symptoms are likely to appear. These may take the form of vomiting and diarrhœa; involvement of the myocardium with tachycardia, and peripheral neuritis with marked weakness of the extremities or even a more or less complete paralysis. The probability of myocardial injury increases at the age of sixty so that it is not uncommon to see evidences of cardiac disturbances after the administration of emetine to older patients. Favorable results have been obtained in chronic cases and in carriers of amœbic dysentery by the use of the double salt, emetine-bismuth iodide, given by the mouth. This is entirely insoluble, the salt containing about 20 per cent of emetine and 15 to 20 per cent of bismuth. It does not act in the stomach, but it is decomposed in the intestine so that the emetine can unfold its action. However, it too, like ipecac, is not infrequently the cause of nausea and vomiting, although these effects do not occur with such frequency as with ipecac. A dose of 3–4 grs. should be given daily until about 40 grs. in all have been taken; this is curative in the majority of cases. In amœbic liver abscess, Rogers removes the pus by aspiration and then injects into the cavity a grain of emetine dissolved in 1–2 oz. of sterile saline solution to destroy the amœbæ. The action of emetine in these amœbic diseases can only be compared with that of quinine in malaria; and, as in the case of quinine, the free protozoa disappear while encysted forms escape, and may give rise to relapses. Emetine is valueless in dysentery from bacillary infection and most other intestinal disorders, but has been recommended in sprue.[1]

Preparations.

U. S. P.

Ipecacuanha. Emetic dose, 1 G. (15 grs.).

Fluidextractum Ipecacuanhæ. Emetic dose, 1 cc. (15 mins.).

Syrupus Ipecacuanhæ. Emetic dose, 15 cc. (4 fl. drs.); expectorant, 0.75 cc. (12 mins.).

Pulvis Ipecacuanhæ et Opii, Dover's Powder. 0.3 G. (5 grs.).

Emetinæ Hydrochloridum, 0.02 G. (⅓ gr.).

B. P.

Ipecacuanha.

Ipecacuanha Pulverata, powdered ipecac. Emetic dose, 1–2 G. (15–30 grs.).

[1] Many other drugs have been recommended in amœbic dysentery, but though some destroy the amœba in test-tube experiments, they have not proved valuable in treatment. An extract of Castela nicholsoni or Mexican bitter bush (Chaparro amargosa) has sometimes proved effective in cases in which emetine was unsuccessful.

EXTRACTUM IPECACUANHÆ LIQUIDUM. Emetic dose, 0.6–2 mils. (10–30 mins.).

TINCTURA IPECACUANHÆ. Emetic dose, 15–30 mils. ($\frac{1}{2}$–1 fl. oz.).

PULVIS IPECACUANHÆ ET OPII, Dover's Powder. 0.3–0.6 G. (5–10 grs.).

TROCHISCUS MORPHINÆ ET IPECACUANHÆ, each lozenge contains 0.002 G. morphine hydrochloride and 0.006 G. ipecac.

EMETINÆ HYDROCHLORIDUM, emetine hydrochloride, is the salt of the alkaloid obtained from ipecac. 0.03–0.06 G. ($\frac{1}{2}$–1 gr.).

EMETINÆ ET BISMUTHI IODIDUM, a complex iodide of emetine and bismuth. 0.06–0.2 G. (1–3 grs.).

IPECACUANHA of the U. S. P. is the root of Cephaelis ipecacuanha or of C. acuminata and contains at least 1.75 per cent of alkaloids. The B. P. preparation is the root of Cephaelis ipecacuanha and contains 2 per cent of alkaloids.

PULVIS IPECACUANHÆ ET OPII, Dover's Powder, contains 10 per cent each of ipecacuanha and opium.

EMETINÆ HYDROCHLORIDUM ($C_{29}H_{40}O_4N_2$ 2HCl) is a white crystalline powder freely soluble in water. It may be obtained from ipecac or prepared synthetically.

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II. CARBARSONE.

Following the success which attended the introduction of the organic arsenic compounds in the treatment of syphilis an attempt was made by Marchoux to employ these products in the therapeutics of amœbiasis. For this purpose he used acetarsone, the acetyl derivative of amino-hydroxylphenyl-arsonic acid. More recently 4-carbaminophenyl-arsonic acid ($AsO_3H_2 \cdot C_6H_4NHCONH_2$), under the name of Carbarsone, has been substituted for acetarsone. This compound has shown itself to be superior to acetarsone, being less toxic and at the same time more actively amœbacidal.

Carbarsone is a white, almost odorless powder, very slightly soluble in water. It is usually administered in capsules in doses of 0.250 G. twice daily for ten days. The treatment may be repeated if necessary after a ten day rest period. The drug may also be given in a retention enema, 2 G. being dissolved in 200 cc. of a warm 2 per cent sodium bicarbonate solution. These enemata are given on alternate nights for 5 doses, the oral doses being omitted while the enemata are being employed.

Administered to animals in minimal lethal doses carbarsone produces symptoms of lethargy, loss of weight, abdominal distention and diarrhœa. Post mortem examination shows renal necrosis with tubular degeneration. When doses within the therapeutic range are administered no toxic symptoms are observed and no tissue injury has been described. A possible toxic effect upon the optic nerve has to be considered, as the

modified amino group in the molecule is in the para position in relation to the arsenic.

The excretion of the drug has been studied in the human subject and it has been found to follow closely the excretion curve of acetarsone. The excretion in each case is rather slow and therefore there would appear to be a possibility of cumulative action of the drug if its use were continued over a prolonged period. This would not seem to be important in the treatment of amœbiasis, as in such cases it is only given over a period of a few days.

Although carbarsone appears to be a relatively non-toxic drug for use in amœbiasis a few cases of poisoning have been reported. The symptoms were in one case a local dermatitis while others have shown diarrhœa, localized œdemas, and some visual disturbance.

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III. CHINIOFON.

Among the halogenated quinoline derivatives which have been employed for the treatment of amœbiasis, chiniofon is one of the most extensively used. Chemically it is sodium iodohydroxyquinolinesulphonate. It is prepared from a mixture of about 80 parts of iodohydroxyquinolinesulphonic acid and 20 parts of sodium bicarbonate, which yields when dissolved in water about 85 parts of the sodium iodohydroxyquinolinesulphonate. It is a yellow powder with a slight odor and a bitter taste. It dissolves in water with effervescence due to the reaction of the uncombined bicarbonate upon the acid. It is given to adults in doses of 0.25 to 1 G. three times daily or by enema in 1 to 5 G. doses dissolved in 200 cc. of warm water.

Chiniofon causes diarrhœa in a considerable percentage of cases, but aside from this disturbance symptoms of intolerance seem to be rare. Apparently the drug is not as active an amœbicide as is vioform, making large doses necessary. Some authorities state that chiniofon therapy requires rest in bed and a restricted diet, with either oral or rectal methods of administration, so that for these reasons also vioform is often preferred. Chiniofon is sometimes used in connection with emetine in the treatment of amebiasis.

Iodohydroxyquinolinesulphonic acid has been employed for the treatment of amebiasis under the name Yatren and also Loretin. This combines with sodium carbonate to form the sodium salt or chiniofon.

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IV. VIOFORM.

Among the various drugs which have been introduced for the treatment of amœbic dysentery, Iodochlorhydroxyquinoline, $C_9H_4N.OH.I.Cl$, under the name of Vioform, occupies an important place. It is a grayish-

yellow powder with a faint odor and is almost insoluble in water. It is usually given in capsules in 0.25 G. (4 grs.) doses repeated three or four times daily for a period of ten days. If it is desired to repeat the series of doses a rest period of ten days is recommended.

Vioform was introduced into therapeutics as a remedy for amœbiasis by Anderson and Koch, who found it was very efficient in the treatment of monkeys infected with Entamœba histolytica. Seven of the eight animals were cleared of the infection and no evidence of toxicity was noted.

Doses of 100 mgs. per kilogram given daily to rabbits for ten days gave no gross or microscopical sign of disease. Single doses of 0.250 G. per kilogram produced fatty infiltration and small necrotic areas in the liver and some injury to the renal tubules.

On account of the favorable experimental results the drug was introduced into the treatment of human amœbiasis with quite favorable results, a large majority of the cases being rendered parasite-free and in only very few instances were there any untoward symptoms, these being merely those of gastro-intestinal irritation. The drug seems to be superior to the closely related compound, Chiniofon, in that it requires a smaller dosage and does not require treatment in bed, which is recommended when chiniofon is to be used. On account of the hepatic lesions which have been described as a result of the administration of toxic doses the drug should be used with care in cases with suspected liver damage.

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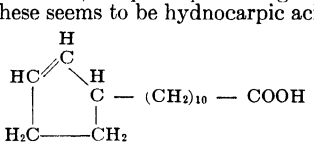
X. CHAULMOOGRA OIL.

Chaulmoogra oil is a fatty oil expressed from the seeds of Taraktogenos Kurzii, a tree growing in Burma and adjacent countries. An oil having similar chemical and therapeutic properties is also obtained from the seeds of Hydnocarpus Wightiani, H. anthelmintica and other species of Hydnocarpus. It has long been used especially in China as a remedy for leprosy, but, given by mouth, it produced so much nausea and gastric irritation that it was not possible to give doses large enough to do anything more than produce amelioration of the disease. In the last twenty years, owing to better knowledge of the nature of the active principles of the oil and to improvements in its preparations, with the consequent possibility of administering such preparations by injection, much more encouraging results have been obtained in the treatment of leprosy.

In 1901 Power and his co-workers determined that chaulmoogra oil consists chiefly of the glycerides of a group of unsaturated fatty acids which are optically active and are, so far as is known, unique in possessing a closed five-carbon ring. The most important of these seems to be hydnocarpic acid.



Chaulmoogric acid, which is similarly constituted but possesses twelve instead of ten CH_2 groups in the side chain, is more abundant in the oil but is believed to be less potent therapeutically.

In 1913 Heiser reported apparent cures of leprosy from intramuscular injec-

tions of the oil. This was a distinct advance but had the serious drawback that the injections were painful and liable to produce local necrosis. Rogers got better results from the use of sodium salts of the acids by subcutaneous or intravenous injection, and Dean introduced treatment by intramuscular injection of ethyl esters.

Though, owing to the very chronic nature of the disease and the fact that spontaneous remissions are of common occurrence, the estimation of the value of remedies is slow and difficult, reports from leper institutions in different parts of the world seem to have established beyond doubt that, by these newer methods of use, derivatives of Chaulmoogra oil have had in certain cases a remarkable effect in checking the disease and in possibly affecting a cure in some early cases. Treatment must be carried out for months or even years.

In 1920 Walker and Sweeny showed that, in respect to acid-fast bacilli and these only, sodium-salts of chaulmoogra acids are 100 times more powerfully bactericidal than phenol. It is supposed that this remarkable bactericidal action is due to the action of the unsaturated acids upon the waxy envelope of acid-fast bacilli, and that this underlies the efficacy of chaulmoogra acids in leprosy.

Read mentions the following, among other toxic actions, as liable to occur from chaulmoogra oil or its derivatives; nausea and emesis (from local irritant action on the stomach but also from central action), hæmolysis, renal irritation, and fatty infiltration of the liver. Continuous administration of small doses favors calcium retention, while larger doses increase calcium excretion and diminish the blood calcium.

Rogers has used other unsaturated acids in leprosy and has obtained favorable results with sodium morrhuate, the sodium salt of the unsaturated fatty acids of cod-liver oil.

A 5 per cent solution of sodium gynocardate or a solution of the sodium soap of chaulmoogra oil is used as a sclerosing agent to produce thrombosis in varicose veins. It is said to be superior to the 5 per cent solution of sodium morrhuate for this purpose. The injection of 2 cc. of chaulmoogra oil solution will result in thrombosis of a vein for a distance of about 5 cm. (Ochsner).

Preparations.

U. S. P.

Oleum Chaulmoogræ, the fixed oil expressed from the seeds of Taraktogenos Kurzii or from certain species of Hydnocarpus; a yellow or brownish-yellow liquid, with characteristic odor and acrid taste. Dose, 1 cc. (15 mins.).

Read recommends for oral administration 6 drops once daily or less frequently if progress can thereby be obtained.

Æthylis Chaulmoogras, ethyl chaulmoograte, the ethyl esters of the fatty acids of chaulmoogra oil. A clear, pale yellow liquid, having a slight fruity odor. Insoluble in water. 15 mins. by mouth or intramuscular injection.

B. P.

Oleum Hydnocarpi, the fatty oil obtained from the seeds of Hydnocarpus Wightiana, a yellowish or brownish oil or soft cream-colored fat, with characteristic odor and acrid taste.

Oleum Hydnocarpi Æthylicum, consists mainly of ethyl esters of chaulmoogric and hydnocarpic acids, a colorless or yellowish limpid oil, with characteristic odor and slightly acid taste. Doses of both above preparations: 0.3–1 mil., increasing gradually to 4 mils.; (5–15 mins. increasing gradually to 60 mins.) Slightly larger doses can be given by subcutaneous or intramuscular injection.

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PART IV.

ANTHELMINTICS.

ANTHELMINTICS are drugs which are used to kill or remove intestinal worms. They are often divided into vermicides and vermifuges, according as they kill or merely cause the expulsion of the worm, but this is determined largely by the quantity which comes in contact with the parasite and the rapidity with which the bowel is evacuated.

In order to possess any value as an anthelmintic, a drug must, of course, act more strongly on the parasite than on the host, and this more intense effect may be attained either by a specific action on the parasite, or by the drug failing to be absorbed from the alimentary canal. As a matter of fact, the anthelmintics, with few exceptions, have not been shown to possess any such specific action, but seem to injure most forms of living matter; this has been demonstrated more particularly for muscle tissue. Their use is thus rendered possible only by their slow absorption which permits of their acting on the parasite in greater concentration than on any of the tissues of the host.

Before the administration of most of the anthelmintics, the bowel ought to be emptied of its contents as far as possible by a light, easily digested diet and a laxative, and a brisk purge ought to follow some hours later, in order to remove the dead or stupefied worms. The anthelmintic is often prescribed along with a purge.

A number of drugs belonging to other groups are used occasionally as anthelmintics. Thus several of the volatile oils—tansy, turpentine—have some reputation; and chloroform is also administered occasionally by the mouth for its action on the parasites, but, like the volatile oils, is apt to produce gastric and intestinal irritation. The less easily absorbed antiseptics, such as naphthol, have been used with good results. Large enemata of salt solutions, or of infusion of quassia, are thrown into the rectum when the worms infest the large intestines. Many other drugs enjoy some popular reputation as "worm-cures," but have proved inferior to the recognized remedies.

Male fern, cusso and pomegranate are those most largely used for tapeworm; thymol has been used with great success in hook-worm (uncinariasis) but in recent years has been largely replaced by the oil of chenopodium or by carbon tetrachloride. Santonin and the oil of chenopodium are the chief anthelmintics in infection with round worm.

Lamson and his co-workers conducted an extensive *in vitro* study of the anthelmintic action of the alkylhydroxybenzenes against pig ascaris and they found that certain of the chlorinated alkylphenols had under the conditions of the experiments marked ascaricidal properties. In

their early paper they report that their studies showed hexylresorcinol was a very effective ascaricide, being active against human ascaris and hookworm. The disadvantage it possessed was the slight irritation it caused in both stomach and intestine, but in neither case was this severe. (Page 817.)

I. MALE FERN (ASPIDIUM, FILIX-MAS).

A number of ferns contain bodies which present considerable resemblance to each other from a chemical as well as from a pharmacological point of view, and which may therefore be classed together, at any rate until further information is available regarding them. The best known of these is the male fern (Aspidium, Filix-mas).

The active constituent of this remedy was supposed to be *Filicic Acid* by Poulsson, but Boehm has found other neutral and acid bodies present, *Aspidinin*, *Flavaspidic Acid*, *Albaspidin*, and *Aspidinol*—and Kraft has added *Filmaron* and *Flavaspidinin*. These bodies are all derivatives of phloroglucin and butyric acid, and it is still uncertain whether the effects of male fern are to be attributed to any one of them or whether all of them may not share in the action. Jacquet holds that the chief therapeutic factor is the filmaron, but that the others also have some effect.[1]

Action.—The extract or oleoresin of male fern, which is the only one of these plants used in regular medicine, as a general rule passes through the bowel without causing any symptoms whatever. The quantity of active substance dissolved, while sufficient to destroy the parasite, is too small to produce any effects on the host, and escapes with the other contents of the bowel, or if absorbed does not cause any symptoms. In rare cases, however, where large quantities are administered, or where some unknown conditions favor the absorption and retention of an unusually large amount of the active constituents grave and even fatal symptoms may supervene. These consist in vomiting and purging, with acute pain in the abdomen, muscular weakness, confusion and somnolence, with occasional twitching of the muscles, or slight convulsive movements, collapse, coma, and death. The stomach and intestine are found congested and swollen, and sometimes covered with small ecchymoses. In some cases icterus has been observed to follow the administration of male fern, probably from the duodenal catarrh, but possibly from destruction of the red blood cells, the number of which has been found to be diminished in some instances (Georgiewsky). In other cases permanent or temporary blindness has resulted from neuritis and subsequent atrophy of the optic nerve.

In the rabbit, filicic acid produces very similar symptoms. The congestion of the stomach and intestine is evidently due to the local irritation produced by the poison, while the other symptoms point to changes induced in the central nervous system. The spinal cord is stimulated, for the reflex excitability is increased, but the higher parts of the central nervous system seem to be depressed, and the paralysis of the respiratory centre is the cause of death,

[1] Nearly related bodies have been found in Aspidium athamanticum (Uncomocomo), which contains two forms of *Pannic Acid*, and in Aspidium spinulosum, while smaller quantities of acids occur in a large number of ferns. Several of these ferns enjoy a reputation as anthelmintics for tapeworm, and their virtues are generally considered due to these bodies.

although the heart is also weakened by filicic acid. Inflammation of the kidney is said to occur by some authors, and in some cases Poulsson found evidence of glycuronic acid in the urine.

In the frog, a mixture of depression and stimulation of the central nervous system is produced by filicic acid, along with distinct diminution in the strength of the skeletal muscles and the heart.

Aspidin (from Aspidium spinulosum) causes dyspnœa and paralysis of the spontaneous and respiratory movements in frogs; fibrillary twitching of the muscles sets in after some time and is succeeded by convulsive movements or tonic spasms, which indicate an increased activity of the reflexes of the spinal cord. The heart is depressed and eventually paralyzed, and the peripheral muscles are also weakened. The muscular tissue of the invertebrates is more powerfully affected by the constituents of male fern, and Straub attributes its action on the tapeworm to its paralyzing muscle. Mammals do not seem to be affected by aspidin injected hypodermically or administered by the mouth, but when it is introduced directly into the blood-vessels, it proves fatal by paralyzing the respiratory centre. Aspidinin induces very similar symptoms in the frog, while the other constituents are less active.

The blindness which has been observed in some cases of male fern poisoning has also been produced in dogs; it occurs chiefly in young, weakly, and anæmic individuals.

Pannic acid differs from filicic chiefly in its acting more strongly on muscle and less on the central nervous system of the frog.

Therapeutic Uses. – Male fern is used exclusively in the treatment of tapeworm and of Anchylostoma duodenale. Previous to its administration the bowel ought to be emptied, as far as possible, by a moderately light diet for one or two days and, where necessary, by a purgative. The oleoresin, or liquid extract, is then to be administered in capsules and a saline purgative is given about six hours later. In case the parasite fails to be dislodged, several days ought to be allowed to elapse before a second dose is given. Poulsson recommends that oily substances be avoided during the "cure," as they dissolve the active bodies, and thus promote their absorption. Other authorities dispute this view and some consider that oils in dissolving the active principles render them more poisonous to the parasites, but it is certainly suggestive that in many cases of poisoning with male fern castor oil had been given along with it or soon after. Marked anæmia, general debility and chronic alcoholism seem to predispose to male-fern poisoning, and the drug is accordingly to be used with care in these conditions.

Preparations.

U. S. P.

Aspidium or Male fern consists of the rhizome and stipes of Dryopteris filix-mas and yields not less than 6.5 per cent of the oleoresin.

Oleoresina Aspidii, 4 G. (1 dr.). The oleoresin of aspidium yields not less than 24 per cent of crude filicin.

B. P.

Filix Mas, Male fern or aspidium consists of the rhizome and leaf-bases of Dryopteris filix-mas, 4–12 G. (60–180 grs.).

Extractum Filicis, extract of Male fern or the Oleoresina aspidii, contains 25 per cent of Filicin, 3–6 mils (45–90 mins.).

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II. CUSSO.

Cusso, or Kousso, contains a neutral body, *Kosotoxin*, which is soluble in alcohol and in alkaline fluids, but is insoluble in water; it is a compound of phloroglucin and butyric acid like the constituents of male fern, which it resembles somewhat in its pharmacological action.

Cusso has a bitter, somewhat astringent taste, and sometimes causes nausea and vomiting and some looseness of the bowels. In rare cases prostration and collapse, with irregularity of the pulse, are said to have occurred from its use.

In the frog, kosotoxin paralyzes the nerve ends like curare, and has a specific action on the striped muscular tissue, which it weakens and eventually paralyzes. The heart muscle undergoes similar changes. In mammals the muscular action is well developed, but is accompanied by some stimulation of the medullary centres, indicated by rapid, dyspnœic breathing, salivation and vomiting. The stools are often fluid, and the urine is increased in amount. When it is injected directly into the circulation, some convulsive movements are often observed, and the heart is weakened and paralyzed. Kosotoxin seems to be a general protoplasm poison, as is indicated by its action on muscles and by its retarding the growth of yeast.

Cusso (Kousso or Brayera), the pistillate flowers of Brayera anthelmintica, is generally given by suspending 15 G. ($\frac{1}{2}$ oz.) of the powdered flowers in water. Kosotoxin has not yet been prescribed for therapeutic purposes. The usual preliminary treatment ought to be instituted, but no purge is required after Cusso as a general rule. It is used exclusively as an anthelmintic in cases of tapeworm.

Kamala is a reddish-brown powder which consists of the minute glands and hairs obtained from the surface of the fruits of Mallotus Philippinensis. It contains a neutral crystalline substance *Rottlerin*, which, like the active principles of male fern and Cusso, is a derivative of phloroglucin. Kamala is used in cases of tapeworm in doses of 2–8 G. (30 grs.–$\frac{1}{4}$ oz.) suspended in water. It acts as an intestinal irritant, causing purging and, more rarely, nausea and vomiting. No purge is necessary, therefore, after the powder. An alcoholic tincture of kamala has been found quite as efficient as the powder. Rottlerin resembles the active constituents of several other anthelmintics in possessing a strong action on muscle tissue whether striated or unstriated, in which it induces rigor; it also has some depressant effect on the central nervous system, particularly on the motor areas.

Areca Nut, the seeds of the palm Areca Catechu, is used in veterinary medicine as a remedy in tapeworm. It contains a fluid alkaloid, arecoline ($C_8H_{13}NO_2$), which resembles pilocarpine in action. In addition, it contains several inactive alkaloids and tannic acid.

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III. PELLETIERINE.

The bark of the pomegranate contains a very large amount of tannic acid (20–25 per cent), along with several alkaloids, of which *Pelletierine* or *Punicine*, and *Isopunicine* alone are active in ordinary doses. All the pomegranate alkaloids are closely related chemically to each other and to tropine (see atropine). None of them can be classed among the more active poisons as far as man and the higher animals are concerned.

In man, large doses cause heaviness, confusion, giddiness, and very marked weakness of the limbs. The consciousness is but little affected but the sight is often dim and uncertain, and in one case complete blindness persisted for several days. Occasionally nausea and discomfort in the abdomen are complained of, and more rarely vomiting, tremors, and cramps of the leg muscles are produced; the gastric symptoms are perhaps due to the large quantity of tannic acid in the drug rather than to the alkaloids.

In the frog and in most mammals, pelletierine causes a distinct increase in reflex irritability of the spinal cord and medulla oblongata, along with some depression of the higher divisions of the central nervous system. Very large doses weaken or paralyze the conductivity of the nerve plates in the frog, like curare. The heart muscle is also acted on and its pulsations are slowed in the frog, although they may be temporarily augmented in force.

Pelletierine and isopunicine have a specific action on tapeworms, for Schroeder found that a solution of 1 part in 10,000 was sufficient to kill them in ten minutes, while a stronger solution had practically no effect upon other intestinal worms.

Therapeutic Uses.—Pomegranate has been used exclusively as an anthelmintic, but the crude bark has now been displaced almost entirely by the tannate. The preliminary treatment is the same as that given under male fern, and a purge ought to be given one to two hours after the vermicide.

PELLETIERINÆ TANNAS (U. S. P., B. P.), a mixture in varying proportions of the tannates of four alkaloids (punicine, isopunicine, methylpunicine and pseudopunicine), obtained from pomegranate bark. Dose, U. S. P., 0.25 G. (4 grs.); B. P., 2–8 grs. (0.12–0.5 G.).

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v. SCHROEDER· Arch. f. exp. Path. u. Pharm., vol. **18**, p. 381; vol. **19**, p. 290.

IV. THYMOL.

Thymol ($C_{10}H_{14}O$) is a crystalline substance obtained from the volatile oil of thyme and other plants, and chemically is a homologue of phenol. It is very insoluble in water and when taken in solid form appears to be absorbed from the alimentary tract with difficulty.

In man, thymol has caused depression, nausea, vomiting, headache

and confusion with roaring sounds in the ears and alarming weakness of the heart resulting in giddiness and collapse. In a few cases death has occurred. Its irritant action on the mucous membrane may cause burning sensations in the stomach and vomiting.

In poisoning in animals it induces a condition of weakness and apathy which passes into collapse and death, generally without any convulsions. Fatty degeneration of the liver, congestion or even consolidation of the lungs, and irritation of the intestine are found *postmortem*. One-half or more of the thymol ingested is destroyed in the tissues; the rest is excreted in the urine in combination with sulfuric and glycuronic acids; it is said to have caused renal irritation in some cases, as shown by the appearance of albumin and even of blood in the urine.

Therapeutic Uses.—Thymol has been used widely as an anthelmintic in hook-worm disease (anchylostomiasis or uncinariasis) but has been largely replaced by carbon tetrachloride and oil of chenopodium. It is given in capsules or cachets in doses of 15 to 30 grs. repeated in two hours and followed in six or eight hours by a brisk saline purge. The bowel should be emptied as far as possible by light diet and an aperient before the treatment is begun. Thymol in $\frac{1}{10}$ per cent solution is also used as an antiseptic (see p. 786).

PREPARATIONS.

THYMOL (U. S. P., B. P.) ($C_6H_3C_3H_7CH_3OH$) occurs in common thyme and other plants, and forms large colorless crystals which have the odor of thyme and are very insoluble in water. It may also be prepared synthetically. The dose as an anthelmintic is 2 G. (30 grs.), U. S. P., 1-2 G. (15-30 grs.) B. P.

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V. CHENOPODIUM.

The oil of chenopodium, the so-called "Oil of American Wormseed" is a volatile oil obtained by distillation from Chenopodium ambrosioides anthelminticum, a weed which is found more or less extensively over the entire United States but which is especially abundant in the southeastern section.

The active constituent of the oil is Ascaridol ($C_{10}H_{16}O_2$) which is present in amounts varying from 45 to 70 per cent. It is obtained from the oil by fractional distillation in a partial vacuum. The remainder of the oil is mainly a mixture of terpenes which apparently are devoid of anthelmintic properties. Ascaridol has been shown to be about 30 per cent more toxic than the whole oil. The drug is very active as an anthelmintic against the hook-worm and ascaris infections, but it is, in common with some other anthelmintics, less efficient against oxyuris. The reports are contradictory concerning its value in amœbic dysentery.

The drug is probably as safe as any which is used for this purpose but even so, disagreeable symptoms not infrequently follow its administration and a number of deaths have been reported. In many of the cases which terminated fatally there is evidence that there was overdosage. The symptoms most commonly encountered in the use of the drug are nausea and vomiting with pain in the abdomen and some drowsiness, followed at times by ataxia, convulsions and coma. By far the most common of the more serious signs of intoxication from the drug is due to a disturbance of the ear. This may be merely a tinnitus such as is often seen following the use of quinine but it may go on to more or less complete deafness. The deafness is usually temporary, passing off in a few days or weeks but in some cases it has persisted for years. It is advised that the drug be used with caution in cases of hook-worm infection with long-standing anæmia and with signs of cardio-renal disease as in such patients severe untoward reactions are most likely to occur.

In dogs and cats the oil of chenopodium produces signs of depression of the central nervous system followed by clonic convulsions. In rabbits excitement is not uncommon. Given by mouth to dogs it produces somnolence with incoordination of the muscles of the extremities, coma and paralysis with death in a few hours. In some animals tremors of the muscles appear, passing on to convulsions and opisthotonus. The oil appears to be more toxic for cats than for dogs and rabbits. Given intravenously it causes a fall of blood-pressure which is probably due to an action on the heart. There is also depression of the respiration.

In cats it is slowly absorbed from the stomach but if given in an emulsified condition it is taken up quickly from the duodenum. Given intravenously the odor is detected very soon in the breath, indicating its rapid excretion by the lungs, but it has not been detected in the urine or bile.

Therapeutic Uses.—In the treatment of hook-worm infection with the oil of chenopodium the preliminary preparation of the patient by the use of laxatives and a period of starvation for the previous day seems not to be necessary. The adult dose is 3 cc. This dose is divided into two parts and given in hard gelatine capsules two hours apart and the final dose is followed in two hours by a purgative dose of castor oil. Food should not be taken before the anthelmintic is administered as it seems to markedly lessen the efficiency of the treatment.

To children the drug can be given most easily by dropping it on sugar, 1 drop of the oil for each year of the child's age; this dose to be repeated in two hours and followed in three hours by castor oil.

Smillie and Pessoa recommend that Ascaridol itself be substituted for the whole oil as it is a pure substance of definite chemical composition while the oil is a mixture. The main objection to Ascaridol is the high cost. It should be given to adults in a single dose of 1 cc. upon an empty stomach and followed in one-half hour by a purge of magnesium sulfate.

Against ascaris infections the oil may be given in 5–10 drop doses three times daily for two days and followed by a brisk purge.

PREPARATION.

OLEUM CHENOPODII (U. S. P., B. P.), Oil of Chenopodium, Oil of American Wormseed. A volatile oil distilled from the plant of Chenopodium ambrosioides var. anthelminticum. The oil yields not less than 65 per cent of Ascaridol ($C_{10}H_{16}O_2$). Dose, U. S. P., 1 cc. (15 mins.); B. P., 0.2–1 mil. (3–15 mins.).

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VI. CARBON TETRACHLORIDE.

Following the introduction of chloroform as a general anæsthetic in 1847, the closely related carbon tetrachloride was studied also as to its narcotic properties but it proved to be unsatisfactory and it was discarded as a medicinal agent. In 1921 it was recommended by Hall as a highly efficient and apparently safe remedy for the treatment of hookworm infections and since that time it has been used in many thousands of such cases, showing a high degree of effectiveness.

The drug has a mild local irritant action and its use may be followed by eructations and a feeling of warmth in the epigastrium. More rarely nausea and vomiting may follow its administration. Not uncommonly following these symptoms of local irritation there may be evidences of the general action of the drug such as headache which may last for two or three days, dizziness, and not infrequently drowsiness. These symptoms usually pass off in a brief time and are not important. Pain in the back and hematuria have also been described as occurring in man following the use of the drug. The drug, therefore, is not entirely safe and several deaths have already been reported from its use. The principal pathological lesion which has been described is a central necrosis of the liver. Different species of animals appear to vary considerably in their susceptibility to the poison; the dog and probably man are relatively tolerant while the rabbit is more susceptible. Certain factors seem to lessen human resistance among which may be mentioned the use of alcohol, starvation and in general a poorly nourished condition of the individual. A rich carbohydrate diet appears to lessen the likelihood of poisoning. As the drug has a distinct cathartic action some of it passes out in the fæces not having been absorbed at all, this being especially true if the dose administered has been large. Therapeutic doses (3 cc.) are probably largely absorbed from the intestine and excreted by the lungs.

The toxicity of carbon tetrachloride has been studied by Lamson and his co-workers. They found that it could be administered to dogs in large quantities if it were given upon an empty stomach and that only slight transient symp-

toms were produced, this lack of toxicity being apparently due to failure of absorption. However, even small doses given in this way have caused definite liver lesions. In rabbits it was much more toxic. Repeated large doses given to dogs by mouth caused chronic poisoning with symptoms of depression, bilirubinemia, bile in the urine and changes in the liver. Administration of substances such as alcohol (97 per cent) and fatty articles of food (cream and olive oil), apparently aid the absorption of the drug and definitely increase its toxicity.

Inhalation of the vapor of carbon tetrachloride is quite toxic to dogs and produces effects similar to those which follow intravenous administration. These symptoms in an unanæsthetized dog consist of excitement, muscular hypertonicity, evidences of anxiety and fright followed by anæsthesia and sleep from which the animal may recover in a few minutes. Under ether the injection of the drug causes a stoppage of respiration and a marked fall in blood-pressure which is maintained at a low point for some time. The lesion which is found at autopsy is a massive pulmonary œdema with focal hæmorrhages.

If the drug is injected into the portal vein there is extensive necrosis of the liver and following this the animal shows depression and becomes markedly jaundiced.

Wells has shown that in dogs 3 cc. doses are completely absorbed in from twenty-four to thirty-six hours and that the rate of excretion, which is high at first, drops rapidly until the fifth hour, after which it remains fairly constant. The odor of the drug appears on the breath early and the lungs are apparently the main avenue of excretion. Traces have been found in the urine.

Due to the widespread use of carbon tetrachloride in various industries as a solvent for rubber, paint, grease, etc., and as a cleansing agent in the dry cleaning industry, cases of poisoning are being encountered from time to time. The substance is usually inhaled, due to its presence in the air in the factories, but it is also absorbed through the skin. The early symptoms are those of headache, nausea, loss of appetite, slight anæmia and mental confusion. A mild degree of jaundice is not uncommon as are also various visual disturbances. Removal of the individual from the offending fumes is usually sufficient in the early stages of intoxication and adequate ventilation of rooms where the substance is being used should always be provided.

It is believed that a concentration of carbon tetrachloride of 100 parts per 1,000,000 is safe for continuous exposure of workmen during the working day, and that a concentration ten times as great is safe for short periods of say one-half hour. If there is a concentration of 100 parts per 1,000,000 it is noticeable by a faint characteristic odor. If the odor is more than a faint one an increase in ventilation is called for.

Long continued exposure to the fumes of carbon tetrachloride leads apparently to liver changes which may result in hepatic cirrhosis.

Therapeutic Uses.—Carbon tetrachloride is used most extensively in the treatment of hook-worm infection, being given to adults in a dose of from 2–3 cc. To children it is given in doses of 2 minims for each year of age up to fifteen years. Special preparation of the patient is not necessary unless there is marked constipation, when a laxative may be given. The drug may be given in divided doses but is commonly administered as a single dose. It may be enclosed in gelatine capsules but the simplest method is to give it in a fluid vehicle—usually water. Milk is also extensively used as a vehicle as it aids in forming an emulsion with the drug, thus covering up the taste. For this purpose, the dose of the drug is shaken up with a small quantity of milk and this emulsion is then poured into a larger quantity of milk. A saline purge may be given two to three hours later if it is thought to be desirable.

It has been recommended that the drug be administered in a 50 per

cent solution of magnesium sulfate. It is thought that in this way absorption may be limited and thus its toxicity lessened.

Carbon tetrachloride is also used in Ascaris infections but it is not so effective in this condition as it is against the hook-worm infection. It is quite effective against Oxyuris. Here it is advised that it be not only given by mouth but also in the form of an emulsion as an enema. For this purpose 6 cc. emulsified in warm milk is employed, the same being retained two hours.

In Kala-azar the drug has also proved effective and it is better tolerated here than is the oil of chenopodium. In this condition a single dose of 70 minims is recommended.

PREPARATION.

CARBONEI TETRACHLORIDUM (U. S. P., B. P.), Carbon Tetrachloride. Tetrachlormethane. Dose, U. S. P., 2.5 cc. (40 mins.); B. P., 2–4 mils. (30–60 mins.).

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VII. SANTONIN.

Santonin ($C_{15}H_{18}O_3$) is an anhydride or lactone of santoninic acid, a derivative of naphthalene. It occurs in Artemisia pauciflora along with a nearly related body (artemisin) and a volatile oil (cineol). Santonin is very insoluble in water, but is dissolved by alkalies, with which it forms santonates.

Action.—Owing to its insolubility in water, santonin has only a slightly bitter taste in the mouth. It is partially dissolved in the stomach and passes into the bowel, where it effects the removal of some forms of intestinal worms. Under special conditions part of the santonin may be absorbed in the bowel, however, and general poisoning results without the parasites being affected. A certain amount of absorption occurs in every case, as is shown by the disorders of color vision and by the yellow coloration of the urine. At first objects appear of a bluish color to the patient, but this aberration is of comparatively short duration and may in fact pass unnoticed. It is followed by a much longer period of "yellow sight" or xanthopsia, during which objects that are brightly illuminated seem to have a yellow tinge, blue seems green, and violet is indistinct, although in dimmer lights the violet may still

predominate. In severe poisoning the appreciation of the darker colors becomes very imperfect, and violet and even blue may fail to be distinguished from black. In general the violet end of the spectrum is shortened, while the yellow impresses the retina more vividly than normally. In some cases the senses of taste and smell, and more rarely, of hearing, are also deranged. These symptoms all pass off in the course of a few hours, a second stage of "violet sight" occasionally intervening before complete recovery.

The symptoms produced by the absorption of large quantities of santonin are so uniform in man and the other mammals that it is sufficient to enumerate those observed in experiments on the dog. The first distinct effects are generally twitching of the muscles of the head, frequently beginning on one side. These are followed by rolling of the eyes, grinding of the teeth, flexion and extension of the neck and rotation of the head from side to side, later by regular epileptiform convulsions in which the animal is first thrown into opisthotonos and then into clonic spasms of the limbs and trunk. These are interrupted by intervals of repose during which a curious momentary contraction of all the muscles of the body is often noticed. During the convulsive seizures the respiration is irregular and insufficient, and in fatal cases it fails to return after the convulsion passes off, and the animal dies of asphyxia. In man, some confusion, nausea and vomiting occasionally occur after quantities which are too small to produce convulsions, and in several cases aphasia has been observed. In frogs, convulsions are produced by santonin as in mammals, but they are preceded by a prolonged stage of depression, which is entirely absent in the higher animals.

These symptoms manifestly point to changes in the central nervous system. The xanthopsia is generally referred to a specific action on the retina, though some hold that the central apparatus of vision in the brain is the seat of the action. The condition has been ascribed to a preliminary stimulation and subsequent depression of the sense organs for the perception of the violet and eventually of the blue rays of the spectrum, or more precisely to some obstruction to the regeneration of the substance in the retina which normally appreciates violet rays (Filehne). According to Marshall, whatever may be the intimate mode of action of santonin in causing color vision, it is fundamentally one affecting violet receptivity and is of the same nature as that occurring after exhaustion of violet vision by violet light. It appears, therefore, to diminish the perceptibility of the most refrangible rays of the spectrum and possibly to a slight extent that of all rays.

The clonic nature of the convulsions at once points to an affection of the brain rather than of the cord, and the epileptiform convulsions are generally regarded as arising from stimulation of the cortex in the higher animals and man, though the basal cerebral ganglia may also be involved; the sudden contractions observed in the intervals of repose are ascribed to stimulation of the gray matter in the region of the pons.

Santonin undergoes some oxidation in the tissues and is excreted in the fæces and urine in several forms, two of which have been isolated from the urine of animals by Jaffe and found to be oxysantonins. After medicinal doses santonin is probably excreted almost wholly as a colored substance and chiefly in the urine. After larger doses traces of unchanged

santonin have been found in the urine. The colored compound is yellow in acid urine changing to scarlet upon addition of a caustic alkali, but the constitution of the compounds is unknown. The same colored compound is excreted after the administration of a colorless alkaline santoninate so that the organism in forming the colored compound from santonin and from a santoninate reverses the reaction in the two cases. The colored substance has also been found in the sweat after santonin has been given by mouth, in the blood plasma and in the fæces after the administration of potassium santoninate. A close relationship has been shown to exist between the presence of this compound in the urine and the occurrence of the xanthopsia but whether the disturbance of vision is due to the compound is still undecided.

Santonin is universally used as a remedy for the round worm, Ascaris lumbricoides, and most clinicians believe that it has a specific poisonous action on these animals, and that its undoubted effects are due to its killing them. In experiments on the entozoa outside the body, santonin was not found to be very toxic to them, but this appears to have been due to its not having been completely dissolved in the absence of bile, for Sollmann found it fatal to earthworms in low dilution when bile salts were added. Santonin, like other anthelmintics, often causes active movements in the worms before killing them and they are often expelled in this condition, although this movement ceases very soon afterward from the exposure to cold.

Therapeutic Uses.—Santonin is used almost exclusively to remove Ascaris lumbricoides from the intestine. It is much less effective against tapeworm or other intestinal parasites. It may be prescribed as a powder, or lozenge, or in solution in oil.

The bowel ought to be emptied by suitable diet and a laxative before the santonin is administered, and a sharp purge ought to be given afterward in order to bring away the entozoa.

A 5-grain dose is said by Caius and Mhaskar to be the optimum dose for adults and to be safe. They recommend that the dose should be taken three hours after a light evening meal and that the purge be given the next morning. For children the dose should not exceed 1 grain in twenty-four hours. It is often prescribed in a powder or capsule with calomel.

Santonin has been advised in some retinal diseases, but the results have generally been unsatisfactory.

PREPARATION.

SANTONINUM (U. S. P., B. P.) ($C_{15}H_{18}O_3$), a neutral principle derived from Artemisia pauciflora, is colorless when freshly prepared, but assumes a yellow color when exposed to the light. This does not seem to impair its activity materially, but it is preferable to avoid it by keeping santonin in amber-colored vials. Dose, U. S. P., 0.06 G. (1 gr.); B. P., 1–3 grs. (0.06–0.2 G.).

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SPIGELIA.

Another remedy used in cases of round worm is pink root, Spigelia maritima, the active principle of which is unknown, although an alkaloid, *spigeline*, is said to occur in it. Occasional cases of poisoning have been observed, especially in children, the symptoms consisting in flushing and dryness of the skin, often with some œdematous swelling of the face, delirium and sopor followed by dimness of sight or temporary blindness. In frogs spigelia appears to depress the brain and spinal cord, and the heart beats more slowly and weakly, while in rabbits the most prominent symptoms arise from the respiration, which becomes slow and labored and finally ceases in a convulsive attack. In the dog and cat its injection is followed by vomiting, great weakness and incoordination of the movements, restlessness, rapid dyspnœic respiration and finally by stupor, coma, and death from failure of the respiratory centre.

The fluidextract is used to remove round worms, which it seems to affect in very much the same way as santonin. It ought to be preceded and followed by a purge.

PART V.

ANTISEPTICS AND DISINFECTANTS.

VARIOUS balsams, tars and other aromatic bodies have long enjoyed a certain reputation in the treatment of wounds, but the whole course of surgery was changed about 1870 when Lister introduced the systematic application of antiseptics to wounded tissues. The general principle underlying this treatment was that infection arises from the invasion of the tissues by microörganisms and that it can be combated either by preventing them from reaching a wound or by retarding their growth on the injured surface by means of antiseptic drugs. The first of these which he introduced was carbolic acid, and this held its position unchallenged for several years, when it was discovered that many other substances were equally destructive to the microörganisms and were less poisonous to the invaded tissues. Of late the tendency in civil practice has been rather to prevent the infection of the tissues by a very careful technique (asepsis), but when this is impossible the use of antiseptics and disinfectants is still necessary, and even the newer aseptic surgery depends in part on the use of disinfectants to cleanse the skin and instruments. It may be interesting to recall that during the World War the study of the action of antiseptics and of antiseptic methods in surgery received a new impetus due, of course, to the unprecedented prevalence of infected wounds. As a result of these studies much valuable information was gained and some important modifications of established surgical antiseptic methods were introduced.

A disinfectant, in the strict use of the term, is a substance used to destroy microbes, whereas an antiseptic, while not actually killing the germs, prevents their growth as long as it remains in contact with them. A disinfectant is accordingly only intended to act for a short time, for if the infected matter be once rendered sterile it can only become dangerous by being again contaminated. For example, a room requires only to be disinfected after a case of infectious disease. A wound, on the other hand, even though completely disinfected may become contaminated again very easily and an antiseptic may be required to prevent the further growth of microbes. Many substances are disinfectant in large quantities and antiseptic in more dilute solutions, but others are too weak to disinfect thoroughly though they retard the growth of pathogenic organisms, and still others may be employed to disinfect but are unsuitable for use as antiseptics, either because they are too poisonous to be applied for a sufficient time, or because they lose their activity on contact with living matter (*e. g.*, oxidizing disinfectants).

A very large number of substances possess disinfectant properties, that is, are capable of destroying microbes when they can be applied in sufficient quantity. They have no specific action on the microbes, however, but act as general protoplasmic poisons, destroying living tissue of all kinds wherever they come in contact with it. On the other hand, drugs such as strychnine, which act on specialized parts of the vertebrate organism and have less effect on the less differentiated tissues, are equally harmless to the undifferentiated protoplasm of the microbes. It is of importance to note that the ordinary antiseptics do not act more strongly on microbes than on the tissues in which they are embedded or on the phagocytes with which the organism is combating the infection. The destruction of the septic organisms in a wounded surface entails the destruction of the surrounding cells also. Thus disinfection can only be carried out in a part in which the superficial cells are not of vital importance and may be restored by new growth. It is therefore impossible to disinfect the tissues of the body as a whole unless a drug has a specific affinity for the parasite.[1] A drug without such a specific action circulating in the blood in sufficient quantity to destroy the bacteria in the body would be equally detrimental to the organs in which they are embedded. Some progress has been made in the quest for such a drug possessing specific bactericidal properties, for Browning and his associates state that certain basic substances, notably *Flavine* or *Acriflavine* (diamino-methyl-acridinium chloride), act more strongly as disinfectants in serum than in water and kill bacteria in a concentration 400 times lower than that required to interfere seriously with phagocytosis. These findings in regard to the effects of the presence of protein upon the antiseptic strength of acriflavin, however, have not been confirmed by some of the other workers upon the subject (Wright and Hirschfelder). Similarly, Morgenroth has shown that some alkaloidal substances of the quinine series possess a selective action on the pneumococcus, which they are able to destroy in the mouse without injury to the host. This use of basic substances seems to be promising, for there is more probability of their being freed in the body fluids and thus penetrating more readily into the organisms than is possible for acidic substances.

A most important step forward was announced in 1935 in the paper of Domagk upon the chemotherapy of bacterial infections. In this paper Domagk reported that a relatively non-toxic dye, Prontosil (4-sulfonamido-2, 4-diamoazobenzene) was highly effective in hemolytic streptococcal infections in mice and in staphylococcal infections in rabbits. Previous to this time a few clinical papers had appeared following the original report by Foerster in 1933, but Domagk was the first to report the highly successful experimental findings in mice. Simultaneously there appeared three clinical reports testifying to the value of the drug. Confirmation of this work immediately followed, and since then numerous papers, both experimental and clinical, have

[1] A drug which has a specific affinity for a parasite as compared to the organs of the host is said to be parasitotropic, while the affinity for the organs in general is called its organotropic tendency.

appeared treating of the theoretical and practical aspects of the subject. Other compounds were studied and the most important among these were neoprontosil, sulfanilamide and sulfapyridine. It was known from the earliest work that these compounds exerted a specific action upon only certain types of bacteria, and investigations still continue in order to ascertain not only the conditions in which the drugs are valuable but also where they are ineffective. An interesting and important phase of the work has been the attempt to explain the mode of action of these compounds upon bacteria, and several theories have been advanced to elucidate their effects.

While there is perhaps no final answer to the question at the present time, it may be said that they do not appear to stimulate the production of antibodies or to have an action upon phagocytosis. It does seem clear, however, that they act not only *in vitro*, but also *in vivo* to inhibit the growth of bacteria, thus lessening their invasive power and permitting the defensive mechanism of the body to exert itself. Domagk believes the bacteria are not always killed by the drugs, but are so degraded that their elimination by the tissue phagocyte and white blood cells is made possible. However, even without a complete explanation of their mode of action and of their limitations in clinical medicine, the knowledge of them which has been thus far gained has shown that they mark a definite and very important step in the control of diseases due to bacteria (p. 737).

The antiseptics and disinfectants act upon most forms of living matter, and in many instances their effects are obviously due to their possessing powers of oxidizing or of coagulating proteins. In other instances their destructive action is not so open to explanation. And the amount of destruction induced varies with the degree to which the poison penetrates the tissues to which it is applied. For example, mercuric chloride diffuses deeply into tissues brought in contact with it and causes wide destruction, while the oxidizing disinfectants lose their efficacy on meeting proteins and thus affect only the most superficial cells. If microbes were confined to the surface, the latter would be sufficient for their destruction, but in order to disinfect a wound it is necessary to penetrate more deeply and thus efficient disinfection implies a certain amount of destruction of the tissues in which the microbes are harbored. This local destruction of cells and nervous structures induces pain and irritation and most efficient disinfectants are irritants. Their action as irritants arises from the same qualities as their disinfectant power, namely, from their general toxicity to living matter, and it is probably impossible to dissociate the one from the other and to produce non-irritant effective disinfectants.

When a surface has been poisoned by means of disinfectants, it heals less quickly, and this has led to the more sparing use of antiseptics and to the development of the aseptic method, in which organisms are excluded instead of being admitted and then destroyed.

In addition to their local effect, many of the antiseptic and disinfectant drugs have a further poisonous action when they are absorbed and circulate in the blood, and this has led to a further limitation of their

use. This general action does not necessarily arise from the qualities which render them antiseptic, and may be avoided by care in the choice of the drug and in its use.

The action of different drugs upon the microörganisms varies in nature in the same way as the action on other living cells. Some apparently penetrate into the interior by virtue of their solubility in lipids, and this penetration is facilitated by anything which decreases their solubility in the surrounding medium. Others accumulate on the surface of the organisms by adsorption, so that the microbe is surrounded by a dense layer of disinfectant. Yet others appear to enter into true chemical combination with the constituents of the parasites. Some of the antiseptics (*e. g.*, carbolic acid) enter the cell by simple diffusion and do not accumulate in its interior in greater concentration than in the solution surrounding it. Others (*e. g.*, corrosive sublimate) tend to accumulate in the cell and on its surface by adsorption, and thus are withdrawn from the solution if a sufficient number of microbes is present.

The efficiency of any disinfectant naturally depends on the concentration in which it comes in contact with the microbes and the time during which it remains in contact with them. Thus a solution of mercuric chloride of the strength of 1 in 3000 is much more efficient than one of 1 in 10,000, and after exposure to a solution for five minutes far fewer microbes escape than after exposure for two minutes. Another factor is the temperature at which the microbes are exposed to the disinfectant, for it is found that when the latter is kept at about 30° C. far fewer bacteria escape than when ordinary room temperature prevails. Different species of microbes vary in their resistance, and different cultures of the same microbe and even different individuals of the same culture exhibit marked variations in susceptibility. The effect also often varies inversely with the number of microbes present, because each of these withdraws a certain amount of the disinfectant and thus reduces the general concentration of the solution. And other proteins have the same influence as the microbes themselves, for they offer the disinfectants the same surface for adsorption or combine with some of them in the same way as the proteins of the microbes. Thus a concentration which is sufficient to sterilize water infected with bacteria, may have little or no effect if applied to a suppurating wound, because the greater part of the disinfectant is taken up or otherwise rendered inactive by the proteins of the secretion, leaving only a low concentration to act on the microörganisms. Thus Bechhold has shown that many substances which are powerful disinfectants in ordinary fluids lose their activity in protein solutions (commonly called the "protective action of colloids"), owing to their forming combinations with the proteins, so that though they are not dangerous to the host, they are comparatively innocuous to the microbes in the tissues. The inhibiting action of the proteins may also be due partly to their limiting the diffusion of the disinfectant. In fact the antiseptics and disinfectants act on proteins and not specifically on microbes. Wright and Hirschfelder, however, have pointed out that the reduction of antiseptic efficiency due to the presence of protein, in the triphenylmethane series at least,

does not run parallel to the amount of dye adsorbed on the protein as the antiseptic efficiency of these dyes under these conditions is greater than the degree of efficiency representing the free concentration of dye. This would indicate that the adsorbed dye also exerts an antiseptic action as well as the free dye. They showed that, in a 1 to 10,000 solution of crystal violet in the presence of 1 per cent egg albumin, the adsorbed dye exerted 3.5 times the antiseptic activity of the free dye. Also if the solution should be made still more dilute a point is reached where most of the antiseptic action would be exerted by the bound dye. When the proteins are present in small amount, as in an emulsion of bacteria in water, these disinfectants are active enough, but when the bacteria are distributed among the proteins in an infected wound, the amount of the disinfectant that falls to the share of the bacterial proteins is too small to be effective. For example, a disinfectant which prevented the growth of diphtheria germs in broth when added in the proportion of 1 in 500,000, had no action on the germs in the tissues when it was present in the proportion of 1 in 5000, because it combined with the tissue proteins in preference to those of the bacilli. Recently it has been shown that lipids, like proteins, lower the potency of antiseptics.

This again indicates the limitation of disinfectant therapeutics, which cannot be overcome as long as the drugs have no elective affinity for the invading organisms but act equally strongly on the tissues of the higher animals.

If a poison is to penetrate into the interior of an organism in quantity, it must be as soluble in the protoplasm as in the fluid in which it is applied, for it is obvious that it will not leave a medium in which it is readily soluble for one in which it is dissolved with difficulty. Accordingly, it is found that fats and oils in which the members of the aromatic series are very soluble are not suitable as media for their application, for the poisons remain in the oily menstruum and fail to penetrate the microbes in which they are less soluble. Mercuric chloride dissolved in alcohol has little germicidal power but this is due to the fact that mercuric chloride, and indeed salts of the other heavy metals as well, are not dissociated in alcohol (95 per cent) and it is necessary in order that the salt be active that it should be so dissociated. On the other hand, if the mercuric chloride (or silver nitrate) is dissolved in dilute alcohol (25 per cent) its action is strengthened, probably due to the penetration of the salt being favored. The addition of inorganic salts to an aqueous solution of carbolic acid often increases its antiseptic power, because the poison becomes less soluble in the water and shows a greater tendency to escape from it into the interior of the microbes.

There is reason to believe that solutions containing several disinfectants are more strongly antiseptic than those containing an equal percentage of the individual pure bodies; for example, a mixture of carbolic acid and mercuric chloride, is more efficient than a much stronger solution of either alone. This appears to be due to a change in the solubility of the disinfectant, at any rate in some cases. Churchman

showed that a combination of gentian violet and acriflavine ("acri-violet") is more germicidal than either alone.

Disinfectants and antiseptics are used for a large variety of purposes and it may be well to consider the principles which underlie their uses before discussing the special features of each drug.

1. **In Surgery,** Lister advised that not only infected wounds should be treated with disinfectants but that infection of any wound should be guarded against by the application of antiseptics which would retard the growth of microbes. It is now recognized, however, that a clean wound requires no antiseptics and heals more quickly if they are avoided. Disinfection in surgery is now applied only to tissues already the seat of infection, and to objects which may come in contact with a clean wound. Among the latter, those which offer the greatest difficulty are the skin of the patient and of the operator, and a large number of drugs have been employed to disinfect these and render them harmless. Among the disinfectants more commonly used to disinfect the skin or to destroy the organisms in a wound already infected are the carbolic acid group; 70 per cent ethyl alcohol or a mixture of ethyl alcohol 50 per cent by weight, normal propyl alcohol 20 per cent by weight and water 30 per cent by weight (Price); mercuric chloride; the oxidizing disinfectant group; iodine and picric acid, of which iodine has perhaps recently been the most popular. Propyl alcohol (50 per cent) has been used to some extent and it has the advantage of dissolving some of the fatty substances on the skin. For use in disinfecting the skin in certain locations which are especially difficult to render sterile, such as the perianal region, Bonney and Browning have found that a mixture of crystal violet and brilliant green (violet-green) in a 1 per cent solution is especially effective. The disinfectant must be applied in solution or suspension in water, and should induce as little irritation as is compatible with its fulfilling its purpose. This is of special importance in dealing with the delicate, sensitive mucous membranes such as the eye, which cannot be subjected to such treatment as would be necessary in other parts of the body. A danger which is smaller now than formerly is from the absorption of the disinfectant giving rise to general poisoning. This arose as a general rule not from the drug applied during the operation, but from its too lavish use in the subsequent dressings. But cases of poisoning are still met from the use of powerful disinfectants to wash out large abscesses, the uterus, or other organs.

Instruments, ligatures, etc., are generally disinfected by heat, but are often kept in dilute solutions of carbolic acid or other disinfectants until required.

The relative disinfecting power of the drugs used in surgery has been investigated repeatedly but no satisfactory ratio can be given as yet, because it is impossible to imitate the conditions in a septic wound closely enough in experimental determinations. And estimations of the relative power in destroying organisms in water or in broth cultures depend upon a variety of conditions, such as the number of organisms and the completeness with which the disinfectant is removed before test growths are made. It is generally held that among the disinfec-

tants used in surgery mercuric chloride is superior to the carbolic acid group, and that both of these penetrate more efficiently than do the oxidizing disinfectants. For disinfection of the skin 70 per cent ethyl alcohol or the mixture of ethyl and propyl alcohol is quite efficient, especially if the skin is rubbed with gauze at the same time that the alcohol is being used. The solutions containing iodine, such as the mild tincture of iodine U. S. P., hold high rank as surgical disinfectants of the skin although their use is limited by their staining properties. In the case of mucous membranes the silver compounds are extensively used.

2. **In the Treatment of Skin Diseases,** a number of disinfectants have been employed, and where the area of infection is small it may be permissible to use the more powerful ones if necessary. But in widespread disease the dangers of local irritation and of absorption preclude all except the least noxious, and it remains a question how far these act in retarding the growth of an infecting organism, and how far their effects may be due to their causing slight irritation and improved nutrition. Some dermatologists hold the view that these mild skin remedies owe much of their value to their reducing properties. Among the remedies used are chrysarobin, pyrogallol, resorcinol, salts of mercury and the tar series.

3. **To Disinfect the Intestine.**—Septic processes may occur either in the contents of the intestine or in its walls, the former affecting the general organism only by the production of poisonous or irritant substances which may be absorbed, while in the latter the tissues of the wall themselves become the seat of active disease. It is possible that an admixture of a disinfectant with the contents of the bowel may retard their putrefaction, and this method of treatment has been largely employed. When the evidence of its efficacy is examined, the results prove to be disappointing; the amount of double sulfates or of indol in the urine is said to be diminished, and the number of microbes in the fæces to be reduced under the use of these intestinal antiseptics, but this is no longer regarded as unequivocal evidence that the disintegration of the food by microbes is retarded; and in addition these changes in the urine and the fæces have not been confirmed by many observers. There is some rather unconvincing clinical evidence of improvement under this treatment, but it is now recognized to be more in accord with general aseptic procedure to remove the putrefying contents by means of a purgative, than to attempt to render them sterile in the bowel by means of disinfectants.

When the bowel wall itself is the seat of bacterial infection the use of antiseptics and disinfectants is still less supported by the results. It seems very unlikely that a drug powerful enough to destroy the microbes harbored in the mucous membrane will leave the latter uninjured. In typhoid fever, in which this treatment has been carefully followed, the number of typhoid bacilli in the stools has not diminished to any noticeable extent, and the use of these drugs does not relieve the symptoms nor shorten the duration of the disease.

Any drug used for the disinfection of the intestine must not be irritant, nor very poisonous. It must not be too soluble, since other-

wise it may be absorbed from the upper part of the bowel, and on the other hand it must be soluble to some extent, or it cannot mix very intimately with the contents of the intestine. Carbolic acid is scarcely fitted for this purpose, for it irritates the stomach and is also rapidly absorbed. Some of the cresols have been recommended of late years, and the naphthol preparations have also enjoyed some reputation. Salol and its congeners have the advantage of being almost completely insoluble and harmless in the stomach and of being dissolved and rendered active by the intestinal juices. The purgatives are the most efficacious treatment and, among these, the mercurials and castor oil are largely used.

4. **To Destroy Pathogenic Germs in the Tissues After Absorption.**—It is now recognized to be hopeless to attempt to find a single body which will destroy all forms of bacteria in the tissues, while leaving the host uninjured, but evidence is accumulating to justify the hope that clinical substances may be found which possess properties which will exert a specific action upon certain bacteria in the same manner as some of the diseases due to protozoa are controlled. (See page 21.) Such a specific action is seen in the effects of quinine on the organism of malaria, of mercury, arsenic, bismuth and antimony in various protozoal infections, and of emetine, chiniofon and vioform in amœbic dysentery, all of these apparently acting more strongly on the cause of the disease than on the tissues of the patient. However, in malaria, syphilis, dysentery, and trypanosomiasis, in which specifics have been obtained, the disease is due to invasion by protozoa, while many of the infections of which the cause is known, arise from bacteria, and these appear to be much less susceptible to the action of chemical agents. Nevertheless in spite of the difficulties a great advance has been made in the introduction of the sulfanilamide group of drugs which has proved so effective in the treatment of certain diseases of bacterial origin. This group is discussed earlier in the section (p. 770) and under the general article on Sulfanilamide (p. 737).

5. **In the Treatment of Septic Genito-urinary Diseases.**—The treatment of general infections in the tissues with non-specific disinfectants is hopeless for the reasons given above. On the other hand, good results are obtained in infection of the genito-urinary tract through which many of the antiseptics are eliminated from the body. In the course of their elimination they are concentrated; thus a quantity of disinfectant which is inactive when distributed through the protein-rich tissues of the body, may very well be efficacious when it is dissolved in the comparatively small quantity of the urine, and especially since here it finds no protein to combine with except that of the tract through which it passes. On the other hand, in their passage through the body the antiseptics are generally formed into combinations which are less irritant and also less poisonous to the microörganisms. There is, however, no question that the continual washing of the genito-urinary tract with the antiseptics in the course of their excretion reduces the number of the organisms in the urine and relieves septic conditions. The drugs used for this purpose must not be too irritant to the mucous

membranes of the alimentary tract, and must be easily absorbed and not dangerously poisonous. Many of the aromatic series, such as salicylates, have been employed, and some of the volatile oils, such as the oil of sandalwood. An important advance was made in hexamethylenetetramine (methenamine), which is harmless and inactive itself but frees formaldehyde in acid urine, and more recently hexylresorcinol has been introduced.

In addition to the administration of drugs for the purpose of disinfecting the urine and the urinary tract, an effort was made a few years ago to render the urine sterile by means of its acidification produced by the giving of a ketogenic diet. The results were very encouraging, but this method of rendering the urine more acid is roundabout and clumsy and has been superseded by the use of mandelic acid—a hydroxy acid, relatively non-toxic, excreted unchanged in the urine which it renders bacteriostatic. At present mandelic acid and its salts are still under trial—some finding them highly efficient while others report disappointing results (p. 815).

In addition to the oral method of treatment, antiseptics and disinfectants may be applied by injection into the urethra and bladder by the ordinary surgical procedure. For this purpose the silver compounds are extensively employed either as silver nitrate or as the newer organic silver preparations. In addition to silver some other disinfectants are used in cases of infection of the bladder or urethra: among these may be mentioned boric acid, potassium permanganate, chloramine and acriflavine.

6. **In the Treatment of Pulmonary Infections.**—Traces of some of the more volatile antiseptics are eliminated in the breath, and this has suggested their internal use to destroy microbes in the lungs, especially the tubercle bacillus. It may be stated, however, that careful observers are united in the belief that this form of medication is entirely useless. The case of the lungs differs entirely from that of the kidney, for in the former there is no concentration of the disinfectant in the organ, but it is excreted in even greater dilution than that in which it circulates in the general tissues; the surface of lungs has been estimated at about 70 square meters, and it is impossible to conceive that small quantities of antiseptic spread over this surface can affect bacteria harbored on it. Again, chloroform is a fairly efficient disinfectant which is absorbed and excreted by the pulmonary endothelium, yet no improvement occurs in lung disease from the inhalation of chloroform during an operation; on the contrary, the endothelium is more likely to suffer from the remedy than the microbes. Antiseptic remedies have also been inhaled in vapor or spray, and have been injected into the trachea or even into the lung directly, but as far as the tubercle bacillus is concerned, they have had no result in the hands of most careful observers. In fact this bacillus appears to be peculiarly refractory to most chemical disinfectants which can be administered by the mouth. In cases of gangrene of the lung, fœtid bronchitis, etc., the inhalations relieve the patient to some extent and certainly lessen the offensive odor.

Here again, however, an important advance has been made in the

treatment of certain pulmonary diseases, notably certain types of pneumonia by the use of the newer members of the sulfanilamide group of drugs as described elsewhere (p. 744).

7. **In Infections of Other Secretions and Organs,** the use of antiseptics has not proved successful. In the bile, thymol and methenamine (hexamine) have been found after administration by the mouth, and the latter has been shown to occur in the cerebrospinal fluid and in many other excretions, but it is to be noted that methenamine (hexamine) is in itself inactive and is disinfectant only through its liberation of formaldehyde, which does not take place except in the urine.

8. **To Disinfect Rooms, Furniture, Clothing, Excrementa,** the strongest and cheapest drugs which are available are employed. It is quite futile to attempt to carry out such disinfection unless with concentrations which would be immediately fatal to all higher organisms. For rooms and furniture, formaldehyde or sulphur dioxide are best adapted as they are volatile and penetrate fairly well, but the latter bleaches all dyed material. Clothes are best disinfected by washing or by steam or dry heat, or formaldehyde solution may be employed. Excrement may be disinfected by chlorine or lime; crude carbolic acid and tar are less certain, and the oxidizing disinfectants are expensive when used in quantity.

9. **To Disinfect Drinking-water.**—Water may be freed from infectious organisms by heat or filtration, but when these are not available, chemical disinfection may be necessary, as for example in military expeditions. The disinfectant must not be present in such quantities as to render the water poisonous, or even disagreeable to the taste. Fortunately, the organisms are not protected by the presence of colloids and are therefore destroyed by very small quantities of disinfectants. The most convenient is chlorine which may be used in the form of the hypochlorite or as Halazone (p-sulphonedichloramidobenzoic acid). Hydrogen peroxide has also been employed.

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Many antiseptics and disinfectants are used for a variety of purposes and might be classed under several of these headings. The following arrangement is therefore an arbitrary one, and merely points to the use for which the drug has been considered most adapted.

I. SURGICAL ANTISEPTICS AND DISINFECTANTS.

1. Carbolic Acid.

Carbolic acid, or phenol, the first of the modern antiseptics to be introduced, acts like the rest of the simpler benzol compounds as a **General Protoplasm Poison,** although in the vertebrates it affects the central nervous system more powerfully than the other tissues.

Its poisonous effects are well seen when it is applied to unicellular organisms, such as the *protozoa*. Even dilute solutions cause immediate arrest of all movements; the organism assumes a spherical shape and loses its transparency, and, unless the solution be very attenuated, dies in the course of a few minutes. *Plant cells* are acted on in the same way, and the individual cells of more highly organized animals, such as the *ciliated epithelium* of the air passages and the *spermatozoa*, are killed at once when brought in contact with carbolic acid. There is some evidence, however, that very dilute solutions of carbolic acid, as of other antiseptics, tend to increase the activity of protoplasm, for while solutions of phenol, such as are used as surgical antiseptics, are immediately fatal to the yeast plant, very dilute solutions increase its activity. The effect of carbolic acid on protoplasm has, however, been studied chiefly in the *bacteria*. Its antiseptic power, while always considerable, is found to vary greatly with the species of microbe. Thus, while it is fairly poisonous to the ordinary pyogenic organisms, it has to be present in very concentrated form to destroy the more resistant spores of anthrax, and like other antiseptics, is much less poisonous to the microbes than to the protozoa and other simple forms of life. The development and reproduction of many microörganisms have been found to be much delayed, or altogether prevented, as long as they remained in a solution of 1 part of carbolic acid in 400 to 600 parts of water, but in order to kill them very much more concentrated solutions (5 per cent) were required, and Koch found that the spores of the anthrax bacilli were destroyed by 5 per cent carbolic solution only after they had remained in it for two days.

It seems to vary considerably in its action on the *unorganized ferments;* thus it is said not to retard appreciably the fermentations produced by emulsin, diastase and myrosin, even when present in the solution up to 5 per cent, while pepsin, ptyalin, and the rennet ferment are weakened by somewhat smaller quantities.

Carbolic acid precipitates **Proteins** in solution and also in the cells. It does not seem to enter into any firm combination with them, for it can be washed out of the precipitate with comparative ease. It results from this that carbolic acid penetrates more thoroughly than the metallic antiseptics, which are rendered insoluble by the protein

they meet, and whose action therefore tends to remain confined to the surface.

This coagulation of the proteins occurs whenever carbolic acid is brought in contact with the tissues. On the **Skin** a white, opaque lesion is formed by concentrated phenol, which becomes red and shining afterward and then falls off in a few days, leaving a light brown stain which may remain for several weeks. Even a 5 per cent solution applied to the fingers produces tingling and warmth, which is often followed by opacity and shrinking of the epidermis and a sense of numbness. This numbness may amount to almost complete anæsthesia if more concentrated solutions are applied, no pain being felt even when the skin is cut through. When applied for some time and prevented from evaporating, carbolic acid may cause extensive dry gangrene of the part, from its penetrating through the surface layer and reaching the deeper tissues. Applied to a **Wound** in 5 per cent solution, phenol induces pain and irritation followed by local anæsthesia, and a white pellicle of coagulated proteins is formed. It causes irritation and necrosis of the **Mucous Membranes**, and if applied in sufficient quantity may lead to sloughing and acute inflammation. This local effect may prove fatal from shock and collapse when large quantities of the undiluted acid are swallowed, the effects resembling exactly those produced by other corrosive substances. Carbolic acid is rapidly absorbed from the stomach and bowel, but after some time the absorption is much slowed owing to local changes in the vessels of the intestine.

General Action.—In *man* delirium and excitement have been observed in some cases, but convulsions are comparatively rarely seen. When large quantities are taken, immediate unconsciousness may result and death follow within a few minutes. How far this is due to the local corrosion, and how far the direct action on the central nervous system is involved, cannot be determined. In more gradual poisoning, depression and weakness, headache, nausea and vomiting are followed by giddiness, noises in the ears, pallor and collapse, with irregular pulse and respiration, and cold perspiration; fainting and unconsciousness then lead to failure of the respiration and death. Fatal poisoning may arise from swallowing a concentrated or a dilute solution, or from absorption from wounds and abscesses. It has also occurred in man from absorption through the unbroken skin.

The autopsy sometimes gives no special indications of the cause of death, save the local corrosion of the alimentary canal. Inflammation and necrosis of the intestine is said to have been observed in some cases in which the poison was absorbed from skin wounds, and fatty degeneration is sometimes induced in the liver and the renal epithelium, but is not constant.

In the *frog* carbolic acid first causes depression and loss of the spontaneous movements, and later fibrillary twitching in the muscles, augmented reflex excitability and finally tonic convulsions. These may last for some time and then complete paralysis of the central nervous system supervenes, while the heart and the peripheral nerves and muscles remain active. A dilute solution of carbolic acid applied

directly to the exposed spinal cord paralyzes the sensory elements immediately, while leaving unaffected the motor fibres and the cells of the anterior horn (Baglioni).

In *mammals* very similar symptoms are produced, save that there is often no noticeable preliminary stage of depression. Some weakness and lethargy may be present, however, and is followed by marked muscular tremor, which resembles the shivering produced by cold. At intervals this is interrupted by sudden twitches in different muscles, and later by clonic convulsions. The respiration and the pulse are at first accelerated, but afterward are slow, irregular, and weak. The movements become feeble and appear at longer intervals, the respiration is shallow and irregular, and the animal passes into a condition of collapse, in which, however, the sensibility to pain is often preserved. Eventually death occurs from asphyxia. After very large doses the collapse may be immediate, no convulsions being observed, the heart and respiration often ceasing simultaneously. In most cases salivation is a marked symptom, and the temperature often falls far below the normal.

Central Nervous System. The convulsions in the frog arise from increased irritability of the spinal cord, especially of the anterior horn cells, for they are not arrested by section of the medulla oblongata. In mammals the sudden contractions of isolated muscles appear due to a similar action on the spinal cord, but the clonic convulsions and the persistent tremors are probably of cerebral origin, and Berkholz found the cerebral cortex abnormally irritable after carbolic acid. The rarity of convulsions in man has not been satisfactorily explained. In some cases the course of the intoxication is too short, the large amount of poison swallowed inducing immediate collapse, while in others their absence may be due to the debility of the patient from disease; but in a considerable number of cases of poisoning in which neither of these conditions was present, no convulsions were observed. The primary stimulation of the central nervous system in animals is followed by depression and paralysis if large doses are administered.

The acceleration of the **Respiration** and of the **Heart** seen in mammals has been supposed to be an indirect result of the increased muscular movement and convulsions, but this seems to be incorrect, for the heart is found to be accelerated before the convulsive movements and tremor appear, and the frog's heart is accelerated in cases where no movements whatever occur. It would seem probable that the acceleration of the heart is due to direct action on the muscle or on the regulating nerves. The subsequent slowing is undoubtedly due to muscular action.

The acceleration of the respiration precedes the increased movement, and would therefore seem to be due to action on the medullary centre, which is first stimulated and later paralyzed. The vasomotor centre is depressed by the injection of carbolic acid into the blood, and this, together with the weakness and slowness of the heart, causes a fall in the blood-pressure and collapse.

The peripheral **Nerves and Muscles** do not seem to be affected in

general poisoning in mammals, although in the frog their irritability and the capacity for work of the muscle may be somewhat reduced.

On the direct application of solutions of carbolic acid to the nerves or muscles, these are killed at once, like other forms of living matter; even dilute solutions paralyze the nerve fibrils and terminals and thus induce local anæsthesia.

The increased **Secretion** of saliva, perspiration and tears which is seen in poisoning in mammals is probably of central origin, and may possibly be associated with the nausea and vomiting.

The fall in **Temperature** in carbolic acid poisoning seems, for the main part, to be due to the collapse, although it is impossible to state how far this may be aided by some alteration of the regulating function, such as is seen in the closely related group of the antipyretics.

Carbolic acid added to the defibrinated **Blood** leads to the slow formation of methæmoglobin, but this does not occur in the living animal. Occasionally some destruction of the red blood cells is caused in animals through the injection of carbolic acid directly into the blood-vessels, and in one case of poisoning in man hæmoglobin was detected in the urine, indicating that some of the red cells of the blood had been destroyed.

Excretion.—Some of the carbolic acid absorbed is oxidized to hydroquinone and pyrocatechin, and these and also the unaltered carbolic acid are excreted in the urine in combination with sulfuric and glycuronic acids. The hydroquinone and pyrocatechin tend to become further oxidized to colored substances and the urine therefore assumes a dark, dusky-green color which may change to brown or even black. This change may occur in the body, and the urine is very often passed of a greenish-brown color, but further oxidation takes place on exposure to the air, resulting in deeper coloration which commences at the surface of the fluid and gradually extends downward. The depth of the shade depends not on the amount of phenol sulfate in the urine, but on that of the dioxybenzols, and a darker urine is often observed, therefore, when the absorption has occurred from an open wound (in which the conditions are especially favorable to oxidation) than from much larger quantities absorbed from the alimentary canal.

The presence of glycuronates in the urine may lead to its reducing Fehling's solution, and thus give rise to the suspicion of glycosuria. On the other hand, the passage of these bodies through the kidney often causes some irritation and albuminuria. The double sulfates of the urine are, of course, much increased, and the inorganic sulfates are correspondingly diminished.

The **Chlorphenols,** in which chlorine is substituted for one or more of the hydrogen atoms of carbolic acid, are much more poisonous to microörganisms than the original substance, while their toxicity in mammals is not increased in the same ratio. A similar intensifying effect is seen in the chlorine substitution products of the narcotic series, *e. g.*, chloroform. The most poisonous of the monochlorphenols is parachlorphenol. *Bromol* or tribromphenol has been used to a limited extent in therapeutics as a disinfectant and caustic.

Therapeutic Uses.—Carbolic acid is used as an antiseptic in surgical operations in 2–5 per cent solution in water. It now plays a much less important rôle in surgery than it did in the first days of antisepsis; in fact in many clinics it is now employed only to protect the instruments from infection. Its irritant action and the danger of absorption have also rendered it unpopular as a dressing or lotion after operations or injuries, where there is any large absorbent surface, or where irritation is liable to be injurious, as in most forms of skin disease.

It is still used as a disinfectant in septic wounds, though greater reliance is now placed on corrosive sublimate. Strong carbolic acid has been applied to disinfect wounds, its poisonous effects being avoided by immediately washing it off with alcohol.

Harrington drew attention to the danger of applying dilute solutions in bandages to injured fingers and hands; he found records of over 100 cases in which this had led to gangrene, necessitating amputation.

Carbolic acid has a limited use as a caustic in the form of the liquefied preparation, and is less painful than most other caustics. It has also been employed in itching skin diseases.

PREPARATIONS.

U. S. P

PHENOL.
PHENOL LIQUEFACTUM contains 88 per cent of phenol. 0.06 cc. (1 min.).
GLYCERITUM PHENOLIS, 20 per cent phenol. 0.3 cc. (5 mins.).
UNGUENTUM PHENOLIS, 2 per cent phenol.

B. P.

PHENOL.
GLYCERINUM PHENOLIS, 16 per cent phenol. 0.3–1 cc. (5–15 mins.).
PHENOL LIQUEFACTUM, 80 per cent phenol. 0.06–0.2 cc. (1–3 mins.).
TROCHISCUS PHENOLIS. Each lozenge contains $\frac{1}{2}$ gr. of phenol.
SUPPOSITORIUM PHENOLIS. Each suppository contains 1 gr. of phenol.
UNGUENTUM PHENOLIS, 3 per cent phenol.

PHENOL, or carbolic acid (C_6H_5OH), forms colorless, deliquescent crystals when recently prepared, but often assumes a reddish tinge from oxidation. It has a characteristic odor and is intensely corrosive. It is soluble in about 15 parts of water, but becomes liquid when 10 parts of water are added to 90 of the crystals, forming PHENOL LIQUEFACTUM of the U. S. P. This must be carefully distinguished from the ordinary solution of carbolic acid, which contains only 2 to 5 per cent of phenol, while the liquefied carbolic acid contains from 80 to 90 per cent.

Carbolic acid is generally used in 2–5 per cent solution. A crude, impure form may be employed to disinfect stools, latrines, etc. The glycerite may be used as a very weak caustic. Solutions of carbolic acid in oil have little or no antiseptic action, because they fail to penetrate into the microbes.

Poisoning.—In carbolic acid poisoning, when it has been taken by the mouth, the first treatment is the removal of the poison by the stomach tube and the thorough lavage of the stomach with water to which 10 per cent of alcohol may be added; the alcohol dissolves the poison more readily than water and thus facilitates its removal, but has no other antidotal action, and should be removed from the stomach

as completely as possible; when absorption has occurred from the skin or from a wound the dressing should be removed at once. The combination of phenol with sulfuric acid in the tissues forms a comparatively harmless body, and Baumann and Preusse therefore suggested the administration of sodium sulfate in large quantities. It is found, however, that this is of little or no use, because the phenol does not combine with sulfates as such in the body, but with organic sulfur compounds which are only in process of being oxidized to sulfuric acid. When coma and collapse set in, the patient is to be sustained by the application of warmth externally, and by the administration of such central nervous stimulants as caffeine or strychnine; artificial respiration may eventually be used, although there is little prospect of resuscitation if the intoxication has advanced so far. The corrosion induced by carbolic acid locally may be treated by washing the part with alcohol, which dissolves the acid readily.

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2. Cresols.

Of late years the cresols or cresylic acids ($C_6H_4 \cdot CH_3 \cdot OH$) have been substituted for carbolic acid to a considerable extent in surgery. There are three isomeric cresols which all resemble carbolic acid closely in action, and which present only minor points of difference from each other. Metacresol is said to be less poisonous and less irritant than carbolic acid, while it is credited with a more powerful antiseptic action; orthocresol, on the other hand, is said to be more dangerous than carbolic acid, and paracresol to be the most poisonous of all. But the differences in toxicity between the cresols are too small to be of practical importance, and their germicidal action is approximately equal when they are used in suspension with soaps, as is usually the case.

Many cases of suicidal poisoning with cresol preparations have occurred and have presented symptoms similar to those of carbolic acid poisoning—collapse and exhaustion followed by coma and death;

in some cases marked alterations have been found in the liver along with nephritis and hæmolysis. Much of the cresol absorbed undergoes complete oxidation in the tissues, but about one-third of that ingested is excreted in the urine in combination with sulfuric and glycuronic acids.

The cresols are constituents of tars and other crude disinfectants. In pure form they are only slightly soluble in water, and it has been found necessary to form them into emulsions or suspensions for surgical use. A large number of these cresol preparations are available and differ chiefly in the way in which they are suspended in water (*creolin*, *solveol*, *solutol*, *lysol*). These preparations are not devoid of poisonous properties, as is often stated; on the contrary they are little if at all less dangerous than carbolic acid. Their germicidal action has been overrated by some authorities and has been denied by others. On the whole they appear to be more powerfully antiseptic than carbolic acid when they are used in emulsion form; their insolubility in water facilitates their passage into the bacteria, in which they are more soluble; and the emulsion form has a further advantage as the fluid coming in contact with the bacteria must always be saturated with the antiseptic. In spite of these facts recent work has indicated that the disinfectant effect on the skin is not as powerful as would be expected from the results as obtained in the test-tube. Cresol has been given as an intestinal disinfectant, but has not proved more useful than the other drugs used with this object.

The chlorcresols are said to be more strongly germicidal than the cresols themselves, while their toxicity is not increased in the same degree or may even be reduced; a suspension of chlorcresols has been introduced as an antiseptic, but has not yet been widely used.

Triorthocresyl Phosphate.

In 1930 a peculiar form of flaccid paralysis (ginger paralysis) appeared in various parts of the United States. After a careful study this was shown to be due to the presence in certain lots of fluid extract of ginger of triorthocresyl phosphate. The paralysis in most cases affected adult males who gave a history of having partaken of the beverage some five to ten days before the muscular symptoms developed. The immediate effects after taking the fluid extract were merely those of alcoholic intoxication accompanied at times by evidences of gastro-intestinal irritation. About ten days later soreness of the leg muscles was noticed and some numbness of the fingers and toes. Paralysis of the toes followed, succeeded shortly by bilateral foot-drop. Weakness of the fingers and wrist-drop occurred later, but the symptoms on part of the upper extremities were never so marked as they were of the lower. The paralysis affected the victims with all degrees of severity from slight disability to practically complete helplessness, the patient being confined to bed and even unable to feed himself. There were few or no sensory disturbances.

Laboratory studies have shown that a similar set of symptoms can be produced in certain species by the administration of the triorthocresyl phosphate. The symptoms are especially characteristic in chickens in which flaccid paralysis of the legs is often followed by some weakness in the wings. In the cat and dog paralysis is marked in the hind legs while the fore legs may not be so much affected. Similar paralytic manifestations have been produced in calves and in monkeys. Chemical examination of the adulterated fluid extract were in harmony with the pharmacological findings in showing that the offending compound was present to the extent of about 2 per cent. It appears that the neurotoxic

property of the compound does not reside in the cresol portion of the molecule but in the entire cresyl phosphate aggregate. Triorthocresyl phosphite and triphenyl phosphate resemble the triorthocresyl phosphate closely in that they are also neurotoxic, possessing a delayed action. However, in the case of the triphenyl phosphate the process is more diffuse and the paralysis, therefore, more generalized. In the case of triorthocresyl phosphite certain paths in the spinal cord are affected in addition to the peripheral motor nerves. In general the phenyl ester seems to affect more particularly the motor nerve cells while the cresyl compounds exert their action upon the myelin substance of the conducting fibres—peripherally in the case of orthocresyl phosphate and centrally as well as peripherally in the case of the phosphite, which produces degeneration of certain tracts in the spinal cord. The phosphoric ester is more restricted in its effects while the phosphorous compound is more diffuse and generalized.

PREPARATIONS.

CRESOL (U. S. P., B. P.), a mixture of the three cresols, forms a colorless or straw-colored fluid with a phenol odor. Soluble in 60 parts of water. Dose, U. S. P., 0.05 cc. (1 min.); B. P., 1–3 mins. (0.06–0.2 mils.).

LIQUOR CRESOLIS SAPONATUS (U. S. P.) (B. P.). Cresol 50 per cent suspended in water by means of soap, is used diluted to about 2 per cent as a surgical disinfectant.

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3. Other Aromatic Surgical Disinfectants.

Many other members of the benzene or aromatic series have enjoyed a more or less transient reputation as surgical disinfectants and antiseptics. Thus *Thymol* ($C_6H_3CH_3C_3H_7OH$), obtained from oil of thyme, was used to a limited extent as an antiseptic lotion in $\frac{1}{10}$ per cent solution and also as a mouth wash and gargle, but in this strength it is only feebly active and it is too insoluble in water to form a really effective germicide. It is used as an anthelmintic chiefly (p. 759).

Salicylic acid ($C_6H_4OHCOOH$) and *sodium salicylate* ($C_6H_4OHCOONa$) were at one time used as antiseptic washes in surgery, and indeed promised to supplant carbolic acid for this purpose as they are less irritant and less poisonous. The acid is destructive to the pyogenic microorganisms suspended in water but has much less effect than carbolic acid when proteins are present, and its use has been abandoned in practice by most surgeons. The salicylates are used almost exclusively for their specific action in acute rheumatism.

Picric acid or trinitrophenol, $C_6H_2(NO_2)_3OH$ (U. S. P.), is used as an application to wounds or burns in the form of a saturated watery solution (1 per cent) on lint. It has approximately the same disinfectant action as carbolic acid, but enters into a more stable combination with proteins and is thus slightly astringent. Larger quantities are irritant

and in some cases have given rise to gastro-enteritis and nephritis; the skin and mucous membranes are stained yellow even when the picric acid is carried to them in the blood, and this coloration has sometimes been confused with jaundice. Violent convulsions occur sometimes, in other cases, collapse. The urine is yellow or red and contains casts, but little albumin and no bile, the absence of the latter serving to distinguish the condition from jaundice; picric acid tends to destroy the red blood cells in animals but no marked fall in these has been observed in man. It is excreted as picramic acid ($C_6H_2OHNH_2(NO_2)_2$) in the urine.

The *sulphocarbolates* (or *phenolparasulphonates*) of sodium and zinc are less poisonous than carbolic acid, as the sulphon group lessens the toxicity in the same way as the carboxyl one, but they are at the same time very much weaker in germicidal power. They have been used as external antiseptics, and the sulphocarbolate of sodium has been administered to arrest fermentation in the stomach with little success. *Aseptol* or *sozolic acid* is a 33 per cent solution of phenol-ortho-sulphonic acid in water, but very often contains some of the para-acid. Of the three phenol-sulphonic acids, the ortho- is the most strongly antiseptic and the para- the least useful.

Sodii Phenolsulphonas, or sodium phenol-para-sulphonate ($C_6H_4OHSO_2ONa,-2H_2O$), forms colorless, transparent prisms, without odor, and with a saline taste. Soluble in 5 parts of water. 0.25 G. (4 grs.).

The *oxynaphthoic acids* ($C_{10}H_6OHCOOH$) possess antiseptic properties, which are said to be somewhat greater than those of carbolic and salicylic acids, but they are less soluble in water, while the sodium salt is less antiseptic. The acids are irritant and produce diarrhœa and symptoms similar to those of salicylic acid. They seem to be at least as poisonous as carbolic acid, and have been used as external antiseptics only to a very limited extent.

Turpentine oil and many of the other volatile oils enjoy a reputation as antiseptics and disinfectants, and have been applied to disinfect the skin before operations and for similar purposes.

Chloroform may also be mentioned as a disinfectant in use in the laboratory though it has never been adopted in surgical operations.

Alcohol is a disinfectant when used in 70 per cent dilution by weight or 78 per cent by volume, and has been used to clean and disinfect the skin and hands before operation. The disinfectant action diminishes rapidly as this strength is departed from either by dilution or by the use of more concentrated solutions. Normal propyl alcohol has also considerable disinfectant power and a mixture of 95 per cent ethyl alcohol 675 cc. with pure propyl alcohol 250 cc. and distilled water 250 cc. prepared at 25° C. has been shown to be more effective as a skin disinfectant than ethyl alcohol alone. The disinfectant action of alcohol can be aided to a considerable degree by gently rubbing the skin with sterile gauze while the alcohol is being employed. (Price.)

4. Mercuric Chloride.

Soon after the treatment of wounds with carbolic acid was established, its rival, corrosive sublimate, was introduced as a more powerful disinfectant. There is no question that the claim was justified and that corrosive sublimate in ordinary surgical practice has greater germicidal and antiseptic powers than carbolic acid. At the same time bacteria must be exposed for a longer time to its action before they are destroyed, and it has a more injurious effect on the tissues with which it comes in contact and is more poisonous when it is absorbed. A certain amount of mercury remains attached to the proteins of the microbes and restrains their reproduction even when it does not actu-

ally kill them; owing to this fact corrosive sublimate has been credited with greater disinfectant power than it merits, for it is found that on the complete removal of the mercury many of the inactive organisms recover; in practice its action is therefore partly disinfectant and partly antiseptic. The symptoms of mercuric poisoning and the general action have been discussed under the chapter on mercury.

Mercuric chloride solution (1 in 2000–4000) is used extensively in surgery to disinfect the hands, skin, and wounds, but is very irritant even to the unbroken skin and must not be applied to more delicate tissues. It corrodes steel and this precludes its use to protect instruments before use. It is sometimes employed in the form of a soap and to impregnate bandages, cottonwool, gauze, catgut, etc., but it renders all of these irritant and corrosive so that they should not be applied directly to wounded surfaces. It differs from the carbolic acid group in preserving its disinfectant powers in oils and fatty vehicles, in which it is only slightly soluble and which it therefore leaves readily for the fluids of the microbes. It also differs from carbolic acid in the fact that the presence of sodium chloride reduces its disinfectant action because it lessens the amount of the free Hg ion. The disinfectant action of corrosive sublimate is much diminished by the presence of protein and it has less penetrating power than carbolic acid. Mercuric chloride dissolved in 25 per cent alcohol is more active as a disinfectant than when in water probably due to the fact that the dilute alcohol may favor the penetration of the poison.[1] On the other hand, this salt loses its disinfectant power in 95 per cent alcohol because it is not dissociated in the alcohol and as is well known the free ion is necessary for the disinfectant property. It precipitates protein like other metallic salts and has a further specific toxic action on living tissue.

Various other mercurial salts have been suggested as disinfectants, for example the cyanide, the periodide and potassium mercuric iodide.

Preparations.

U. S. P.

Hydrargyri Bichloridum, 0.004 G. ($\frac{1}{15}$ gr.).

Toxitabellæ Hydrargyri Bichloridi Magnæ. Each large tablet of the bichloride of mercury contains 0.5 G. of corrosive chloride of mercury. They are colored and are of an irregular shape in order to distinguish them from tablets which are intended for internal administration, these tablets being used only for the preparation of disinfectant solutions. They form a solution of the strength of 1 to 2000 when one tablet is added to a liter of water.

Toxitabellæ Hydrargyri Bichloridi Parvæ. Small tablets of mercury bichloride contain on an average 0.125 G. of the bichloride of mercury. These tablets must be colored and of an irregular shape.

B. P.

Hydrargyri Perchloridum, Corrosive Sublimate. 0.002–0.004 G. ($\frac{1}{30}$–$\frac{1}{15}$ gr.).

Liquor Hydrargyri Perchloridi. The solution of mercuric chloride contains 0.1 G. of mercuric chloride to 100 cc. of water; 4 mils. contain 0.004 G. of mercuric chloride. 2–4 mils. (30–60 mins.).

[1] Harrington's solution consists of 640 cc. of 95 per cent alcohol, 60 cc. of hydrochloric acid, 300 cc. of water and 0 8 G. of bichloride of mercury.

Unofficial Preparations.

A more recent introduction is Mercurochrome, the disodium salt of dibromo-hydroxymercurifluorescein, a compound containing between 24 and 26 per cent of mercury. It is recommended as an antiseptic and disinfectant in the most diverse conditions. For use in ophthalmia neonatorum a 2.5 per cent solution is advised. On the skin a 2 per cent aqueous solution is said to be less efficient than an aqueous alcohol-acetone solution of the same strength. On mucous membranes a 1 to 2 per cent solution may be employed. In infections of the kidney pelvis a 1 per cent solution is instilled and in the bladder the same strength is used, the solution being retained for an hour or more. In the acute stages of urethritis a 1 per cent solution is used which in later stages of the disease may be replaced by a stronger concentration. The drug may be also injected intravenously in the dose of 5 mg. per kilogram of body weight in the treatment of septicemias. Some favorable reports have appeared from such use, but in many cases it has been without value. Such intravenous use is sometimes followed by severe reactions such as fever, vomiting, diarrhœa and prostration and by severe stomatitis and enteritis.

Owing to the comparative newness of the drug a final estimate of its value is not possible at this time. It would appear to have some value as a local antiseptic, but many of the claims which were originally made for it do not seem to be justified in the light of subsequent research.

Merthiolate is a germicide containing about 49 per cent of mercury in organic combination. Chemically it is sodium ethylmercuri-thiosalicylate. It is recommended for application to the skin or to mucous membranes and for the disinfection of instruments. For such local application a 1 to 1000 solution is employed, but if large quantities are to be used as in irrigation of infected wounds or of the nasal sinuses or for introduction in the the bladder, solutions of 1 to 5000 to 1 to 10,000 are recommended.

Metaphen is the anhydride of nitro-hydroxymercuri-ortho-cresol and contains about 56 per cent of mercury. Laboratory tests have shown that it is a more powerful germicide than mercury bichloride, and at the same time it is relatively non-irritating and relatively non-toxic. Solutions in water are prepared with the aid of sodium hydroxide and for application to the skin it is used in the strength of 1 to 5000 to 1 to 1000. Solutions of similar strength are used for the disinfection of instruments, while for the eye or for application to the urethra solutions from 1 to 5000 to 1 to 10,000 are employed.

5. **Other Metallic Disinfectants.**

The salts of several other metals have been used as disinfectants and antiseptics. Silver nitrate is the most important of these and plays a large rôle in the treatment of infections of the mucous membranes, especially that of the eye. This disinfectant action is accompanied by intense irritation, but silver nitrate has very slight powers of penetration because it is rendered insoluble and therefore inactive by the chlorides of the tissues. Silver nitrate is used in solutions of 1 to 2 per cent as a disinfectant in infectious ophthalmia, or in more dilute form (1 in 200–400) for more frequent application. It has also been used as an injection in gonorrhœal infection of the urethra in the strength of 1 in 500–2000, and in various other conditions. General poisoning is unknown from this use of silver, but its intensely caustic action and the limited extent to which it penetrates have prevented its wider employment. This irritant action of the nitrate has led to the introduction of various organic compounds (see Silver, p. 146), which are less dissociated in solution and thus are less corrosive. But these lose their disinfectant

power in the same ratio as they become less irritant, for the tissue destruction arises from the same factor as the disinfectant action, the free silver ion. The effects of silver after absorption have been discussed.

6. Oxidizing Disinfectants.

Peroxide of Hydrogen.

Hydrogen peroxide or dioxide (H_2O_2) tends to break down into water and oxygen very rapidly in the presence of many substances, which in themselves may be either oxidizing or reducing. Among the bodies which induce this decomposition are the peroxidase ferments, which are found in all forms of living matter, and the peroxide of hydrogen is therefore decomposed when brought in contact with the tissues; the oxygen thus liberated tends to oxidize its surroundings and its chief effects are therefore due to its oxidizing properties. It is generally met with in dilute solution in water, and in this form alone is used in medicine. Brought in contact with the skin, peroxide of hydrogen solution is decomposed, and numerous bubbles of oxygen are formed,[1] but this decomposition proceeds much more rapidly when it is applied to denuded surfaces or to mucous membranes. The oxygen is formed in such quantity that some irritation may follow, and thus dogs often vomit when it is administered in quantity by the mouth. When it is injected subcutaneously, a large amount of oxygen is formed in the subcutaneous tissue, but some of the peroxide escapes decomposition and is absorbed into the blood. Here the decomposition proceeds more violently, the red-blood cells having a strong catalytic action, and the oxygen set free may cause emboli and lead to sudden death. The formation of emboli is seen most frequently in the rabbit, but was in all probability the cause of death in one case of fatal poisoning in man, in which a solution of hydrogen peroxide had been used to wash out the pleural cavity.[2] Emboli are not formed in the dog on hypodermic injection, nor in either dogs or rabbits poisoned by the stomach—in the latter case probably because the liquid is more slowly absorbed and is almost entirely decomposed in the mucous membrane. Even in the blood and tissues the whole of the peroxide is not decomposed, for several observers have found traces of it excreted in the urine.

The catalysis of hydrogen peroxide occurs in the lower forms of life as well as in the higher. Thus germinating seeds, yeasts, infusoria and the microbes all free oxygen from the solution, and in fact, a rough estimate of the number of microbes in water may be formed from the amount of oxygen given off by it on the addition of the peroxide (Gottstein). This decomposition is fatal to most of these lower forms, from the nascent oxygen, and peroxide of hydrogen is therefore a powerful disinfectant in water, a 3 per cent solution proving as strongly bactericidal as a 1 per mille solution of corrosive sublimate; but when the microbes are contained in a medium with much organic substance,

[1] A concentrated solution corrodes the skin, leaving a white eschar.

[2] In several other instances hemiplegia has been observed, apparently from embolism of the cerebral arteries.

as in wounds, the bactericidal action is very much reduced. This appears to be due to the too rapid decomposition of the peroxide, which escapes as bubbles of oxygen, comparatively little oxidation taking place. This may be exemplified by its action on the blood; when normal blood in a test-tube is treated with peroxide, it froths up and the oxygen escapes, leaving the blood unaltered. If, however, some hydrocyanic acid has been added to the blood some time previously so as to weaken the ferment, there is little or no effervescence and the hæmoglobin is changed to methæmoglobin by the peroxide remaining and freeing its oxygen more slowly. The peroxide therefore oxidizes most powerfully when it is slowly decomposed, while the rapid action of the ferments tends to dissipate the oxygen in the molecular form which has comparatively slight oxidizing and disinfectant powers.

In recent years, attention has been drawn to other bodies analogous to hydrogen peroxide, some of which possess powerful microbicidal properties. The peroxide is represented by the structural formula H—O—O—H and one of the hydrogens may be replaced by benzoyl or acetyl, forming $C_6H_5CO—O—OH$ (benzo-peracid) or $CH_3CO—OOH$ (aceto-peracid). These bodies give off oxygen more slowly than hydrogen peroxide and surpass it in germicidal power; in fact they are as powerful disinfectants as corrosive sublimate in favorable conditions. Unfortunately these peracids are too unstable for practical use; and the organic peroxides, such as diacetyl peroxide ($CH_3CO—O—O—COCH_3$), which form the peracids in water, have not proved so useful clinically as the laboratory results seemed to promise.

Therapeutic Uses.—Hydrogen peroxide is used locally as a disinfectant solution in suppuration, diphtheria, and urethral infection. In pus cavities the oxygen is freed with great rapidity, and the pus corpuscles are said to be disintegrated. The catalysis is due in part to these corpuscles, in part to the microbes, and the extent of the suppuration may be estimated from the amount of effervescence. Peroxide solutions differ from most other disinfectants in the short duration of the action, which passes off as soon as all the oxygen is liberated. In addition to its microbicidal action proper, this agent loosens and destroys masses of infected material by the mechanical effect of the liberation of the gas, and the wound or cavity is thus cleaned by it more perfectly than by washing with ordinary disinfectant solutions. Most surgeons believe that this mechanical action is of more importance than the direct germicidal effect. The solution has been recommended for use in ophthalmic practice, and for this purpose may be diluted one half.

Peroxide has been used to destroy the bacteria of drinking water and 10–15 cc. of the pharmacopœial solution is found to reduce the bacteria in a liter of water more than 100 times; about twice as much is required to have the same effect in milk.

Preparations.

Liquor Hydrogenii Peroxidi (U. S. P., B. P.), solution of hydrogen dioxide or peroxide, contains about 3 per cent by weight of the pure dioxide. Each volume of this solution is capable of setting free 10 volumes of oxygen when completely decomposed. Some acid is added to the peroxide solution in order to retard its decomposition, but it gradually changes when kept, so that only freshly prepared solutions are of full strength. The solution is colorless and odorless, but has an acid taste from the added acid, and the oxygen freed in the mouth gives a curious sensation and forms a froth.

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OTHER OXIDIZING DISINFECTANTS.

Some older disinfectants also owe their powers to liberated oxygen, and among these that most largely employed is the *Permanganate of Potassium*.

When a solution of this salt comes in contact with organic matter, such as albumin, the permanganate at once parts with some of its oxygen, which attaches itself to the albumin. Permanganate is thus poisonous to protoplasm, not through the presence of the whole molecule, but in consequence of the oxidation of the proteins. As soon as the permanganate is reduced, it of course loses this action, so that the oxidizing effect is limited to the skin and the surface of the mucous membranes. Concentrated solutions irritate and even corrode the skin, and induce gastro-enteritis when swallowed. Permanganate solutions are disinfectants of considerable power, owing to their oxidizing bacteria and thus destroying them. They fail to penetrate deeply in an active form, and this renders them of less value than many other disinfectants, except in very superficial infection.

Therapeutic Uses.—Permanganate is used for its disinfectant and deodorant action, as an application to gangrenous ulcers, cancerous sores, diphtheria, and gonorrhœa. In dilute solution it may be used as a gargle and mouth wash ($\frac{1}{4}$ per cent), to disinfect the hands (1 per cent), which it stains brown, and for other similar purposes. The stain on the skin may be removed by lemon juice or vinegar.

It has recently been recommended in poisoning with phosphorus, prussic acid, morphine and other alkaloids, on the theory that these poisons are oxidized by it in the stomach, and thus rendered harmless. For this purpose it is given in $\frac{1}{3}$ per cent solution. But permanganate also oxidizes the gastric mucous membrane, and it has not been shown that it attacks morphine in preference to the proteins; the treatment is certainly less reliable than the use of the stomach tube; permanganate has of course no action on morphine after absorption. In snake-bite, permanganate has been used to wash the wound and also to inject around it; it has no effect upon the poison already absorbed.

Potassium permanganate has also proved to be of value in the dermatitis due to poison ivy. For this purpose it is used in rather strong concentrations, 1 per cent solutions sometimes being effective where weaker strengths have failed to give relief.

Condy's Fluid is a strong solution of impure permanganate, which is of use to disinfect and deodorize urinals and fæces, but must be poured on them, and cannot be employed to disinfect rooms.

PREPARATIONS.

POTASSII PERMANGANAS (U. S. P., B. P.) ($KMnO_4$) forms slender crystals of a dark purple color and a sweetish, afterward disagreeable and astringent taste, soluble in sixteen parts of water, reduced by alcohol and other organic bodies. Dose, U. S. P., 0.06 G. (1 gr.); B. P., 0.06–0.2 G. (1–3 grs.).

Some of the caustics owe part of their action to the oxygen liberated when they come in contact with organic matter. Thus CHROMIC ACID destroys tissue in part through its acidity but this is reinforced by its oxidizing powers.

Other oxidizing bodies have been used as antiseptics and disinfectants. Thus CALCIUM PEROXIDE or GORIT has been recommended as a gastric and intestinal disinfectant for children in doses of 0.2–0.6 G. in milk. Zinc peroxide and magnesium peroxide have also been suggested, the former for external, the latter for internal use.

Similarly the Persulfates of potassium and sodium ($Na_2S_2O_8$), PERSODINE, possess strong oxidizing properties from their liberating oxygen in contact with organic matter. They are only feebly poisonous but have not been extensively used as yet.

7. Boracic Acid and Borax.

Boracic or boric acid ($B(OH)_3$) is a very weak acid, and it is doubtful whether the hydrogen ions or acidity play any part in its action, or whether the whole is not to be referred to the rest of the molecule. The ordinary sodium compound, borax, $Na_2B_4O_7$, is stated by some authors to be equally active, but is alkaline in reaction, so that the exact relative importance of the two ions of boric acid cannot be determined. Boracic acid and its sodium salt have some antiseptic power, for in $2\frac{1}{2}$ per cent solution almost all forms of bacilli stop growing; but they are not destroyed, even the delicate anthrax bacilli being found capable of further growth after exposure to a 4 per cent solution for twenty-four hours. Boracic acid is therefore valueless as a disinfectant, but has been used as an antiseptic dressing; it has the advantage over many other antiseptics of inducing very little irritation and of being only slightly poisonous, but experience has shown that it cannot be used with impunity in very large quantities.

Action.—Boracic acid and borax are only feebly toxic, but large quantities taken by the mouth cause gastric and intestinal irritation, as is evidenced by vomiting and purging, and even smaller amounts are said to act as mild aperients in some cases. Not infrequently repeated small doses of boric acid have induced albuminuria, especially in persons predisposed to it. Moderate doses are without effect on the metabolism, but larger quantities (5–10 G. per day in dogs) increase the nitrogen excretion in the urine. A dose of 30–60 grs. of boric acid is found to increase the bulk of the fæces in man by retarding the absorption of the proteins and fats.[1] Both borax and boracic acid are rapidly absorbed by the bowel, and do not affect the intestinal putrefaction.

Boracic acid has been widely used as an antiseptic dressing and also internally, and a number of cases of serious poisoning have been recorded from its absorption. The symptoms arose in part from the alimentary

[1] The body weight often falls under borax treatment, and this has been attributed to augmented fat destruction by Rost and Rubner, who state that a corresponding increase in the carbonic acid elimination accompanies it.

canal: uneasiness in the abdomen, vomiting, diarrhœa, dryness of the throat, and difficulty in swallowing; sleeplessness, great muscular weakness and depression, dimness of sight and headache were also complained of, and in severe cases collapse and death followed. The prolonged use of boric acid, internally or externally, has repeatedly led to falling of the hair, eczema, and psoriasis. Papular eruptions are common in cases of poisoning and local œdemas and swelling of the skin sometimes appear. A gray line on the gums, similar to that seen in lead poisoning, is stated to occur, along with irritation of the mouth. Chemical examination of the organs in cases of fatal poisoning has shown that the largest amount of boracic acid is stored in the brain, which in turn is followed closely by the liver.

Boracic acid and borax are excreted in the urine, in which they appear within a few minutes after ingestion; over half the quantity taken is excreted within twelve hours, but afterwards the elimination proceeds more slowly, so that traces may be found in the urine for five days or more; the urine becomes alkaline after sufficient amounts of borax, as after any other alkaline preparation.

Boracic acid has been used as a surgical antiseptic in solution (4 per cent), ointment, or on lint, and the solution of the acid or of borax is also used as a wash in aphthæ and other forms of irritation of the mouth. Boracic acid solution has been given internally in dilute watery solution as a genito-urinary disinfectant, has also been injected into the bladder, and is frequently used in ophthalmic surgery, as being less irritant to the eye than the more powerful antiseptics. Boracic acid and borax are sometimes added to milk or other food as preservatives, and it has been much discussed whether the habitual use of such preserved food is likely to prove deleterious to the health. The general result of the investigations is that, while no preservative should be added to food unless it is absolutely unavoidable, boric acid is less liable to derange the health than most other preservatives. Foods preserved with boracic acid should not be used by delicate individuals or by children, however, and the quantity of the acid used must be strictly limited.

Preparations.

U. S. P.

Acidum Boricum, 0.5 G. (8 grs.).

Glyceritum Boroglycerini, contains 31 per cent of boric acid in glycerin.

Unguentum Acidi Borici, ointment of boric acid, contains 10 per cent of boric acid.

Sodii Boras, sodium borate or borax, contains about 54 per cent of $Na_2B_4O_7$, corresponding to not less than 99 per cent of the crystallized salt. 0.75 G. (12 grs.).

B. P.

Acidum Boricum, boric or boracic acid (H_3BO_3). 0.3–1 G. (5–15 grs.).

Glycerinum Acidi Borici, contains about 30 per cent of boric acid in glycerin. 0.6–2 mils. (10–30 mins.).

Unguentum Acidi Borici, contains 10 per cent boric acid in paraffin ointment.

Borax, sodium borate. 0.3–1 G. (5–15 grs.).

GLYCERINUM BORACIS, contains 12 per cent of borax in glycerin. 2–4 mils. (30–60 mins.).

MEL BORACIS, contains 10 per cent of borax in honey and glycerin.

Boric acid consists of colorless crystals, with a faintly bitter taste, soluble to about 5 per cent in water, or in alcohol, and to about 25 per cent in glycerin.

Borax ($Na_2B_4O_7 + 10H_2O$) forms colorless crystals with a sweetish alkaline taste. It is soluble in water to the extent of about 6 per cent, giving the water an alkaline reaction.

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8. Potassium Chlorate.

The chlorate of potassium introduced into therapeutics on the erroneous theory that it would supply oxygen to the tissues, has been used very extensively for its effects in certain diseases of the mouth. It was supposed to be entirely devoid of poisonous properties, but was shown by Jacobi to give rise to very grave and even fatal symptoms in some instances. But the conditions which determine their appearance are not universally present, for very often large quantities have been taken with impunity.

Symptoms.—The chlorates have a cool, saline taste, which persists for a long time owing to their being excreted in part in the saliva. Concentrated solutions may cause nausea and vomiting from their local salt-action in the stomach, and their absorption is often followed by considerable diuresis from a similar action in the kidney. In the great majority of cases no further effects are observed.

In some individuals, however, symptoms arise from a single large dose, or from smaller quantities taken repeatedly. In **Acute Chlorate Poisoning**, the first symptom is often prolonged and violent vomiting, with pain in the stomach region; diarrhœa and a dark cyanotic color of the skin and mucous membranes follow, the respiration is at first dyspnœic and then weak, the pulse quick and feeble, sometimes irregular. The patient complains of headache, giddiness and muscular weakness, is restless, and eventually becomes comatose before death.

In **Subacute Poisoning**, vomiting and diarrhœa are also observed, and the vomited matter often contains large quantities of bile, less often blood. There may be complete anuria for some time, or the urine is scanty and at first dark colored, then deep reddish-brown; it contains hæmoglobin, methæmoglobin, and hæmatin in solution. On standing, it deposits casts of brown amorphous particles, which arise from the destruction of the red cells of the blood, and chlorates are contained in it in considerable quantity. The methæmoglobin may disappear from the urine after one or two days, but the casts remain longer. The skin is often icteric in color, and in some cases erythematous eruptions have been observed. Headache, muscular

weakness and abdominal pain are complained of, and uræmic symptoms may arise—delirium and convulsions, or confusion and coma. Death has followed from these last as late as a week after the first symptoms of poisoning were observed, but in several cases complete recovery has followed even the gravest symptoms.

Action.—These symptoms arise from the action of chlorates on the red cells of the blood and especially on the hæmoglobin. When chlorate solution is added to blood in a test-tube it slowly forms methæmoglobin and hæmatin, and the blood assumes a chocolate brown color. Later, the red cells tend to become laked and the methæmoglobin is freed in the serum. This action on the blood is generally ascribed to the oxidizing properties of the chlorates, for other oxidizing agents have the same effects; some oxidizing agents induce marked hæmolysis with little methæmoglobin, while in others the latter feature is the predominating one. There is, however, some difficulty in explaining the chlorate action by oxidation, for these salts are very stable and have practically no oxidizing action at body temperature.

When this transformation of the hæmoglobin takes place in the vessels, asphyxia results from the inability of the blood to carry available oxygen, and this is probably the chief cause of the symptoms and of the fatal issue in the most acute form of intoxication. When a considerable amount of hæmoglobin is transformed, but sufficient remains to continue the respiration of the tissues, the subacute form of poisoning results from the hæmolysis; the hæmoglobin and fragments of the corpuscles obstruct the renal tubules with masses which may appear as casts in the urine, or may cause complete suppression; the fatalities in subacute chlorate poisoning appear to be the result of these renal changes. Some of the products of the hæmoglobin are deposited in the liver and spleen and often cause enlargement of these organs; the bile pigment is increased in amount and the bile passes through the ducts with difficulty and this leads to the absorption of bile and jaundice.

The hæmoglobin of most animals seems equally easily transformed to methæmoglobin by chlorates when it is dissolved in water, but the blood-corpuscles of the rabbit and guinea-pig resist their action much more than do those of the dog and of man, which are more readily permeable by the chlorate.

Recently the generally accepted view that the blood changes, and especially the formation of methæmoglobin, are responsible for the symptoms seen in chlorate poisoning has been called in question. Potassium chlorate administered to animals so as to produce either acute or subacute poisoning is said to produce methæmoglobin in only a small percentage of the cases. In some instances it will appear in the blood postmortem and it forms more often when death is delayed for some hours. Frequently it only appears very late, even when the animals are moribund, In case of death the kidney activity previous to death is more or less completely inhibited while survival is dependent upon immediate and continued diuresis.

Sodium chlorate seems more prone to produce methæmoglobin *in vivo* than does potassium chlorate, while such formation does not occur when magnesium or calcium chlorate is administered. *In vitro* the action is just the reverse, the magnesium and calcium salts being more active than either the sodium or the potassium salt.

Chlorate has little or no direct effect on the central nervous system or the circulation, though these are secondarily affected by the asphyxia and renal changes.

Very little chlorate is reduced in the blood and tissues, for 90-96 per cent of the amount administered has been recovered from the urine. Small quantities appear also in the saliva and in other secretions, such as the perspiration, milk, tears, and nasal mucus, and some has been found to pass from the mother to the fœtus *in utero*.

Chlorates hardly retard the growth of bacteria in cultures more than other indifferent salts, and no adequate explanation has been offered for their use in infections of the mouth and throat.

The **Bromates** and **Iodates** have been less often the subject of investigation than the chlorates, and are not used in therapeutics. The iodates are more poisonous than the bromates and these again than the chlorates; the iodates destroy the red cells more rapidly but form less methæmoglobin than the chlorates in test-tube experiments. Iodates induce fatty degeneration of the liver and congestion and extravasation in the alimentary tract. Some iodide is formed from them in the body.

The action of the **Perchlorates** has been examined by Kerry and Rost. In the frog the perchlorate of sodium ($NaClO_4$) induces fibrillary twitching and clonic contractions of the muscles; the muscle curve is prolonged in the same way as by veratrine, and rigor eventually follows as in caffeine poisoning. The reflex excitability is increased and the heart is slow and irregular. The effects of the perchlorate on mammals differ considerably in different species; in the rat, mouse, and guinea-pig the reflex excitability is enormously increased and tetanic convulsions may arise from this action; in the cat a certain stiffness, muscular paresis and tremor can be made out after the injection of large quantities of perchlorate, but these animals as well as the rabbit and dog are not easily killed by it.

Therapeutic Uses.—The chlorate of potassium is used chiefly as a mouth wash and gargle in irritated conditions of the mouth and throat, such as aphthæ, and in the tenderness and ulceration of the gums and mouth induced by the prolonged use of mercury. It may also be given as a prophylactic to lessen stomatitis when mercury is being prescribed. In catarrh of the throat it is often used with apparently good effects. It is rarely employed in diphtheria now.

It is used in 2-4 per cent solution, or the official lozenge may be prescribed. In children a somewhat stronger solution with syrup or honey may be used to brush out the mouth, but care should be taken that none is swallowed. The local action of the chlorates has not been explained, and it may be due to the salt-action in part, though not wholly. It has been suggested that they are oxidizing disinfectants, but there is no reason to suppose that they are changed here any more than in the tissues in general. It is not impossible that equally satisfactory results might be obtained by the use of the chlorides or nitrates. Chlorate of potassium has been given internally in cases of diphtheria and in some diseases of the mouth, but it does not seem to have any therapeutic value unless when applied locally. Some benefit may arise from its contact with the mouth and throat in the process of swallowing and from its excretion in the saliva. In addition the internal administration of the chlorate is liable to induce dangerous poisoning.

PREPARATION.

POTASSII CHLORAS ($KClO_3$) (U. S. P.), 0.25 G. (4 grs.); B. P., 5–10 grs. (0.3–0.6 G.).

The chlorates are colorless prismatic crystals with a saline taste, and are given in solution or in lozenges when used internally. The dry salts form explosive mixtures with organic or other reducing substances, and such mixtures are therefore to be kept cool, and ought not be be ground together, as heat and pressure are liable to cause explosions.

Poisoning.—The fatal dose of chlorate varies extremely, as little as 1 G. (15 grs.) having proved fatal in a child, while 40–50 G. (10–12 drs.) have been swallowed by adults without marked symptoms. Chlorate poisoning is now very rare; it is said to be more liable to occur in nephritics than in normal persons. As a general rule symptoms appear only two to three hours after the drug has been taken, and the treatment is purely symptomatic—central nervous stimulants, ice for vomiting, etc.; alkalies may be given to lessen the formation of methæmoglobin and diuretics and large amounts of fluid to flush out the kidneys.

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9. Iodine.

Iodine has recently been used largely to disinfect the skin before operation, as it is found to penetrate readily into the pores and has a powerful germicidal action. Its irritant effects preclude its more general use. It is generally employed in the strength of $2\frac{1}{2}$–5 per cent in 10 per cent potassium iodide solution or in alcohol, and is painted on the site of operation a few minutes before the incision is made.

A solution which is recommended as being relatively non-irritant and yet efficient as a germicide, contains 2 per cent of iodine and 2.4 per cent potassium iodide in 50 per cent ethyl alcohol.

U. S. P.

TINCTURA IODI. Tincture of Iodine contains 7 per cent of iodine and 5 per cent of potassium iodide in about 85 per cent alcohol.

TINCTURA IODI MITIS. The mild tincture of iodine contains 2 per cent of iodine and 2.3 per cent of sodium iodide in diluted alcohol.

B. P.

LIQUOR IODI FORTIS. The strong tincture or solution of iodine contains 10 per cent of iodine and 6 per cent of potassium iodide in approximately 80 per cent alcohol.

LIQUOR IODI MITIS. The weak solution or tincture contains 2.5 per cent of iodine and 1.5 per cent of potassium iodide in approximately 85 per cent alcohol.
LIQUOR IODI SIMPLEX. The simple solution of iodine contains 9 per cent of iodine in 95 per cent alcohol.

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10. Iodoform.

A number of iodine compounds have been introduced into therapeutics as applications to wounded surfaces. The most widely known of these is Iodoform (CHI_3), which corresponds in its chemical structure to chloroform, and has been used very extensively in surgery; it formerly gave rise to poisoning repeatedly.

Iodoform has no marked **Local Action** on the skin or mucous membranes. Some persons have a special idiosyncrasy for it which betrays itself in an eruption developed in the skin near where iodoform has been applied; Bloch states that a skin graft from these persons implanted in a normal individual continues to show this reaction, but believes that the idiosyncrasy is not limited to iodoform but extends to many other methyl compounds. It seems to have some anæsthetic action when applied in large quantity to wounded surfaces. Iodoform was at first applied to wounds in the belief that its **Antiseptic** properties were equal to or even exceeded those of carbolic acid. But cultures of bacteria are not prevented from developing by the addition of iodoform. It has therefore been suggested that while iodoform in itself possesses no antiseptic virtues, the iodine formed from it in the wound may retard the growth of septic germs; but microbes drawn from wounds under iodoform treatment are not retarded or weakened in their development. Some of the advocates of the iodoform treatment therefore suppose that it diminishes the secretion of the wounded surface and thus affords a less suitable medium for the growth of the germs; in this relation it may be mentioned that Binz found the emigration of the leucocytes from the blood-vessels hindered by the local application of iodoform. Finally iodoform may retard the growth of microbes to some extent by forming a crust over the wounded surface, and mechanically preventing them from penetrating into it.

Symptoms.—The symptoms of iodoform intoxication in man generally set in with anxiety, general depression and discomfort. The patient becomes sleepless and restless, complains of giddiness and headache and often of the taste and odor of iodoform in the mouth and nose. The pulse is generally greatly accelerated, and a rise of temperature is said to have occurred in some cases in which no septic poisoning could be found to account for it. The depression deepens into true melancholia accompanied by hallucinations, the patient often suffering from the delusion of persecution, which may induce him to attempt suicide. As a general rule this melancholia is followed by attacks of violent delirium and mania, lasting for hours or days, and in fatal cases, by collapse and death. In other cases the condition has passed into permanent insanity

and dementia. A rarer result of the absorption of iodoform is deep sleep passing into stupor and collapse without any symptoms of cerebral excitement.

In milder cases of poisoning the patient suffers only from the unpleasant taste and odor, from headache and not infrequently from nausea and vomiting.

In the dog and cat iodoform generally causes deep sleep and stupor, with lessened excitability of the spinal cord and of the motor areas of the brain; but after large doses excitement and convulsions of clonic and tonic types have been observed. In the frog it paralyzes the central nervous system and the heart without eliciting any symptoms of excitement. No narcosis is observed in the rabbit even after fatal doses. After prolonged administration albuminuria is often observed in animals, and the iodine of the thyroid has been found to be increased by iodoform, as by other bodies which free iodine in the tissues.

After fatal iodoform poisoning in man and animals, the liver, kidney, heart, and muscles are generally found to have undergone fatty degeneration. In addition, irritation of the gastric and intestinal mucous membrane has been observed, and the epithelial cells are often degenerated. Ecchymoses occur beneath the endocardium, in the kidney, and elsewhere; and congestion of the meninges is described.

Absorption and Excretion.—Iodoform is readily decomposed in the presence of alkaline fluids and in protein solutions, and some decomposition undoubtedly takes place in wounds; the iodine liberated combines with the alkalies of the fluids to form iodides, for these have been shown to be present, and iodalbuminates are presumably formed in the same way as by free iodine. Some of the iodoform is perhaps absorbed unchanged. After iodoform absorption, iodine has been shown to be present in the saliva, perspiration, and bronchial secretion, as after the ingestion of iodine or iodides; but it is chiefly excreted in the urine in the form of iodides and partly in organic combination. The tissues apparently retain it very tenaciously, for iodides have been found in the urine for more than a month after the administration of iodoform.

In considering the symptoms of iodoform intoxication, it must be recognized, therefore, that a very complex condition is present. Some iodoform may circulate in the blood unchanged and give rise to the cerebral symptoms. Other symptoms are due to the presence of iodine and iodides in the blood and tissues. Lastly, the acceleration of the heart and some other symptoms are due to abnormal activity of the thyroid secretory cells. It is possible that the cerebral symptoms may arise from the thyroid gland through the action of iodoform on it, but this has not been demonstrated.

The intensely disagreeable odor of iodoform and its toxicity have led to the introduction of numerous substitutes. None of these seem to be very poisonous, and in most of them the iodine of the molecule is not liberated in the wound or tissues. It is of course impossible to state how far they are capable of replacing iodoform, as long as their exact action in wounds is unknown.

The first of these substitutes was *iodol* or tetraiodopyrrol (C_4I_4NH), which has no odor or taste, is insoluble in water, but is absorbed from mucous surfaces and from wounds. It is decomposed in the tissues, and leads to the excretion of iodides in the urine, and in very large doses gives rise to symptoms in animals resembling those produced by iodoform. Others are *aristol* or dithymol-diiodide ($(C_6H_2CH_3C_3H_7OI)_2$, and the potassium, sodium, mercury, and zinc salts of soziodolic acid ($C_6H_2I_2HOSO_2OH$). Iodine compounds of phenolphthalein are known by the trade names of *nosophen*, *antinosine*, and *eudoxine*. Triiodocresol is known as *losophan*, while *europhen* is a more complex combination of cresol and iodine; *loretin* and *vioform* are derivatives of quinoline containing iodine. (See also under Bismuth and Alum.) These later "substitutes" for iodoform differ entirely from it and from iodol in the fact that iodine is not liberated by the tissues; what value they possess is probably due to their acting as absorbent powders, and precipitated chalk would presumably be as efficient.

Therapeutic Uses.—Iodoform has been used to a very limited extent internally in the treatment of syphilis, and as an intestinal disinfectant. It is chiefly employed in surgical treatment as an application to wounds, skin diseases and burns. In granulating surfaces with a profuse secretion, and in slowly healing abscess cavities, it seems to be especially valuable. It may be applied as a dusting powder, as an ointment, or in gauze or bandages saturated with it. It has been shown that it has very weak antiseptic properties, and many surgeons take the precaution of disinfecting the powder before applying it, and use it for its effect on the tissues of the wound and not for its effects on the germs. Applied in ordinary quantity to small surfaces it seems to be a perfectly safe remedy, cases of poisoning occurring only when large cavities are treated with it, or when it is applied to very large absorbing surfaces.

Iodoform has been credited with some specific action in tuberculous disease, but has proved almost inert toward the bacillus. The favorable results in the local treatment of tuberculous abscesses, laryngeal ulcers, and similar conditions may with greater probability be attributed to its action on the granulation tissue. In syphilitic ulcers and chancres, iodoform has been used very largely and with good effects.

PREPARATIONS.

U. S. P.

IODOFORMUM, 0.25 G. (4 grs.).

THYMOLIS IODIDUM. Aristol ($(C_6H_2CH_3C_3H_7OI)_2$, a yellowish brown powder; tasteless, odorless, insoluble in water and containing not less than 43 per cent of iodine.

B. P.

IODOFORMUM, 0.03–0.2 G. ($\frac{1}{2}$–3 grs.).

OCULENTUM IODOFORMI. The iodoform ointment for the eye contains 4 per cent of iodoform.

SUPPOSITORIUM IODOFORMI. Each suppository contains 0.2 G. or 3 grs. of iodoform.

IODOL. Not official. C_4I_4NH, a light grayish-brown crystalline powder, tasteless, odorless, insoluble in water. Dose, 0.25 G. (4 grs.).

IODOFORM (CHI_3), forms small, lemon-colored crystals, possessing a very penetrating, persistent, and disagreeable odor and taste, practically insoluble in water, soluble in alcohol, ether, fixed oils, glycerin, etc.

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11. Chlorine Preparations.

The disinfectant action of many organic substances is intensified when chlorine is substituted for hydrogen; for example, chlorphenol is more powerful than carbolic acid. This is not owing to chlorine being freed from the molecule, but from some chemical property which is not understood and which in chemistry renders trichloracetic acid a more readily dissociated and therefore stronger acid than acetic acid.

But several chlorine compounds have been introduced as disinfectants recently, which owe their value to the chlorine liberated by them. Chlorine itself is a powerful poison to all living matter, including the bacteria, and has been used for the disinfection of water and inanimate objects. It cannot be employed in surgery, owing to its intense irritant action, and volatility. Compounds which give off chlorine more slowly than the solution have therefore been introduced; solutions of sodium hypochlorite have been largely employed to irrigate septic wounds (*Eusol* or *Dakin's solution*) and have proved highly efficient as disinfectants.

Dakin's solution is prepared by adding chlorinated lime to a solution of sodium carbonate and after filtration of this solution boric acid is added. The solution, which is nearly neutral, should contain between 0.45 and 0.5 per cent of sodium hypochlorite. *Eusol*, made by adding boric acid to a solution of chlorinated lime, contains the equivalent of 0.27 per cent of hypochlorous acid.

As the chlorine escapes the fluid becomes slightly alkaline but it is not strongly irritant. It penetrates well as it does not precipitate proteins, and it dissolves necrotic tissue and pus to some extent.

A firmer combination is met with in the *chloramines*, in which the chlorine is attached to the nitrogen of an organic molecule. The best known of these is the chloramine-T (*Chloramina*) of Dakin, a toluene derivative of the formula $(CH_3)C_6H_4SO_2NNaCl$, containing about 12.5 per cent of active chlorine. This chloramine is a white crystalline substance smelling faintly of chlorine, and is used in 1–2 per cent solution in water for the same purposes as hypochlorite solution, especially on wounds as an irrigating fluid and as a mouth wash. It is more stable than the hypochlorite, does not dissolve necrotic tissue in the same way, nor become alkaline, nor does it give up its chlorine so rapidly; it is less irritant to the skin surrounding the wound.

Dichloramina (U. S. P.), *Dichloramine-T.*—Paratoluene-sulphondichloramide contains from 28 to 30 per cent of active chlorine. The yellowish powder is almost insoluble in water but is soluble in eucalyptol and in chlorinated paraffin (*Paraffin Chlorinatum* (U. S. P.), *Chlorcosane*). It is an active germicide possessing a gradual sustained action. It is more irritant than chloramine and also more solvent.

Dichloramine dissolved in chlorinated paraffin may be used for nasopharyngeal work in a 1 to 2 per cent solution; on wounds a 5 per cent solution is used. Such solutions are not very stable and should not be kept for more than two or three days.

Therapeutic Uses.—Hypochlorite solution, chloramine-T and dichloramine-T have been used extensively in infected wounds and with good results. They owe their activity entirely to the chlorine which they liberate and which is a general poison to all living matter, but if they are properly applied, the action on the microbes more than makes up for their tendency to damage the tissues of the host. On the other hand their use is necessarily limited to local infections; they cannot be applied to disinfect the tissues as a whole, for they act at least as strongly upon the proteins of the human body as upon the microbes invading it.

PREPARATIONS.

U. S. P.

LIQUOR SODII HYPOCHLORITIS. This solution is the strong solution of sodium hypochlorite and contains about 5 per cent of NaOCl. It is not suitable for application to wounds but is diluted with water and made neutral with sodium bicarbonate forming the dilute solution of Sodium Hypochlorite.

LIQUOR SODII HYPOCHLORITIS DILUTUS. Dilute solution of the hypochlorite of sodium, corresponding to Dakin's solution, is an aqueous solution of chlorine compounds of sodium, containing the equivalent to from 0.43 to 0.48 per cent of available chlorine.

CHLORAMINA-T. Chloramine-T is sodium paratoluenesulphonchloramide and contains about 12 per cent of active chlorine.

DICHLORAMINA-T. Dichloramine-T is paratoluenesulphondichloramide and yields about 30 per cent of active chlorine. It is almost insoluble in water but soluble in eucalyptol and in chlorinated paraffin hydrocarbons.

PARAFFINUM CHLORINATUM. Chlorinated paraffin, or Chlorcosane, is a solvent for dichloramine.

B. P.

LIQUOR SODÆ CHLORINATÆ CHIRURGICALIS. Dakin's solution. Contains between 0.5 and 0.55 per cent of available chlorine.

CHLORAMINA. Chloramine-T. Chloramine is sodium p-toluenesulphonchloramide.

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12. The Acridine Dyes—Acriflavine and Proflavine.

Acriflavine was introduced by Ehrlich in 1912 as having therapeutic properties in trypanosome infections. It was therefore called trypaflavine, but the name was later changed to acriflavine. It is a derivative

of acridine, a coal-tar base, being diamino-methylacridinium chloride hydrochloride, while the base is often known as neutral acriflavine. Proflavin or proflavine sulfate differs from acriflavine in not possessing the methyl group attached to the nitrogen.

These flavines or acridine dyes have been shown to possess considerable antiseptic and bactericidal properties, and on this account they have been introduced into medical and surgical practice as wound and surface disinfectants. They have a relatively low degree of toxicity and are comparatively free from local irritant properties. Acriflavine is apparently more active than proflavine, but it acts more slowly. Acriflavine base is particularly recommended where freedom from irritation is desirable, such as might be produced by the acid reactions of acriflavine hydrochloride or proflavine solutions.

Neutral acriflavine administered orally is eliminated in the urine, giving it a yellow fluorescence and exerting an antiseptic action in the urinary tract which begins in about two hours and may last eight hours. It is more marked in an alkaline urine, so that sodium bicarbonate is frequently given at the same time. Gastric distress may result if the use of the drug is prolonged.

Therapeutic Uses.—These dyes have come into use in a large variety of conditions in which an antiseptic or disinfectant is required. For wounds a strength of 1–1000 is used in physiological salt solution, which may be applied by swabbing or as an irrigating fluid, and if desired the wound may be packed with gauze saturated with this solution. Evaporation should be prevented by the use of a protective dressing. Fresh wounds may be freely irrigated with the solution, and some being left in the wound, it may be closed and be permitted to heal.

In the treatment of gonorrhœal urethritis a dilute solution—1:4000 or 6000 may be used as an irrigating solution or a 1:1000 solution may be injected. In the throat or mouth a 1:1000 solution may be used.

Solutions may be sterilized by boiling or by heating in an autoclave. They should be preserved in amber bottles, but solutions will not keep long, and those over a week old should be discarded.

Preparations.

U. S. P.

Acriflavinæ Hydrochloridium. Acriflavine hydrochloride. This is a brownish-red crystalline powder soluble in 3 parts of water and in alcohol.

Acriflavina. Neutral acriflavine or acriflavine base is a brownish-red granular powder soluble in 3 parts of water and incompletely soluble in alcohol.

B. P.

Acriflavina. Acriflavine is the hydrochloride of diamino-methylacridinium chloride.

It will be seen that in the U. S. P. acriflavine is the base while in the B. P. the term is used to designate the salt.

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II. ANTISEPTICS USED CHIEFLY IN SKIN DISEASES.

1. Pyrogallol.

Pyrogallol, $C_6H_3(OH)_3$ the only trioxybenzol that has been largely used, produces nervous symptoms resembling those of carbolic acid, when given in very large doses to animals. In the cases of poisoning which have been observed in man, the symptoms arose almost exclusively from changes in the blood corpuscles. The red-blood cells become shrunken and angular and lose most of their hæmoglobin, which escapes into the plasma and is changed into methæmoglobin; the blood therefore assumes a chocolate-brown color, which may be detected in the living animal by the discoloration of the skin and mucous membranes. If the intoxication is not too acute, icterus follows, and hæmoglobin and methæmoglobin are excreted in the urine. In the blood, fragments of red cells and "shadows," or red cells deprived of their coloring matter, are seen in large numbers, and the spectrum of methæmoglobin can be obtained easily. The kidneys are also affected, and the resulting nephritis is indicated by the presence in the urine of albumin, epithelium and casts, along with the products of the decomposition of the blood. The nephritis may lead to uræmic convulsions, which are sometimes accompanied by the nervous tremors characteristic of this series, and also by dyspnœa and cyanosis from the lack of hæmoglobin in the blood. The formation of methæmoglobin is due to the reducing properties of the drug. Pyrogallol is excreted in part in combination with sulfuric acid in the urine, in part as unknown oxidized products, which give the urine a dark brown or black color, even when no blood pigments are contained in it.

The skin is dyed brown when pyrogallol is applied to it, from the products of oxidation formed.

Therapeutic Uses.—Pyrogallol is used in the treatment of several forms of skin disease, especially in psoriasis, in which it is applied in ointment (5 20 per cent). It is dangerous to apply it to very large surfaces, however, and many authorities therefore advise the use of chrysarobin in its stead. Pyrogallol ought never to be used internally. Its curative action in skin diseases may be due to its slight irritant and antiseptic properties, but is referred by some to its reducing action.

PYROGALLOL (U. S. P.), pyrogallic acid ($C_6H_3(OH)_3$), light, colorless crystals or laminæ when freshly prepared, which rapidly assume a darker color on exposure to light and air. It is very soluble in water and reduces the salts of the heavy metals even in the cold. It is used only externally.

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2. Chrysarobin.

Chrysarobin is a mixture in varying proportions of neutral bodies which are closely related to the active principles of the anthracene purgatives. It is found in an impure form (Goa powder) in cavities in

the Andira or Vouacapoua araroba, a tree growing in India and Brazil. Chrysarobin applied to the skin in a concentrated form, or in susceptible persons, causes itching, redness and swelling, less frequently papular or pustular eruptions; the skin and clothing are stained a reddish-brown color where it is applied. When swallowed, chrysarobin acts as a gastro-intestinal irritant, causing vomiting and purging; some of it is absorbed, and in its excretion by the kidneys it causes nephritis in the rabbit with albumin and even blood in the urine. In man, slight albuminuria has been observed in some instances after its application to the skin; in animals the epithelium of the renal tubules has been found to be necrosed, the glomeruli being less frequently affected. Part of that absorbed undergoes oxidation to chrysophanic acid in the body, but most of it passes through the tissues unchanged.

Therapeutic Uses.—Chrysarobin is used in skin diseases, especially in psoriasis, in which it is applied in ointment. Its effects, like those of pyrogallol, have been ascribed to its reducing action. Chrysophanic acid might be used also for this purpose were its isolation not attended with such expense. Some confusion has arisen from chrysarobin having been at first supposed to be chrysophanic acid.

PREPARATIONS.

CHRYSAROBINUM (U. S. P., B. P.), a substance obtained from Goa powder, which is found in the trunk of Andira araroba (Vouacapoua araroba, U. S. P.). It is a yellowish powder without odor or taste and is almost insoluble in water.

UNGUENTUM CHRYSAROBINI (U. S. P.), 6 per cent (B. P.), 4 per cent.

3. Naphthol.

The naphthols, $C_{10}H_7OH$, resemble carbolic acid in their antiseptic action but are much less soluble and less corrosive. Alpha-naphthol has been found to be more strongly antiseptic than the beta compound, and may be more poisonous, as is generally stated, but no satisfactory investigation has appeared regarding this point. Beta-naphthol is several times as strongly germicidal as carbolic acid, and is the form used in therapeutics.

The naphthols are irritating to the mucous membranes when they come in contact with them in solution or in vapor; thus they cause sneezing and coughing when applied to the respiratory passages, and in the course of excretion induce pain in the bladder and urethra with strangury and swelling of the mucous membrane. Large doses cause symptoms similar to those of carbolic acid poisoning, except that in the dog no convulsions have been observed, and in the other mammals they seem less pronounced. Injected subcutaneously or absorbed from the alimentary canal in animals, they induce acute nephritis with the appearance of albumin and hæmoglobin in the urine, and some nephritis has been caused in man from their external application. They seem to have less effect on the circulation and respiration than the other aromatic antiseptics, but resemble them in tending to destroy the red cells of the blood.

The drug has been given in rather large doses (6 G. repeated on two succeeding days) in the treatment of hook-worm infection. In some instances it produced severe anæmia due to the action on the red blood cells, and icterus resulted, with enlargement of the spleen and liver and hæmoglobinuria.

Occasionally naphthol has given rise to imperfect sight and partial retinal degeneration in man, and changes in the eye have been observed repeatedly in experiments on animals in which naphthol was absorbed. The retina is seen to be dotted over with bright points or to contain large yellow plaques. Atrophy of the optic nerve may follow, or subretinal effusion, and cataract has been developed in some experiments, from an inflammatory infiltration beginning in the ciliary body and iris and extending into the lens and finally into the posterior surface of the cornea. While the ocular effects in man have never reached this intensity, Hoeve has observed some defects of vision induced by the use of naphthol internally or externally, and cautions against its prolonged use.

The naphthols are excreted in the urine in combination with glycuronic and sulfuric acids, and these combinations and their oxidized products give the urine a reddish-brown color which may become deeper on exposure to the air.

Naphthalene, $C_{10}H_8$, the hydrocarbon from which naphthol is derived, is less soluble and does not give rise to acute symptoms in animals, but after prolonged treatment with it animals suffer from diarrhœa and nephritis, with albumin and casts in the urine. The same changes in the retina are induced by naphthalene as by the naphthols. The antiseptic value of naphthalene is small, but it is oxidized to naphthols in the tissues and these acquire a toxic action. It is excreted in the urine as naphthol and further oxidation products, in combination with glycuronic and sulfuric acids.

Therapeutic Uses.—Beta-naphthol was at first introduced as an external application in various forms of skin disease, in which it is used in ointment (5–10 per cent). Naphthalene was also employed in the same way, but has not proved so popular. Beta-naphthol has also been given internally as an intestinal disinfectant, but has not been efficacious. It has been employed as an anthelmintic especially against hook-worm infections and apparently with some success, though it has not proved so reliable as some of the other drugs used for this purpose; it may be prescribed as a powder or in capsules. Naphthalene and naphthol ought to be avoided in irritation of the kidneys, bladder or urethra.

PREPARATION.

BETANAPHTHOL (U. S. P., B. P.), NAPHTHOL. Beta-naphthol ($C_{10}H_7OH$), white or yellowish-white, insoluble crystals or powder, with a faint phenol odor and a hot taste. U. S. P., 0.25 G. (4 grs.); B. P., 5–10 grs. (0.3–0.6 G.).

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4. Resorcin.

The three dioxybenzols—resorcin, pyrocatechin and hydroquinone—resemble carbolic acid in their effects, but produce a more intense stimulation of the central nervous system, for convulsions have been observed in man after their use. This is especially true for the last two, resorcin being much less toxic than these. Resorcin seems to be equally or more strongly antiseptic than phenol, and is somewhat less poisonous, while the others are more dangerous; it is less irritant and caustic than carbolic acid. All three dioxybenzols are excreted in the urine in combination with sulfuric and glycuronic acids. They are in part subjected to further oxidation, leading to coloration of the urine similar to that seen in carbolic acid poisoning.

Resorcin has been applied in ointment (5–10 per cent) in skin diseases, and has been injected in cystitis and gonorrhœa in solution (1–3 per cent), but in both cases is liable to produce irritation and pain. As an internal remedy it was formerly used as an antipyretic and as an intestinal disinfectant but has fallen into complete disuse.

RESORCINOL, resorcin, metadioxybenzol ($C_6H_4(OH)_2$), colorless, very soluble crystals with a faint aromatic odor. U. S. P., 0.125 G. (2 grs.); B. P., 0.06–0.3 G. (1–5 grs.).

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5. Tar.

Long before carbolic acid and its congeners were known, tars and other crude preparations enjoyed a reputation in the treatment of wounds, and some of these have been retained in medicine and are widely used. Among these the tar obtained by the dry distillation of different woods is included; its constituents vary with the source, but the creosols ($C_6H_3CH_3{\cdot}OH{\cdot}OCH_3$). guaiacols ($C_6H_4OH{\cdot}OCH_3$), and other less poisonous aromatic compounds are present in larger quantity than the phenols and dioxybenzols, and wood-tar is therefore less poisonous than carbolic acid, and its simpler homologues. At the same time these higher combinations seem to have the same antiseptic powers as the simpler benzol derivatives, so that several of the crude preparations possess considerable value in surgery and medicine.

Therapeutic Uses.—Tar has been used with considerable success as an antiseptic in skin diseases, in which it may be applied either alone or as an ointment. It is only slightly irritating to the skin, and some absorption occurs, as is often seen by the dark color of the urine. Internally it has been used occasionally as an anthelmintic and intestinal disinfectant, much more frequently as an "expectorant" in cough mixtures. Whether it has any effects on the lungs in these cases may be questioned.

Tar is a valuable disinfectant, which is very generally available and is much cheaper than the purer bodies of the aromatic series. It

may be used for the disinfection of excrementa, latrines, etc., where the cost of even crude carbolic acid would be prohibitive.

PREPARATIONS.

U. S. P.

PIX PINI, pine tar, 0.5 G. (8 grs.).

UNGUENTUM PICIS PINI. Tar ointment contains 50 per cent pine tar.

OLEUM PICIS RECTIFICATUM. 0.2 cc. (3 mins.).

SYRUPUS PICIS PINI. 10 cc. (2½ fl. drs.). The syrup of pine tar is prepared from the rectified oil of tar.

B. P.

PIX LIQUIDA, tar. 0.12–0.6 G. (2–10 grs.).

Tar is a thick, dark-colored liquid obtained from the wood of Pinus palustris and other species of Pinus by destructive distillation, and contains a very large number of aromatic bodies mixed with others of less importance.

OLEUM PICIS RECTIFICATUM, oil of tar, is a volatile fluid distilled from tar, and consists almost entirely of guaiacols and their compounds.

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Ichthyol is derived from the tar of a bituminous shale which is found in the Tyrol, and which contains the remains of many fossil fishes. It has a high percentage of sulfur, and possesses some antiseptic action, although it is believed to be less powerful than carbolic acid. Applied to the skin, ichthyol causes slight irritation, which is apparently of benefit in some cutaneous diseases, and it has therefore been used extensively for this action. In more dilute form it possesses a demulcent or emollient effect. A certain amount of absorption occurs when it is rubbed into the skin, for the sulfur of the urine has been found to be augmented. Taken internally in large quantities, it acts as a gastric and intestinal irritant and produces diarrhœa, but it is only very feebly poisonous.

Ichthyol has been strongly recommended in the treatment of a number of skin diseases and in erysipelas. It has also been extensively employed to aid the absorption of chronic infiltrations and also the products of inflammation, especially in gynecological practice. The local irritant action is probably responsible for any benefits resulting from its use in these conditions. It is generally used as an ointment containing equal parts of ichthyol and petrolate, but may be used in 10 per cent or even weaker dilution. Ichthyol has been enthusiastically praised as a remedy in the most diverse conditions, but its sphere of utility has been much restricted of late, and it threatens to disappear from therapeutics altogether.

PREPARATION.

B. P.

ICHTHAMMOL. Ammonium Ichthosulphonate consists of the ammonium salts of the sulphonic acids of an oily substance, prepared from a bituminous schist, together with ammonium sulfate, and contains about 10 per cent of organically combined sulfur. It is a dark, viscid liquid with a strong odor. It is soluble in water and in alcohol and miscible with glycerin and fixed oils. 0.3–0.6 G. (5–10 grs.).

U. S. Bureau Mines Cir. 7042, 1938. (Ichthyol, Source and Properties. References.)

6. **Balsams.**

Another ancient treatment of wounds comprised the application of various balsams and some of these still maintain a position in therapeutics, though with increasing difficulty. Balsams are mixtures of resin, volatile oil, benzoic and

cinnamic acids and their esters. The chief survivors are *Benzoin*, obtained from Styrax Benzoin and other species, *Styrax* from Liquidambar orientalis, *Balsamum Peruvianum* from Toluifera Pereiræ or Myroxylon Pereiræ and *Balsamum Tolutanum* from another species of the same genus.

Benzoin and Balsam of Peru are applied in parasitic skin diseases, notably in scabies. And the compound tincture of benzoin (containing benzoin, styrax, aloes, and balsam of Tolu) is still used in doses of 2 cc. (30 mins.) as an ingredient of expectorant mixtures where the mucus is tenacious and coughed up with difficulty. It was formerly known as traumatic balsam and resembles in composition a number of old remedies which were known as Friar's balsam, Turlington's balsam, Jesuit's drops, etc. Syrup of Tolu is used merely as a flavoring agent.

PREPARATIONS.

U. S. P.

BALSAMUM PERUVIANUM. Balsam of Peru.
BENZOINUM, 1 G. (15 grs.).
ADEPS BENZOINATUS. Benzoinated Lard.
TINCTURA BENZOINI, 1 cc. (15 mins.).
TINCTURA BENZOINI COMPOSITA, 2 cc. (30 mins.).
STYRAX, 1 G. (15 grs.).
BALSAMUM TOLUTANUM. Balsam of Tolu.
SYRUPUS BALSAMI TOLUTANI, 10 cc. (2½ fl. drs.).
TINCTURA BALSAMI TOLUTANI, 2 cc. (30 mins.).

B. P.

BALSAMUM PERUVIANUM. Balsam of Peru. 0.3–1 mil. (5–15 mins.).
BALSAMUM TOLUTANUM. Balsam of Tolu. 0.3–1 G. (5–15 grs.).
SYRUPUS TOLUTANUS. Syrup of Tolu. 2–8 mils. (30–120 mins.).
TINCTURA TOLUTANA. Tincture of Tolu. 2–4 mils. (30–60 mins.).
BENZOINUM. Benzoin. 0.6–2 G. (10–30 grs.).
TINCTURA BENZOINI COMPOSITA. Compound Tincture of Benzoin or Friar's Balsam. 2–4 mils. (30–60 mins.).
STYRAX, 0.6–2 G. (10–30 grs.).

Many other drugs applied to the skin may exercise some germicidal action along with their other properties, but are discussed elsewhere. (See zinc, lead, sulfur ointments.)

III. INTESTINAL DISINFECTANTS.

1. Salol.

Salol, or phenyl-salicylate ($C_6H_4.OH.COO.C_6H_5$), may be taken as a type of the drugs used to disinfect the intestine, or at any rate to retard the growth of bacteria in the contents and the wall of the bowel. It is a very insoluble, crystalline body, which has little or no local action in the mouth or stomach, but is decomposed in the intestine by the fat-splitting ferment of the pancreatic juice. Some decomposition also appears to occur in the stomach, at any rate under certain conditions. The products of its decomposition, salicylic acid and phenol, are supposed to act as antiseptics in the bowel and are then absorbed and produce their usual effects. Salol is regarded chiefly as a substitute for salicylic acid, but the formation of phenol from it in the body must not

be overlooked, for in several cases of dangerous poisoning which have been observed under it, the symptoms were those characteristic of carbolic acid, and the urine became dark in color from the phenol oxidation products. In moderate quantities, salol produces the disturbances of hearing observed under salicylic acid, without any symptoms of carbolic poisoning.

Salol has been used to lessen putrefaction in the bowel, and even to act upon the bacilli of typhoid fever and of tuberculosis of the intestinal wall. Kumagawa, however, states that the putrefaction in the bowel as measured by the indican in the urine is unchanged by its administration, and he found enormous numbers of bacteria in the fæces afterward. It certainly seems of little value in typhoid fever or in tuberculosis of the intestine. Intestinal calculi have been formed in a few instances from prolonged treatment with salol which failed to be decomposed in the intestine and formed masses of considerable size.

Salol has been used to diagnose stenosis of the pylorus, as it was supposed that in these cases the reaction for salicylic acid in the urine would be delayed when salol was given. But some salol is absorbed from the stomach, and the interval before salicylic acid appears in the urine varies widely in normal persons, so that the test is of little value.

Salol has some value as a genito-urinary disinfectant, partly owing to the salicylic acid component and partly to the phenol developed.

It has been used as a substitute for salicylic acid in rheumatic fever, and has the advantage of being tasteless and of producing no irritation in the stomach. On the other hand, the considerable amount of carbolic acid freed by its decomposition has given rise to poisoning and in any case the presence of the phenol sharply limits the amount of salol which can be given, thus diminishing the dose of salicylic acid. Externally it is of little or no value as an antiseptic, as it is only active when it is decomposed.

PREPARATIONS.

PHENYLIS SALICYLAS (U. S. P.), phenyl salicylate ($C_6H_4OHCOOC_6H_5$), salol, a white crystalline powder, odorless or faintly aromatic, almost tasteless, almost insoluble in water, decomposed by the pancreatic juice into salicylic acid and phenol. 0.3 G. (5 grs.), in powder or capsule.

Other salicylic acid compounds, similar to salol, are BETA-NAPHTHYL SALICYLATE, CRESALOL (cresol salicylate), THYMOSALOL (from thymol), GUAIACOL-SALOL. They are less poisonous than salol, but have not been largely used. Phenetsal breaks up in the intestine into salicylic acid and paraminophenol. It is claimed that it is useful not only as an intestinal antiseptic but also on account of its antipyretic qualities.

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2. Other Intestinal Disinfectants.

Most of the drugs possessing disinfectant properties have been used at one time or another in the hope of reducing the intestinal putrefaction, but have generally been abandoned after a shorter or longer vogue. Among these may be mentioned carbolic acid, corrosive sublimate, resorcin, naphthol and thymol. As has been stated (p. 775), there is

little prospect of destroying bacteria imbedded in the wall of the intestine without serious injury to the mucous membrane. On the other hand putrefaction of the contents of the bowel is better treated by their evacuation than by attempts to retard the process in the body.

IV. GENITO-URINARY ANTISEPTICS.

1. Volatile Oils.

A group of volatile oils is used chiefly for genito-urinary disinfection. The best known of these are the *Oils of Copaiba, Cubebs and Sandalwood*, which resemble each other closely in character. Oil of cubebs and oil of copaiba contain a large proportion of a sesquiterpene ($C_{15}H_{24}$), and the oil of sandalwood has two oxidized substances (santalol and santalal), which can be reduced to a sesquiterpene identical with that of copaiba. In copaiba the volatile oil is associated with one or more resinous acids, and in cubebs there is in addition to resinous acids a bitter substance, *Cubebin*, which is not absorbed from the stomach and bowel and is entirely inactive. Cubebs and copaiba have long been used as genito-urinary disinfectants, while sandalwood oil is a more recent addition to the group, which is less disagreeable to take and has less tendency to disturb the digestion. These oils have the irritant effects on the skin, stomach and intestine common to the class of volatile oils, are absorbed readily and are excreted partly by the lungs, but chiefly by the kidneys in combination with glycuronic acid; some oil is unchanged, some is partially oxidized in the tissues.

The products of the oils excreted in the urine appear to have some antiseptic action, for the urine of persons treated with them putrefies more slowly than ordinary urine and the growth of many of the more common germs is retarded by it; thus Jordan found that the urine was powerfully germicidal to a staphylococcus after sandalwood oil had been taken, and this action persisted even when the urine was rendered alkaline; on the other hand the colon bacillus grew luxuriantly; others have found that gonococci grow readily in media made up with such urine. Winternitz therefore attributes the undoubted efficacy of these oils in gonorrhœa to their glycuronic compounds precipitating proteins and thus acting as slight astringents along the urinary tract, as well as to their antiseptic action.

In large quantities, these oils cause irritation in the bladder and urethra, which leads to a constant desire to micturate, and to much pain and difficulty in doing so; sometimes the pain is so great as to lead to complete retention. When the urethra or bladder is in a state of inflammation, these symptoms are produced by even small doses, so that these oils are generally avoided in the acute stages of inflammation, and only given later when the disease has passed into the subacute or chronic stage. They are used in some inflammatory affections of the bladder, but much more extensively in gonorrhœa.

Copaiba and cubebs both contain resinous acids in addition to the volatile oil, and these possess considerable diuretic powers, and are

also credited, along with the oils, with some action on the bronchial mucous membrane, so that they often form constituents of "expectorant" mixtures, prescribed to lessen the secretion of the bronchi. These resins are excreted in the urine, and are precipitated by the addition of acids; this precipitate has sometimes been mistaken for albumin, but can easily be distinguished from it by the addition of alcohol, which redissolves the resin but not the protein. The urine is often found to reduce Fehling's solution, from the glycuronic acid combined with the oil. The oil of sandalwood is excreted more rapidly than the others. Copaiba and cubebs are less irritant to the stomach than many of the other volatile oils, but after their prolonged administration (especially in the case of copaiba) symptoms of gastric disturbance sometimes appear in loss of appetite and uneasiness in the stomach. Sandalwood oil is said to be less irritant than the others. Occasionally skin eruptions occur after the use of these oils; they are generally of the nature of urticaria, sometimes of erythema nodosum, and only very rarely is eczema seen. The cause of these skin eruptions is unknown. Sandalwood oil is credited with being less likely to cause the eruptions of the skin than the other members of the group.

Therapeutic Uses.—As has been mentioned, these drugs find their most extensive application in the subacute stages of cystitis and gonorrhœa; less often copaiba is prescribed along with other diuretics to promote the secretion of urine. They are also used in bronchial disease with an excessive flow of mucopurulent secretion. The cubeb lozenges are sucked in hoarseness and relaxed sore throat, and often give relief owing to the pungent peppery action.

In gonorrhœa the therapeutic agent is undoubtedly the volatile oil, the resin having little or no antiseptic action. The oils and the oleoresins are often administered in capsules, as they have an unpleasant odor and taste, especially those of copaiba. They may also be given in emulsions, and cubebs is sometimes prescribed as a powder suspended in mucilage.

Several other oils have been used as substitutes for Copaiba and Cubebs. Among these may be mentioned Gurjun Balsam, which is obtained from Dipterocarpus alatus, and contains a sesquiterpene and a resin. It has been used in gonorrhœa and as a local application in leprosy. Various peppers have been employed as substitutes for cubebs in gonorrhœa, among them *Matico*, but they have not proved so useful as the three typical oils.

Preparations.

U. S. P.

Copaiba, 1 cc. (15 mins.).
Oleum Santali, Oil of Sandalwood, 0.5 cc. (8 mins.).
Balsam of Copaiba is an oleoresin derived form various species of Copaiba.
Oil of Sandalwood is the oil distilled from the heartwood of Santalum Album

B. P.

Copaiba, 0.6–2 mils. (10–30 mins.).
Oleum Santali, 0.3–1 mil. (5–15 mins.).
Oleum Santali Australiensis, Oil of Australian Sandalwood, 0.3–1 mil. (5–15 mins.). Oil distilled from the wood of Eucarya spicata.

COPAIBA, Balsam of Copaiba, Copaiva, is the oleoresin of Copaiba Langsdorffi and of species of Copaifera.

CUBEBA (Cubebs) is the unripe fruit of Piper cubeba.

OLEUM SANTALI, Sandalwood oil is distilled from the wood of Santalum album.

Oil of Sandalwood yields about 90 per cent of SANTALOL ($C_{15}H_{24}O$), a mixture of sesquiterpene alcohols, and recently compounds of santalol have been introduced as genito-urinary antiseptics with the claim that they are less irritant to the stomach than the oil. Santalol itself has been prescribed under the name ARHEOL and its salicylic acid ester under the name of SANTYL.

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See also the bibliography of the volatile oils in general.

2. Hexamethylenetetramine, Methenamine, Hexamine.

Hexamethylenetetramine ($(CH_2)_6N_4$), official as *methenamine* (U.S. P.) and *hexamine* (B. P.) has no important action itself, but is of interest from its liberating formaldehyde in the course of its excretion in the urine; formaldehyde is a powerful disinfectant, and the small quantities liberated from methenamine are sufficient to prevent putrefaction of the urine for many hours. It seems a superior urinary antiseptic under certain conditions, microbes in the urine decreasing in number or sometimes disappearing altogether within a few hours of its administration. Formaldehyde is formed from methenamine only in the presence of acid, and the only fluids in the body which are acid enough to liberate it are the gastric juice and the urine. A certain amount of the drug swallowed is decomposed in passing through the stomach, but enough is absorbed unchanged to act in the urine if it is acid; when it is alkaline, methenamine has no disinfectant action in the urinary passages; when, however, in those cases the reaction of the urine is rendered acid by the administration of acid phosphates or ammonium chloride or nitrate, formaldehyde is formed from methenamine and satisfactory results follow. It follows therefore that in order that the treatment with methenamine be successful the pH of the urine shall be controlled and should in general be kept below 5.6. Methenamine is readily soluble and permeates freely into most organs and secretions of the body; thus it has been found in the bile, pancreatic juice and cerebrospinal fluid, and this has suggested its use in infections of these fluids. But there is no evidence that formaldehyde is liberated from it in any of these, and there is equally little ground for believing methenamine is of benefit in infections of the gall-bladder, pancreas, or central nervous system. No symptoms arise from ordinary doses of methenamine, but large quantities have occasionally given rise to gastric discomfort and to pain and discomfort in the bladder, and more rarely to hæmaturia; the irritant here is not the unchanged drug but the formaldehyde liberated by it.

Formaldehyde forms some soluble combinations with uric acid, and this suggested the use of methenamine in gravel, calculus, gout, and similar conditions, but the results have been disappointing. Methenamine is not diuretic.

Therapeutic Uses.—Methenamine is used in cystitis and urethritis and to destroy typhoid bacilli which are eliminated by the kidney. It should not be used in acute gonorrhœa or tuberculosis. It may be given as a prophylactic before a catheter is passed. In order to secure that the urine shall be acid, methenamine is often given along with acid sodium phosphate (1 G. [15 grs.]), ammonium nitrate or ammonium chloride.

Numerous compounds of methenamine have been introduced of late years but none of these has proved superior to the original drug, and none of them forms formaldehyde in alkaline urine.

PREPARATIONS.

U. S. P.

METHENAMINA, 0.3 G. (5 grs.).

B. P.

HEXAMINA, 0.6–2 G. (10–30 grs.). Hexamine or methenamine is hexamethylenetetramine.

METHENAMINA (U. S. P.), HEXAMINA (B. P.), $((CH_2)_6N_4)$ is a white crystalline powder, very soluble in water and giving off formaldehyde in acid solution. It should be taken in a glass of water.

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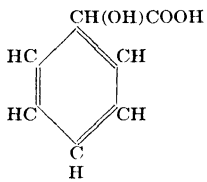
3. Mandelic Acid.

While it has been known for a long time that acid urines are less favorable for the growth of bacteria, it is only recently that serious attempts were made to utilize a high fat, low carbohydrate diet to produce a state of ketosis in order to control urinary infections. The results were so successful that the simpler method of inducing the same condition by the use of a low calorie or starvation diet was employed to avoid the difficulties associated with the ketogenic diet first used. It was soon pointed out by Rosenheim that while the results thus obtained by these diets were due to the beta-hydroxybutyric acid, the method of attaining this end were unnecessarily complicated and could be reached by the more direct means of administering an acid at once. It was not feasible to administer the hydroxybutyric acid itself by

mouth because when given in this manner it is largely oxidized to carbon dioxide and water before reaching the kidney. From the various organic acids which were studied, mandelic acid was selected as being most suitable for the purpose, inasmuch as it is relatively non-toxic and is excreted unchanged by the kidneys.

Mandelic acid (alpha-hydroxy-alpha-toluic acid) is a white crystalline



powder relatively soluble in water (16 per cent at 20°) and is usually given dissolved in water in doses of 3 G. four times daily. The sodium salt has been used, but lately the ammonium salt has largely replaced it.

While mandelic acid has not been employed for long, the reports of its use are quite favorable. In uncomplicated cases of urinary infection it has been said to be bactericidal in 80 per cent of cases (Braasch). It is true that not all reports are quite so optimistic and a longer trial with the drug will be necessary in order to assign it its correct place in the group of urinary antiseptics.

In order to insure its greatest degree of effectiveness several precautions are necessary. The fluid taken by the patient should be restricted to 1200 cc. per day and the pH of the urine must be observed daily and kept below 5.6. If the desired degree of acidification is not attained it may be necessary to give some drug such as ammonium chloride. If these conditions are obtained the urine usually becomes bactericidal in two or three days and free from infection in six or seven. It is seldom necessary to continue this therapy longer than ten or twelve days and indeed it is inadvisable to do so because of the possibility of renal irritation. In some patients a return of the infection has been seen after the drug has been stopped and in such cases it may be necessary to repeat the treatment after allowing a rest interval of a week or so.

The administration of the drug produces at times nausea but rarely does it cause diarrhœa. It also may cause renal irritation with the presence of hyaline casts. Small numbers of red blood cells are found in the urine at times and more rarely gross hematuria. The drug is contraindicated in cases of renal insufficiency as it might act as an additional source of irritation to the kidney and in addition it might not be excreted in sufficient amounts to make the urine bactericidal.

Preparation.

U. S. P.

Acidum Mandelicum ($C_8H_8O_3$), racemic mandelic acid. Dose, 3 G. (45 grs.).

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4. Minor Genito-Urinary Antiseptics.

Hexylresorcinol.—Recent study of resorcinols has demonstrated that the introduction of the alkyl group into resorcinol brings about a sharp drop in toxicity together with a rise in bactericidal power. These changes appear to be in direct proportion to the molecular weight of the alkyl chain which reaches its maximum influence at the n-hexyl derivative which is said to show a phenol coefficient of 46. This compound, hexylresorcinol (introduced also under the name of Caprokol), has been recommended as a genito-urinary disinfectant. It is non-toxic in therapeutic doses and non-irritating to the urinary tract and while most of the drug administered is excreted in a conjugate form which is inert, a sufficient amount is excreted in the urine to give a definite bactericidal action. The disinfectant action is especially effective against infections of the urinary tract with streptotoccus albus and aureus while B. coli infections are more resistant. The activity of the drug is not influenced by the reaction of the urine but the administration of sodium bicarbonate by mouth when hexylresorcinol is being taken seems to entirely destroy its disinfectant action in the urine. This action of the bicarbonate is said to be due to the fact that it raises the surface tension of the urine. It is recommended also that large amounts of water should not be taken for the same reason.

The drug appears to be relatively non-toxic as rabbits tolerate large single doses (1–2.5 G.) without showing ill effects and even daily doses of 0.5 gram given for some weeks were followed by no toxic effects. When given to man it is not infrequently followed by diarrhœa for a few days but this effect soon passes off. Hæmaturia has also been reported.

Hexylresorcinol is given in gelatine capsules in doses ranging from 0.15–0.6 G. dissolved in olive oil, three times a day.

The drug is recommended to be used in cases of pyelitis and cystitis and it may be necessary to give it over a considerable period of time—even two or three months. Its use is still in the experimental stage and reports regarding its value are contradictory.

More recently crystalline hexylresorcinol has been recommended as an anthelmintic to be used against ascaris and uncinaria. The crystalline drug is administered in capsules in doses of from 0.4–1 G. according to the age of the patient. It should be given on an empty stomach and no food should be taken for some hours afterward, and a saline purge given about twenty-four hours later.

The comparatively limited number of cases which have been studied up to the present time seems to offer evidence of an effective anthelmintic for the treatment of cases infected with round- or hookworms and at the same time the drug appears to be relatively non-toxic, few symptoms having been encountered in its use beyond signs of a mild gastric irritation in certain individuals.

Further experience with the drug would seem necessary before final judgment can be given as to its efficiency in these conditions.

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The salicylates have some effect in retarding the growth of microorganisms in the genito-urinary tract and sodium salicylate and salol have been used for this purpose. Benzoic acid and ammonium benzoate have also been used to disinfect the urine, and, as in the case of salicylate, act well when it is acid, but lose their effect largely when it is alkaline. Arbutin, a glucoside contained in the uva ursi, is also credited with some antiseptic properties, but is not used now. Boric acid and borax are both good genito-urinary antiseptics and differ from the other more active drugs of this class in retaining their disinfectant action when the urine is alkaline.

V. ANTISEPTICS IN PULMONARY DISEASE.

Creosote.

Creosote may be regarded as a wood-tar from which the more poisonous phenols and the less volatile bodies have been eliminated, leaving guaiacols and creosols as the chief constituents. Its action is similar to that of carbolic acid, except that it has less tendency to induce nervous symptoms, and is less irritant and poisonous. On the other hand, it seems at least as strongly antiseptic as carbolic acid, and, according to some investigators, far excels it as a germicide. Its chief constituents, the *Creosols* ($C_6H_3CH_3OH.OCH_3$) and *Guaiacols* ($C_6H_4OH.OCH_3$), resemble carbolic acid and the other aromatic phenols in their action. They are excreted in the urine for the most part in combination with sulfuric and glycuronic acids.

Guaiacol is readily absorbed from the skin when rubbed into it and considerable amounts can be regained from the urine afterwards. When large quantities are thus taken up from the skin, they often cause a rapid fall of fever temperature with exhaustion and all the symptoms of mild collapse, followed by shivering and rigor and a return of the high temperature. This condition of poisoning is exactly similar to that seen under other benzene derivatives of simpler constitution.

Guaiacol carbonate ($(C_7H_7O)_2CO_3$) is almost insoluble and tasteless, and liberates guaiacol in the intestine.

Therapeutic Uses.—Creosote is seldom used now except perhaps in the treatment of pulmonary phthisis and gangrene, and chronic bronchial inflammation. It is generally given by the mouth in these cases, but the vapor has been recommended as an inhalation, and some practitioners have injected creosote solution into the trachea, in order to ensure its reaching the lungs. None of these methods is believed to give such good results as the ordinary administration by the mouth. Guaiacol and guaiacol carbonate have been substituted for the creosote and are more pleasant forms.

The results of creosote medication are still disputed. A few clinicians state that a general improvement follows in phthisical patients, that the appetite is improved, the cough and expectoration lessened and that the patient feels stronger and better. On the other hand, most are extremely skeptical as to any benefits arising from creosote, and regard it as merely one of the countless remedies which have been recommended in this condition, and which, after a shorter or longer period of popularity, have passed into oblivion.

It was generally supposed by the advocates of the creosote treatment that the remedy destroyed the tubercle bacillus in the lungs through its antiseptic properties. On the other hand, animals infected with tubercle bacilli and treated with creosote die as soon as controls which are untreated, and the sputum of phthisical patients treated with creosote is as virulent as that of others not so treated. Besides, the administration of creosote by other ways than by the mouth was said to be much less efficacious. Another explanation of the creosote action was

that it acted as an intestinal antiseptic and prevented the secondary infection of the bowel; but it was pointed out that the other intestinal antiseptics were of little value in tuberculosis. It seems useless to speculate on the method of action until it has been definitely determined that creosote does have value in phthisis, and this can be done only by careful statistical inquiry. The medical profession has much less faith in the efficacy of the creosote treatment than it had some years ago, when it was not generally recognized that pulmonary tuberculosis is curable by hygienic measures in a considerable proportion of instances.

PREPARATIONS.

U. S. P.

CREOSOTUM, 0.25 cc. (4 mins.).
CREOSOTI CARBONAS, 1 G. (15 grs.).
GUAIACOL, 0.5 cc. (8 mins.).

B. P.

CREOSOTUM, 0.12–0.6 mil. (2–10 mins.).
GUAIACOL, 0.3–0.6 mil. (5–10 mins.).

CREOSOTUM is obtained from wood-tar, preferably from beech tar, and is an almost colorless, oily liquid with a smoky odor and hot, burning, acrid taste. It is slightly soluble in water, and mixes readily with alcohol. It tends to darken in color when exposed to the light.

CREOSOTI CARBONAS is a mixture of the carbonates of the constituents of creosote, chiefly guaiacol and creosol.

Creosote may be administered in pills, capsules, or in solution in alcohol. It ought not be allowed to reach the mucous membranes in a concentrated form, as it is liable to irritate them.

GUAIACOL ($C_6H_4OH{\cdot}OCH_3$), consists of colorless crystals, or a fluid, with an agreeable aromatic odor, soluble in 80 parts of water and in alcohol. It is given in solution in alcohol or cod-liver oil, or in pills.

GUAIACOLIS CARBONAS ($(C_7H_7O)_2CO_3$), an almost tasteless powder, is occasionally given in cachets in 1 G. or 15-grain doses.

VI. DISINFECTANTS FOR ROOMS, FURNITURE, ETC.

1. Formaldehyde.

Formaldehyde (HCHO), the aldehyde derived by oxidation from methyl alcohol, is a very powerful germicide, while it is not very dangerous to the higher animals. The aldehyde is a colorless gas and has been used either in solution in water (*formalin*) or as a vapor. As a germicide it is estimated to be as efficient as corrosive sublimate, and its volatility enables it to penetrate much more rapidly so that it may be used for purposes for which the latter is unsuitable.

Action.—The vapor is very irritant when inhaled, causing stinging and prickling in the nose and throat, salivation and tears, and bronchial irritation and catarrh. In the few cases of poisoning in man recorded, the symptoms were those of gastric irritation and consequent collapse. When swallowed by animals the watery solution produces nausea and

vomiting, which are followed by narcosis, coma, and in the rabbit by convulsions and opisthotonos. The respiration in the dog is very greatly accelerated some time before death, while in the rabbit this is not as marked or is entirely absent. The blood-pressure is increased at first, and the heart is slow from direct action on the cardiac muscle. Formaldehyde is rapidly absorbed from the alimentary tract and also by the lungs but quickly disappears from the blood owing to its oxidation and excretion; some formic acid is said to be formed from it, and formaldehyde has been detected in the urine, the gastro-intestinal secretions, and the expired air.

The powerful action of formaldehyde on microbes and on mucous membranes is believed by Loew to be due to its combining with the amino groups in the proteins, and as a matter of fact, a number of changes have been described in the reaction of proteins exposed to this gas. For example, egg albumen and serum to which formaldehyde solution has been added are not precipitated by heat and are less easily digested by ferments, while casein is not coagulated by the rennet ferment. Some of the ferments (pepsin and diastase) are not affected by small amounts of formaldehyde, while trypsin and papain lose their activity wholly or in part.

Uses.—Formaldehyde is too irritant to admit of its use as an antiseptic in medicine and surgery, but it has been largely employed to disinfect instruments, furniture, clothes and rooms, which cannot be sterilized by heat. Diluted liquor (4 per cent) may be used for some of these purposes, or the vapor may be disengaged by distillation from the liquor or by heating paraform. Large rooms filled with formaldehyde vapor and left for some hours are found to be almost completely sterilized, so that cultures of the pathogenic microbes exposed in them cease to grow even when removed from the atmosphere. Novy makes the room to be disinfected as nearly air-tight as possible and distils the formaldehyde into it through the key-hole of the door. He states that the gas disengaged from 150 cc. (5 oz.) of 40 per cent liquor is sufficient for each 1000 cubic feet of space, if the room is closed for ten hours. The odor of formaldehyde may then be removed by sprinkling ammonia solution with which it forms hexamethylenamine. The disinfectant action of formaldehyde is increased by moderate warmth, and a longer time must be allowed for it to act if the temperature of the room is below 50° F. Formaldehyde not only destroys the microbes, but also alters the toxins formed by them so that they are no longer poisonous, even in very large quantities.

The action of formaldehyde against bacterial toxins has taken on great importance recently as these detoxified products are being used very largely under the name of "toxoids" for the production of immunity, especially against diphtheria. The pharmacopœias recognize such a product in Toxinum Diphthericum Detoxicatum, where the diphtheria toxin is treated with 0.3 to 0.5 per cent formaldehyde at body temperature until its toxicity is so reduced that five human doses injected into guinea-pigs cause no local or general symptoms of poisoning within thirty days. Such a product retains its property of inducing

active immunity. It is usually given in two 1 cc. doses, administered with an interval of three or four weeks between the doses.

Formaldehyde has been added to food, especially to milk, as a preservative. Tunnicliffe and Rosenheim found that, in the proportion of 1 to 5000, formaldehyde did not seem to be deleterious to healthy children, but in the case of a weakly child the protein waste was increased, and it is certainly not to be regarded as a harmless method of preserving food and its use for this purpose has been virtually given up as it is likely to produce gastric disturbances.

Formaldehyde is not alone in its germicidal action, although it is much more powerful than the other less volatile and less active aldehydes, such as acetaldehyde.

PREPARATIONS.

LIQUOR FORMALDEHYDI (U. S. P., B. P.), formalin, a solution of formaldehyde in water containing not less than 37 per cent of the gas, which may be obtained from it by distillation.

PARAFORMALDEHYDUM $(HCHO)_3$, paraform, a solid polymer of formaldehyde, which is partly decomposed by heat and liberates formaldehyde in gaseous form.

Some formaldehyde may be formed by the incomplete combustion of methyl alcohol, and several lamps have been devised with this object in view, but have not proved satisfactory.

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2. Sulfur Dioxide.

Sulfurous acid is a powerful reducing agent, as it becomes oxidized to sulfuric acid, and this renders it poisonous to protoplasm in general, quite apart from its acidity. Sulfurous acid anhydride has accordingly been used occasionally to disinfect rooms and furniture after infectious diseases; for this purpose sulfur is burned in the room, which ought to be rendered as air-tight as possible, and the fumes are allowed to act for several hours before the room is ventilated. The value of this method of disinfection has been called in question, and though sulfurous acid gas is fairly germicidal when it is applied along with moisture, it may be doubted whether it has ever been used efficiently in practice; unless efficient, the procedure is open to the objection that it may lend a sense of security which is quite unwarranted, and may lead to the neglect of other measures. Sulfur dioxide bleaches and rots most materials, and the fumes are fatal to the higher animals, even when much less con-

centrated than are necessary to destroy bacteria. In order to be of service, at least 1 volume of SO_2 ought to be present in each 100 volumes of air, and even this concentration is insufficient to destroy the spores of bacteria. Novy[1] recommends 3–6 pounds of sulfur to be burned for each 1000 cubic feet of space; the walls and floor should be sprayed with water, and the room must be kept perfectly closed for at least twenty hours.

The chief symptoms of poisoning with sulfurous acid solution are those of irritation of the mucous membranes, and if the solution is swallowed these may not differ from those of other irritants.

In poisoning from the inhalation of the anhydride, the symptoms arise chiefly from the respiratory tract. Even in 5 parts in 10,000 it acts as an irritant, causing sneezing, coughing and lacrimation, and in somewhat greater concentration it becomes entirely irrespirable; smaller quantities in the air cause bronchial irritation and catarrh, when inhaled for some time. Sulfurous acid is neutralized and oxidized for the most part to sulfates in the tissues, or probably partly in the course of absorption.

Sodium sulfite (Na_2SO_3) and thiosulfate or hyposulfite ($Na_2S_2O_3$) are rapidly changed to the sulfate when given by the mouth; the liberation of SO_2 in the stomach may cause some gastro-intestinal irritation in man, and in animals vomiting has occurred from it. Injected subcutaneously in the frog they cause muscular weakness and finally central nervous paralysis; in the cat and dog a preliminary stage of vomiting, dyspnœa and restlessness is seen, apparently from direct action on the centre in the medulla and on the heart and vessels. When applied in this way the sulfite is excreted in the urine as sulfate, while the thiosulfate is changed more slowly and from a third to a half may escape by the kidneys unchanged. Solutions of these salts have been used to some extent as antiseptic mouth washes. Their earlier reputation as blood and tissue disinfectants in septicæmia is unmerited and they are no longer employed for this purpose.

3. Chlorine and Bromine.

Chlorine and bromine resemble each other closely in the effects which they induce in all forms of living matter. These may be explained in part by their replacing hydrogen in its combinations in the proteins and forming hydrochloric or hydrobromic acid with the hydrogen set free, in part by their combining with the hydrogen of water and thus liberating oxygen, which then acts on the tissues. These processes are believed to account for the fact that chlorine is a much more powerful disinfectant in moist air than in dry. In the higher organisms all of these reactions probably occur together.

Action.—Chlorine and bromine are general protoplasm poisons; thus 3 parts of chlorine in 1000 parts of moist air are sufficient to destroy the spores of most bacteria in the course of three hours, and the infusoria and the higher plants have been shown to be equally susceptible to the influence of the gas. Even smaller quantities of bromine are disinfectant.

In the higher animals and in man chlorine and bromine act as irritants, causing irritation and redness and even blistering of the skin

[1] Novy and Waite. Medical News, vol. **72**, p. 641.

when applied to it in solution, and eliciting when swallowed intense inflammation and corrosion of the mouth, throat, and stomach, with collapse and all the ordinary effects of gastric irritation. Air containing 1 part of chlorine in 100,000 irritates the eyes, nose, larynx and the deeper respiratory passages; bronchitis, pulmonary congestion and hæmorrhages, coughing and pain in the thorax are induced by somewhat higher concentrations, and exposure to about 1 part in 3000 for fifteen minutes causes acute œdema of the lungs, which may prove fatal immediately. More dilute vapor may be equally dangerous if the exposure is longer. Chlorine and bromine as such are not used in therapeutics, but have given rise to poisoning in their industrial use, and the former has more recently acquired notoriety from its being used in warfare.

These symptoms of chlorine and bromine poisoning are caused by their local action only; they are changed to hydrochloric and hydrobromic acids, and these again to chlorides and bromides in the course of absorption. Attention has been drawn to a number of cases in which symptoms arose in workmen in chemical factories where chlorine is liberated by electrolysis, or more rarely in others where hydrochloric acid is formed in large quantities. The most marked symptom is an affection of the sebaceous glands, from which the condition receives its name of chlorine acne, but this often induces headache, sleeplessness, loss of appetite, and anæmia. No satisfactory explanation of the symptoms has been given, nor is it known whether the chlorine or some unknown body is the cause (Lehmann, Jacquet).

The **Hypochlorites** disengage chlorine more slowly than solutions of chlorine and are correspondingly less toxic to microbes and the higher forms of life. (See p. 802.)

The chlorine preparations are chiefly used to disinfect fæces, urinals and to a less extent rooms and houses; for this purpose chlorinated lime is the most suitable, especially when acid is added to it in excess. The room ought to be hermetically sealed, and the fumes are of no value as disinfectants unless they are present in such quantity as to render the air quite irrespirable. They have the disadvantage that they bleach most of the colors used in dyeing, and fail to penetrate in sufficient quantity into the clothing, which they also corrode to some extent. Chlorinated lime exposed in the sick-room serves merely as a deodorant, and has no disinfectant value, but has the disadvantage of giving a false feeling of security like other similar measures. Chlorine seems inferior to sulfurous acid anhydride, and still more so to formaldehyde as a disinfectant, not from its being weaker in action, but because it is more difficult to apply in sufficient quantity. Chlorinated lime can, however, be applied in urinals and closets, where both these disinfectants are unavailable. Here again it acts as a deodorant, while its disinfectant value is smaller.

Chlorine in the form of hypochlorite has proved effective in destroying the germs in drinking water; it should be added in such amount as to leave about 1 part of free chlorine in 1,000,000 of water. A compound which has recently been introduced for the same purpose is parasulphone dichloramido-benzoic acid or *Halazone* ($Cl_2N{\cdot}O_2SC_6H_4COOH$)

which is efficacious in about 4 parts per 1,000,000 and is more stable and more easily transported in small quantities than the hypochlorites. In the presence of alkaline carbonates, borates, and phosphates it will sterilize in thirty minutes water contaminated with typhoid and other bacilli when used in the strength of 4–8 mg. per liter. Tablets containing halazone and the necessary carbonate are available on the market.

PREPARATIONS.

U. S. P.

LIQUOR SODII HYPOCHLORITIS. This solution is the strong solution of sodium hypochlorite and contains about 5 per cent of NaOCl.

LIQUOR SODII HYPOCHLORITIS DILUTUS. The dilute solution of the hypochlorite of soda is a modified Dakin's solution, containing the equivalent of about 0.45 G. of available chlorine per 100 cc.

B. P.

CALX CHLORINATA. Chlorinated lime.

LIQUOR SODÆ CHLORINATÆ CHIRURGICALIS. Dakin's solution. Contains not less than 0.5 nor more than 0.55 per cent of available chlorine.

CALX CHLORINATA, chlorinated lime, bleaching powder, sometimes erroneously called chloride of lime, is a mixture of calcium hypochlorite ($Ca(ClO)_2$), calcium chloride ($CaCl_2$), lime and water. The hypochlorite is very unstable and gives off chlorine in air, and especially in the presence of an acid. Chlorinated lime forms a white or grayish-white powder, with the odor of chlorine. It is only partially soluble in water and must contain not less than 30 per cent of available chlorine.

LIQUOR SODII HYPOCHLORITIS, solution of the hypochlorite of soda, Labarraque's solution or Javelle's solution, is formed from chlorinated lime and contains hypochlorite of sodium (NaClO) and chloride of sodium. Like the corresponding lime salts, it has the odor of chlorine and bleaches vegetable colors. It must contain at least 2.5 per cent by weight of available chlorine.

For preparations containing chlorine to be used for surgical disinfectants and similar purposes, see page 802.

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4. Other Disinfectants.

Many other substances may be employed as disinfectants of urinals, latrines, fæces, etc., the chief determining consideration being the cost of the material in most cases. Thus tar, or crude carbolic acid may be used to disinfect fæcal matter, and unslaked lime is applied to bodies in epidemics in the hope of preventing the liberation of infectious organisms. The most certain disinfectant, where it is available, is moist heat, which is generally used to disinfect clothes and bedding which have been in contact with infected persons.

PART VI.

VACCINES, TOXINS, ANTITOXINS (VEGETABLE TOXALBUMINS).

THE prophylactic or therapeutic effects of vaccines, toxins and antitoxins belong to the domain of bacteriology rather than of pharmacology, but, as these substances now find a place in our Pharmacopœias, a very brief account of their mode of action may be given here.

Vaccines.—It has long been known that spontaneous recovery can occur in man and in the lower animals from diseases now proved to be due to infection by pathogenic organisms. It was also early recognized that one attack of such disease might confer a partial or complete insusceptibility to subsequent infection. Thus a person who had suffered from an attack of smallpox was very unlikely to have a second attack, however much he might be exposed to infection. There would be no gain, however, in artificially subjecting a person to such a disease, merely to prevent a second attack, as obviously he would run all the usual risks and would be compelled to undergo a disease which in the normal course of events he might have escaped. It was a great and fruitful advance when Jenner showed that a person who had suffered from cowpox—a disease closely allied to, but much less severe than, actual smallpox—was less susceptible to smallpox itself. In other words, cowpox infection conferred an immunity against smallpox, as shown by the fact that a person who had had cowpox was less likely to acquire smallpox, or, if he did acquire the latter disease, suffered from it in a milder form. Advantage is taken of this fact in "vaccination" against smallpox. This is done by means of vaccine lymph, which is obtained from the vesicles produced by inoculation of vaccine virus on the skin of healthy animals. One minim of the lymph is applied by scarification to the skin, *e. g.*, of the arm or leg. This produces the local and constitutional reactions typical of cowpox and confers a high degree of immunity, lasting with diminishing intensity for many years, against smallpox infection.

Attempts have been made in the case of many other diseases to confer immunity by means of an attenuated virus. It has been found, for example, that injected bacteria, even when they are killed, can still provoke immunity. Immunization with dead bacteria can often be induced with relatively little risk or even inconvenience, because the organisms cannot multiply in the body and a safe but effective immunizing "dose" can be found by experience. Such a vaccination is used as a prophylactic against typhoid fevers. There are at least three bacilli, *viz.*, B. typhosus, B. paratyphosus *A*, and B. paratyphosus *B*, which are responsible for different kinds of typhoid fever. Though these bacilli are closely allied, an attack due to infection by one of them will not confer immunity against the others. By the use of a vaccine containing

all three a person can be simultaneously immunized against them all. This is now the usual practice. Vaccinum typho-paratyphosum is a standardized sterile suspension of those three bacilli which have been killed by heat. Two doses are usually given by subcutaneous injection, one of 0.5 cc. and the second, seven to ten days later, of 1 cc. Such vaccination has been practised on a large scale in many countries and has done much to lessen the incidence and gravity of typhoid fevers.

Rabies vaccine is prepared in a different way. The active causal organism of the disease is unknown. Pasteur, however, discovered that the virus of the disease is present in the central nervous system of animals which have suffered from it, and that a suspension of such nervous tissue, suitably prepared, can be used as a vaccine for prophylaxis of the disease. In practice the vaccine is used chiefly to confer an active immunity against rabies in cases of known or suspected infection, and this is possible owing to the relatively long incubation period. The attempt is made to render the bitten person sufficiently immune during this period to confer protection against the disease before the virus has had time to affect the nerve centres.

Other vaccines have been used both in the prophylaxis and treatment of many organismal diseases, but the value of those mentioned above is most certainly established and they are the only vaccines at present official.

The pathological disturbances of structure and function resulting from infection by pathogenic organisms are as a rule due not so much to mechanical or other effects of the bacteria themselves as to the action of toxins which they form. These toxins may act locally and generally. Escaping into the blood they may produce effects on organs remote from the actual seat of infection. The process of recovery of an animal from a bacterial disease is accompanied by the appearance in the blood and tissues of "antibodies," which in various ways inactivate the bacteria or neutralize their toxins. Antibody formation is not a reaction peculiar to bacteria or toxins but occurs when any foreign protein is injected. It is a reaction which occurs to all proteins and proteoses and to these only. It does not occur readily if at all when they are given by mouth, because the proteins are broken down by digestive processes in the alimentary canal into amino-acids which do not provoke this reaction. Antibody formation is one of the most important natural mechanisms for resisting invasions of bacteria or for neutralizing the protein-like toxins which they produce. It is perhaps the most general method by which a bacterial disease is overcome and "immunity" to it acquired. When an animal acquires immunity to bacteria or their toxins by being exposed naturally or artificially to their actions, the immunity so acquired is called "active immunity" because the animal manufactures its own antibodies, and the immunity so acquired may be lasting, depending upon the duration of antibodies in the tissues and other factors.

Toxins.—Just as active immunity can be induced by the injection of devitalized bacteria, as in the case of typhoid vaccines, so can similar immunity against toxins be induced by injection of attenuated toxins. Various methods are in use for reducing the virulence of a toxin without

destroying its power of provoking immunity. This can in some cases be successfully achieved by the addition to the toxin of the specific antitoxin or of formaldehyde. This procedure is adopted in the case of *Toxinum diphthericum detoxicatum*, B. P. and U. S. P. Active immunity to diphtheria, which may last for years, can be induced by injecting small doses of this toxin. It is therefore used as a prophylactic against diphtheria in much the same way as typhoid vaccine is used against typhoid fever.

It is not necessary artificially to immunize people who have already a high natural resistance to diphtheria and these can be excluded by the Schick test. This test consists in the intradermal injection of a specially prepared toxin (*Toxinum diphthericum diagnosticum*, B. P. and U. S. P.). Sensitivity to diphtheria is indicated by an area of redness at the site of injection. Such a reaction may be given, however, by non-specific substances in the toxin which is not a pure toxin. To exclude this possibility an intradermal injection is given simultaneously (*e. g.*, into the skin of the opposite arm) of the same amount of diagnostic toxin previously heated so as to destroy the toxin (*Toxinum diphthericum califactum*, B. P.). Persons showing a positive skin reaction with the diagnostic toxin and a negative reaction with the heated toxin are presumed to be susceptible to diphtheria infection. The Schick test is therefore merely a test diagnostic of susceptibility. Susceptible persons can then with advantage be actively immunized by injections of *Toxinum diphthericum detoxicatum*, as previously explained.

A very similar procedure is adopted in the diagnosis and treatment of scarlet fever. A toxin (*Toxinum Scarlatinæ Streptococcicum* U. S. P.) can be used by intracutaneous injection for determining susceptibility (Dick test) or by repeated subcutaneous or intramuscular injections to confer an active immunity. For purposes of treatment of scarlet fever, the antitoxin (*Antitoxinum Scarlatinæ Streptococcicum* U. S. P.) is used to confer a passive immunity.

Antibacterial Sera and Antitoxins.—As has already been explained, natural cure of many bacterial diseases results largely from the formation in the tissues of antibodies which inhibit the multiplication of bacteria or neutralize their toxins; and especially for prophylaxis, artificial immunity can be actively induced by suitable injections of attenuated bacteria or toxins. When a bacterial infection is severe or if the patient has a low resistance to it, antibody formation may not take place sufficiently rapidly or adequately to save the patient from the effects of the toxins. Once the toxin has combined with the tissues, antitoxin is incapable of dislodging it. It would be clearly of advantage, therefore, if the patient could be quickly supplied with the necessary antitoxin from extraneous sources. This can be done by injecting antitoxin obtained from a horse or other suitable animal which has been immunized against the toxin. The details of procedure for obtaining antitoxin varies in the case of different toxins. Generally, however, a horse is immunized by repeated injections of the toxin at intervals of a few days for a period of several months until the blood acquires a sufficiently high antitoxin content. The animal is then bled and the

separated serum collected and standardized according to its power of neutralizing toxin. This power is expressed in "units" compared with a standard antitoxic serum. The serum may be used as such or the separated globulins, which contain practically all the antitoxins. A person can be immunized against a toxin by an injection of such an antitoxic serum. Immunity conferred in this way is called "passive immunity" because the person does not manufacture his own antitoxins as a personal reaction to the toxin but receives the antitoxin ready made. Immunity passively produced in this way is more transient and usually less complete than active immunity, but has the advantages of speed and safety of induction. Antitoxins are used both as prophylactic and curative agents. In the latter case their value depends largely upon their being given sufficiently early and in sufficient doses, so that the toxin can be neutralized before it combines with the tissues and before it produces its toxic effects.

Official antitoxins are *Antitoxinum diphthericum, Antitoxinum tetanicum, Antitoxinum welchicum,* and *Serum antidysentericum,* which are used in the prophylaxis and treatment of diphtheria, tetanus, gas gangrene and bacillary dysentery, respectively. The B. P. Supplement 1936 introduced further *Antitoxinum œdematiens* (gas-gangrene antitoxin), *Antitoxinum staphylococcicum,* and *Antitoxinum vibrio septicum.* The B. P. has, therefore, three gas-gangrene antitoxins to antagonize the toxins of three pathogenic organisms which may cause gas gangrene, viz.: A. Welchicum (Bacillus perfringens or Welchii), A. œdematiens (Clostridium œdematiens), A. vibrio septicum (Vibrion septique).

These are the most important sera which are used to neutralize toxins. Sera can also be obtained to combat bacteria themselves, in which case the serum is obtained by immunizing a horse against the particular bacterium and is used much in the same way as an antitoxic serum. Of such sera those which have proved most successful in treatment are *antimeningococcus serum* and *antipneumococcus serum.*

Preparations.

U. S. P.

Vaccinum Rabies, rabies vaccine. Average dose: the contents of one container, to be repeated at proper intervals.

Vaccinum Typhosum, bacterial vaccine made from the typhoid bacillus. Average dose, by hypodermic injection, 0.5 cc. and 1 cc., the latter dose to be repeated once.

Vaccinum Typho-paratyphosum, bacterial vaccine made from the typhoid bacillus and the paratyphoid "A" and "B" bacilli. Average dose as for Vaccinum Typhosum.

Vaccinum Variolæ, smallpox vaccine.

Toxinum Diphthericum Detoxicatum, diphtheria toxoid. Average dose by hypodermic injection, prophylactic, 1 cc.

Toxinum Diphthericum Diagnosticum, diphtheria toxin for the Schick test. Average dose, intracutaneous, 0.1 cc.

Toxinum Scarlatinæ Streptococcicum, scarlet fever streptococcus toxin. Average dose for determining susceptibility (Dick test), intracutaneous, 0.1 cc.

Antitoxinum Diphthericum, diphtheria antitoxin. Average dose by parenteral injection: therapeutic, 10,000 units; prophylactic, 1000 units.

ANTITOXINUM SCARLATINÆ STREPTOCOCCICUM, scarlet fever antitoxin. Average dose, by parenteral injection: therapeutic, 6000 units; prophylactic, 2000 units.

ANTITOXINUM TETANICUM, tetanus antitoxin. Average dose by parenteral injection: therapeutic, 20,000 units; prophylactic, 1500 units.

SERUM ANTIMENINGOCOCCICUM, antimeningococcic serum. Average dose by parenteral injection, therapeutic, 20 cc.

SERUM ANTIPNEUMOCOCCICUM-1, antipneumococcic serum, Type 1. Average dose, by parenteral injection, therapeutic, 30 cc.

B. P.

VACCINUM VACINNIÆ, vaccine lymph. 0.06 mil.; 1 min., by scarification.

VACCINUM TYPHO-PARATYPHOSUM, antityphoid-paratyphoid vaccine; by subcutaneous injection, 0.5 mil. (first dose), 1 mil. (second dose after seven to ten days interval).

TOXINUM DIPHTHERICUM DETOXICATUM, diphtheria prophylactic. The requisite dose is indicated on the label and is given by subcutaneous injection on two or three occasions at intervals of two to four weeks.

TOXINUM DIPHTHERICUM DIAGNOSTICUM, Schick test toxin, and

TOXINUM DIPHTHERICUM CALIFACTUM, both by intradermal injection. 0.2 mil. (3 mins.).

ANTITOXINUM DIPHTHERICUM, diphtheria antitoxin. Doses by injection: prophylactic, 500 1000 units; therapeutic, 10,000–20,000 units.

ANTITOXINUM ŒDEMATIENS, gas-gangrene antitoxin (œdematiens). Doses by injection, prophylactic, 20,000 units; therapeutic, 50,000–100,000 units.

ANTITOXINUM STAPHYLOCOCCICUM, staphylococcus antitoxin. Doses by injection, 5000–20,000 units.

ANTITOXINUM TETANICUM, tetanus antitoxin. Doses, by injection: prophylactic, 1000–2000 units; therapeutic, 20,000–40,000 units.

ANTITOXINUM VIBRIO SEPTICUM, gas-gangrene antitoxin (vibrion septique). Doses by injection, prophylactic, 5000 units; therapeutic, 10,000–20,000 units.

ANTITOXINUM WELCHICUM, gas-gangrene antitoxin. Doses, prophylactic, 4000 units by injection; therapeutic, 10,000–20,000 units by intravenous injection.

SERUM ANTIDYSENTERICUM (SHIGA), antidysentery serum. Doses by injection, 4000–10,000 units.

SERUM ANTIPNEUMOCOCCICUM I, antipneumococcus serum (Type I). Doses by intravenous injection, 50,000–150,000 units.

SERUM ANTIPNEUMOCOCCICUM II, doses similar to those for Type I.

VEGETABLE TOXALBUMINS: RICIN.

Some albumins found in plants and of a highly poisonous nature resemble the toxins produced by bacteria both in their physiological actions and in their immunity reactions. Indeed, the investigation of their effects has played an important part in the advancement of knowledge of the corresponding effects of bacterial toxins. The most important of these vegetable toxins are Ricin, Abrin and Crotin, and they can be conveniently considered in juxtaposition to the bacterial toxins.

Ricin is an intensely poisonous albumin found in the seeds of Ricinus communis along with castor oil, which does not itself contain this principle, however. Ricin is poisonous in doses of about $\frac{1}{10000}$ milligram per kilogram body weight injected subcutaneously, but seldom causes any symptoms when swallowed, as it is apparently destroyed for the most part by the digestive ferments. It is thus among the most powerful of the vegetable poisons when it is injected subcutaneously. Death often occurs only several days after the injection in animals, and in the interval no symptoms make their appearance except some loss of appetite, and toward the end, diarrhœa and vomiting. Post mortem, the bowel is found inflamed and congested and contains ecchymoses; blood

is found in the serous cavities, and extravasations may occur in various other organs, although not so uniformly as in the bowel. Among the most obvious lesions are the innumerable ecchymoses in the great omentum and the swelling of the abdominal lymph glands, which generally contain numerous small hæmorrhages. Microscopic examination reveals small foci of necrosed tissue in the liver, spleen, intestine, stomach, and other organs. Ricin seems to be excreted by the intestinal epithelium, which may explain the violence of its action here, although it acts as a poison in many other tissues. It is a powerful irritant, inducing inflammation and suppuration when it is injected subcutaneously, or is applied to the conjunctiva. On the other hand it has little or no irritant action on the mouth and throat, and is usually digested and rendered harmless in the stomach. The mucous membrane of the nose is irritated by the inhalation of the powder in many persons. This toxalbumin has a very characteristic action on the blood. When a drop of a dilute solution is added to a test-tube of defibrinated blood, the corpuscles soon fall to the bottom, leaving the clear serum above, and the blood does not filter through paper any longer, the corpuscles all remaining on the filter, the serum passing through colorless. This is due to the agglutination of the red cells, which are formed into masses and thus fail to pass through the pores of the filter. Fibrin does not seem to be formed in the process, as was at one time supposed, but the nature of the cementing substance is unknown. Stillmark supposed that ricin formed these masses of red cells in the blood-vessels, and that the symptoms were due to the emboli resulting, but this is certainly incorrect, for the blood of immune animals reacts in the same way, yet these are not poisoned by many times the usual fatal dose of ricin. Gunn has shown that ricin similarly agglutinates any suspended particles which, like the red cells, possess a negative charge and that this agglutination is accompanied by an abolition of the negative charge on the particles or red cells. He has suggested, therefore, that the agglutination of red cells by ricin may be, partly at least, non-specific and of the nature of the precipitation of one colloid by a colloid of opposite sign.

Ehrlich found that animals rapidly acquire immunity to the action of ricin, if they receive for some time small non-toxic doses. From this discovery has arisen the Ehrlich side-chain theory, which plays such an important rôle in medicine at the present time. By gradually increasing the daily amount of ricin, rabbits have attained an immunity of 5000, that is, they are not affected by 5000 times as much ricin as would have killed them had no preliminary treatment been instituted.

Ricin and its antitoxin are not used in therapeutics, but ricin has repeatedly given rise to poisoning, from the beans being taken as a substitute for the oil. Cattle have also been poisoned by being fed on the refuse of castor oil beans after the oil had been expressed.

Another vegetable toxin which resembles ricin very closely in its effects is **Abrin,** which is obtained from the seeds of Abrus precatorius or jequirity, the familiar scarlet and black beans, which are often formed into necklaces. Abrin contains two poisons, a globulin and an albumose, of which the former is the more powerful. It induces the same symptoms as ricin, but is less poisonous, and immunity can be acquired in the same way. Animals which are immune to ricin are not more resistant to the action of abrin than others, because the two poisons form different antitoxins. Abrin or jequirity has been used as an irritant to the eye in cases of granular lids and of corneal opacities. It causes an acute inflammation which improves the condition in some cases, but it must be regarded as an exceedingly dangerous remedy, as the inflammation is entirely beyond the control of the surgeon. In animals the eye is often completely destroyed by the application of abrin, while in other experiments enough of the drug is absorbed to cause fatal poisoning.

Crotin is another toxin, which is found in the Croton Tiglium, but which does not pass into croton oil. It is less poisonous than ricin and abrin, but resembles them in most other points, except that it does not cause agglutination of the blood cells of certain animals, while ricin and abrin have this effect in all kinds of blood hitherto examined.

CLASSIFICATION OF DRUGS ACCORDING TO THEIR THERAPEUTIC USES.

I. Drugs applied for their local action to the skin, wounds, or visible mucous membranes.

Corrosives or caustics.

Nitric acid, 101
Silver nitrate, 148
Zinc chloride, 134
Chromic acid, 167
Alum, 136
Arsenic, 195
Trichloracetic acid, 102
Phenol, 783
(Salicylic acid, 716)
Iodine, 82
Carbonic dioxide snow, 110

Irritants.

Chloroform, 345
Turpentine oil group, 229
Mustard, 230
Cantharides, 232
Camphor, 240
Menthol, 241
Iodine, 82
Ammonia, 94

Disinfectants and antiseptics.

Hydrogen peroxide, 791
Permanganate of potassium, 792
Phenol, 783
Mercuric chloride and other mercury salts, including organic mercury compounds, 787–789
Silver nitrate and organic silver compounds, 789
Boric acid, 794
Iodine, 798
Iodoform, 801
Cresol, 785
Hypochlorites, chloramine, and dichloramine, 803
Tar, 808
Salicylic acid, 786
Picric acid, 786
Alcohol, 306
Volatile oils (thymol, eucalyptol, etc.), 234
Acridine dyes, 803

Disinfectant or irritant ointments in parasitic skin diseases.

Mercury ointments, 164
Sulphur ointment, 266
Tar, 808
Benzoin, styrax, and Peru balsam, 810
Naphthol, 807
Resorcin, 808
Pyrogallol, 805
Chrysarobin, 806

Astringents.

Tannic acid series, 258
Iron preparations, 127
Bismuth preparations, 176
Zinc sulphate and oxide, 134
Copper sulphate, 131
Alum, 136
Alcohol, 306

Styptics.

Soluble astringents (see above).
Ferric chloride, 127
Alum, 136
Silver nitrate, 148

To contract vessels and reduce hemorrhage and swelling.

Epinephrine and substitutes, 533–536
Ephedrine, 538
Benzedrine, 539

Emollients or protectives.

Adeps, petrolatum, 218
Plasters and Collodia, 220
Dusting-powders — starch, talc, chalk, iodoform, and many insoluble metallic powders, which may also be slightly astringent, 221

Local anodynes and analgesics for pain and itching.

Bicarbonate of potassium or sodium, 89
Cocaine, Procaine, Eucaine, Orthoform, etc., 454
Phenol, 783
Chlorbutanol, 372
Belladonna, 520
Some volatile oils (in dentistry).

Local anesthetics.
Cocaine, procaine, etc., 454
Cold by evaporation of ethyl chloride, 345

Drugs administered internally to increase the secretion of perspiration (diaphoretics or sudorifics).
Pilocarpine, 498
Ipecacuanha, 749
Ipecacuanha and Opium (Dover's powder), 749
Camphor, 240

Drugs administered internally to lessen secretion of perspiration.
Atropine and Belladonna, 518

II. Drugs used for affections of the alimentary tract.

MOUTH AND THROAT.

Demulcents.
Liquorice, 217

Astringents.
Tannin group, 258
Iron, 126
Alum, 136

Antiseptics.
Boric acid, 794
Volatile oils, 235
Hydrogen peroxide, 791

To lessen salivation.
Atropine, 518

Flavoring substances.
Sugars, 243
Volatile oils series, 245
Acids, (Citric), 103
Saccharin, 245

STOMACH.

Digestives.
Dilute hydrochloric acid, 101
Pepsin, 252
Pancreatin, 253

Emetics.
Apomorphine, 404
Ipecacuanha, 749
Sodium chloride, 48
Mustard, 230
Warm water.
Tartar emetic, 182
Copper sulfate, 131
Zinc sulfate, 134

To lessen irritation or vomiting
Opium, 395
Chlorbutanol, 372
Bromides, 412
Lime-water, 65
Bismuth, 176
Cold (ice).
Carbon dioxide waters, 108
Demulcents, 215

To lessen acidity,.
Sodium bicarbonate, 89
Magnesium oxide and carbonate, 281
Lime-water, 65
Calcium carbonate, 65

To Increase secretion.
Simple bitters, 250
Nux vomica, 424
Cinchona, 731

Carminatives
Volatile oils, 245
Ether, 345
Alcoholic preparations, 309
Carbon dioxide waters, 108
Bicarbonates, 89
Camphor, 240
Charcoal, 261

INTESTINE.

To promote digestion.
Pancreatin, (?) 253

To promote evacuation — purgatives.
Mild aperients—Castor Oil, 265
Sulfur, 266
Phenolphthalein, 270
Agar-agar, 283
Liquid petrolatum, 266
Rhubarb and Aloes group, 268
Saline purgatives, 279
Mercurial purgatives—Calomel and Metallic mercury preparations, 162
Glycerin suppositories, 267
Enemata.

In intestinal atony.
Pituitary extract, 574
Physostigmine, 494
Turpentine, 229

To lessen movement.
Opium, 395
Tannic acid series, 258
Bismuth salts, 176
Atropine (to relax spasm) 519

To destroy parasites—anthelmintics.
Male fern, 757
Santonin, 766
Pelletierine, 759
Carbon tetrachloride, 763
Oil of chenopodium, 761
Hexylresorcinol, 817
Thymol, 760
Naphthol, 807
Quassia enema, 250

Antiseptics.

Mercurial purges—Calomel, 162
Vegetable purgatives (Castor oil), 265
Salol, 810

III. Drugs used for their effects on the circulation.

HEART.

To strengthen contraction.

Digitalis, 647
Strophanthin, 654

In auricular fibrillation and flutter.

Digitalis, 645
Quinidine, 736

To accelerate pulse.

(Atropine, 518)
(Caffeine, 438)

To slow the pulse.

Digitalis, 645

VESSELS.

To contract vessels or raise blood-pressure.

Epinephrine (intravenously or subcutaneously), 533
Ephedrine and substitutes, 539

Pituitary extract, 574

To relax vessels and lower blood-pressure (angina pectoris).

Nitrites, 667
Theobromine and Theophylline preparations, 438

To arrest internal hemorrhage.

Opium and Morphine (to allay restlessness), 395
Ergot, 549

To remove fluid (dropsy, anasarca).

Digitalis, 647
Diuretics.
Theobromine, 438
Saline cathartics, 279
Sudorifics—Pilocarpine, 498
Merbaphen and Salyrgan (Mersalyl), 162

IV. Drugs used for their effects on the genito-urinary system.

To increase the flow of urine (diuretics).

Caffeine and Theobromine, 438
Digitalis, 647
Saline diuretics, 52
Citrates, acetates, 52, 93
Mercury—calomel, merbaphen, salyrgan (Mersalyl), 162

To lessen the flow of urine in diabetes insipidus.

Pituitary preparations (subcutaneously or into nasal cavity), 574

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