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PHYSIOLOGICAL PRINCIPLES IN TREATMENT

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BY

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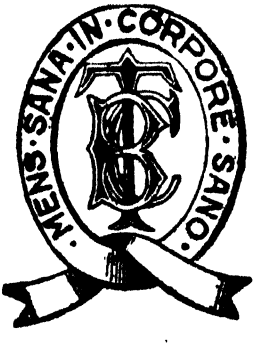

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PREFACE TO THE EIGHTH EDITION

FOR the second time in the life of this book, the appearance of a new edition has been delayed by a great war. It was originally written (as the preface to the first edition says) to acquaint the busy practitioner with the leading changes in physiology and to deduce therefrom the points on which his clinical conceptions should be modified. While that is still our aim, the scope and method have necessarily been enlarged with the passage of time. Indeed, the enormous and growing amount of factual information in the textbooks of both physiology and medicine increases, in our opinion, the need for a book of moderate size in which the emphasis is laid on principles rather than on details. As before, it has sometimes been difficult to decide the moment at which new experimental work should be sponsored in a clinical book. It has happened in the past that we have been reproved for omissions in this direction, only to find by the time the next edition was required that the work in question had been discarded in the laboratory.

Although the book has been thoroughly revised, the general plan as modified in the seventh edition has been maintained. The sections on the following subjects have, however, been considerably altered: the pituitary hormones, the treatment of gastric ulcer, nephritis, diabetes (with special reference to slowly acting insulin), the carotid sinus reflexes and hypertension. An entirely new chapter has also been added on the action of drugs, interpreted as far as possible in accordance with the views expressed earlier in the book. No attempt has been made to alter the diet tables to conform with the fluctuating food restrictions necessitated by war.

Thirty-four years is a long life for a book of this character. It is gratifying that another edition should be called for, since it provides evidence that it still fulfils a useful purpose. That it may continue to do so in its revised form is the earnest hope of the authors.

W. LANGDON-BROWN.
R. HILTON.

December, 1942.

FROM THE PREFACE TO THE FIRST EDITION

In the last decade our ideas have undergone fundamental alterations on many points of cardinal importance in physiology. The same period has seen a much wider use of exact scientific methods in clinical work. The result has been a closer harmony between physiology and practical medicine. The researches of Pavlov and his followers, which have led to the rewriting of the physiology of digestion, the clinical applications of Gaskell's work on the heart by Mackenzie and others, the introduction of convenient methods of registering blood pressure in man, the increased knowledge of the chemistry of uric acid and its congeners, of nitrogenous metabolism and internal secretion, are examples which will occur to anyone.

The busy practitioner is aware that the physiology of his student days has been largely supplanted or supplemented, but has not time to acquaint himself with the changes, nor to deduce therefrom the points on which his clinical conceptions should be modified.

This book does not aim at being a complete treatise on applied physiology; but as it has been my lot during the decade in question to combine the practice of medicine with the teaching of physiology, I have set down here some of the considerations which I think have helped me, in the hope that they may help others. . . .

Though the days are past when the student entering the wards often received the superfluous advice to 'forget his physiology,' the physiologist is still regarded a little suspiciously at the bedside. Perhaps he is in part himself to blame for that, for he is sometimes inclined to forget that

observations made in the laboratory are not infallible, and are not necessarily more correct than clinical evidence. When I reflect that I am now teaching the exact opposite to many of the views held ten years ago, I feel that physiology can only come to the aid of medicine with becoming modesty, and without overweening dogmatism. There is no finality about either, but that they can co-operate usefully I trust the following pages serve to illustrate.

W. LANGDON-BROWN.

October, 1908.

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PHYSIOLOGICAL PRINCIPLES IN TREATMENT

CHAPTER I

THE PRINCIPLES OF ORGANO-THERAPY

WHENEVER we give a drug, we imply thereby a belief that the functions of the body can be influenced by chemical means. And we can find support for this confidence in the fact that the body itself produces chemical substances whereby it regulates its own functions.

Nothing could be more reasonable than to use intelligently in disease those very drugs by which the body is enabled to do its own work in health. This is the basis of a rational organo-therapy, as Starling has so clearly indicated.

Though the use of organic extracts has enormously increased during recent years, it is but the renaissance of a very ancient method. Celsus and Galen testify to the antiquity of organo-therapy. The first Pharmacopœia, published by the College of Physicians in 1618, contains several prèparations of animal extracts.

The success of thyroid extract in treatment led to a great revival of interest in the subject, an interest not always intelligently displayed. Indiscriminate use of gland extracts in every sort of disease, without consideration of the underlying principles, only brings discredit on a valuable method of treatment. There is no scientific sanction for the employment of brain extract in insanity, and extracts of bronchial glands for phthisis. Powdered heart muscle was a favourite prescription in the old days; it is no advance to squeeze it into a tablet and call it cardin.

The stimuli to which the most primitive forms of life

respond are chemical; the development of a nervous system comes later and enables very rapid reactions to occur. Recent work has shown how closely these chemical and nervous mechanisms are interwoven throughout the body. That a gland may secrete a chemical substance in answer to a nervous stimulus is a commonplace of physiology; it is now recognized that it is the general rule for nervous impulses to exert their effect on the tissues through liberating chemical substances there. In Hopkins' phrase, chemical substances produced locally and temporarily translate for the tissues the messages received through the nerves. Among these chemical products the secretions of the endocrine glands—the hormones, as Starling labelled them—occupy a specially important place. Their link with the nervous system is through its lowest level, the autonomic or vegetative portion of that system. The hypothalamus or diencephalon, as it is often called today, has long been regarded as the head ganglion of the sympathetic portion of this autonomic system. It is now recognized that this region of the brain is the site of the primitive instincts and of emotional expression. It appears capable of acting directly upon the pituitary body, which may well be termed the leader of the endocrine orchestra. The brain therefore exercises control over these chemical mechanisms either directly through the sympathetic nervous system or indirectly through the pituitary. The endocrine glands are structures for elaborating chemical stimulants which were formerly more widely diffused throughout the body, and which have gradually come to a greater or lesser extent under the control of the nervous system in the course of evolution.

The work of E. C. Dodds has thrown new light on the *general characteristics of hormones*. They would appear to be of two grades. The first are produced by the anterior lobe of the pituitary and are of extreme complexity, belonging to the protein class. They act upon such organs as the

thyroid, adrenals, testes, and ovaries, and to a less extent upon the pancreas and possibly the parathyroids; these in their turn give rise to the second grade of hormones, which are bodies of comparatively small molecular weight. Their chemical constitution has been determined in some instances and actually prepared synthetically. Dodds has shown that their biological effects can be produced to a greater or less extent by similar chemical substances of even simpler constitution, and that in some cases these effects are interchangeable with those of other biologically active substances.

Unlike ferments, they are not destroyed by simple heating. They are not readily absorbed unaltered from the alimentary canal. Thyroxin, the active principle of thyroid secretion, is an exception to the rule, probably because the thyroid gland originally discharged its secretion into the alimentary canal by the thyroglossal duct. Recent work seems to show that pituitrin is absorbed from the nasal mucosa.

Hormones are employed in treatment—

1. In substitution therapy—*i.e.*, to replace the absent or deficient secretion of a gland that is involved in a destructive lesion—or where there is relative insufficiency owing to over-action of some antagonistic gland. Here the hormone is intended to produce a chronic effect.

2. Where their known physiological action may be useful quite apart from any defect in the patient's own glands. Here a sudden effect is usually aimed at.

3. In a purely empirical manner.

For successful substitution therapy the gland from which the extract is prepared must contain the hormone in an amount much in excess of the body's immediate needs, while the hormone must be fairly stable so as to resist chemical changes during extraction, and be capable of absorption from the alimentary canal. Also it must be possible for intermittent doses to replace satisfactorily the constant slow secretion which normally occurs. The secretion of the

thyroid is the only one which fulfils all these criteria, but insulin and the parathyroid hormone fulfil most of them. The recently introduced method of subcutaneous implantation of tablets of pure hormones which are slowly absorbed is a hopeful advance.

The Pituitary Gland.

The anterior lobe contains cells which resist staining—the chromophobe cells, which are probably the parent cells, from which arise eosinophil cells and basophil cells. An adenoma composed of chromophobe cells diminishes pituitary function. Fröhlich's syndrome of obesity of the limb-girdle type and genital hypoplasia was originally recognized in a case of this sort. But extreme obesity may also result merely from division of the pituitary stalk either experimentally or by disease. Milder cases occur without the presence of an adenoma. They may be attributed to a delay in the differentiation of these chromophobe cells; puberty may be delayed, but the outlook is not so serious. Overgrowth of the eosinophil cells leads to gigantism, general or local, when it occurs early in life, or to acromegaly when it occurs, as is more usual, after bony union is complete. Lack of this eosinophil secretion, on the other hand, will lead to failure of growth and an extraordinary degree of premature senility (Simmonds' disease). A similar condition may occur from damage to the pituitary by puerperal sepsis. Large doses of œstradiol and progesterone may help, but a subsequent pregnancy seems more curative. The condition should be carefully distinguished from anorexia nervosa. Over-activity of the basophil cells, together with hyaline changes (Crooke), is associated with a remarkable condition termed 'pituitary basophilism' by Cushing, which is characterized by a plethoric obesity (with polycythæmia, large red cutaneous striæ on the abdomen and hips, and ecchymoses on the legs), general dystrophy, including osteoporosis, and hirsu-

ties of the male type with frontal baldness and vascular hypertension. Glycosuria is not uncommon. Most of the cases described have been in women, as their bearded condition and other evidences of virilism at once attract attention, but it is not unknown in men. The prognosis is bad, as the hypertension may be followed by renal changes; but improvement under deep X-rays to the pituitary fossa has been recorded.

The **anterior lobe** has been credited with the production of at least fourteen different hormones, and it is true that certain purified fractions have different metabolic effects. Yet it seems improbable that a gland containing only three types of cells should be capable of elaborating so many, and J. B. Collip has suggested that it only produces three attached to a large protein molecule, which are modified to meet the immediate needs of the organism just as the biochemist modifies them in the laboratory. It is simpler, however, to discuss the various activities as if they were due to independent hormones.

1. *Growth hormone* is certainly associated with the eosinophil cells on the evidence adduced above.

2. The *gonadotropic hormone* is a more complicated subject; its source has been stated to be the basophil cells, but that is by no means proved. It can stimulate the maturation of the ovarian follicles and their subsequent luteinization. Although two separate hormones have been postulated for these two functions, it is more probable that there is only one substance, prolan, acting at different stages in the cycle. The abundant presence of this in the urine of pregnancy enables it to be employed therapeutically. In the male it may stimulate both spermatogenesis and interstitial cells. Its bisexual character is therefore established. Many successes from its uses in cryptorchidism have been reported, but Ronald Smith advises caution in this interpretation of results, since so many testes descend spontaneously at puberty, and those

that do not are often held up by mechanical obstructions requiring operation. Nevertheless, there seems to be a residue of instances where success may fairly be attributed to treatment by injections of pregnyl.

3. *Thyrotropic hormone.* It is clear that a purified fraction has a stimulating effect on the thyroid. It can only act if there is sufficient thyroid tissue to respond, and therefore has no effect in myxœdema, though it can excite a normal thyroid up to a state of Graves' disease.

4. *Diabetogenic hormone.* Houssay showed that if a dog is previously deprived of its pituitary, subsequent removal of the pancreas does not cause glycosuria, but if anterior pituitary extract is then injected it produces both glycosuria and ketonuria. F. G. Young, by using large doses of extract, has rendered dogs permanently diabetic, with degeneration of the cell-islets in the pancreas.

5. *Adrenotropic hormone.* The close association between the adrenal cortex and the anterior pituitary is well known. Implantation of anterior pituitary or injection of its extract causes marked hypertrophy of the adrenals.

6. *Lactogenic hormone* (prolactin). There is good evidence of a special hormone governing the secretion of milk, and it has been biologically estimated by its effect on the milk-like secretion of the pigeon's crop. This is quite distinct from the expulsion of milk by oxytocin. Œstrogenic substances deprive the secretion of prolactin during pregnancy; the expulsion of the placenta releases that inhibition and lactation follows.

7. *Parathyrotropic hormone* is less proven. There is, however, a striking similarity between the decalcification and bone pains in pituitary basophilism and hyperparathyroidism.

The secretion of the **posterior lobe,** pituitrin, consists of two factors—oxytocin, which stimulates uterine contraction, and vasopressin, which raises blood pressure, affects diuresis, and antagonizes insulin. Oxytocin acts directly on uterine

muscle. Dixon and Marshall showed that œstrin stimulates, while progestin inhibits its production. In this way the corpus luteum provides for the maintenance of pregnancy, and when it begins to degenerate its inhibitory effect ceases, so that œstrin can then contribute to the onset of parturition by stimulating the production of oxytocin. Thus the use of pituitrin in obstetrics reinforces a natural mechanism. Evidently there is a close interlocking of pituitary and ovarian hormones.

It is now clear that either a pituitary lesion or a diencephalic one, or even a disturbance of their interaction, may cause diabetes insipidus. Since vasopressin will control the output of water even by a denervated kidney, the logical conclusion is that, even when the diencephalon is responsible, it must act through this chemical intermediary.

J. H. Burn has shown that vasopressin antagonizes insulin, the former diminishing and the latter increasing the storage of glycogen, which is another factor in the lowering of carbohydrate tolerance and in the intermittent glycosuria sometimes found in hyperpituitarism. The galactagogic effect of pituitrin, probably due to oxytocin, is merely the stimulation of a muscular contraction of the mammary ducts, but the lactation, sometimes prolonged for years, which may occur in cases of pituitary tumour, must be attributed to the anterior lobe; nevertheless, relief may sometimes be given by the luteal hormone.

The post-pituitary evidently plays an important part in fat metabolism. Injections of pituitrin cause fat to be transferred from the outlying tissues to the liver, where it is metabolized. Hence the accumulation of fat in the liver in hepatic toxæmias, and hence the obesity of hypopituitarism. In the first case there is a failure of fat combustion; in the second a failure in fat transport. From the close association between the gonads and the pituitary we can understand why castration or gonadal defects lead to obesity.

Dodds has shown the irritative effect of repeated doses of pituitrin on the gastric mucosa, which may throw some light on the increasing frequency of peptic ulcer, in view of the association between the pituitary and the hypothalamic centres for emotional expression.

Tumours of the pituitary lead to a characteristic enlargement of its fossa, often accompanied by optic atrophy and loss of the temporal fields of vision, and sometimes by third nerve paralysis. A definite chromophobe adenoma calls for operation, as it is so likely to cause blindness, but other tumours should be treated by X-rays at any rate before attempting operation.

Therapeutics.—The value of oral administration of anterior lobe extracts has been questioned, yet benefit certainly seems to follow their use in some cases. Combined with thyroid, it appears to act better than does either gland extract separately. A number of preparations of the gonadotropic hormone for intramuscular injection are on the market now. The secretion of the posterior lobe, pituitrin or either of its constituents, should be injected intramuscularly, or applied to the nasal mucosa as a spray or snuff or on pledgets of cottonwool packed into the nostril. The success of the nasal route is due to the fact that the pituitary originally opened into the naso-pharynx, just as the thyroid opened by the thyroglossal duct into the mouth. It is convenient where a more prolonged effect is required, but the intramuscular route is better where a quicker response is needed, as in uterine inertia, in the low blood pressure of shock, or in post-operation atony of the gut. The ordinary dose is 1 c.c., which contains 10 units.

The Thyroid Gland.

Organo-therapy won its first and most conspicuous triumph with thyroid extract in the treatment of myxœdema and cretinism. The ease with which thyroid preparations are

absorbed from the alimentary canal has greatly contributed to this, but at the outset it was not realized that so simple a method could be effective, and subcutaneous injections were employed.

The only active principle that has been isolated from the gland is thyroxin, which Harington and Barger have synthesized and shown to be an iodine compound of tyrosine. The presence of iodine is the striking peculiarity of this hormone, which is interesting in view of the formerly purely empirical use of iodine in diseases of the thyroid. It certainly appears to allow the gland to return to a resting state, and its use as a prophylactic in districts where goitre is endemic, such as certain Swiss valleys, has been very successful. The first effect of a shortage of iodine is enlargement of the thyroid. This also explains the enlargement of the gland which occurs in pregnancy, since the mother has to supply iodine to the fœtus.

The thyroid gland is to the human body what the draught is to the fire (McCarrison). It is a general accelerator of metabolism and growth; this has been demonstrated mathematically by observations on the basal (*i.e.*, resting, fasting) metabolism.

Thyroxin has the effect of reducing weight, but it has been stated that only one-sixth of the loss is due to increased nitrogenous waste, the remainder being due simply to diuresis, apparently from dehydration of fats. It lowers sugar tolerance and may produce glycosuria. It accelerates the heart-beat without augmenting its force. It is therefore not very effective in the treatment of ordinary obesity, and is not free from risk, as a fatty heart may not be able to maintain the accelerated rhythm. Moreover, as in obesity there is often a tendency to glycosuria, the use of a drug which can excite this demands caution. But if the obesity is associated with other signs of hypothyroidism, careful administration of thyroid extract may be very helpful.

The thyroid not only stimulates metabolism, but plays an important part in the differentiation of tissues. Therefore with thyroid insufficiency there will be defective growth, which will be most noticeable in the young subject, while in the adult there will be accumulation of material which should be katabolized. Congenital thyroid deficiency leads to cretinism, which must be treated by adequate doses of thyroid extract before growth has been arrested thereby. It must be distinguished from mongolism and achondroplasia. Cretinism is more apt to occur when the mother has a thyroid which is below normal standard. Thyroxin passes readily into the mother's milk. Hertoghe attributed to a minor degree of thyroid insufficiency such symptoms as relaxation of the articular ligaments, particularly in the knee, heel, ankle, and thoracic vertebræ, causing knock-knee, painful heel, flatfoot, and lordosis. Infiltration of tendons and fascia may produce rheumatoid pains. He attached considerable importance to the loss of hair in the outer half of the eyebrow. Enuresis he believed to be sometimes due to the same cause. Changes in the nerve centres cause mental slowness, partial or entire loss of memory, and difficulty in expressing ideas. Sometimes there are hallucinations of sight and hearing. Headache, giddiness, and somnolence are not uncommon. The liability of myxœdematous subjects to develop atheroma suggests the use of thyroid extract in premature arterial degeneration.

The striking changes occurring in the skin in myxœdema implies that the thyroid plays an important part in regulating its nutrition. Byrom Bramwell therefore employed thyroid extract in various diseases of the skin, but its use should be restricted to chronic conditions. It is often useful in Raynaud's disease.

Among the less-known effects of thyroxin on metabolism is its influence on the liver. Apart from the discoloration, the chief sufferings of a jaundiced patient are due to the toxic

effects of the bile-salts; prominent among these is the intense itching, which is sometimes so troublesome. Administration of thyroid extract may relieve this. This is apparently associated with a diminished output of bile-salts in the urine.

The striking contrast between Graves' disease and myxœdema suggests naturally that while the latter is due to hypothyroidism, the former is associated with hyperthyroidism. In Graves' disease the gland is enlarged by an increase in the secreting cells, so that the basal metabolism is increased, the excitability of the nervous system is increased, the pulse is rapid, the temperature is raised, the skin is moist, the bowels relaxed, and there is usually emaciation. In myxœdema the gland is atrophic and basal metabolism is diminished; therefore the excitability of the nervous system is lowered, the pulse is slow, the temperature subnormal, the skin dry, constipation and increase of weight is the rule. Moreover, the administration of excessive doses of thyroid extract may cause symptoms analogous to those of Graves' disease. Hector Mackenzie drew attention to the resemblance between the symptoms of Graves' disease and the expression of the emotion of fear. In both we have the staring eyes, the rapid pulse, and the tremors. It is therefore doubtful how many of the phenomena of Graves' disease are directly due to hyperthyroidism and how many to disorder of the pituitary diencephalic control. A continued emotional disturbance certainly plays a large part in the production of Graves' disease, especially when combined with a toxic factor. Myxœdema following Graves' disease we can understand, for the gland may become exhausted as a direct result of its excessive activity; but the coexistence of active Graves' disease with some of the symptoms of myxœdema, such as the characteristic condition of the skin, is more difficult to account for on the basis of thyroid changes alone.

The best drug in the treatment of Graves' disease is un-

doubtedly iodine, given either as the liq. iodi simplex or as Lugol's solution in a little milk. A suitable dose is 5 minims twice a day. When the gland becomes firm or the pulse accelerates again after a temporary fall, the dose of iodine should be reduced. Some authorities limit the administration of iodine to the pre- and post-operative periods; others give it for a fortnight and then suspend administration for six weeks. If the weight continues to fall, 10 units of insulin daily after administration of 30 grammes of sugar is a rational treatment in view of the antagonism between the thyroid and the pancreatic cell-islets. Three to five grains of quinine hydrobromide with 20 minims of dilute hydrobromic acid three times a day is often decidedly helpful. The barbiturates first used empirically have been shown by Zondek to have a rational basis, since they hinder the entrance of thyroxin into the tissue cells. But none of these measures will be fully effective unless septic foci—*e.g.*, in the tonsils—are eliminated, and complete rest is an essential part of the treatment. In any case, medical treatment has to be prolonged, and operation may be necessary. In acute cases medical treatment should be tried first, and will be successful in a certain number, particularly in the younger patients. But the majority will need operation, especially when (i.) for economic reasons a more rapid recovery is important, (ii.) auricular fibrillation, to which all long-standing cases are liable, has supervened. Cases of so-called toxic adenoma, or secondary Graves' disease, fall into this group. Here the cardiac condition may be the only obvious sign of the thyroid disease. Indeed, thyrotoxicosis is often masked. If after operation normal rhythm is not restored in a few weeks, quinidine should be given (see Chapter IX).

The Parathyroids.

In the early experiments of Schiff it was pointed out that removal of the thyroid gland was fatal in the dog and cat,

whereas in the rabbit no obvious symptoms resulted. A rational explanation for these divergent results was found by Gley, who showed that in the dog and cat the parathyroids were embedded in the substance of the thyroid, so that 'thyroidectomy' in these animals had included parathyroidectomy as well. Thereafter all workers have agreed that the removal of the parathyroids is followed by a fall of blood calcium, muscular spasms, weakness, convulsions, and death. Today, owing to the increasing frequency of thyroidectomy, post-operative tetany is not very rare. It may, however, be due to a temporary disturbance of the parathyroids at the operation.

Clinically a level of blood calcium distinctly below the normal average of 10 milligrams is found in tetany of parathyroid origin.

The preparation by Collip of a consistently active parathyroid extract which on injection raises a low blood calcium has provided us with the means of checking symptoms of tetany. To this extract the name parathormone has been given. The increase in the electrical excitability of the nerves is due to the decrease of blood calcium in the ionized state. There are four physiological ways of dealing with such a condition. The first is by raising the calcium content of the blood directly. This may sometimes be achieved by oral administration of calcium salts. In many cases intravenous injection is necessary. A second method is by injecting parathormone. The dose is 25 to 50 units subcutaneously once or twice a day. This mobilizes the calcium from other parts of the body. It is considered better to give calcium by the mouth at the same time, to prevent it being taken excessively from other tissues such as bone, where it is needed. This combined method is the one usually employed. A third method is to give acids, which are supposed to increase the ionization of the blood calcium. Even in a normal person tetany may be produced by voluntary hyperpnœa, which

produces a state of alkalosis. Although the blood calcium may be normal in quantity, the calcium ions must decrease if the blood becomes more alkaline. Acid therapy has the reverse effect. The fourth method is to give calciferol (vitamin D). Empirically parathormone has been found very useful in hepatic and intestinal colic. It has not proved of much clinical value in other conditions than the above, and should not be given over any length of time, because it depletes the calcium stored in the bones.

A spontaneous *hypoparathyroidism* causing similar symptoms to post-operative tetany and relieved by parathormone occasionally occurs. It is characterized by lesions of ectodermal tissues, such as cataract, ridging and brittleness of nails, loss of hair and of dental enamel.

Hyperparathyroidism.—The isolation of parathormone led to the recognition of a new clinical entity—hypercalcæmia. Generalized osteitis fibrosa is associated with a fall in blood phosphorus and a rise in blood calcium, together with deposits of calcium salts in the pelvis of the kidney. This has now proved to be due generally to a parathyroid tumour, removal of which has greatly benefited the condition.

The Adrenals.

In their double origin—in part nervous, in part epithelial —these structures offer an interesting parallel to the pituitary.

Following on Addison's clinical observations, Brown-Séquard showed that experimental removal of the adrenals was rapidly fatal to animals. Schäfer and Oliver in 1893 prepared from these glands an active substance possessed of powerful tonic properties. That this substance was only formed from the medulla of the gland was shown by Swale Vincent from observations on certain fishes in which the cortical and medullary portions are separate glands. Attempts to isolate the active principle from the extract culminated in 1901 in the preparation by Takamine of a

crystalline body, to which he gave the name of adrenalin, and to which he attributed the formula $C_{10}H_{15}NO_3$. This name has now been adopted by the British Pharmacopœia.

Four years later Dakin synthesized it artificially from pyrocatechin, and made a series of similar bodies, showing that their activity depended on the presence of a catechol nucleus. This suggests an origin from the aromatic radicles present in the protein molecule.

We owe to Langley the important generalization that the action of adrenalin on any part is the same as stimulation of the sympathetic nerves to that part. It will not act on a structure that at no time in its history has been innervated by the sympathetic. Elliott, in extending these observations, has brought forward some facts which suggest that, after excision of the adrenals, the muscles innervated by the sympathetic cannot be thrown into activity even by electrical stimulation of the nerves. Adrenalin appears, then, to be a chemical body whose presence is essential to the activity of the sympathetic. This is specially interesting when we remember that the medulla of the adrenals is developed as a direct outgrowth from the sympathetic nervous system. Nor is this the only example of such an association, for sympathetic paraganglia and structures, such as the carotid body, contain *paragangline*, a similar but more stable body, which does not lose its effect even if left in contact with the stomach wall for twenty-four hours.

In applying adrenalin therapeutically, we have to consider what would be the effect of stimulating the sympathetic nerves to the part in question. The application of adrenalin to internal medication is greatly limited by two facts:

1. If mixed with alkalies, its activity is lost; if the alkali be neutralized, the specific effect can be obtained again. It is certainly rapidly destroyed on circulation through the tissues.

2. It is doubtful whether in healthy persons it is absorbed

unaltered from the alimentary canal. The most striking action of adrenalin is the rise of blood-pressure that it causes, but many observers have failed to detect any rise when the drug has been given by the mouth. Yet it is not destroyed by gastric juice in a test-tube. Probably the intense vaso-constriction it produces prevents its own absorption. Rolleston found that, given by the mouth to persons suffering from Addison's disease, it did raise the blood-pressure, though this is by no means always the case.

Alimentary Canal.—Since Leyton suggested adrenal extract for hæmatemesis, many instances of its successful use have been reported. Doses of 20 minims of the 1 in 1,000 solution of adrenalin chloride in ½ ounce of water, given every three or four hours, not only constrict the bleeding-point, but also stop peristalsis. If an isolated loop of intestine be placed in a bath of warm salt solution, vigorous peristaltic waves may be seen; the addition of two or three drops of adrenalin solution to the bath at once renders the coil quiescent. Like the sympathetic, adrenalin inhibits the movement of a hollow viscus, while keeping the sphincter controlling the exit closed. Herein lies its advantage over ergotin and the like. For these reasons it will often check vomiting or hiccough, in doses of 10 to 15 minims of the 1 in 1,000 solution diluted with water. It may be usefully combined with 1 minim of carbolic acid and 3 minims of dilute hydrocyanic acid.

Though it may be open to doubt whether the drug can get past the pyloric sphincter, it has been successful in checking severe intestinal bleeding in typhoid fever in doses of 30 minims of the solution by mouth three hourly. It may be added also to an enema of starch and opium. As a precautionary measure it may be given about a quarter of an hour before getting the bowels opened by enema after an intestinal hæmorrhage. By keeping the bloodvessels of the small intestine constricted, the walls flaccid, and the ileo-cæcal

sphincter closed, it affords the ideal condition for emptying the large bowel by enema.

In view of the inhibitory action of adrenalin on peristalsis, it is contra-indicated in the treatment of gastro-intestinal atony.

Intraperitoneal injection of adrenalin delays the absorption of poison introduced into the stomach or peritoneal cavity; thus strychnine required twenty times as long to produce its toxic effect. The gain of time is most valuable, and suggests the administration of a full dose of adrenalin pending the employment of other remedies.

Heart and Bloodvessels.—Adrenalin is a powerful stimulant to the heart, augmenting and accelerating its action like the sympathetic; but, as we have seen, to produce this effect it must be injected subcutaneously. We must remember, however, that as it also constricts the bloodvessels, thereby raising the pressure, it may stimulate the cardio-inhibitory centre in the medulla, so that slowing of the heart through the vagi might be caused instead. With moderate doses, however, this danger is not likely to arise. The sudden vaso-constriction greatly increases the work of the heart. Fortunately, it has been shown experimentally that adrenalin dilates the coronary vessels, for if it constricted them it would almost certainly produce anginal attacks; 3 to 5 minims is a large enough dose to inject at one time. In cases of shock, where the blood-pressure is lowered from dilatation of the splanchnic bloodvessels, adrenalin may sometimes be useful, though most of the fall of pressure is due to capillary stasis.

Owing to the realization of this, adrenalin is now much less used in the treatment of shock and toxæmic states than it was. However, in cases of collapse under an anæsthetic an injection of 10 minims directly into the cavity of the ventricle should be given. In the extreme bradycardia of heart block a subcutaneous injection of 5 minims is often helpful.

In accordance with the general law that adrenalin only acts on structures which have a sympathetic innervation, Baum found it had no effect in blanching nævi, and only a very transitory effect on unsound flesh.

Respiratory System.—A paroxysm of *asthma* may often be cut short by the subcutaneous injection of liq. adrenalin hydrochlor. In the first instance only 3 minims should be given, and it is rarely necessary to give more than 5 minims at a time. It is far more effective if given at the very onset of an attack. To produce a more prolonged effect the adrenalin is sometimes given in oil. The vagus and sympathetic are opposed in their action, and as the former is constrictor in its effect on the bronchial muscles, the latter inhibits bronchial spasm; moreover, it constricts the turgid vessels in the bronchial mucosa. Both these actions would be produced by adrenalin.

In hay fever the drug has a similar action. It is sometimes combined with pituitrin, but this is of doubtful advantage. Adrenalin injections are of great assistance in other allergic states such as giant urticaria and serum rashes.

In the chapter on the Vasomotor System in Disease, it is pointed out that the changes in the pulmonary circulation are passive, and are controlled by the systemic circulation. On perfusion of adrenalin through the pulmonary vessels Brodie and Dixon could not find any evidence of vaso-constrictors, a conclusion with which most subsequent observers have concurred. The thoracic viscera from an animal killed by a fatal dose of adrenalin show that while all the other tissues are anæmic, the coronary vessels are distended with blood, and the lungs intensely congested, being a deep plum colour. Adrenalin is therefore obviously inadvisable in *hæmoptysis*. In so far as any result is obtained it will be a harmful one. The blood which is being squeezed out of the rest of the circulation will be forced into the pulmonary vessels, which are unable to protect themselves by adequate

vaso-constriction, and hæmorrhage will be aggravated unless the sole source of the bleeding is a bronchial vessel. The only reason why serious harm has not been done more frequently is that the drug has been administered by the mouth, so that it has had little effect; but if injected into the circulation, it would have an injurious effect in hæmoptysis, because of the pulmonary engorgement that results.

Cerebral Hæmorrhage.—For similar reasons adrenalin is contra-indicated in cerebral hæmorrhage. Even though there are vaso-constrictors in the vessels of the brain, the systemic rise of blood-pressure certainly outweighs any advantage to be reaped from a possible local constriction in the cerebral vessels; and local application is out of the question.

Surgical Applications.—Adrenalin has been very useful in certain surgical conditions. For removal of foreign bodies and other operations on the eye, Darier recommends 10 drops of the 1 in 1,000 solution added to 10 c.c. of a 1 per cent. solution of cocaine. MacCallan thinks it is risky in glaucoma, as he has seen it cause a rise in tension.

Its blanching action has rendered adrenalin of considerable service both for diagnosis and treatment of diseases of the nose, for it is rapidly absorbed by the nasal mucous membrane.

In affections of the urinary tract it has been used with novocaine for anæsthetic purposes, for the pain and strangury of acute gonorrhœa, and for the hæmaturia of enlarged prostate. In the form of ointment it certainly seems to alleviate hæmorrhoids. In uterine bleeding it may be looked to to produce a double effect, constricting the bleeding vessels and causing contractions of the pregnant uterus. Cushny and Dale have shown the curious and interesting fact that adrenalin relaxes the non-pregnant and contracts the pregnant uterus. Such contractions are, however, inadequate to induce labour.

In **local anæsthesia** the rôle of adrenalin is to prevent the escape of the anæsthetic from the field of operation by constricting the bloodvessels in the neighbourhood. In this way its general toxic effect is diminished, while its local anæsthetic effect is increased. Cocaine, novocaine, and alypin either have no influence on its action or slightly increase it; while eucaine, tropocaine, and possibly stovaine, are markedly antagonistic, considerably decreasing its activity.

It is important that there should be no trace of soda in the fluid used for boiling the syringe employed, since adrenalin is rapidly destroyed in alkaline solutions.

In spinal anæsthesia adrenalin is not so satisfactory, as it limits the spread of the injection too much. Also its use has been followed by convulsions due to petechial hæmorrhages in the brain, which may well be due to the blood being driven to a part which is unable adequately to protect itself by vaso-constriction.

Deleterious Effects.—Like all powerful drugs, adrenalin has its dangers. We need not fear these bad results from local application or subcutaneous injection, since the vaso-constriction it produces so greatly interferes with its absorption. They have only been noted after intravenous injection.

1. *Mechanical Effects of High Blood-Pressure.*—The great pulmonary engorgement produced seriously limits the use of the drug as a cardiac stimulant in inflammatory diseases of the lung. As the brain cannot adequately protect itself against this rise of pressure by vaso-constriction, damage may be done here also, while sudden heart-failure may occur.

Repeated injection of adrenalin into rabbits has been thought to cause atheroma, aneurysmal dilatations, and hypertrophy of the heart. Anything causing a persistently high pressure leads to arterial degeneration, and although rabbits are very liable to arterial degeneration without such injections this remains a possible risk. An increase in the

medulla and chromaffin material in diseases associated with high blood-pressure has also been noted.

2. *Glycosuria.*—This will be discussed in the chapter on Glycosuria in general.

3. *Toxic Effects on the Tissues.*—Necrotic areas have been found in the centre of the lobules of the liver, outside which were areas of fatty degeneration. They have been attributed to the shutting off of the arterial blood by the intense vaso-constriction. In the kidney, cloudy swelling and desquamation of the tubular epithelium have been seen after injections of adrenalin both experimentally and clinically. However, frequent injections of the drug, as in asthma, have not been followed by any such ill-effects.

Summary.—Adrenalin, which is formed in the medulla of the adrenal, is a benzene compound probably derived from the aromatic group in the protein molecule. It is not destroyed by simple boiling, but is rapidly destroyed by oxidizing agents, which turn it brown; apparently it is quickly dealt with thus in the tissue it excites. It loses its activity in the presence of alkalies. It is probably absorbed with great difficulty from the alimentary canal. Its application to any part produces the same effect as if the sympathetic nerves to that part had been stimulated. It may be freely applied locally, though some observers think that caution is needed in the case of the nasal mucous membrane and (in old people) the eye. Subcutaneous injections are usually safe, though repeated injections may cause necrosis in ill-nourished parts from the local anæmia produced. Intravenous injections are not free from risk. The best results have been obtained in asthma, hay fever, and giant urticaria, but it is also useful in bleeding from any part of the alimentary tract, in vomiting, and in heart-block. It is contra-indicated in hæmoptysis and in cerebral hæmorrhage. It may be used as an adjuvant to local anæsthesia.

The Adrenal Cortex.

As the cortex of the adrenals arises from similar cells to those which provide the interstitial cells of the gonads, it is only to be expected that lesions of it may involve the reproductive system remarkably. Tumours of the adrenal cortex will produce virilism of a similar type to that caused by a pituitary basophilic adenoma. The type of virilism resulting from such tumours depends on the time of onset; the earlier in life they occur, the more they influence structure; later on they chiefly affect function.

Addison's Disease.—It was formerly considered that the symptoms of Addison's disease, in which the adrenals are fibro-caseous or atrophied, were due to destruction of the medulla. Stewart and Rogoff, however, found that dogs from which the adrenals had been removed could be kept alive by injections of a cortical extract, but not by adrenalin. There is no doubt that many cases of Addison's disease have been greatly benefited by cortical extracts. The chief difficulty is their high cost. A preliminary dose of ½ to 1 c.c. should be given intramuscularly to test for idiosyncrasy; if no rise of temperature occurs, 5 to 10 c.c. should be injected twice a day for a time, the dose being gradually reduced to a point at which the symptoms are held in check. The patient's subjective state often improves out of all proportion to the physical signs. A relapse calls for a repetition of the larger injections without waiting for any serious symptoms to occur. The synthetic product desoxycorticosterone acetate (D.O.C.A.) has also yielded good results; 5 mg. of it are equivalent to 10 c.c. of cortical extract. Plenty of fluids with salt and glucose should also be given. Ephedrin gr. ½ three times a day will help to maintain blood-pressure, and adrenalin by the mouth, as already said, may check vomiting. But the prognosis remains very serious.

The discovery that in this disease there is an excessive

excretion of sodium salts has, however, improved the treatment. They should be given in as large doses as the patient can tolerate; 10 grammes a day at least is required in the form of chloride, bicarbonate or citrate. The dose of cortical extract can, at any rate, be much diminished by this procedure. It appears that the extract influences the high level of the potassium in the blood rather than the leakage of sodium. It is important to avoid any potassium salts as medicine, while vegetables should be thoroughly boiled to extract as much of such salts as possible.

The Ovary.

Our knowledge of ovarian hormones has been made much more accurate by means of Allen and Doisy's method of testing the effect of an ovarian extract in producing sexual maturity and œstrus in rats. It would appear that prolan produced in the anterior pituitary initiates the ripening of the Graafian follicles. The fluid in the follicles contains œstrin, which leads to hypertrophy of the uterus; the follicle ruptures and the ovum slowly descends the Fallopian tube; meanwhile the corpus luteum left in the ovary forms progestin, which stimulates the uterine mucosa to prepare a cradle, as it were, for the ovum. If fertilization occurs, the corpus luteum persists and the building up of the uterine cradle continues; if it does not occur, progestin rapidly disappears, the endometrial construction breaks down under the revived influence of œstrin, and this constitutes menstruation. Ovulation occurs midway between two menstrual periods and is followed either by pregnancy or 'pseudo-pregnancy.' In the earlier stages of a true pregnancy, progestin is necessary for the retention of the products of conception, and the destruction of the corpus luteum which produces it is inevitably followed by abortion. In the later stages, however, the presence of a corpus luteum is less essential, at any rate in human beings. The part played by

œstrin in initiating parturition through the post-pituitary has already been explained.

A further advance was made by Aschheim and Zondek's discovery that œstrin is excreted in the urine in large amounts during mammalian pregnancy. At the same time they noted the presence of prolan in the urine, on which they based their test for pregnancy, which has proved reliable very early on, and which is now widely used. Although œstrin may appear apart from pregnancy, the presence of prolan in any quantity in the urine is a specific sign of pregnancy or of hydatidiform mole.

It may be deduced from these physiological data that œstrin is indicated for amenorrhœa, scanty or painful menstruation, and for some of the disturbances of the climacteric. Progestin, on the other hand, is indicated for menorrhagia and repeated abortion. For primary amenorrhœa, the sex hormone of the anterior pituitary would appear to be more suitable.

Cook and Dodds synthesized œstrin and have shown that it contains the condensed phenanthrene ring, which is also at the basis of calciferol (vitamin D) and the carcinogenetic substance obtained from coal tar. It is of great interest to find that two forms of normal and one of abnormal growth should be associated with the same chemical grouping. As the synthetic product stilboestrol is more powerful than the natural one the future is evidently with the organic chemist in this matter, who may be able to supply synthetic hormones at reasonable prices; in the meantime the clinical results are much more encouraging than they were a few years ago. The natural products are given in doses of 50 to 100 rat units by injection and in considerably larger doses by the mouth. The benzoate compound is often the most convenient.

The Male Sex Hormone.

As in the female, prolan from the pituitary is necessary for sexual maturity. The contrast between the condition of a person in whom the testes are undescended and one from whom they have been removed naturally suggests that these structures form an internal secretion responsible for the production of the secondary male characters, which persist in the former case. The efficacy of any testicular extract can be tested by its producing the comb and wattles which would otherwise fail to appear on a caponized cockerel. The earlier experiments cannot be described as conclusive, but the recent discovery that the male sex hormone, like œstrin, can be obtained freely from urine has enabled the active principle to be obtained in a crystalline form, testerosterone, generally given as the propionate. It proves to be a phenanthrene compound only differing from œstrin by the presence of an additional methyl group. With this definite knowledge at our disposal, reliable clinical results cannot be far off and discussion of the validity of earlier observations becomes unnecessary.

Thymus.

The thymus is an infantile organ which tends to disappear spontaneously, and whereas there is an association between the cortex of the adrenal and sexual development, there appears to be an antagonism between the thymus and the sexual organs. The statement that thymus extract accelerates the rate of growth and sexual maturity in rats has not been confirmed, but pineal extract appears to retard the rate of growth and accelerate sexual differentiation, producing a precocious dwarf. These results are now attributed to glutathione.

Growths of the thymus have been associated with a syndrome similar to pituitary basophilism, but without any changes in the pituitary.

The enlargement of the thymus in cases of Graves' disease is interesting in view of the development of both thyroid and thymus from branchial clefts. Hassall's corpuscles (usually regarded as remains of the epithelium of the gill-slits) may be enormously hypertrophied.

The association of enlargement of the thymus with sudden death is, strictly speaking, outside our present subject. The pardonable scepticism which exists as to this association is due to its being invoked to explain too many mis-adventures.

The important therapeutic results obtained by administration of liver and stomach extracts are discussed in the chapter on anæmia, while reference is made to kidney extracts in the section on blood-pressure. Many other organic extracts have been used empirically, but it cannot be said that they have achieved, or, for that matter, have deserved, much success; for the preliminary proof that the extracts contained any active principle whatever has been lacking. Recent work shows that the medium in which the hormone is dissolved has an important influence, that the benzoate salt is sometimes more potent than the pure hormone, and that certain activators may intensify its effect. All this is of hopeful import.

Antihormones.

Originally it was assumed that hormones, belonging as they do to the natural defences of the body, would not act as antigens. Doubt on this generalization was first thrown by Collip's observation that parathormone gradually lost its effect on repeated injection. Subsequently the existence of antihormones was established in some instances and suspected in others. Patients soon become resistant to the thyrotropic hormone, and it seems advisable also to give the growth hormone periodically with intervals of rest to avoid the development of its antihormone.

Although they may in the future be utilized by injecting an antihormone developed in an animal in order to neutralize the oversecretion of a hormone by the patient, it must be admitted that so far antihormonal action has proved a hindrance rather than a help in organo-therapy. The spontaneous secretion of a hormone seems to be checked if the body is continuously supplied with it artificially.

Starling looked forward to an important future for organo-therapy conducted on right lines when he said: 'If the mutual control . . . of the body be largely determined by the production of definite chemical substances in the blood, the discovery of the nature of these substances will enable us to acquire an absolute control over the working of the human body. Such a control is the goal of medical science.'

Far though we may be from such a goal, the study of hormones offers a profitable field for research. For it is only by an exact knowledge of the bodily processes in health that we can learn to intervene effectively in disease. Progress will only be delayed by the uncritical administration of extracts which have not been shown to contain the necessary active principle.

CHAPTER II

VITAMINS AND THE DEFICIENCY DISEASES

At the end of the nineteenth century it was held that the calorie value of the food consumed was the all-important factor in nutrition. Then Hopkins showed that a dietary of pure protein, fat, and carbohydrate, with the addition of appropriate mineral salts, could be well digested, normally absorbed, and duly oxidized in the body of an animal, and yet wholly fail to support it in the absence of certain organic substances present in minute quantities, and easily overlooked. Funk believed that he had isolated some of these as basic crystalline bodies, and therefore called them *vitamines*. As they are not all of amine constitution, the non-committal term of *vitamin* has been substituted. They are differentiated from the ordinary foodstuffs in that they are intensely active in minute quantities.

In this respect they resemble hormones, and as animals are almost entirely dependent on vegetable life for their production, they have been called 'exogenous hormones.' We now recognize that their absence from the diet may lead to definite disease just as effectually as the presence of a germ may do. While the germ theory of disease was in full favour it was difficult to realize that, so to speak, a *minus* could be as operative as a plus. But it is now also recognized that, in addition to the fully developed pictures of deficiency disease, there exist minor degrees of vitamin lack which have a definite effect on the growth of the body and its resistance to disease.

The literature of this subject is now so enormous that it is impossible to do more in this book than to allude to certain general principles.

It is usual to classify the vitamins according to their solubilities in water or fats. The accompanying table also indicates the principal source of each group of vitamins, together with the principal diseases which result from lack thereof.

1. FAT-SOLUBLE VITAMINS.

	Principal Sources.	*Principal Diseases.*
A.	Milk and its derivatives, cod or halibut liver oil.	Xerophthalmia.
D.	Cod or halibut liver oil, egg yolk.	Rickets.
E.	Lettuce, wheat germ.	Sterility.
K.	Alfalfa grass.	Certain hæmorrhagic states.

2. WATER-SOLUBLE VITAMINS.

	Principal Sources.	*Principal Diseases.*
B_1.	Germ of cereals, yeast, egg yolk.	Beri-beri.
B_2.	Liver extract, yeast.	Pellagra.
C.	Lemons, oranges, cabbage.	Scurvy.

Vitamin A.—This vitamin is an alcohol. When a molecule of carotene is split into two, with the addition of 2 molecules of water it gives rise to 2 molecules of vitamin A. The precursor, carotene, is abundantly present in green plants, carrots and egg yolk. The fully formed vitamin is present in milk and its derivatives, but its richest-known sources are fish-liver oils (*e.g.*, cod and halibut), which derive them from the minute green infusoria floating on the sunlit surface of the sea. The fats of mammalian livers are also rich in it. The vegetable fats have generally a low content of this vitamin, and consequently margarine is deficient in this respect unless fortified. It is not destroyed by prolonged cooking, even in the presence of bicarbonate of soda.

Although it had been known since 1848 that cod-liver oil could cure xerophthalmia, which is the chief cause of preventable blindness in children in various parts of the world, it was not until the outbreak in 1917 in Denmark, when milk products were being exported to Germany, that the condition was recognized as due to a vitamin deficiency. Vitamin A is necessary also for the regeneration of visual purple in the retina, lack of which causes night blindness in adults. It is interesting to note that Hippocrates found that this condition could be cured by ox liver, which we now know to be rich in vitamin A.

The effect of vitamin A on the cornea is a special case of its general action on epithelium and mucous membranes. In its absence they become keratinized and break down, allowing of penetration by micro-organisms. Hence its importance in the prophylaxis of renal calculi. This does not mean, as was formerly thought, that the vitamin has any anti-infective property, but that in its absence the body is deprived of one of its natural defences. The normal individual has a considerable reserve of it in his liver, but the damage caused by an insufficient supply of it in early life apparently cannot be made good by an adequate supply later on. A child requires food containing vitamin A as soon as it is weaned. Much chronic ill-health in later life may have its origin in an early deficiency in this respect. Thus Lady Mellanby believes that this keratinization of the periodontal membrane in youth is a predisposing cause of pyorrhœa in later life. Degeneration of nerve cells following a lack of this vitamin has been reported by several observers, including Sir Edward Mellanby, who attributes this in part to excess of cereals in the diet. At least 3,000 international units are required daily. Four to six thousand can be supplied by a pint of milk, two ounces of butter and one serving of green vegetable. High temperatures in cooking readily destroy this vitamin.

Vitamin B.—This is now known to consist of a complex including two substances of special importance, which can be distinguished by the effect of the autoclave upon them.

Vitamin B_1.*—The classical example of a lack of this vitamin was seen in those races whose staple diet was polished rice and who consequently suffered from beri-beri. The embryos of seeds and yeast are rich sources of vitamin B_1. In the preparation of white flour and polished rice, in which process the germ is removed, the greater part of the vitamin is lost. Takaki was able to reduce the incidence of beri-beri in the Japanese Navy from 1,485 cases to nil within nine years by remodelling the diet, although he did not understand the real nature of the disease. It was only after Eijkman's observations on the development of polyneuritis in hens fed on milled rice that the conclusion was gradually reached that beri-beri was a deficiency disease. Finally, the vitamin was isolated in a crystalline form and found to be a sulphur-containing compound (aneurin or thiamine hydrochloride) readily destroyed by heat, especially in an alkaline medium. It appears to be an essential factor in the oxidation of carbohydrates; when insufficient the metabolism of the central nervous system and the heart is seriously impaired. Hence it has been recommended for dropsy in alcoholics with marked benefit and for polyneuritis with varying success. Although beri-beri is practically unknown in this country, it is quite possible for urban populations to suffer from a partial shortage of vitamin B_1. Wholemeal bread is certainly a richer source of it than is white bread. Brown bread contains more germ, but frequently has bran added to it, which has a relatively low content of this vitamin. Yeast extracts such as are used for soups and flavouring are valuable sources. But a good mixed diet usually contains a sufficiency. There is no danger of excess, and the average daily

* Sometimes called vitamin F in American literature.

requirement is 1 mg. of the crystalline substance, though more is needed in febrile states and thyrotoxicosis.

*Vitamin B_2.**—Pellagra is the principal disease caused by lack of this vitamin. Although the florid form does not occur in this country, thousands of people die from it annually in the United States. Leslie Harris points out that it is characterized by three *d*'s—dermatitis, diarrhœa, and dementia; and is due to a diet of the three *m*'s—maize meal, molasses, and meat (salt pork). He says: 'It is a sad commentary on our civilization that while these people are dying from a dietetic deficiency, at the same time in other parts of the continent food is being burned or thrown into the sea because of "over-production."'

Minor degrees of this trouble may appear after gastrectomy, or even when maize predominates in the staple diet, and may be merely manifested by glossitis, diarrhœa and vague nervous disturbances. Liver extract is a rich and wheat germ a poor source of vitamin B_2—exactly the opposite distribution of B_1. Heating in an autoclave destroys B_1, but not B_2. B_2 contains at least four active principles, and for that reason it is sometimes referred to as the B_2 complex. Of these riboflavin and nicotinic acid are the most important. Lack of the former leads to dermatitis and stomatitis, while the latter is the anti-pellagra factor.

Vitamin C.—The value of fresh fruits and their juices in the prevention of scurvy has been known for centuries. The history of the recognition of this as due to lack of vitamin C is full of interest. Holst and Fröhlich caused fatal scurvy in guinea-pigs by feeding on barley, oats, or rye. Timely addition of fresh potatoes, apples, carrots, or cabbage would cure the disease. Although popularly supposed to be a valuable anti-scorbutic, lime juice is actually far less efficient than lemon juice. The 'lime juice' of the Navy was obtained from lemons in the Mediterranean area, where true

* Sometimes called vitamin G in American literature.

limes do not grow. During the Napoleonic wars it was difficult to get fruit from this district, and just then we wished to develop the newly acquired West Indian Islands, where limes grow, but not lemons. Quicker voyages, cold storage, and other improvements prevented serious outbreaks of scurvy until the siege of Kut.

The anti-scorbutic principle is found in most fruits. The richest sources are blackcurrants, lemons, oranges, and grapes, but in emergency use may be made of the fact that on germination of seeds such as peas and beans considerable amounts of it are formed. Outbreaks of scurvy were prevented and stopped on several occasions during the recent war by this means.

In 1883 Sir Thomas Barlow recognized an infantile form of scurvy due to sterilized foods. Human milk contains four times as much vitamin C as the cow's milk ordinarily supplied, though a sufficient supply of the latter is adequate to prevent a baby from developing scurvy. The juice of raw swedes is particularly useful for babies fed on dried or sterilized milk when oranges or lemons are too dear. Unlike most other vitamins, C can be made by animals, except men, monkeys, and guinea-pigs. Some authorities believe that in addition to frank scurvy a minor degree of this condition is not uncommon in some parts of the world where the consumption of fresh fruits, vegetables, and milk is insufficient. Vague ill-health due to this cause may be recognized by Göthlin's method. On applying pressure to the skin, small capillary hæmorrhages occur.

The isolation of vitamin C was arrived at by noticing that stale fruit juice would not bleach certain dyestuffs in the way that fresh juice would do. Tillmans and Hirsch found that this was associated with the disappearance of a reducing agent (hexuronic acid) from the juice. Szent-Györgi isolated large quantities of this acid from paprika and found that it would prevent scurvy, and it has therefore been renamed *ascorbic*

acid. The anti-scorbutic power of a food is in direct proportion to its content of this acid, which has now been synthesized. This power is dependent on its reducing activity, in the absence of which the balanced chemistry of the cell cannot go on. Among other things, it appears to be necessary for the maturation of the red blood corpuscles in all its stages. In its absence the healing of wounds is impaired. It is so powerful that a single dose of 50 mg. by the mouth will produce a marked effect in infantile scurvy within forty-eight hours. Persons suffering from a deficiency of vitamin C excrete less of it in the urine than normal, nor do they excrete more when given the vitamin until their tissues have reached saturation point.

The longer vegetables are heated, the more vitamin C is destroyed, especially in the presence of alkalies, which are often added by the cook to preserve their colour. Copper utensils also destroy it rapidly even at pasteurization temperature. Essentially it is oxidation which is responsible for their destruction. The daily minimum requirement is 30 mg., but the optimum dose is twice that amount.

Vitamin D.—The steps by which vitamin D was proved to be concerned with calcium metabolism, and that rickets is due to lack of it, constitute one of the triumphs of twentieth-century medicine. Rickets was first described by Glisson in 1650, and perhaps for that reason was called on the Continent the English disease, since it is by no means uncommon elsewhere. For years cod-liver oil was recognized as the best treatment, but there were two prominent schools of thought as to the causation of rickets. The first held that the disease was due to a faulty dietary containing excess of cereals, but too little fat; the second that a lack of fresh air, sunlight, and exercise was responsible. These two theories were difficult to reconcile. Mellanby's dietetic results at first appeared convincing, but supporters of the other school showed that if exercise in fresh air was provided rickets

would not appear in experimental animals, although they were given Mellanby's rachitic diet. It was then found by Huldschinsky in Vienna that rickets could be cured just as well by sunlight or ultra-violet rays as by diet containing such things as cod-liver oil. Harriette Chick and her collaborators, from their study of post-war conditions in Vienna, confirmed the fact that the cure is apparently identical in character in both cases.

The clue to the reconciliation of the two views was found by Steenbock at Wisconsin, who found that a rachitic food mixture would no longer produce rickets after it had been exposed to ultra-violet light. The constituents of the food were examined one by one until fat was found to be the precursor of the substance responsible. Further examination proved that the actual substance was the ergosterol associated with the fat. Under the action of ultra-violet rays it forms the active anti-rachitic vitamin D. When the body is exposed to these rays vitamin D is synthesized from ergosterol in the superficial layers of the skin, and subsequently absorbed into the circulation. The vitamin was finally isolated in a crystalline form by Bourdillon and his colleagues in 1932 and styled calciferol. It is now put up in a standardized form, and 500 units daily is an effective prophylactic dose, while 1,200 to 3,000 units daily are curative. Some authorities prefer to begin treatment with massive doses for a short time. Its action in assisting the normal deposition of calcium in growing bone is due to an improved absorption from, and a diminished re-excretion of, calcium phosphate into the bowel. A low level of either calcium or phosphorus in the blood will cause rickets, the latter being the common type in babies; tetany only occurs with low calcium. The anti-calcifying action of certain cereals is now attributed to their phosphorus content being in an unassimilable form. Lady Mellanby has further shown that vitamin D not only prevents dental caries, but can actually arrest the process when it has begun. There

is no need for special preparations of vitamin D during the summer months, and at any time it is easy to prevent rickets with small doses of cod-liver oil or of irradiated milk. It is not injuriously affected by cooking. Excessive doses of any anti-rachitic agent can do harm by raising the blood calcium too high. The amount of cod-liver oil necessary to do this is much more than an infant would normally get, but a concentrated vitamin preparation could do it. Leslie Harris has shown that 10,000 units may be a distinctly toxic dose, raising the blood calcium to a dangerous level, and leading to the deposit of calcium salts in various parts, including the kidney, where it forms calculi.

Osteomalacia in adult women is due to a similar deficiency of vitamin D, and should be treated like rickets. J. P. Maxwell has shown that osteomalacia in the mother may lead to prenatal rickets in the offspring.

Since an ordinary diet usually contains sufficient calcium, it is clear that any shortage of it in the blood is usually due to lack of assimilation or increased excretion. The various ways in which this can be corrected have been described in the section on the parathyroids. If it is thought advisable for any reason also to administer calcium salts, 15 grains of the lactate or 25 grains of the gluconate appear to be the most suitable forms.

Vitamin E (Tocopherol).—In 1922 Evans of Berkeley, California, detected a third fat-soluble vitamin which appears to be essential to normal reproduction in some animals. It is present in wheat germ and certain green leaves, particularly lettuces. In its absence, with the female rat fertilization and implantation occur as usual, but there is subsequent death and reabsorption of the fœtus. An adequate dose of vitamin E will restore fertility to the female, but sterility once thus induced in the male is permanent. This vitamin is a stable substance, but it has not yet been isolated, though it can be prepared in a concentrated form. It has been recommended in doses of 10 to 50 mg. daily for

the treatment of habitual abortion, if other causes have been excluded.

Vitamin K (Methyl-naphthaquinone).—In obstructive jaundice fats and fat-soluble vitamins are badly absorbed. The lack of vitamin K is thought to be responsible for the hæmorrhages which are apt to occur in this condition, because it is necessary for the elaboration of blood prothrombin. It is extracted from alfalfa grass or hog's liver, and is fairly stable. It is therefore useless for hæmorrhagic conditions in which the prothrombin content is normal, such as thrombocytopenia purpura and hæmophilia. It is useful as a prophylactic against hæmorrhage in preparing for operation on jaundiced patients, provided that there is no extensive liver damage.

These aspects of the science of nutrition have taught us a good deal about the intimate chemical mechanisms of the cell. They also give scientific sanction for our belief in the necessity of sunlight and a mixed diet drawn from as many sources as possible, and should discourage fads, extremes, and one-sided views and practices in dietetic matters. The best sources of vitamins are the dairy and the garden. An ordinary good mixed diet contains a sufficient supply of all the vitamins to maintain health except possibly of B in the case of urban populations. In certain diseases it is necessary to add them to the restricted diets employed in such conditions as peptic ulcer, gall-bladder disorders, and obesity. In vomiting, diarrhœa and possibly in achlorhydria their absorption is impaired. Their actual requirements may be increased in pregnancy, lactation and fevers. It should be emphasized in conclusion that for every case of obvious clinical lack there are many of minor deficiency with symptoms too vague for diagnosis without a critical examination of the patient's usual diet. But a protest should be made against the absurd and pseudo-scientific propaganda which is sometimes indulged in.

CHAPTER III

MECHANICAL FACTORS IN DIGESTION AND INDIGESTION

It should hardly be necessary to insist on the cardinal importance of the teeth in the due performance of mastication, without which the food cannot be insalivated. It may appear paradoxical to assert that the inevitable tendency to swallow soft carbohydrates is a more serious consequence of defective teeth than the bolting of meat. For such carbohydrates do not lead to the secretion of sufficient saliva to promote their digestion, which would otherwise continue until the gastric contents became thoroughly mixed with acid.

The Mechanism of Swallowing.

Apparently swallowing is not the simple peristaltic act it was formerly thought to be. As a result of the use of radiographic methods on normal persons and also on certain animals, Barclay has put forward the interesting hypothesis that during the act of swallowing a sub-atmospheric pressure is developed in the pharynx and upper œsophagus, so that the bolus is transferred by suction. Anrep has recorded and measured these changes of pressure by means of a rubber catheter introduced through the nose into the lower pharynx. This demonstration helps to explain why it is that the swallowing mechanism is so completely disturbed by paralysis of the constrictors of the pharynx on one side only.

The different conditions obtaining in the swallowing of liquids and solids explain some of the symptoms in malignant stricture of the œsophagus. At the necropsy it may appear as if there could have been no difficulty in swallowing food

or in the passage of a bougie, but, of course, much of the obstruction is due to spasm. It is common for the dysphagia to begin suddenly during a hearty meal. A spasm has been evoked and will recur on each attempt at deglutition. The same thing may occur in congenital œsophageal stricture. As the act of swallowing liquids excites no spasm, but rather an inhibition of peristalsis, it is easily performed long after all solids are unable to pass. It is important to note that a spasm may result from a growth lower down the œsophagus or at the cardiac orifice, which, like the gastric spasm to be referred to later, is presumably protective in nature.

When the intragastric pressure rises above 25 centimetres of water, eructation or regurgitation occurs, to be followed promptly by œsophageal peristalsis forcing back any food into the stomach again.

Hurst showed that so-called cardiospasm is really a failure of the cardiac orifice to open, and he suggested the term achalazia as a more accurate name. Degeneration of Auerbach's plexus at this point was subsequently demonstrated. The passage of a blind tube filled with sufficient mercury can often overcome this difficulty and temporarily relieve the symptoms. The value of vitamin B_1 in the treatment of such conditions has already been referred to.

Movements of the Stomach.

Our present knowledge of the movements of the stomach in man has been derived from radiology after an opaque meal. With the shifting of the emphasis formerly laid on secretory disorders to changes in motility, the X-ray screen has become indispensable in the routine examination of disorders of the stomach.

Not only can peristalsis and rate of emptying be studied, but also it is possible to determine the presence of residual fluid when the stomach should be empty, and to see the

pattern of the mucous membrane itself. Peristalsis varies considerably even in the same individual, but normally in man it is quite unlike that forcible churning movement described in some physiological textbooks. Deep waves of contraction are evidence of obstruction at the pylorus, whether functional or organic, such as is commonly seen in pyloric ulceration.

The causes of pyloric spasm will be considered later. Normally, peristaltic waves begin high up on the greater curvature, taking about twenty seconds to pass from end to end. By the time the wave reaches the lower third of the stomach it is also evident on the lesser curvature. It becomes deeper as the pylorus is reached. Normally, about three waves a minute can be observed, which persist with short periods of rest until the stomach is empty. It is probable that, even when empty, peristalsis persists to some degree, so that withholding food does not rest the stomach. The pangs of hunger have been shown to be accompanied by contraction of that organ. Emptying of the stomach begins very quickly and does not depend only on peristalsis; sometimes the pylorus is seen to relax when no wave is evident; on the other hand, vigorous peristalsis may fail to pass any barium onwards into the duodenum for minutes at a time, unless the food is pushed up against the pylorus by hand. If there is food in the small intestine the opening of the pylorus is delayed; if the patient has been starved beforehand, emptying is much more rapid.

Changes in the acidity or alkalinity of the food seem to have no effect on the rate of emptying—an observation which is difficult to reconcile with the long-held theory of the acid control of the pylorus. The size of the food particles has a definite effect, the presence of larger particles apparently slowing down the emptying of the stomach.

The common occurrence of pain in dyspeptics at a time when the stomach is nearly empty has been ascribed to a

change in the type of contraction, although no such change has been demonstrated on the X-ray screen. It is possible that with the development of X-ray cinematography the causation of the pain may be revealed.

The length of time the stomach takes to empty varies considerably, not only from person to person, but in the same individual. When a fine barium emulsion is used, the stomach is often almost empty in two hours; it may be considered to be definitely abnormal if not emptied in six hours.

Hour-Glass Contraction.—A spasmodic constriction is liable to be mistaken for an organic hour-glass contraction. Jellasse, in 1906, suggested, and it is generally agreed, that a spasmodic ring of constriction is most usually due to the presence of an ulcer, which is generally situated on the lesser curvature, and may be quite small. The spasm can sometimes be made to disappear by the injection of $\frac{1}{100}$ grain of atropine. The contracted area varies in degree; there is no sagging or peristaltic wave in the proximal half of the stomach. These three points serve to distinguish spasmodic from organic constriction.

Perigastric adhesions are now well recognized as a mechanical cause of indigestion. There is generally a previous history of gastric ulcer or biliary colic; the pain is much influenced by the position of the patient and little by diet; and local tenderness is common, while vomiting is rare (E. P. Paton). To this we may add that the X-rays may show the stomach to be held up somewhere, so that the normal alterations in its position on change of posture or on vigorous contractions of the abdominal wall do not occur.

Dilated Stomach.—There are important differences between the atonic and the obstructive form of dilatation:

1. *Atonic Dilatation.*—There is sometimes a long history of chronic gastritis, or of a disease like typhoid fever which leads to muscular enfeeblement. But the most frequent cause

is an emotional one which leads to sympathetic irritation. This would check gastric peristalsis and cause pyloric spasm. It may show a familial tendency. To such cases this term is not really appropriate. One of the most characteristic symptoms, which can generally be elicited on inquiry, is that the patient feels full up as soon as he starts eating. Hurst points out that both the atonic stomach and the contracted stomach give rise to this sensation. The contracted stomach feels full up because it cannot expand. The atonic stomach feels full up because it has already expanded, and a further relaxation of the stomach as it fills, which would avoid a rise of intragastric pressure, cannot take place. As soon as food is taken into this relaxed stomach the pressure begins to rise and the patient feels full. After taking food there is a general sense of misery and discomfort rather than actual pain. The patient frequently complains of a disagreeable taste in the mouth, and there is often a brown fur on the back of the tongue. There is seldom vomiting. On inspection of the abdomen there may be some dropping of the stomach, a hollowing out under the costal margin, and a fulness below and to the left of the umbilicus.

A succussion splash which is elicited only on deep palpation is only significant at a time when the stomach should be empty. A superficial splash may be suggestive of atony. But neurasthenics and hypochondriacs have an extraordinary power of producing splashing by vigorous contraction of the abdominal walls. The test-meal may show diminished hydrochloric acid in the cases following gastritis, but not in the nervous type. An atonic stomach gives, on X-ray examination after barium, a shadow reaching some distance below the umbilicus, with a broad meniscus at the bottom and a straight line at the top. Peristaltic waves are feeble or absent. Gastro-jejunostomy is definitely contra-indicated, but an appropriate abdominal support, such as Curtis', may be decidedly helpful.

We must distinguish between this type of atony and gastroptosis, which is usually part of a general enteroptosis. In the latter the stomach is increased in the vertical diameter, whereas in the dilated stomach it is increased chiefly in the horizontal diameter. It is now, however, recognized that great variations in the position of the stomach and colon occur without pathological significance.

Treatment.—Acute dilatation is a rare but dangerous condition of toxic origin, for which lavage should be performed without delay. Chronic dilatation may exist unsuspected in an alcoholic subject. In the ordinary dyspeptic type there has usually been a long-continued mucous gastritis. Treatment is likely to be ineffective in this type if lavage be not performed at the outset; otherwise our remedies are apt to be lost in the fermenting slimy mass that is already there. Sodium bicarbonate should be added to the water because of the solvent action of alkalies on mucus. The last part of the fluid employed may have an antiseptic added, such as 2 volumes per cent. of hydrogen peroxide. Starchy foods are contra-indicated; they should certainly never be given in the form of pap, as is so often done. Dry toast, biscuit, or rusk, is preferable, because in the act of mastication some of the starch will become converted into malt-sugar; but any form of starch should be reduced to a minimum.

As Sir Clifford Allbutt said, 'There is no superstition more tenacious of life than that which prescribes carbohydrates to all dyspeptics as "so digestible," and into weak stomachs, ready to dilate, is thrown a mass of such a dish as rice pudding.'

In bad cases the diet, at first, should be restricted to meat-juices and meat-extracts (because of their stimulating effect on the secretion of hydrochloric acid), and to lightly cooked minced meat, which does not ferment, and leaves but little residue. From the rapidity with which egg-albumen leaves

the stomach it might be imagined that eggs would be a suitable diet in this condition; but patients generally protest that they cannot digest them, although some cases have improved on a Lenhartz diet. If hypochlorhydria is present, hydrochloric acid or oxyntin (acidol) should be given after food, combined with arsenic and strychnine, which seem to have a tonic effect on the gastric musculature. In the nervous type, alkalies with bromide will do more good than acids, while the emotional cause will require investigation.

Abdominal massage is useful, as it increases peristalsis in the stomach. Rest before and after meals should be enjoined, since fatigue before or exercise immediately after can be shown to delay the discharge of food from the stomach.

2. *Obstructive Dilatation.*—The characteristic symptoms are vomiting of large amounts and steadily increasing discomfort between the attacks. After the stomach has been emptied by a large vomit, the patient is comparatively comfortable for hours or even days, and then discomfort begins and increases until it culminates in vomiting again. A point of practical importance is that the vomit is highly acid, if the obstruction is not of a malignant nature. Ordinarily, though the secretion of gastric juice may be normal or even slightly hyperacid, the vomit will not show free hydrochloric acid unless there is obstruction, because the other conditions which excite vomiting are almost certain to have previously inhibited gastric secretion. But when there is obstruction to the pylorus the vomiting occurs from quite a different reason. Secretion has been taking place as usual, but onward progress and consequent neutralization are delayed so that the vomited contents will be highly acid. Gastro-enterostomy is generally indicated, but as œdema at the pylorus may have contributed to the obstruction, routine lavage should be employed first.

Gastro-Enterostomy.—Increased knowledge of the gastric movements has shown clearly the limitations of this operation. It does not 'drain' the stomach. Even when the pylorus is partly occluded, the food passes through it rather than through an opening remote from the greatest pressure. Berg operated on two cases of duodenal fistula, in both of which gastro-enterostomy was done, but the discharge of chyme through the fistula ceased only in one in which he tied the pylorus as well. We are not justified in assuming that the region between the new opening and the pylorus is placed completely at rest. The operation is therefore rarely indicated except in cases of definite obstruction to the pylorus. But we must bear in mind the effect of the hyperchlorhydria associated with gastric and duodenal ulcer. Bolton has proved experimentally that hyperacidity facilitates the production and prevents the healing of a gastric ulcer. After gastro-enterostomy hyperchlorhydria usually passes off, though sometimes a jejunal ulcer may form in the area against which the acid is now projected. The diminution in acidity results from regurgitation of alkaline bile and pancreatic juice into the stomach through the new orifice, which is not provided with a sphincter. Retention of food in the stomach with repeated vomiting, the so-called 'vicious circle,' is an occasional bad result of the operation. This is not due to the repeated entrance of the food from the duodenum into the stomach, but to an obstructive kink or other demonstrable obstacle. Although, according to Cannon, sharp turns in the intestine are normally straightened without difficulty by the material driven on by peristalsis, this force is not at hand to straighten a kink immediately beyond the ostium, since the division of the circular muscular fibres at the operation has abolished the peristaltic wave there. The rational procedure is therefore to attach a narrow band of the distal gut continuously to the stomach wall for an inch or so

beyond the ostium. The gut is then kept straight throughout a distance which permits peristalsis to become an effective force.

Another unfavourable result may be too rapid emptying of the stomach, as shown by Hurst. The chief symptom complained of is a feeling of fulness slightly lower down than the site of the discomfort before the operation. The distension of the jejunum is probably responsible. The patient has generally found that a dose of castor oil shortens the duration of this discomfort, because it hastens the onward progress of the contents of the distended jejunum. Hurst advises the recumbent posture after meals in these cases to delay the emptying of the stomach. If this is not sufficient, small doses of belladonna to relax the muscle fibres of the intestine, and of codeine to diminish the excitability of the sympathetic nervous system, should be given half an hour before meals. An abdominal support often helps to prevent this jejunal distension.

The possibility of these various untoward consequences renders the operation far from an ideal one, and its performance in unsuitable cases is fraught with disaster. Jejunal ulcers, troublesome adhesions, and many neuroses are frequent sequels. Pernicious anæmia has occurred too often to be explained as a mere coincidence, and is still more common after partial gastrectomy, which has now become the operation of choice in the surgical treatment of intractable gastric ulcer.

Congenital Hypertrophic Stenosis of the Pylorus.—This cause of vomiting and marasmus in infants presents some interesting problems. The diagnosis rests upon the combination of vomiting, constipation, and wasting with visible peristalsis of the stomach and a palpable pylorus. That the condition may really be congenital is proved by its having been found in a seven-months fœtus, but the vomiting usually begins about the fourth week, and not later than

the ninth week, after birth. It is generally sudden, copious, and forcible, so that a quantity representing more than one feed may be shot out a foot or more from the mouth, and perhaps through the nostrils also. With increasing dilatation the vomiting becomes less frequent, while the amount becomes greater. For the two characteristic signs of visible peristalsis and palpable pylorus, it is very important to examine the abdomen immediately after feeding, for it is sometimes only then that the abnormal peristalsis can be seen, and the thickened pylorus felt. It may be necessary to examine for ten to fifteen minutes before these signs can be elicited. Sometimes the waves appear spontaneously, at other times only after repeated stroking or gentle kneading of the epigastrium. *Post mortem* the stomach is found greatly dilated, and the pylorus is much thickened for about $\frac{3}{4}$ inch, yet a probe can usually be passed through it readily, and water injected into the duodenum quickly finds its way into the stomach. Microscopically the only change found is hypertrophy of the muscular tissue.

The pathology of the condition is a vexed question. Congenital stenosis appears to be a misnomer, since the hyperplasia may occur after birth, and there is no true narrowing of the lumen. Pyloric spasm leading to muscular hypertrophy seems to be the sequence of events. But what causes the spasm? John Thomson suggests that it is due to an inco-ordination of the muscles of the stomach, the central nervous system having not yet acquired proper control. It would thus be comparable to the stuttering of a child who is learning to talk. It is commonest in male first children and is often associated with phimosis.

Treatment.—The usual procedure is for Rammstedt's operation to be performed as soon as the diagnosis is made. The stomach should be washed out through a No. 15 catheter first to remove curds and other food residues. The injection of a solution of glucose *per rectum*,

or into the loose tissues of the axillæ, diminishes the risk of acidæmia, and keeping the infant very warm during and after operation lessens shock. A combination of local with general anæsthesia appears to be favoured by surgeons. Both speed and gentleness are essential. The operation simply consists in a clean cut through the peritoneal and muscular coats along the white non-vascular line on the pylorus, allowing the mucous membrane to herniate through the muscles. There is an unexplained liability to hyperpyrexia after operation, which may be due to the excessive zeal in trying to prevent shock. The troublesome and even dangerous diarrhœa which may follow operation is probably due to its having been delayed until the intestine has become atrophic, or to the bulk of the feeds having been increased too quickly. For it is essential that food should be given frequently in quite small amounts, beginning with not more than a teaspoonful at a time, while it is probably wise not to give any milk in the feeds for thirty-six hours. Whey and raw-meat juice are apparently the best foods to start with.

Of late there has been a return to medical methods since the successful experience with eumydrin (atropin methyl nitrate) reported from Copenhagen. It is important not to employ it while the infant is in an extremely dehydrated condition, and not until the introduction of saline has been followed by satisfactory diuresis. Then 5 ml. (75 minims) of a 1 in 10,000 solution (which must be fresh) is given seven times a day half an hour before food; half these doses are often sufficient. Treatment should be maintained until vomiting has ceased for at least a week. It is claimed that this method gives better results than surgery, gastric lavage, or atropin.

The Intestines.

Discharge of Food into the Duodenum.—The discharge of the gastric contents normally begins at once, but may be reflexly delayed. Murphy and Cannon found,

after high intestinal section and suture, that for almost six hours after recovery from anæsthesia the pylorus remained tightly closed. There is a remarkable coincidence between the period of delay in the discharge and the time required for the primary cementing of the intestinal wound. This is clearly protective, and probably explains the spasm and consequent hyperchlorhydria of reflex dyspepsia. It may occur in duodenal ulcer and in diseases of the biliary passages, both of which we know may be accompanied by hyperchlorhydria, a common result of pyloric spasm. This happens also when the colon is irritated, and it is recognized that hyperchlorhydria is a frequent accompaniment of chronic appendicitis. It is noteworthy how often the focus of an organic dyspepsia is situated on the right side, and that more than one lesion may be present there, such as appendicitis with cholecystitis or with peptic ulcer.

Movements of the Small Intestine.—Although pendular movements, together with peristaltic waves, have been described under experimental conditions in animals, radiological observations in the normal human being seem to show that peristalsis is only evident where the opaque food is in masses, as when the stomach empties very rapidly.

The transference along the small intestine is rapid, especially from the first part of the duodenum through the jejunum. In the latter, indeed, the movement of the opaque food is too rapid to allow of accurate visualization on the screen. There is no movement *en masse*, but the food seems to be reduced to a fine state of division, owing partly to dilution and mixture with intestinal juices. It comes about, therefore, that some pathological phenomena which can be seen on the screen do not persist long enough to allow of their being photographed except by special methods. Films alone are quite inadequate as a means of studying the stomach and duodenum.

The whole of the small intestine is traversed rapidly until

the lower end of the ileum is reached. The opaque meal is seen to halt for some before it enters the cæcum. In the normal person examined at the sixth hour after the meal there is usually some food already in the cæcum. But in a 'nervous' subject the passage may be much more rapid.

Some of these movements apparently depend on an intrinsic nervous mechanism of the bowel, the plexus of Auerbach. At the same time the extrinsic nerves affect these waves, the vagus increasing and the splanchnic inhibiting them. An exception to this general statement is the fact that the splanchnic nerve supplies motor fibres to various sphincters. Elliott has formulated the law of the hollow viscus as follows: 'If the quiet lodgment of the contents be facilitated by the presence of sympathetic inhibitory nerves to the body of the viscus, there will also be sympathetic motor nerves at the sphincter closing the exit.' The pylorus, the ileo-cæcal valve, the internal anal sphincter, and the neck of the gall-bladder are all thus supplied.

Extrinsic mechanisms occasionally interfere with the normal intrinsic ones, usually in the direction of inhibition. This is observed after operations. It has been shown that even gentle manipulation of the stomach and intestines produces a much greater post-operative inactivity than anything else in the operation. That this is due to reflex inhibition is proved by the fact that it is overcome for a time by injection of eserine salicylate ($\frac{1}{100}$ grain four-hourly for six doses), which diminishes these nervous influences, while tincture of aloes, which is particularly effective in promoting peristalsis in the cat, is quite ineffective after such manipulation of the gut as results in paralysis. Some emotional states are a strong stimulus to peristalsis, while others inhibit it. Thus in most animals any sign of rage or distress or mere anxiety is accompanied by a total cessation of the movements of the stomach. In the dog's intestine, on the other hand, after

signs of emotion there is a marked increase of activity lasting for only a few minutes. Emotion as a factor in the production of diarrhœa is well known.

Apart from operative interference or organic obstruction, delay seldom occurs in the small intestine. Cannon never observed it experimentally, and Hurst found it only in lead-poisoning. Peristaltic rush, on the other hand, is not infrequent here, and may be the result of a purgative or an enema. Of the three foodstuffs, carbohydrates normally pass the most rapidly. This may be associated with the presence of cellulose and its well-known mechanical action.

Cannon made some interesting observations on the result of intestinal anastomosis. After an end-to-end union of the intestine there was no evidence of stasis, but after lateral anastomosis there was a more or less complete blocking. In time the tube may be straightened out after a lateral anastomosis, with restitution of functional efficiency, but there is a period when there is a danger of obstruction, because the division of the circular coat of muscle interferes with peristalsis. Further, if the blind ends of the lateral loops are allowed to extend beyond the openings there is a danger of the proximal portion becoming packed with hardened fæces, and of the distal becoming invaginated until it fills the lumen of the anastomosis.

Movements of the Large Intestine.—Functionally the large intestine can be divided into three portions which do not correspond exactly to the anatomical divisions: (1) a proximal part characterized by the presence of antiperistaltic waves, (2) an intermediate part conforming to the type of movements seen in the small intestine, and (3) a distal portion, the rectum, where the central nervous system again assumes control. It is in this last part that disturbances are most likely to occur because the automatic call for the discharge of its contents can be voluntarily suppressed. Anti-

peristalsis is rather a misnomer, for it is really a rhythmical series of reversed segmentation movements depending largely on the degree of tension present, and not peristaltic waves originating from a ring of tonic constriction. It serves to churn the food and delay its onward passage. It necessitates a true muscular sphincter at the ileo-cæcal valve, and the development of a cæcum is a corollary to its occurrence. In animals like the rabbit and the herbivora in general, where the cæcum is long, it can be filled only by the aid of anti-peristalsis.

In the large bowel the absorption of water mainly occurs, and as the contents become more solid, the shadow cast on the X-ray screen becomes more intense, so that the segmentation waves and peristalsis become very distinct. The onward progress also becomes much slower, so that the colon is traversed in about six hours. During the night the movements are considerably slower than this. From the transverse to the pelvic colon the residue is transferred by so-called mass movement. This takes place at intervals and is so rapid that opportunities to observe it rarely occur. The action of some purgatives in producing peristaltic rush in the large intestine is marked. Thus senna causes an evacuation as soon as it enters the colon, and anti-peristalsis is completely inhibited. Enemata, on the other hand, have a markedly stimulating action on the anti-peristalsis of the colon. Small rectal injections are never forced even partially into the small intestine; but with larger amounts, whether fluid or semi-solid, many coils of the small gut become filled. In cases of cæcal fistula the ileum has been transplanted into the transverse colon without stopping the discharge, for here, as elsewhere in the alimentary canal, the contents will continue to follow the direction of the powerful muscular waves, which will be very incomplete where the circular coats have been divided. This has an important bearing on short-circuiting operations designed to exclude the large bowel. If

the normal path be left open, much of the contents will continue to pass along it.

In addition to the study of the opaque meal from above, the barium enema also affords an indispensable method of studying obstruction and other filling defects.

Defæcation.—When the bowels are opened regularly once a day the interval between a meal and the excretion of its residue will vary between nine and thirty-three hours. As the pelvic colon becomes distended it rises, widening the acute angle with the rectum, thus removing an obstacle to the onward progress of the contents. The rectum should normally be empty, except during the act of defæcation, but in constipated persons it always contains some fæces. Although defæcation has become largely a conditioned reflex, the first meal of the day helps to evoke peristaltic waves throughout the whole alimentary tract, opening the ileo-cæcal sphincter and driving some of the contents into the much more sensitive rectum. The resulting stretching of the anal sphincters causes contraction of the upper segment of the rectum, thus distending the lower part. It is this distension which evokes the desire to defæcate, which may be produced either by the passage of fæces from above or by a balloon introduced through the anus. The distension may be increased voluntarily by contraction of the abdominal muscles of the walls. A powerful wave of peristalsis is thus produced, which empties the accumulation in the rectum and completes the emptying of the descending colon. The discharge of contents is facilitated by the recto-coccygeus muscle, which draws the rectum backwards, straightening out the angle in its lower portion, while the anal sphincters are relaxed. The levator ani mainly acts as a voluntary sphincter, but it may also help in defæcation by directing the fæces forward towards the entrance to the anal canal, and by drawing this canal upwards over the fæcal mass, and finally contracting firmly behind it. In multiparous women injury to, and

atrophy of, the levator ani play a distinct part in the production of constipation. Again, the levator ani being a voluntary muscle can resist the call to defæcation. When this occurs the desire soon passes off until the arrival of more fæces again distends the rectum. Repetition of this process blunts the sensibility of the rectum until it habitually retains a considerable amount of fæces. Although such a patient is constipated, X-ray examination shows that there may be no delay in the onward passage of the intestinal contents until the rectum is reached. For this type of constipation Hurst has revived the term *dyschezia*, originally used by Robert Barnes to denote painful evacuation of fæces. As he points out, there is little use in treating such a case by aperients which have to act on a colon which is normal in its response. The rational procedure is the routine use of glycerine suppositories or enemata, by which the rectum can be emptied and its tone regained. Either procedure stretches the anal sphincter, thus aiding peristalsis, as already explained.

In Hirschsprung's disease, or 'megacolon,' the rectum is not involved in the dilatation. The hypertrophy of the muscular coats of the colon shows that atony is not the cause; a more probable explanation is a congenital defect in neuro-muscular control comparable to hypertrophic stenosis of the pylorus. The condition is thus maintained even when the impacted fæces originally present have been evacuated, so the failure to discover the cause *post mortem* is explained, since there is no organic stricture. In the same way it may not be detected at operation. In treatment the most important thing is to empty the colon as completely as possible by enemata, and then to prevent its becoming overloaded again by the use of a rectal tube passed above the kink. Strychnine and abdominal massage are valuable adjuncts to treatment. The operation of sympathectomy has been performed on many patients with so-called congenital megacolon. The

rationale of this operation is that the sympathetic fibres are inhibitory to the large bowel. Satisfactory results are claimed if the operation is performed early, and in some cases a regular daily evacuation is said to be secured, though there is a tendency to relapse.

Intestinal Stasis.—The earlier views of Lane on intestinal stasis consequent on visceroptosis do not command much support today. It must be remembered that Cannon found that peristalsis was able to drive on the contents of the bowel past quite sharp kinks, and in tuberculous peritonitis or malignant disease of the intestine kinks are formed which in many cases produce neither constipation nor stasis. There is a muscular sphincter of some length at the ileo-cæcal valve, which might easily produce the appearance of a narrowing by adhesions, and similar sphincters have been described by Keith in the position of most of Lane's kinks. Again, in healthy persons the transverse colon may be quite as low as in cases of visceroptosis, without any symptoms. And we must remember that though sudden parasympathetic irritation evokes diarrhœa, sympathetic irritation of the bowel inhibits peristalsis and contracts sphincters. Therefore depressing emotions may produce intestinal stasis. Nevertheless, the work of Wilkie on the influence of chronic duodenal ileus in exciting migraines and "bilious attacks" should be borne in mind.

Hygiene of the Bowels.—This includes the inculcation of regular habits as to the bowels, starting in childhood and continued throughout life, the use of low lavatory seats, or of footstools high enough to allow of a squatting posture during defæcation, not getting up too soon after debilitating illnesses and confinements, the avoidance of corsets exerting a downward pressure, and the correction of a tendency towards emaciation. Besides the ordinary measures for the relief of constipation, special mention must be made of liquid paraffin, which has such a vogue in the treatment of con-

stipation. Not being absorbed, it increases the bulk of the fæces, and really does seem to facilitate the onward progress of the intestinal contents. One drawback to its use is that in some cases it produces a slight degree of incontinence; but this is generally because too large an amount has been taken or because the oil is not sufficiently viscous. One should start by prescribing quite a small dose, such as a drachm, and increasing slowly till the quantity suitable for the individual has been found, which may be an ounce or more. Some preparation of Iceland moss, such as taxol or coréine, by its power of absorbing water and swelling up, is often useful by increasing the bulk of hard dry fæces; it may be used in conjunction with paraffin if necessary. The routine use of drastic aperients is to be deprecated. Abdominal massage and exercises designed to develop the abdominal muscles may be helpful. A well-fitting abdominal support is often of assistance. It might be thought that such a support could only do good, and should only be worn when the abdominal muscles are so weak that they are unlikely to recover. Such, however, is not always the case, and Hurst believes that the good effect of the support is due to its increasing the intra-abdominal pressure. It certainly does not alter the position of the viscera.

Some scepticism toward operative interference is natural when one recalls the number and variety of the surgical short cuts to health that have been advocated, and the disillusionment that has too frequently followed. There has been a regrettable tendency for the advocates of each operation to regard their particular method as a panacea to the exclusion of all the others. This is part of a generally uncritical attitude seen too frequently in the profession, and one that has been satirized by the observant layman. Only by a close and accurate study of the normal mechanism of the alimentary canal can we arrive at sound conclusions as to the value and limitations of any procedure, medical or surgical.

CHAPTER IV

GASTRIC AND INTESTINAL DIGESTION

PAVLOV'S experimental observations, followed by the introduction of X-rays and fractional test meals, laid the foundations of the rational treatment of gastric disorders.

The Nervous Factor in Gastric Digestion.—Pavlov, by dividing the œsophagus in dogs, and fixing the divided ends to the skin, completely separated the cavities of the mouth and stomach. Food taken into the mouth would naturally drop out of the gullet: this is termed 'sham feeding,' but 'direct feeding' could also be carried out by passing food into the stomach by way of the lower segment of the œsophagus. In some cases a separate cul-de-sac was made out of a portion of the stomach. This pocket opened on to the surface, so that the digestive processes in it could be easily observed; it was found that they were an exact reflection of those occurring in the main stomach.

He found that in such a dog the taking of food by the mouth was followed after an interval of five minutes by a copious secretion of gastric juice; in fact, it was not necessary for the food even to be swallowed. If the dog were shown the food, secretion would follow, until the animal realized it was not going to get it.

Clearly, a nervous agency must be at work. Now, if one vagus were previously divided below the recurrent laryngeal and cardiac branches, and the other drawn into the wound, the latter could easily be cut while the animal was feeding. It was found that now 'sham feeding' produced no effect. Conversely, if the vagus had been previously drawn into the wound and divided, to allow the cardio-inhibitory fibres to degenerate, stimulation of the peripheral end, too weak to

cause the animal any pain, led to a secretion of gastric juice.

On the other hand, 'direct feeding' into the stomach led to hardly any immediate secretion, if the animal did not see the food.

Bennett and Dodds, however, consider that in modern man, whose stomach is frequently filled before ever appetite has had an opportunity to become awakened, the psychic factor is not of great importance.

The Chemical Factor in Gastric Digestion.—Mechanical stimulation of the gastric mucosa will lead merely to an outpouring of alkaline mucus, but certain chemical stimuli will result in true secretion. The character of the juice which is poured out varies greatly with the diet which excites it. As clinically chemical factors are more under our control than nervous ones, these are also of practical importance.

We may arrange the effect of articles of diet as follows:

1. Substances producing a powerful secretion: Meat extractives such as are contained in soups, broths, and beef-tea. Bickel found that in human beings alcoholic and carbonated fluids, spices, mustard, pepper, salt, cloves, also produced an abundant secretion. Craven Moore and Allanson found that tea was a stimulant to secretion, and coffee still more so in some individuals, though variable in its action. A cigar after meals stimulates secretion in an habitual smoker.

2. Substances producing a slight secretion: Milk, gelatine, water.

3. Substances producing no secretion: Egg white, proteose, peptone, starch, sugar, salts of meat.

4. Substances inhibiting secretion: Fats and sodium bicarbonate. Recent work does, however, suggest that in these instances the secretion is merely delayed.

In fact, secretion occurs in two stages, the first depending on the stimulation of the sense of taste while the food is yet

in the mouth, the second occurring when absorption has begun. The mechanism of this second secretion was attributed by Edkins to a chemical factor, which would explain the occurrence of digestion after division of the vagi. The pyloric glands differ widely in structure from the glands in the fundus of the stomach. Though the latter are simple tubular glands, they are composed of highly differentiated cells, the granular chief cells secreting the pepsin and rennin, the ovoid parietal cells forming the hydrochloric acid. Passing to the pylorus, we find a marked change in the plan of the glands, which have become wide-mouthed and branched; the lining cells are neither granular nor ovoid, but closely resemble those covering the surface of the stomach.

No theory of gastric secretion can be satisfactory that does not account for these striking differences of structure. Edkins found that an extract of pyloric mucous membrane injected into the circulation of a fasting animal would cause the secretion of a juice containing both hydrochloric acid and pepsin. He did not find that a similar extract of fundus glands produced this effect. Pyloric glands, therefore, appear to produce a chemical stimulant to the continued secretion of gastric juice by the fundus glands.

He tested the efficacy of certain substances in evoking this stimulant in the pyloric glands. Meat extract was the most marked and consistent in its effect, the percentage of acid being from 0·05 to 0·16 per cent. After meat extract came dextrose and then dextrin. It has been, however, shown subsequently that many extracts of tissues, both animal and vegetable, have a similar effect. This may be due to the presence of histamine, which is one of the strongest stimulants of gastric secretion.

If the appetite and sense of taste were the only stimulants to secretion, how would digestion be completed when the former was assuaged and the latter no longer exercised? Many animals, their hunger being satisfied, soon fall asleep.

We see now that the secretion, started by nervous impulses, is continued by chemical stimuli, which will act as long as there is food in the stomach.

Practical Deductions.

The nervous factor in gastric digestion affords a scientific explanation of the old adage, 'Hunger is the best sauce.' Indeed, as we have seen, it is a sauce which will greatly increase the rate of digestion. This should lead us to attach great importance to the personal equation in dieting a patient. Too rigid a dietary, albeit compiled on an admirable chemical basis, may prove distasteful and upset the appetite, thereby preventing all the good that might be expected. Nevertheless, in neurotic patients, strictness in itself may cause interest, and thus excite the appetite. The personal equation is too often neglected. Thus, fat has a temporary inhibitory effect on gastric secretion in any case; to force it on a child who loathes it may be good moral discipline, but it is certainly bad physiology. Now that we know that fatty foods tend to produce ketosis and that the neurotic child is apt to have a low blood sugar, the rashness of this moral discipline is more obvious, since sugar is necessary to combat ketosis. The nervous child needs sugar rather than fat (Cameron).

Our dietetic restrictions and prescriptions are too much dictated by fashion. Except in cases where we must forbid something for a perfectly definite reason, our patient's likes and dislikes should be carefully considered; whereas it is our own likes and dislikes which reappear constantly in our dietetic schemes. Given a certain knowledge of the man, one can predict fairly accurately what he will recommend to any patient. The dyspeptic is often a diligent seeker after medical advice, and when he tries to harmonize the various dietetic gospels he has received, his opinion of our profession is not enhanced.

'There is to be observed a sort of fashion running through these restrictions,' says Sir William Roberts, 'yet I know not on whose authority they repose. . . . They are, for the most part, quite unmeaning; they stand on no ground of science or experience, and are gratuitously punitive to our patients. . . . There are cases in which a certain amount of coercion is salutary and even necessary. In neurotic and hysterical persons the stomach sometimes shares in the general instability, or it may even be the chief offender.'

It is curious that often quite opposite methods of restriction should both be successful. A patient goes to one physician, whose opinion is that all purins are deadly poisons. He is put on a purin-free diet, and improves. Tiring of the restrictions, he seeks advice from another physician, whose opinion is that most ills are due to incomplete combustion of carbonaceous foods. These are now restricted, while he takes meat freely, and again he improves.

The explanation is that this is a type of patient who eats and drinks too much. Variety of diet stimulates his appetite, while the monotony entailed by abstention from so many pleasant things results in his eating less altogether.

In fact, there are surprisingly few instances in which the addition of or abstention from some particular article of diet can be relied upon to produce a specific effect. Examples will be considered in their appropriate places.

The late Sir Andrew Clark was accustomed to forbid his dyspeptic patients to take soup, on the ground that by diluting the gastric juice it prevented digestion from proceeding. The advice was good in many cases, though the explanation was unphysiological. Of all the chemical excitants of gastric secretion, meat extracts have proved the most efficacious. To a tired man the warm fluid, causing gastric vaso-dilatation, and containing a stimulant of the gastric juice, while not in itself taxing the digestive organs,

is an excellent beginning to a meal. It is important to note that meat extracts mainly affect the production of hydrochloric acid, and cause little secretion of pepsin. In hyperchlorhydric conditions, therefore, meat soups are distinctly contra-indicated, while to dyspeptics with inadequate gastric secretion they are beneficial.

This explains the discrepancy between the results of analysis of meat extracts and the popular estimate of their value. Their nutritional worth, so far from being accurately represented by pictorial advertisements, is stated to be equivalent to that of a teaspoonful of milk in a tumblerful of water. Yet as stimulants of gastric juice they have a decided place, and a patient may be able by their aid to tolerate a restricted and uninteresting dietary. But we must remember that we are not giving food; we are only preparing the way for food.

The tax which vegetable as compared with animal protein imposes upon digestion should not be forgotten in the construction of a dietary. It is both bulky and slow to leave the stomach. Herein lies the advantage of lightly cooked minced meat; it requires little pepsin, and it does not leave a large indigestible residue. It is for this reason that it has proved useful in dilatation of the stomach. Surely it is a fallacy to administer so much starchy food in dyspepsia, as is frequently done. A preparation that looks like milk does not necessarily become digested like milk! Harry Campbell has protested strongly against starchy food in the form of pap. It has to be swallowed at once, without any chance of salivary digestion, while in the solid form, requiring a good deal of mastication, it excites enough secretion of saliva to initiate its conversion into sugar. For this reason toast, biscuit, and rusk can often be digested when new bread or mashed potatoes cannot.

In many respects the physiologist's discoveries have been anticipated by the chef. We see the advantage of beginning

a meal with soup to excite secretion, and of finishing with sweets, when the cardiac portion of the stomach will retain the food and permit continued digestion of the carbohydrates by the saliva. The postprandial cup of black coffee receives scientific sanction. The surroundings of a meal may have a physiological as well as an æsthetic value.

Pavlov's experiments also explain the different value attached to bitters by the clinician and the pharmacologist. It is true that, introduced directly into the stomach or into the circulation, bitters are ineffective, but by exciting the nerves of taste and arousing the appetite while passing through the mouth they may be a distinct aid.

This has an important application in the treatment of patients on whom gastrostomy has been performed for stricture of the œsophagus. That the stricture is usually malignant is held to be sufficient explanation of the fact that such patients do not thrive. But they are also losing the powerful aid of 'appetite juice,' since the food no longer passes through the mouth. It is easy and rational to place sapid substances in the mouth to excite the sense of taste, while feeding through the gastrostomy wound is going on. In one case the patient himself requested that he might take the food into his mouth and, after mastication, place it in his stomach through the gastrostomy wound. The request was granted, and the change seemed to benefit him. It was considered merely an unpleasant eccentricity on his part, whereas really he had anticipated Pavlov's discovery.

The Acid of the Gastric Juice.

Of all the constituents of gastric juice, hydrochloric acid is the most variable. Pepsin disappears in achylia gastrica, and is much diminished in gastric carcinoma, but otherwise alters but little in disease.

The method of fractional test meals has, however, shown that even in healthy individuals there is a considerable varia-

tion in the secretion of hydrochloric acid. The fasting contents of the stomach are removed before a meal of oatmeal gruel is given. A Ryle tube is passed and small quantities of the gastric contents are removed at regular intervals by suction for analysis. The total amount should as a rule be withdrawn at the end of 2½ hours. (For details see later in this chapter.)

Bennett and Ryle used this method on 100 healthy medical students and plotted out the curves obtained. Of these, 91 showed an iso-secretory curve—that is to say, that in spite of individual variations the percentage of free HCl rose steadily during the first hour and subsequently fell towards its original concentration. Four of these 91, however, showed a much shorter curve of a similar type, the stomach being empty in three-quarters of an hour. Of the remaining nine, four showed a complete achlorhydria, although they had no dyspeptic symptoms and they remained quite well for the six years they were under observation; five showed a climbing type of curve, such as is associated with juxta-pyloric ulcers and pylorospasm. It is important to note that this method gives the *concentration* of the acid secreted, which is a very different thing from actual *amounts*.

The hydrochloric acid of the gastric juice has been held to have the following functions:

1. *Activation of pepsin*, which is inert in a neutral medium. But trypsin can do as much and more than pepsin, and this would operate in the duodenum.

2. *Hydrolysis of starch*, like any other mineral acid. But here again the amylopsin of the pancreatic juice is of greater service.

3. *Regulation of the pyloric sphincter*. Pavlov's observations on dogs suggested that whereas acid on the gastric side of the pylorus tends to open the sphincter, as soon as it reaches the duodenum it leads to closure of the orifice. But

as long ago as 1908 Boldyreff maintained that regurgitation of alkaline juices into the stomach is part of the process of normal digestion, and that the concentration of acid in the stomach is regulated by such regurgitation. In this way the optimum strength of 0·15 to 0·2 per cent. of acidity is secured, the acid fluid which enters the duodenum exciting anti-peristalsis rather than closure of the pylorus. In 1922 Bolton, by comparing the amount of chloride present as hydrochloric acid with that present as mineral chlorides, was able to show that when the former fell the latter rose, thus confirming the fact of alkaline regurgitation. Further, this demonstrates that the curve of acidity does not necessarily indicate the secretory activity of the stomach, but that the only real measure of the amount of acid produced in the stomach is the curve of total chlorides, since this includes the acid neutralized by regurgitation. Maclean, however, does not accept this interpretation.

4. *Stimulation of pancreatic secretion.* But the researches of Boldyreff, and subsequently of J. Mellanby, have greatly modified our views as to the importance of this (*vide* Pancreas).

5. *Antiseptic action.* Although some diseases only occur in the presence of achlorhydria, such as Addisonian (*i.e.*, so-called pernicious) anæmia and subacute combined degeneration of the cord, this has nothing to do with the absence of an antiseptic action. But the frequency of achlorhydria in irregular recurrent diarrhœa and ulcerative colitis in the absence of abnormal intestinal flora is presumably due to weakness of defence rather than to strength of attack, and the extraordinary therapeutic value of hydrochloric acid in this type of case suggests that the weak spot in the defence is the loss of a normal antiseptic. L. P. Garrod has made the interesting observation that gastric juice is more bactericidal than hydrochloric acid of equivalent strength. Achlordydria is not infrequently present in rheu-

matoid arthritis, which would allow of oral sepsis being more damaging. Acne rosacea is generally associated with diminution or absence of HCl, and often yields to therapeutic doses to a marked degree. It is also lacking in sprue. A curious form of dysphagia with glossitis and anæmia has also been described (the Plummer-Vinson syndrome). Glossitis has been well recognized in Addisonian anæmia since it was described by William Hunter, and it would appear from the above that achlorhydria is associated with thinning or loss of the mucous membrane of the alimentary tract.

Achlorhydria is therefore the rule in *achylia gastrica,* certain anæmias such as *Addison's* and the *chronic microcytic type, subacute combined degeneration of the cord,* and *sprue.* It is often found in *other fatty diarrhœas, colitis,* and *acne rosacea,* and sometimes in *rheumatoid arthritis.* It also occurs in *hyperthyroidism* and *Addison's disease.*

There is often achlorhydria in *gastric carcinoma,* and in any case the amount of free acid will be greatly reduced, except in cases of a peptic ulcer becoming malignant. In some cases the output of total chlorides is very low, suggesting a genuine absence of secretion. In others, although there is an absence of free HCl, the total chlorides are not reduced. This points to neutralization of acid by alkaline fluid secreted by the growth. In either event we may expect to find no free HCl, though lactic and butyric acids are almost certain to be present. The gastric contents are foul-smelling and often show altered blood.

The important part played by Castle's intrinsic factor in the production of Addison's anæmia is dealt with in Chapter XI.

Hypochlorhydria.—This is usually met with in chronic gastritis, in addition to the conditions mentioned above. Chronic gastritis may be caused by:

(i.) Oral sepsis.

(ii.) Unsuitable food and drink, especially strong tea and alcohol.

(iii.) Circulating toxins.

(iv.) Venous congestion of the stomach, as in failing heart or portal obstruction.

Before the diagnosis of achlorhydria or hypochlorhydria is finally made, advantage may be taken of the stimulating effect of an injection of $\frac{1}{4}$ to $\frac{1}{2}$ mg. of histamine on the secretion of gastric juice; or the stomach should be washed out with 2 drachms of hydrogen peroxide in a pint of water or of sodium bicarbonate 2 per cent. and the test meal repeated; for, as Hurst has shown, in many cases of gastritis the secretion of HCl is merely masked by the abundant secretion of mucus. But in long-standing cases some atrophy of the glands may occur.

Hyperchlorhydria.—Craven Moore suggests the term 'reflex dyspepsia' for hyperchlorhydria, which has the advantage of emphasizing the method of its production. It implies the existence of a lesion or an increased excitability of the reflex nervous mechanism, often both. If the lesion is severe, it can make itself felt, even though the nervous system is normal; but if the nervous system is unduly irritable, a very small lesion, or even constipation, may produce marked symptoms. Thus we can understand why it occurs in the type of man it does, and why the man 'who in the prime of manhood was a martyr to dyspepsia . . . in his later years, when his nerves are blunted . . . eats and drinks with the courage and success of a boy.' Another factor in the production of hyperchlorhydria is the stimulus of a change of diet, such as occurs during a Continental holiday. Yet, again, excessive smoking is responsible in some cases. But it must never be forgotten that the lesion most commonly associated with hyperchlorhydria is a peptic ulcer. There is much pathological evidence to suggest that excess of acid plays a part in the causation or continuation

of a gastric or duodenal ulcer. Animal experiments also point in the same direction.

Evidently the diagnosis of simple hyperchlorhydria ought not to be reached until every effort has been made to exclude the organic conditions in which hyperchlorhydria occurs. It will be noted that some of these are situated lower down in the alimentary canal. Now, if the intestine be wounded experimentally, there is inhibition of movements for some distance above, and there may also be spasm of the pylorus lasting for several hours. In the same way a duodenal ulcer, gall-stones, old appendicitis, and colitis set up a protective spasm above. This is usually at the pylorus, preventing the escape of acid from the stomach, and the regurgitation of alkaline fluid from the duodenum into the stomach. This would check neutralization and therefore give a higher yield of acid in the test meal (Bolton and Goodhart). Hyperchlorhydria, then, does not necessarily mean increased secretion.

Symptomatology.—A characteristic symptom in hyperchlorhydria, with or without ulcer, is 'hunger pain,' which comes on when the stomach is getting empty and which is relieved for a time by food. Pain recurs sooner after a light meal, such as afternoon tea, than after a heavy meal. Thus, after evening dinner there may be freedom from pain till the middle of the night. But the situation of an ulcer may influence the time at which the pain recurs; generally speaking, the nearer the ulcer is to the cardiac sphincter the more quickly the pain returns after food. Indeed, a useful distinction between a gastric and duodenal ulcer is this: a light meal is followed by pain more quickly than is a substantial meal when there is duodenal ulceration. With a gastric ulcer a substantial meal causes pain more quickly, while after a light meal pain may not occur at all. This pain is not the direct effect of hyperacidity, for Hurst has introduced stronger acids than are ever found in hyperchlorhydria without evoking it.

Moreover, in duodenal ulcer the stomach begins to empty quickly, and although during that time acid contents are passing over the ulcerated surface there is no pain; but later on, when, as X-rays show, active peristalsis is increasing, the pain returns. This seems to associate pain with some alteration of motility.

A sudden gush of saliva into the mouth, which is termed pyrosis, is common in hyperchlorhydria. It may be regarded as an attempt on the part of the body to neutralize the excessive acidity of the gastric juice by the alkaline saliva, but, like so many pathological attempts at repair, it overshoots the mark; for it is impossible for such a quantity of saliva to be swallowed. This is particularly likely to occur in the presence of cardiospasm. 'Heartburn,' on the other hand, is probably excited by regurgitation of acid contents into the lower end of the œsophagus.

The patient sometimes feels more comfortable when the gastric juice is given plenty to do, and therefore he often eats largely. There may be a positive craving for fat, which is comprehensible in view of its inhibitory effect on gastric secretion.

But in every case of dyspepsia which does not yield quickly to simple measures recourse must be had to X-ray examination. In the examination of the fæces for occult blood we have another important guide. This is a simple enough test, and it is also valuable in the diagnosis of malignant disease of the alimentary tract, because by this method blood will be found in practically every specimen of the fæces. Small continuous losses of blood are typical of carcinoma of the alimentary tract. In simple ulcer intermittent and larger losses of blood are more likely to be met with while it is active. If a patient has never had melæna or bright blood in the stools, but gives on three separate occasions a positive result with the test for occult blood, there is probably malignant disease of the alimentary tract. The

increasing accuracy of the diagnosis of organic diseases of the stomach and duodenum by the X-ray screen has rendered the fractional test meal less important. Curiously enough this test has become more valuable in the differential diagnosis of anæmia than in the above conditions. The introduction of the flexible gastroscope has elucidated still further the pathology and diagnosis of diseases of the stomach. It has also enabled us to study the harmful action of drugs, such as aspirin, on the gastric mucous membrane. However, the technique and its interpretation must be left to experts.

Principles of Treatment in Hypochlorhydric Dyspepsia.

It goes without saying that in all forms of gastric affections the condition of the teeth and gums calls for attention. Carious teeth and pyorrhœa mean that mastication cannot be duly performed, and that septic absorption is taking place. This may lead to chronic gastritis and consequent hypochlorhydria. The improvement in gastritis after removal of this source of infection is often surprisingly rapid.

Except as a palliative, the usefulness of alkalies in conditions associated with diminished hydrochloric acid is limited to their administration before meals.

The solvent action of alkalies on mucin is a great help to a stomach hampered by catarrhal exudation, enabling digestion to start with a clean slate. According to Izod Bennett, bicarbonate of soda also excites a subsequent secretion of hydrochloric acid in man, while magnesia does not.

The combined use of alkalies before meals, followed after meals by a good dose of dilute hydrochloric or nitro-hydrochloric acid with nux vomica, gives more satisfactory results than either separately. And we should not be niggardly; for even the full pharmacopœial dose of 20 minims would only confer an acidity of 0·02 per cent. on a pint of fluid. Acidol (betain chloride) has been claimed to have the advantage of gradually giving off hydrochloric acid in

aqueous solutions, and to be more effective than the simple acid. It is quite stable in the dry state, and is readily soluble in water. Pastilles containing 7½ and 15 grains are put up, and are equivalent to about 5 and 8 minims of hydrochloric acid respectively. They should be given freshly dissolved, and not swallowed in the solid form. Patients may tolerate the acid in this form without difficulty. The method is certainly helpful in some cases. J. B. S. Haldane thinks it merely acts by raising the hydrogen-ion content of the blood, the secretion of the acid into the stomach being a secondary event.

In complete achlorhydria up to a drachm of dilute hydrochloric acid in half a pint of lemonade or orangeade should be given during meals. This is a most important therapeutic measure.

In order to obtain appetite juice the idiosyncrasies of the patient must be studied. The condition is commonest in women, who are notoriously indifferent to the pleasures of the table, but whose æsthetic sense is responsive to pleasant surroundings and dainty service.

It is well to allow some food for which the patient has a special liking, even though it may have a bad reputation in dyspepsia. The result seems to justify this course. Articles which obviously disagree will naturally be prohibited, and it will usually be found that fats or meat with much fat in the fibre cannot be tolerated, because of their inhibitory effect on gastric secretion.

Pavlov showed that he could retard the digestion of protein in dogs by mixing it with starch. And Cannon's observations suggest another important reason against this procedure if gastric secretion be inadequate. When carbohydrates are given with protein they are retained in the stomach, but given by themselves they pass on more rapidly into the sphere of influence of the pancreas, where they are digested by the amylopsin. Therefore it is advisable not to give

carbohydrate and protein together, but to give them as separate meals. Protein can often be tolerated as lightly cooked minced meat.

Both in this and in the opposite condition of hyperchlorhydria it will, of course, be necessary to attend to the bowels, while avoiding drastic purgation.

The golden rules which should guide us in the treatment of hypochlorhydric dyspepsia are:

1. Give sodium bicarbonate twenty to thirty minutes before meals; a teaspoonful of this in a tumbler of soda-water is a useful way of breaking up and dissolving tenacious mucus. Moreover, it produces a secondary rise of acid secretion later on. In milder cases 10 to 15 grains with a bitter will be sufficient.

2. In severe cases daily lavage, as described above, is necessary.

3. Encourage the secretion of 'appetite juice' by careful consideration of the patient's idiosyncrasies.

4. Encourage the chemical stimulation of gastric juice by a small amount of meat extracts or beef-tea at the beginning of a meal.

5. Never give carbohydrate in the form of pap, but in a form requiring mastication, and only give very small amounts with any protein meal.

6. Avoid cooked fats and strong tea.

7. Give acids after food.

8. Attend to the teeth and bowels.

By these measures, which may have to be prolonged, it is sometimes possible to restore normal secretion.

Principles of Treatment in Reflex Dyspepsia (Hyperchlorhydria).

The cause of the hyperchlorhydria must be sought for and treated. The administration of alkalies after meals is a rational procedure for the relief of symptoms, and no doubt

to the relief afforded by this treatment, indiscriminately employed as it often is, is due the large number of duodenal ulcers which escape recognition. The best alkali for the purpose will be one that is insoluble, thus having a slow, continued action, and does not distend the stomach by the evolution of carbonic acid gas on neutralization. It is, moreover, possible that the evolution of this gas stimulates the secretion of hydrochloric acid. Accordingly, 1 to 2 drachms of liq. bismuthi hydratis (Parke Davis), with 10 grains of heavy magnesia or 1 to 2 drachms of cream of magnesia, may be prescribed. The combination has the advantage that, while bismuth is constipating, magnesia is relaxing. Moreover, magnesia is the most effective antacid we have. The two drugs can be prescribed in separate bottles with some hydrocyanic acid and cardamoms, and the patient is instructed to regulate the dose of each according as he is constipated or relaxed. The bismuth lozenge of the British Pharmacopœia, as recommended by Sir W. Roberts, or the magnesia lozenge called alkagen, is often effective. They should be sucked slowly, thus providing for the swallowing of much alkaline saliva as well as the alkaline drugs. Their portability is another factor in their usefulness to sufferers, who are often of an active temperament. The addition of tincture of belladonna to a mixture may have a good effect, because it is a powerful inhibitor of secretion. Craven Moore advises the use of bromide at the beginning of treatment to depress the excitability of the nervous reflex, and this is often a useful addition.

Olive oil before meals may help, by reason of the inhibitory influence of fats on gastric secretion. Starting with a teaspoonful, the dose may be increased up to 1 ounce. Liquid paraffin may have a similar effect, and, if so, is preferable for patients with obesity.

As to diet, Walter Broadbent advises on the basis of Pavlov's work that food should be given in a form which

will not excite more secretion of gastric juice than can be helped. In the first stage the patient is only allowed milk and cream. In the second, bread and milk and soft milk puddings, such as cornflour. Thirdly, bread and butter and eggs. Broadbent says—although this is by no means so in all cases—that they are tolerated best in the form of buttered eggs, the butter still further diminishing the secretion of the gastric juice, while the large amount of protein in the egg will tend to fix the hydrochloric acid. But things cooked in ordinary fat often disagree, and poached eggs are usually tolerated better. Fourthly, fish and vegetables; and lastly meat, starting with chicken and mutton; while we entirely forbid the use of meat extracts of all kinds, because these stimulate the flow of gastric juice without giving anything for it to act upon.

The Treatment of Gastric Ulcer.

In 1901 Lenhartz protested strongly against what was then the orthodox treatment for gastric ulcer. He urged that in patients who are already in a poor physical condition consequent on one or more hæmorrhages, and, indeed, often collapsed, the 'starvation treatment' (which is all that rectal feeding amounts to) maintained their wretched anæmic state, and might produce a serious state of inanition, very unfavourable to the healing of an ulcer. On the other hand, if enough milk were given by the mouth to maintain the body-weight, it would overfill the stomach and stretch its walls, thus preventing contraction of the ulcer and tending to renewal of the bleeding.

He maintained that the correct principles were:

1. To promote healing by providing adequate nourishment.

2. To prevent distension of the stomach by limiting the size of the meals and the amount of fluids.

3. To prevent the action of the excess of hydrochloric acid by combining it with food albumen and with alkalies.

The current practice is as follows: For the first twenty-four hours after a hæmorrhage merely sips of water sweetened with a small amount of dextrose are allowed; then feeding by the mouth is started, concentrated foods rich in albumen being employed. Food is given at two-hourly intervals, and four-hourly at night. The patient is fed a teaspoonful at a time, and is not allowed to feed himself at first. No attempt is made to provoke an action of the bowels during the first three or four days, to avoid peristalsis, and allow absorption of outpoured blood in the intestines. Then, if necessary, a small glycerine enema or hot-water enema may be used. He is kept in bed for at least three weeks or longer if occult blood is still present. Other medicinal measures, such as the administration of alkalies and belladonna, can be employed as required.

The principle, then, of the milk and egg diet in gastric ulcer is to provide food at frequent intervals to take captive the hydrochloric acid, which on the experimental grounds already quoted is considered to play a part in the prevention of spontaneous healing. By its insipid nature and its fat content such a diet depresses, at least for a time, the production of acid.

Alkalies are regularly used for the neutralization of acid. The free use of alkalies does not appear to arrest digestion or to alter considerably the emptying time of the stomach. Too intensive alkalinization with sodium bicarbonate may be followed by a condition known as alkalosis or alkalæmia (*q.v.*), which predisposes to attacks of so-called gastric tetany. Probably excessive alkalinity of the blood diminishes its ionizable calcium content. For this reason it is now customary to use a mixture of the alkaline salts of magnesia and bismuth. Aluminium hydrate or magnesium trisilicate has also been extensively used.

The treatment of peptic ulcer by injection of histidine, once much vaunted, has failed to stand the test of time.

Meulengracht advocates a generous normal diet, even after hæmatemesis, and the general tendency, indeed, of recent years has been to give a more generous diet, especially of protein, in gastric ulcer than was allowed when the Lenhartz principle was first enunciated. Such a 'ladder diet' is now not considered to be necessary. It is better to get up to feeds of 5 ounces as quickly as possible and then slowly to increase the calorie value of the feeds up to 2,000.

MEULENGRACHT DIET

Breakfast:

Porridge or Force. Milk or cream.
Cocoa or weak tea to drink.
White bread or toast. Butter. Jelly marmalade.
Egg, poached, boiled or scrambled.

Dinner:

White meat or white fish, chicken, rabbit, veal or tender lamb.
Mashed potato. Vegetable purée.
Milk or steamed pudding. Fruit purée. Juice of one orange.
Bread. Butter.

Tea:

White bread. Butter. Fruit jelly or honey.
Sponge or madeira cake.
Weak tea. Egg, if desired.

Supper:

As at dinner, or vegetarian dish, baked potato, macaroni cheese, scrambled egg, strained vegetable soup, spaghetti and tomato.
Pudding as at dinner, or jelly, junket or custard.
Bread. Butter. Ovaltine or cocoa to drink.

Meals Must be Taken Regularly

Foods to be avoided:

1. Raw fruits and vegetables, using only those that have been cooked and rubbed through a sieve, mashed banana, tinned apricots and pears may be used.
2. Avoid all fried foods.
3. Avoid all coarse foods, such as brown bread, sausages, beef.
4. Avoid all salted and highly seasoned foods such as bacon, ham, tongue, kippers, pickles, chutney, sauces.

The most important points in treatment are prolonged rest in bed, oral hygiene, and dieting. No case can be regarded as cured until the occult blood test has been repeatedly negative and there is no X-ray evidence of ulceration. In convalescence the diet should be on the lines given for hyperchlorhydria. Smoking is inadvisable.

The classical treatment of **hæmatemesis** is morphia in sufficient quantity not merely to depress the movement of the stomach, but also to keep the patient in such a state that he will tolerate the deprivation of food and drink until the bleeding vessel is sealed by a firm clot. Atropin should be given to depress gastric secretion. Of recent years the importance of blood volume after hæmorrhage has been more fully realized. When loss of blood occurs, the circulation adapts itself to a lowered blood volume by vaso-constriction, and also by increasing the minute volume of the circulation, as in anæmia. After an interval the blood left in the vessels is diluted by tissue fluids, hence the great thirst after hæmorrhage. Some persons seem to take much longer than others over this transference. Hence it may come about that some considerable time after hæmorrhage, when the blood volume should be restored to normal with consequent lowering of the hæmoglobin, there is instead a high hæmoglobin with the symptoms of loss of blood persisting. Such patients need saline intravenously and subcutaneously in addition to fluids by the mouth.

Generally speaking, however, the hæmoglobin value is most important as an indication for the need of transfusion, which is usually done in cases of hæmorrhage whenever the hæmoglobin falls below 35 per cent.

The later results of gastric ulcer are chiefly due to recurrence of ulceration and the mechanical difficulties produced by scar tissue, such as pyloric obstruction and hour-glass stomach.

Examination of the Gastric Contents.

In the investigation of the functions of the stomach fractional test meals, with subsequent removal and examination, though of value, have been rendered less necessary by the development of X-ray technique. They are, however, still of great service in the differential diagnosis of anæmia, as has been already said. The swallowing of the fine weighted tube such as Ryle's for this purpose is by no means as difficult as it first seems. The fractional test meal shows not only the character of the 'resting' juice, but also the progress of the stomach secretion and the rate of emptying of the organ. It is usual to give the patient a charcoal biscuit the night before; this can be easily recognized if found in the stomach contents next morning. No food is given until as much as possible of the 'resting' juice has been secured. A pint of gruel is then given by the tube. This is made of two tablespoonfuls of fine oatmeal boiled down in a quart of water to the volume of a pint. It may be flavoured with salt. Straining through a cheese cloth to remove the larger particles helps materially in extracting the fractional samples. These are removed every quarter of an hour by a syringe until no more can be obtained. Too great suction must not be used; in case of difficulty in aspiration, the tube should be advanced or withdrawn a little, paying attention to the marks on the tube which indicate the distance from the teeth of the weighted end of the tube; or a few cubic centimetres of air may be blown in gently in case the tube has become blocked by food particles.

Each specimen is examined for bile, blood, mucus, and starch. The filtered fluid is titrated for free hydrochloric acid by Topfer's reagent, and for total acidity by phenolphthalein.

The normal limits of variation in free hydrochloric acid are shown in the curve. It will be observed that there is

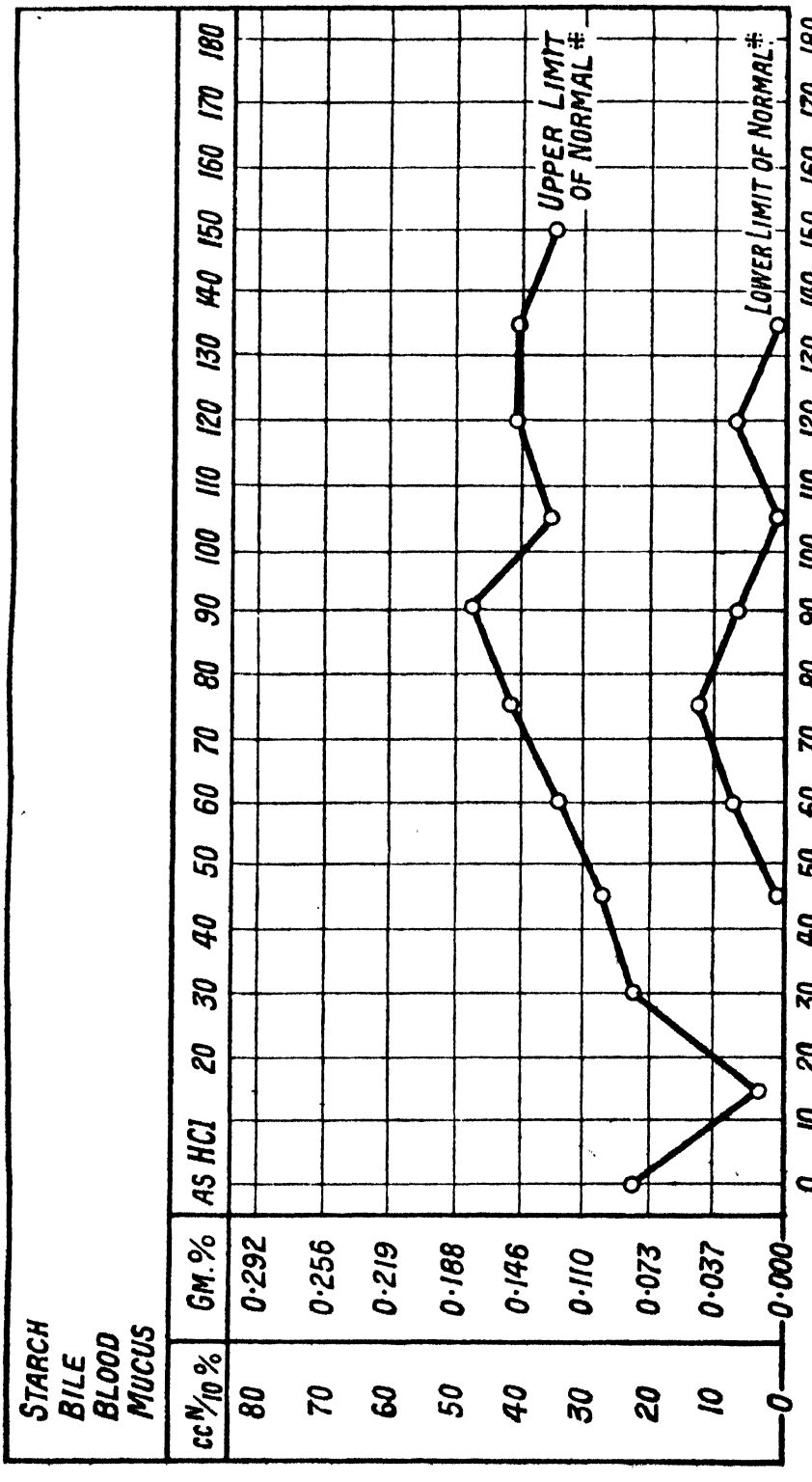


FIG. 1.—FRACTIONAL TEST MEAL.

usually some free hydrochloric acid in the 'resting' juice, and that the first effect of the meal is to dilute this. Then the curve begins to rise again until emptying starts or regurgitation occurs. The disappearance of starch indicates the emptying of the stomach, while regurgitation is indicated by the appearance of bile. The presence of any charcoal taken the night before is clear evidence of delayed emptying. A duodenal or juxta-pyloric ulcer is characterized by a climbing curve maintained at a higher level than normal and without any regurgitation.

Carcinoma of the stomach without evidence of pyloric obstruction often shows complete achlorhydria with a low total acidity, much of which is due to lactic acid. Blood is frequently present, and the contents are often foul. Sometimes the total chlorides are high, indicating neutralization by alkaline secretions from the growth. Other conditions in which achlorhydria occurs have been referred to in the text, but it should be noted that a severe hæmorrhage may cause a temporary achlorhydria.

Gastritis is indicated by hypochlorhydria and excess of mucus, but if the examination is repeated after lavage a normal curve may result. The use of histamine has already been referred to in this connection. The majority of cases of appendix dyspepsia show a normal curve, but occasionally there is hyperchlorhydria.

INTESTINAL DIGESTION

The Work of the Pancreas.

Although the pancreas provides the most active digestive secretion in the body, and plays an important part in general metabolism, disease in it is often overlooked. Its two functions of internal and external secretion are entirely independent; when the latter is deranged, there is com-

monly no disorder of sugar metabolism, and in diabetes the digestive functions of the gland are usually unimpaired.

As soon as the acid chyme enters the duodenum the secretion of pancreatic juice begins. Its alkalinity corresponds almost exactly to the acidity of the gastric juice, so that, allowing for the alkaline bile, the total bulk of pancreatic secretion will be rather less than that of the gastric secretion.

Pavlov thought that the acidity of the chyme acted by stimulating special nerve-endings in the duodenum, but Wertheimer showed that the acid was equally effective after section of all the nerves in the neighbourhood, or even after extirpation of the solar plexus. This paved the way for Bayliss and Starling's important discovery that the hydrochloric acid of gastric juice, when it comes into contact with the mucous membrane of the intestine, leads to the production of a chemical stimulant, *secretin*, which is absorbed from the cells by the blood stream and carried to the pancreas, where it acts as a specific stimulant to secretion.

Dilute hydrochloric acid was placed in a loop of jejunum which had been previously isolated from the rest of the body except for its blood supply. The absorption of acid was accompanied by a secretion of pancreatic juice. If, however, the acid was injected direct into the blood stream, it was ineffective. On the other hand, a saline extract of the intestinal mucosa treated with hydrochloric acid and injected into the blood stream produced an active secretion.

For some years after this discovery it was generally believed that this chemical mechanism was sufficient to account for all the facts of pancreatic secretion. Clayton-Greene, however, recorded a case which seemed to point to nervous influence. During pylorectomy for malignant disease of the stomach a pancreatic fistula was accidentally formed. A few seconds after food was swallowed pancreatic juice began to appear, and this occurred even when the food had only been

seen and not swallowed. Nervous mechanisms are distinguished from chemical by their speed, and here the reaction was very rapid.

In 1911 Cathcart obtained pancreatic secretion in animals by vagal stimulation; so that we must admit a nervous factor.

The position with regard to secretin was further modified when Boldyreff showed experimentally that while the chemically excited juice was rich in alkali and poor in ferment, the juice produced by nervous excitation had exactly opposite characters. This has recently been confirmed by Lagerlöf in human beings. J. Mellanby demonstrated that the presence of acid bile in the duodenum gives a more profuse flow than any secretin preparation. It is well recognized now that when there is no acid to excite the production of secretin, as in achylia gastrica or after gastrectomy, the secretion of pancreatic ferments is apparently normal. Apparently the secretion of these ferments is yet another function which must be ascribed to the vagus.

Inadequate pancreatic secretion may have a striking effect upon growth, for we know that any form of fatty diarrhœa may lead to infantilism merely by interfering with the absorption of the fat-soluble vitamins. Indeed, any chronic disease in early life which interferes with sufficiently important functions may be responsible for persistent infantilism.

The tryptic activity of the pancreas is hedged around with some remarkable safeguards. Fresh pancreatic juice contains inactive trypsinogen. Before this can become active trypsin it must be acted upon by another ferment, *enterokinase*, which appears to be present only in the succus entericus. This activation consists in removing the protein molecule from trypsinogen, thus setting trypsin free. Therefore the fluid present in the duct of Wirsung cannot injure the gland, for it is inactive until discharged from the papilla. And although any mechanical irritation of the

intestine will lead to the outpouring of mucus, true succus entericus is secreted only in the neighbourhood of the food; while, according to Pavlov, its richness in enterokinase depends on the stimulating action of the pancreatic juice. Whatever the exact stimulus to succus entericus may be, it is difficult to extract enterokinase from the intestine of a fasting animal, so that its presence seems to be dependent on the food. This 'double locking' ensures that under normal conditions active trypsin can be liberated only in the presence of food.

For these reasons it may be wondered how pancreatic hæmorrhage or necrosis can be due to self-digestion of the gland by trypsin. But other things besides enterokinase, such as calcium salts, seem capable of activating trypsinogen. A pre-existing pancreatic catarrh might lead to the formation of active trypsin within the ducts of the gland; pancreatic calculi are rich in calcium salts. The toxic symptoms in acute necrosis of the pancreas are probably due to self-digestion by trypsin.

Laparotomy for a ruptured pancreas has been followed by rapid digestion of the rectus abdominis in the neighbourhood of the wound. As no injury to the duodenum was found at the necropsy, there could hardly have been activation by enterokinase. The drainage of pancreatic cysts, too, has occasionally been followed by extensive self-digestion along the track of the fluid.

But such cases are exceptional, and the usual cause of the necrosis is probably the passage of infected bile back along the pancreatic duct. The treatment of an infected gall-bladder, so as to prevent infected bile from reaching the pancreas, is therefore an important prophylactic measure.

Fat Necrosis.—If pancreatic juice be extravasated from the gland, digestion of the body-fat by steapsin will follow. 'Fat necrosis' is due to this splitting of the body-fat into

glycerine and fatty acid, the latter combining with lime salts. These opaque white areas, often surrounded by a ring of inflammation, are usually most abundant in the neighbourhood of the pancreas and omentum, which suggests that they are caused by direct extravasation of the steapsin. The presence of steapsin in the affected areas and in the urine has been demonstrated.

Other Pancreatic Ferments.—Pancreatic juice can act on all three classes of foodstuffs. The starch-splitting ferment, amylopsin, only differs from ptyalin in saliva in being more rapid and in being able to act on unboiled starch.

Pancreatic juice also contains small amounts of erepsin, which completes the digestion of proteins, a milk-curdling ferment, and a malt-sugar-splitting ferment. But they are of subsidiary importance here, being more abundantly present in other digestive secretions.

The Signs of Pancreatic Inadequacy.

1. *Defective External Secretion* is indicated by—

(*a*) *Failure of Tryptic Digestion.*—This is most readily detected by the persistence of cross-striations and nuclei in the muscle fibres in the fæces after a meat meal. For this purpose a small portion of fæces is broken up in water and the centrifuged deposit examined microscopically.

It is claimed that trypsin can be demonstrated in normal stools by placing a small quantity of fæces on a gelatine plate, when a small area of digestion will result. With absence of the pancreatic secretion this would not occur.

(*b*) *Failure of Starch Digestion.*—Though ptyalin can digest boiled starch, amylopsin alone can digest unboiled starch grains. Abelmann found 20 to 40 per cent. of the starch in the fæces after experimental excision of the pancreas. In chronic pancreatitis oxaluria is fairly common, and Cammidge and Mayo Robson have attributed this to faulty carbohydrate digestion.

(*c*) *Failure of Fat Digestion.*—This may result in true steatorrhœa, or in the presence of fat droplets, fatty acid crystals, or soap in the fæces. But a quantitative estimation is necessary to determine this satisfactorily. In normal fæces the saponified and unsaponified fats are approximately equal in amount, the total amount of the two being 15 to 25 per cent. of the dried matter. In chronic pancreatic deficiency, however, this fæcal fat may exceed 60 per cent. As the pancreas provides for the fat-splitting that must precede saponification, unsaponified fat will be largely in excess of the saponified. On the other hand, the bile-salts provide for the absorption of the fat already split by the pancreatic juice, so that if the excess of fat be due to loss of bile simply, the saponified fats and free fatty acids will be in excess, because they cannot be adequately absorbed. It is now realized, however, that gastric lipase plays an important part in the digestion of emulsified fats such as cream. Other fats should therefore be used when this test is applied.

2. *Defective Internal Secretion* is indicated by—

(*a*) *Diminished Sugar Tolerance.*—See Chapter VIII.

(*b*) *Adrenalin Eye Test.*—If the pancreas is inadequate the pupil will dilate in from twenty minutes to one hour after one drop of the liquor adrenalin hydrochlor. is dropped into the eye, and another five minutes later. The dilatation is often an eccentric one. The test may fail if repeated within a week. A criticism of the test is that it is, if anything, too sensitive. It is simple and easily applied, but too much reliance must not be placed on it.

(*c*) *Increase in Urinary Diastase.*—There is normally a diastatic ferment in the urine, and it is found to be much increased in recent pancreatic diseases. The test was originally designed by Wohlgemuth as a measure of renal efficiency, the output being lowered if this were impaired. But subsequent work has shown that the diastase in the urine does not necessarily run parallel with the diastase in the

blood, which is perhaps what we might expect from what we know of the behaviour of the kidney threshold towards substances useful to the body. The test has proved of more value in the recognition of pancreatic disease, because here the alteration of the amount in the blood is so gross that the renal threshold is, as it were, flooded. Normally the figure obtained lies between 10 and 33·3 units. In acute pancreatitis one might find 300 to 500 units, or even 1,000, while in less acute cases 50 to 100 units may be found. In very chronic conditions there may be no excess, but even a deficiency. In ordinary clinical diabetes a low value is the rule. It was at first assumed that this diastase was merely pancreatic amylopsin reabsorbed into the blood stream, and was evidence of some obstruction to the pancreatic ducts, though in that case it would not be easy to explain its presence in normal urine. But Cammidge, with Forsyth and Howard, has adduced cogent reasons for believing this diastase is hepatic in origin. The diastase value rises as more and more of an animal's pancreas is excised, right up to total extirpation. As it is clearly impossible for a non-existent gland to produce an enzyme, diastase cannot come from the pancreas. On the other hand, hydrazine phosphate, which has a toxic effect on the liver but not on the pancreas, reduces and may completely abolish the diastase output. These authors conclude that its production is controlled by the internal secretion of the pancreas. If such control fails there is for a time a greatly increased production of diastase by the liver.

3. *Pressure Symptoms.*—These may be referred to—

(*a*) *The Common Bile-Duct, producing Jaundice.*—In new growth of the pancreas the obstruction may be complete, while in gall-stones it is more likely to be incomplete, so that stercobilin can be extracted from the fæces by acid alcohol or amyl alcohol, even though they appear quite clay-coloured. The extract gives a band in the blue on spectro-

scopic examination, and a green fluorescence with zinc chloride and ammonia if there is any stercobilin present.

(*b*) *The Portal Vein, producing Symptoms of Portal Obstruction.*—This is very uncommon.

4. *Nervous Symptoms, from Irritation of the Solar Plexus.*—In acute pancreatic diseases, such as hæmorrhage, the pain is very severe, the patient feeling as if he were gripped in a vice. Vomiting, meteorism, and collapse follow. In subacute cases there may be periodic seizures of pain and vomiting, like the gastric crises of tabes.

We may say that in the absence of fatty diarrhœa if the adrenalin eye test and the diastase test are negative, it is seldom worth while to undertake more elaborate investigations. If there are fatty stools without jaundice, and the excess of fat is in the unsaponified form, it is very suggestive of pancreatic disease. If there are also muscle fibres in the stools, it strengthens the diagnosis.

General Principles of Treatment in Pancreatic Disease.

Certain considerations govern the treatment of pancreatic diseases in general, which may be discussed here without describing the treatment of particular diseases of the organ.

1. *Dietetic Treatment.*—Pancreatic juice contains ferments which are capable of acting on all foodstuffs, and the only one able to split unemulsified fat to any extent. It therefore follows that when the pancreas is diseased, such fats are badly borne, for not only are they wasted, excess of unsaponified fat appearing in the stools, but by coating over the proteins they hinder their absorption and increase their putrefaction. Fats must therefore be cut down to a minimum, and the fat-soluble vitamins provided in a concentrated form, especially if there are signs of infantilism. The caloric value must be maintained by protein and carbohydrate. Even with no other treatment than this, the condition of the patient may remain satisfactory. Proteins are digested by

pepsin, and can therefore be given so long as a form is chosen in which they can be acted upon rapidly in the stomach, such as minced meat. Certain proteins like caseinogen are also digested by the erepsin of the succus entericus, and can therefore be used—*e.g.*, plasmon. The relatively large amount of sulphur contained in eggs renders them very prone to putrefactive changes. Gelatin, on the other hand, does not contain aromatic bodies, and so is not so liable to these changes, and can replace proteins to a limited extent.

For the digestion of starch we have to rely upon the ptyalin of the saliva; and, to take advantage of this, starchy foods should not be given in a soft form, such as ground rice, but in a dry, crisp form like toast, biscuit or rusk which, requiring thorough mastication and insalivation, reaches the duodenum already largely digested. Sugars like glucose can be absorbed without further digestion, while cane sugar, maltose, and lactose can be digested by the succus entericus. But their use in pancreatic diseases may be limited by diminished sugar tolerance.

2. *Regulation of the Pancreatic Secretion.*—The acid of the gastric juice is a stimulant to the external secretion of the pancreas. Accordingly, if it is deficient, it should be reinforced by the administration of dilute hydrochloric acid, or, better, 15-grain tablets of betain chloride (sold as oxyntin or acidol), freshly dissolved in water after meals. As already stated, this was claimed to liberate nascent hydrochloric acid slowly in the stomach. More probably it merely acts by raising the hydrogen-ion concentration of the blood. On the other hand, if hyperchlorhydria is present it should be corrected by alkalies, including magnesia, after meals. Bile has been shown by J. Mellanby to stimulate the flow of pancreatic juice, and may therefore be given in the form of ox-bile tablets.

3. *Supply of Deficient Ferments.*—This presents difficulties. The simplest method would be to pancreatize the food

before administration, but this is liable to impart a bitter, disagreeable flavour. If ferments are given to act when the duodenum is reached, they will be destroyed in the stomach unless enclosed in capsules capable of resisting gastric digestion, and then we can feel little certainty that they will be set free in the duodenum. Keratin-coated capsules containing pancreatic ferments are supposed to be the best and may be given a trial. Capsules of gelatine toughened in formalin are apt to escape undigested even in the healthy subject. Taka-diastase has been given before meals for the digestion of carbohydrates. Stockton states that many preparations on the market are practically inert, and many combinations are self-destructive, provided they are made as described. It has been repeatedly demonstrated that the internal secretion of the pancreas cannot be absorbed by the intestinal mucosa.

4. *Disinfection of the Pancreatic Ducts.*—Two drugs are known to be excreted by the pancreatic ducts, as well as by other channels. These are hexamine and aspirin, both of them disinfectant in action. Routine employment of them in doses of 5 to 10 grains three times a day is therefore a rational procedure, and should be given a thorough trial. But perhaps the most efficient means of ridding the pancreatic ducts of infection is to drain them by a cholecystostomy, which, if indicated, should not be too long delayed.

Intestinal Toxæmia.

There are fashions in pathology, as in dress, and intestinal intoxications came in for a large share of attention some years ago. Most diseases of unexplained causation were referred to this cause. It is such a fatally easy explanation that it is but human to yield to the temptation in face of perplexity.

Yet since the alimentary canal is an open door for infection, it is worth while to consider what is really meant by

an intestinal intoxication, and what symptoms it might be expected to cause.

Microbes constantly invade the body from the alimentary canal, but are as constantly destroyed. Flexner has shown how frequently a terminal infection occurs when the vital forces of the body are exhausted. The frequent association of diarrhœa with achlorhydria, already alluded to, suggests that the bactericidal action of gastric juice is a means of defence. The body possesses three further lines of defence against intestinal intoxications and infections: Firstly, the epithelium of the bowel; secondly, the blood; thirdly, the liver and the reticulo-endothelial system in general.

One could imagine an intestinal toxæmia arising in one of three ways:

(i.) *Intoxication by Intermediate Products of Digestion.*—There is no satisfactory evidence that this ever occurs.

(ii.) *Intoxication by Products of Putrefaction.*—Whether digestion can be carried on aseptically is a purely academic question, since the opportunity never arises. The infant starts with a sterile alimentary canal, but speedily acquires bacteria therein, chiefly organisms derived from the skin of the mother's nipple.

The great seat of putrefactive change is the large intestine. Proteins putrefy, carbohydrates ferment, and to a certain extent these two processes are antagonistic. Fermentation may be useful to animals that eat a large quantity of uncooked vegetables, because the cellulose resists the ordinary digestive juices. This, however, is not much use in human beings; but fermentation plays another useful part in antagonizing putrefaction. Putrefaction is the disadvantage of a large intestine, the advantage being that, by the absorption of water there, the bulk of the fæces is greatly reduced, so that the emptying of the bowel need not occur normally more than once a day. There is also less need for drinking large amounts of fluids. But we can hardly suppose that

the colon would have appeared in evolution without the development of a compensatory protective mechanism. And we have evidence of its existence.

Putrefaction of proteins leads to the formation of indol and skatol, which are normally conjugated in the liver to form ethereal sulphates which are practically harmless. As one of these, indican, is readily detected in the urine by its striking colour reaction, much of the theory of intoxication by putrefaction has centred round it. But indicanuria is not now regarded as a measure of intestinal putrefaction. Today the symptoms associated with constipation usually receive a mechanical explanation. Distension of the rectum is thought to be responsible at any rate for some of the symptoms.

The discovery by Barger and Dale of diamines set free by putrefactive changes, which raise blood pressure, suggests, however, that intestinal putrefaction may be a factor in the rise of blood pressure in later life. The other two foodstuffs may be held almost guiltless as a cause of intestinal intoxication.

The conclusion is that an intoxication by the ordinary putrefactive products of food digestion is not proven. Yet on this unstable foundation the most airy and far-reaching hypotheses have been reared.

(iii.) *Specific Intestinal Intoxications* may apparently arise in one of three ways:

1. There may be alterations in the intestinal flora, so that bacteria can thrive which produce specific toxic substances.

2. The bacterial processes may spread up from the large to the small intestine.

3. Normal intestinal bacteria may pass into the blood in consequence of lowered resistance of the epithelium or lowered bactericidal power of the blood.

The *Bacillus coli communis* may be regarded as a normal

inhabitant of the alimentary tract, but when it strays beyond its proper domain it may cause cholecystitis, gall-stones, cystitis, pyelonephritis, or phlebitis.

In this connection we may observe that a dose of castor oil may cause a reinfection of the urine with *B. coli* when it had become sterile after a previous attack of bacilluria. This shows the importance of the epithelial line of defence and the unwisdom of damaging it by drastic purgatives.

Another example of the way in which normal inhabitants of the bowel may intrude into damaged tissues with pathogenic results is seen in the engrafting of the *Streptococcus salivarius* or the *S. fæcalis* on to heart valves already crippled by rheumatism, producing infective endocarditis.

In many instances it will be difficult, if not impossible, to draw a hard-and-fast line between intoxications and infections. Indeed, there may be three stages in the same case:

1. Intestinal absorption of toxins only.

2. The organism in the portal blood, soluble toxins in the general circulation.

3. The organism in the general circulation—*i.e.*, septicæmia.

Microbic Cyanosis.—In 1902 Stokvis described cyanosis as a result of intestinal troubles. The abnormal colour was due to the presence of methæmoglobin in the red corpuscles. The patient had great intestinal irritation, clubbing of the fingers, deep cyanosis, and considerable albuminuria. After death it was discovered that he had suffered from parenchymatous nephritis, with ulcerative enteritis.

Van den Bergh found the connecting-link between the intestinal trouble and the resulting blood changes to lie in the presence of nitrites, which lead to the formation of methæmoglobin. He found that the condition would clear up in from twenty-four to forty-eight hours on a milk diet, but returned in four hours after an ordinary meal. He also described four cases of sulphæmoglobinæmia—*i.e.*, a sulphur

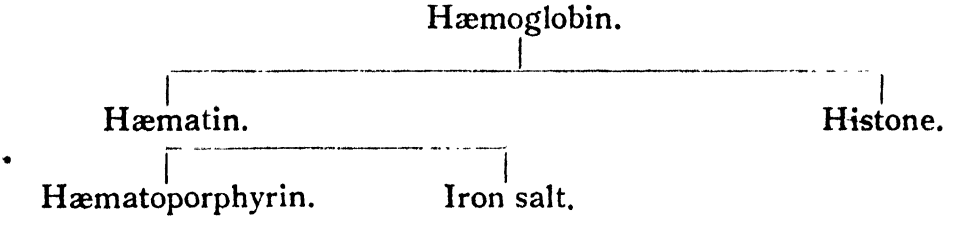
compound of hæmoglobin, which in itself suggests an intestinal source for the intoxication.

The skin is of a leaden hue, resembling that of silver staining. The colour is due to the blood, and not to deposited pigment, for on pressure the skin can be shown, when emptied of blood, to be of the normal hue. The blood can be examined spectroscopically in the circulation by holding the patient's hand in front of an electric light and pressing the web of the thumb between two glass slides until a convenient thickness is obtained. A spectrum closely similar to that of methæmoglobin can then be obtained, with a well-marked band in the red.

Nitrites can be found in the urine, but there is no increase in sulphuretted-hydrogen-forming organisms in the intestine.

Subsequently Mackenzie Wallis claimed to have found in the mouth of five patients with sulphæmoglobinæmia a nitrifying bacillus, which formed a strongly reducing substance, present in the serum of all the patients. It reduced oxyhæmoglobin, an essential step in the formation of sulphæmoglobin. One case was apparently cured by removal of the teeth and the use of an autogenous vaccine prepared from this nitrifying bacillus. The name 'microbic cyanosis' is therefore strictly applicable to the condition.

Hæmatoporphyrinuria.—The decomposition of the hæmoglobin molecule may be tabulated as follows:



A trace of hæmatoporphyrin is a normal constituent of urine, but under certain conditions this is largely increased in amount, such as in sulphonal, trional, and sulphonamide poisoning. But there are other groups of cases where such drugs can be excluded.

One group is congenital. The pigment may stain the bones, and even the enamel of the teeth. Sometimes the spleen is enlarged. Like certain other fluorescent pigments, hæmatoporphyrin increases the sensitiveness of the skin to light, which probably accounts for the recurrent attacks of hydroa vacciniforme to which the subject is liable each summer.

The other group shows an acute onset with toxic symptoms, such as vomiting, thirst, anorexia, abdominal pain, and profound prostration. Ranking and Pardington described two such cases, and one of us had a patient in whom three attacks of this character had led to the suspicion of intestinal obstruction. Ascending paralysis has also been described. Monro has seen hæmatoporphyrinuria in periodic vomiting with acetonuria in a boy. In light-sensitive cases an abnormal intestinal flora rich in yeasts has been found.

All these points are suspicious of an intestinal intoxication, and the suspicion is strengthened when we remember that hæmoglobin will break down into hæmatoporphyrin much more readily in the reduced state than when containing oxygen. In the formation of sulphæmoglobin the blood pigment is also first reduced, and then combines with sulphur.

This suggests that in both cases some reducing agent is at work, and the intestinal symptoms point to the alimentary canal as its source, the liver becoming secondarily involved. It is interesting to compare this condition with methæmoglobinæmia, which may also be caused either by intestinal intoxication or by coal-tar drugs. Fairley has shown that in hæmolytic conditions it is not methæmoglobin but methæmalbumin that is formed.

In the future other conditions may be proved to be due to intestinal intoxication, but the evidence is not convincing at present.

Oral sepsis may play an important part in producing infections via the intestinal tract. If achlorhydria already

exists, the bactericidal effect of the hydrochloric acid is lost; but in any case oral sepsis may lead to gastritis, thereby diminishing or actually preventing the secretion of the acid. This helps to explain various difficulties. Thus, though *cirrhosis of the liver* occurs in alcoholic subjects, direct administration of alcohol experimentally leads to a fatty and not to a fibrotic change in that organ. Consequently the condition has been referred to impurities in the common alcoholic drink of the country. Thus in wine-drinking countries the potassium sulphate with which the *vin ordinaire* is plastered, and in whisky-drinking countries the fusel oil, have been held responsible. Such wide differences of opinion make it all the more probable that the ingredient common to them all, the alcohol, is really the agent at work. Rolleston explains this dilemma by the view that alcoholic excess leads to a prolonged gastric catarrh, which, by lowering resistance, enables toxic substances to be absorbed from the bowel. This might occur in other than alcoholic subjects, and it certainly appears that we cannot explain all cases of multilobular cirrhosis by alcoholism. The chronic peritonitis which produces the ascites in the later stages of cirrhosis means that ultimately the organisms as well as the toxins have been absorbed. Durham has shown that these organisms can always be found in the omentum, although the ascitic fluid is sterile.

It is a reasonable view that many *chronic affections of the joints* are due to a chronic infection or intoxication. Either the alimentary or the genito-urinary tract may be the 'open door' by which the infective agent enters. And so it has come about that pyorrhœa alveolaris must be regarded as a potent cause of rheumatoid arthritis. This should be excluded, if necessary by an X-ray examination, but other septic foci must not be overlooked. *Tetany*, when not dependent on parathyroid defect, may be associated with the fatty diarrhœas which interfere with the absorption of

calcium. This is obviously distinct from its occurrence in alkalosis from any cause.

But we need not multiply the list of diseases for which an intestinal intoxication might be held responsible. For the present this is mere speculation.

Treatment.—Where intestinal infections or intoxications may reasonably be suspected, the indications for treatment are as follows:

1. *Avoidance of Putrefactive Contamination of Food.*—All food should be cooked as far as practicable, and only once. Second dressed meats should be avoided. Cheese, especially the riper varieties, should be avoided. All fruit should be peeled. Careful attention must be paid to the teeth, since anaerobic bacteria lurk in the interstices, and these are a great factor in intestinal putrefaction.

2. *Promotion of Prompt Digestion and Absorption.*—Here again attention to the teeth is important, to allow of proper mastication. Hydrochloric acid should be given if it be deficient in the gastric juice. In the cases where fermentation of starch is suspected, diastatic ferments are advisable before food. Intestinal flatulence especially indicates reduction in the amount of starch, particularly in the form of root vegetables. Pepper, mustard, excess of salt, vinegar, and lemon are irritant to these patients. Vitamin B_1 concentrates help to maintain the normal tone of the bowel. Demulcent drinks may be helpful. Rest before and after meals should be enjoined.

3. *Limitations of the Number of Bacteria.*—Microorganisms form one-third of the total solids of the stools, though the greater number of these are dead. Intestinal asepsis is a counsel of perfection, and we are not now prepared to accept Metchnikoff's dictum that senile changes are the result of an intoxication from the large bowel, so that it is hardly likely that we shall attempt intestinal antisepsis as a routine measure. We must beware of a routine

use of strong purgatives to this end, for, by removing the superficial epithelium of the bowel, they may facilitate septic absorption. Bismuth salicylate, sulphocarbolate of soda or salol in 10-grain doses three or four times a day after meals may be tried. A cachet containing 3 grains of benzo-naphthol with $\frac{1}{4}$ grain of menthol is useful where there is much flatulence. The colloidal emulsion of T.C.P. in doses of half an ounce in water twice a day is unpleasant but sometimes effective. Paraffin is not only aperient, but inhibits the growth of intestinal bacteria to some extent. Kaolin in doses of 2 drachms in water twice a day is also of value. It works best in an emulsified form. Probably the best plan is to combine a selected antiseptic with paraffin and kaolin.

Metchnikoff suggested another way of attacking the problem. Instead of attempting to render the bowel aseptic, he advised the introduction of other organisms which are antagonistic to the growth of the putrefactive bacteria. These are the lactic-acid-producing organisms.

Only fluid cultures or the milk actually soured by the bacilli should be employed. Emulsions containing *Bacillus acidophilus* have also been largely employed for this purpose. Lactose in doses of from 2 to 4 drachms three times a day in hot water before meals often achieves the same end and may do away with the need for aperients. Good results can only be expected in the cases where the fresh fæces are alkaline and remain alkaline after twenty-four hours, yielding hardly any gas to the fermentation tube.

4. Guelpa's method of detoxication by a combination of fasting, purgation, and diuresis has had excellent results claimed for it by various observers and is still fashionable in certain quarters. No doubt it is helpful to such persons as habitually overeat.

5. *Plombières Douches* should be used with caution, if at all. It is important that they should not be given more frequently than three times a week, and that not more than

18 inches of pressure should be used at a time. The treatment should not be continued more than about three weeks. Half an ounce of listerine or 1 grain of potassium permanganate to the pint may be employed. If these precautions are not observed, mucous colitis is almost certain to be produced.

6. *Mechanical Supports.*—When there is definite visceroptosis, help may be derived from a well-fitting abdominal support.

7. *Surgical Procedures,* such as irrigation of the colon through an appendicostomy wound, colopexy, short-circuiting, and even excision of the colon, have all been advised. The only one which is likely to be required is the first-named, and that only when there is ulcerative colitis or chronic dysentery.

8. *Vaccine Treatment of Intestinal Intoxications.*—The most rational procedure would be to isolate the microbe responsible, if possible, but the results have been rather disappointing. If a plate culture from the stools grows definitely pathogenic organisms the effect of the patient's blood in agglutinating or destroying them should be tried. If we get a positive reaction with one or more of these a vaccine may be prepared from such organisms. The prevalent practice of prolonged vaccine treatment with normal intestinal flora should be condemned.

Finally, the psychogenic origin of much indigestion, both gastric and intestinal, must never be forgotten.

CHAPTER V

THE WORK OF THE LIVER

FOR a long time the discrepancy between the great size of the liver and the comparatively small amount of its external secretion, the bile, proved a puzzle. Gradually it was realized that this secretion only represented a small part of its activities. In several respects it shares its duties with the pancreas and the spleen.

The liver and pancreas are both developed as outgrowths of the alimentary tract, and their ducts are innervated in the same general way as the canal from which they develop. Their close co-operation is further shown in the way they pour their secretions into the alimentary tract at the same point, in their complementary rôles in the utilization of fat and in carbohydrate metabolism, as well as by the circulatory conditions which ensure that any internal secretion from the pancreas shall pass straight to the liver. Situated on the path by which all the blood from the digestive organs enters the systemic circulation, it is not surprising to find that the liver helps to prepare all three foodstuffs for utilization by the tissues. The bile it forms is at once an excretion and a secretion. But further, the liver is an important agent in detoxication and in maintaining the constant composition of the blood. On that side it co-operates with the spleen, just as on the digestive and metabolic side it co-operates with the pancreas.

A number of tests have been designed to estimate the functional efficiency of the liver. Many of these failed because its great reserve capacity was not realized. For, like the heart, lungs, and the kidneys, the liver does not normally exert its full activity, and so does not reveal its failure of

function to ordinary tests until this has fallen to so low a limit that grave hepatic damage is no longer in doubt, and the time for successful treatment is past. Moreover, not only must the power of the liver to undergo compensatory hyperplasia be remembered, but, its various functions not being equally inhibited by disease, it is necessary to apply tests covering different fields of hepatic activity.

In the first place we shall consider the action of the liver in preparing the three foodstuffs for the tissues, and the tests related to each.

The Work of the Liver in General Metabolism.

1. *Protein.*—It has been clearly recognized for some years that the protein molecule is broken down into its ultimate amino-acids before absorption, and that these end-products are less toxic than the intermediate proteoses and polypeptides from which they arise. Further, as there is a chemical specificity of tissues, by no means all of such end-products are capable of being utilized for tissue repair at the time of their entering the blood stream. Those which cannot be used at once by the tissues are turned into urea and other excretory products. Indeed, the method of maintaining the nutrition of the body is as far as possible the same on an ample protein diet as in starvation. In both, amino-acids are used to make deficiencies good, though in starvation they are obtained by pooling the autolytic products obtained, as it were, by levying a tax on all the cells of the body. From this pool individual organs are allowed to draw, according to their functional importance to the body. But even in the well-fed body the excess of protein food above what is required for tissue repair is not stored but excreted. Naturally, therefore, much more nitrogen is excreted by the well-fed than by the starving body, any storage being provided from non-nitrogenous sources.

It would appear that each amino-acid has its own method

of breakdown, and very probably its own ferment for achieving that purpose. This has been brought out clearly by Garrod in his study of the inborn errors of metabolism. He says:

'If any one step in the process fail, the intermediate product in being at the point of arrest will escape further change, just as when the film of the biograph is brought to a standstill the moving figures are left, foot in air.'

Now it happens that most of such inborn errors as alkaptonuria, pentosuria, and cystinuria are inconvenient rather than serious. They are also rare, and although their study has established points of great theoretical importance as to protein breakdown, they do not throw light on the estimation of hepatic efficiency. The ferments involved are evidently very resistant normally, since these substances do not appear in extensive degenerations of the liver, although porphyrinuria, which is sometimes an inborn error, may also occur in hepatic disease. The detection of leucin and tyrosin in the urine was thought at one time to be evidence of failure of the liver to turn them into urea, but they are now regarded merely as signs of hepatic disintegration. Though most prominent in acute yellow atrophy, they may be found in other diseases, such as advanced cirrhosis. But it must be admitted that nothing has been found clinically to correspond to the experimental results obtained by Eck's fistula, even, for instance, after the Talma-Morrison operation.

It will be remembered that Eck made a fistula between the portal and hepatic veins in dogs, so that food entering the blood stream after absorption from the bowel could pass into the general circulation without passing through the liver. He found that toxic symptoms resulted, especially after protein foods. The dogs, indeed, learned this for themselves and avoided animal flesh if they could obtain other foods. The liver also appears to destroy purin bodies, ultimately oxidizing them to urea.

A priori one would expect to find that in failure of hepatic efficiency the urea excretion would fall, while the excretion of the precursors of urea such as ammonia and amino-acids would rise. But the following facts must be borne in mind: (1) Quite a small proportion of the total liver substance is adequate to make the normal amount of urea. (2) As so much of the urea comes direct from the food, the total amount excreted varies with the diet. On a liberal protein diet the urea forms about 86 per cent. of the total nitrogen, while in the healthy fasting individual it forms a much smaller proportion. (3) An absolute increase in ammonia formation may be, and usually is, simply a protective step against acidosis.

In normal pregnancy de Wesselow and Wyatt have shown that a low urea excretion is the rule, because nitrogen is being diverted to the use of the fœtus, so much so that a rise of blood urea above 40 mg. per cent., which would be within normal limits otherwise, implies a failure of renal function in pregnancy.

2. *Carbohydrates.*—All sugars are absorbed as monosaccharides. Although they can be rapidly stored in the liver and muscles as glycogen, the absorption from the alimentary tract of any such sugar, with the important exception of lævulose, leads to a rise of blood sugar from the fasting level of 0·08 per cent. to 0·18 per cent., falling again in about one and a half hours. This would imply that lævulose, although its limit of tolerance tends to be rather lower than that of dextrose, can within that limit be stored as rapidly as it can enter the blood stream. Years ago H. Strauss regarded a diminished tolerance for lævulose as evidence of impaired hepatic function, but this did not afford a satisfactory basis for a test. It is not sensitive enough, and the kidney threshold for the excretion of sugars is not a constant. Maclean and de Wesselow, having determined that lævulose when given by the mouth in doses of from 30

to 50 grammes does not raise the blood sugar in healthy subjects with an intact liver, went on to show that when the liver is defective it is not able to deal with lævulose fast enough to prevent it from entering the blood stream, thus increasing the blood sugar proportionately to the hepatic defect. A rise of more than 10 per cent. in the blood-sugar level is regarded as positive evidence of impaired function. The galactose test is somewhat similar. These are the best tests we have for hepatic efficiency. So-called catarrhal jaundice cannot always be due to mere ascending catarrh of the main bile ducts, but must often involve some hepatitis, since administration of lævulose frequently raises blood sugar in this disease even before the onset of jaundice. A similar change occurs in salvarsan poisoning, while Mackenzie Wallis found that in every case where a course of such an arsenical preparation has been given, some degree of hepatic inefficiency exists for at least three months. Clearly a second course should not be given within this interval; while, if lævulose causes a rise of blood sugar of 0·05 per cent. above the fasting level, careful treatment is required, however slight the other clinical manifestations may be. In pure obstructive jaundice this rise of blood sugar does not occur, or is very slight. As further evidence that catarrhal jaundice may involve a toxic hepatitis, allusion may be made to a group of cases one of us saw in 1922, where, in addition to a large and tender liver, with jaundice, there was cyanosis, air hunger, and almost complete suppression of urine, followed by intense albuminuria, sometimes with hæmaturia and casts. Yet the patients made a good recovery, and soon became free from albumen. Sometimes they showed an increased diastase output as well.

The diastatic function of the liver has already been referred to in connection with the pancreas. So far, however, a defect of diastase in the blood has not helped much as evidence of hepatic insufficiency, although Harrison and Lawrence found

in twenty cases of hepatic disease that the blood diastase was low in three severe cases. In two this rose again as the clinical condition improved.

One thing appears clear about the glycogenic function of the liver: in the presence of an ample supply of glycogen the metabolism of the liver proceeds more smoothly. This may be due to the fact that when the glycogen store is low, the liver manufactures it from protein and fat, which throws a strain upon the organ if the cells are damaged. A liver is less liable to post-anæsthetic poisoning if it is well supplied with carbohydrate, while starvation, which would deplete the glycogen store, increases the liability to this catastrophe. And Colonel Harrison, at Maclean's suggestion, has found giving sugar, usually dextrose, of material benefit in preventing toxic jaundice after salvarsan. In a group of patients receiving sugar before injection there were only two or three cases, while in another group not receiving sugar there were nearly fifty cases of toxic jaundice. Glycogen, whether formed from dextrose or lævulose, appears to be the same, and it can be readily drawn upon by the blood and tissues, being converted into dextrose in order to supply sugar to the latter. In this process adrenalin helps in the breakdown of glycogen into dextrose.

3. *Fats.*—Fat in the liver may be obvious as the result of sepsis, broncho-pneumonia, phthisis, rickets, profound anæmias, and poisons, such as phosphorus, chloroform, and trinitrotoluene. But the amount of obvious fat is not an accurate criterion of the total fat in an organ. Combined fat in the heart, kidneys, or liver will not react to stains such as osmic acid or Sudan red, or even yield to fatty solvents, while, when it is set free by degenerative processes, it will do so readily. Rosenfeld showed that 'fatty infiltration' of the liver may really be due to transference from other parts. The condition may fairly be called one of 'fatty congestion.'

Leathes has shown that the fat normally present in the

liver is in the more active unsaturated form, but that the fatty deposit which occurs there in poisoning by phosphorus or tetrachlorethane or after anæsthetics is in the more inert, saturated form. He makes out a good case for regarding as a function of the liver the conversion of saturated fat into the more active unsaturated form for utilization by the tissues. When the liver is thrown out of gear by various toxins the tissues, starving for prepared fats, send unprepared fats to the liver, but in vain, for it is unable to deal with them. The liver may be compared to a miller—the saturated fats are the wheat he grinds, and the unsaturated fats are the flour that results.

Foulerton pointed out that chloroform, ether, and tetrachlorethane are solvents of fat, while phosphorus, dinitrobenzol, and trinitrotoluene are readily soluble in fats, so that the destructive effects of these poisons on the liver may be due to their being conveyed with the fats to the liver in the attempt to carry out this process. In some cases, such as phosphorus or post-anæsthetic poisoning, this carriage of fats may lead to a gross increase in the size of the liver, but we require a much more sensitive test than this. Whipple devised the lipase test to this end. Normally blood contains a small constant amount of fat-splitting ferment, but in diseases of the liver this lipase is increased, as measured by the power of the blood to split ethyl butyrate. It has been supposed, therefore, that normally the liver inhibits the formation of lipase, so that its increase in the blood is a measure of hepatic damage. Whipple has applied this to chloroform poisoning, and Mackenzie Wallis to salvarsan poisoning. The damage has, however, to be rather gross before the lipase increase is enough to be relied upon. But that the fat metabolism in the liver is more complicated than at first appeared is shown by Best's observation that if an animal is injected with lecithin there is a marked reduction in the fat content of the liver.

Mackenzie Wallis further reported that in toxic jaundice due to salvarsan poisoning the cholesterol in the blood is diminished, while in this condition and in phosphorus poisoning the liver is found loaded with cholesterol esters *post mortem*. It may be that the cholesterol is merely on its way to be excreted in the bile, and that the diseased liver cannot accomplish this. Its presence in the kidney under similar conditions may be an attempt at an alternative channel of excretion. In the toxæmia of pregnancy, including a case of icterus gravis, this cholesterol disturbance was not found.

The Antitoxic Functions of the Liver.

At the risk of repeating what has been said under intestinal intoxications, we may say that apart from the reactions against bacterial poisons the antitoxic processes of the body are few and simple—such as oxidation, reduction, hydration, dehydration, and methylation. The protective substances are few, and the process of rendering a poison harmless by conjugating it with a protective substance is most often carried out by the liver. Thus the toxic indol is conjugated with sulphuric acid into a harmless ethereal sulphate, indican. But if the liver cells are diseased such conjugation cannot occur, so that toxic substances like indol, skatol, and phenol can pass direct into the blood, even though the urinary output of ethereal sulphate is low. There does not appear to be any simple test for recognizing this.

Glycuronic acid is another important protective substance, and the formation of harmless glycuronates after administration of camphor, morphine, and the like is a function of the liver. It is claimed that $7\frac{1}{2}$ grains of camphor given by the mouth should be completely conjugated with glycuronic acid and recognized by its reducing action in the urine, but if the liver is diseased no such glycuronic acid is formed. A simpler test is that introduced by Roch. He gives $\frac{1}{2}$ grain of sodium salicylate an hour before food. This should be

turned into a glycuronate, which would not yield a purple colour with 1 per cent. ferric chloride solution. If the urine excreted for the four hours after a meal does give this colour, it is claimed that hepatic insufficiency is present.

The *hæmoclasic crisis* may perhaps be regarded as due to a failure of the antitoxic power of the liver. As C. M. Wilson expresses it, under this rather forbidding name is concealed a test disarming in its simplicity. Widal maintained that when the liver was diseased the normal post-prandial leucocytosis was replaced by a leucopenia, which was accompanied by a fall of blood pressure. This was believed to be due to the hepatic failure permitting the entrance of incompletely digested proteins into the systemic circulation. It recalls the anaphylactic reaction to material unsuitable for assimilation. Before breakfast a white count is taken, then 7 ounces of milk are drunk, and another count taken twenty minutes later. Wilson concludes that, with the possible exception of the lævulose tolerance test, this is the only test which gives an early warning of hepatic insufficiency. But it may fail even in advanced malignant disease of the liver.

The Liver and Hæmopoiesis.—See Chapter XI.

The Liver and Blood Clotting.—See Chapter II.

The Liver and Purin Metabolism.—See Chapter VI.

The Secretion and Functions of Bile.

Bile is partly an excretion which is going on continually, partly a digestive fluid which is only required during digestion. The gall-bladder allows a discontinuity of entry into the bowel of a fluid which is being continuously formed. Furthermore, the gall-bladder, by adding cholesterol and mucin to the bile while absorbing water, alters its composition, making it more concentrated and viscid. Therefore, the longer bile remains in the gall-bladder the thicker

it becomes, while with complete obstruction to the cystic duct the bile entering the intestine is unusually dilute. The bile pigments bilirubin and biliverdin are purely excretory, and their origin will be considered later. Bile also contains lecithin (a complex phosphorized fat) and, as stated above, cholesterol, which is a monatomic alcohol, with mucin, as well as inorganic salts, which render it alkaline. But the important secretory constituents of bile are the bile salts. These are sodium taurocholate and sodium glycocholate. The cholalic acid is secreted by the liver cells, and it is not found when the liver is excluded from the circulation. It is conjugated with taurin and glycin. Glycin is amino-acetic acid, while taurin is a sulphur-containing body derived from cystin. If cholalic acid is given it produces a considerable increase of bile acids in the bile, but as this does not follow the administration of taurin it would appear that under normal conditions of health and diet there is always an excess of taurin present, and that the output of bile acids depends on the amount of cholalic acid available. Normally the outflow of bile is strictly parallel with the pancreatic secretion, though smaller in volume, the total amount secreted in the day averaging 30 ounces. The outflow of bile into the intestine depends upon—

1. *The Rate of Secretion.*—Secretin will double the secretion of bile, thus illustrating the co-operation of the liver with the pancreas. The absorption of bile salts also increases secretion, and they are, indeed, the only direct cholagogues, while salicylate of soda promotes a flow of dilute bile.

2. *Diet.*—Fat has the most effect, protein next, while carbohydrate has the least influence.

3. *The Activity of the Muscular Walls of the Adjacent Passages.*—The gall-bladder shows rhythmical contractions, resembling peristalsis in being independent of the central nervous system. When peristalsis is increased in the bowel these contractions of the gall-bladder are increased. Thus it

comes about that most so-called cholagogues, such as calomel, are merely indirect in their action. They do not increase the secretion of bile; they merely help to empty the gall-bladder by increasing peristalsis. Olive oil and magnesium sulphate when introduced into the duodenum will also cause contraction of the gall-bladder.

4. *The Influence of Extrinsic Nerves.*—As with the bowel and other hollow viscera, the sympathetic relaxes the body of the gall-bladder while closing the sphincters at the neck of the gall-bladder and at the point of entrance into the bowel. Hence the effect of reflex irritation—*e.g.*, in the appendix—in holding up the output of bile. The stimulation of the vagus, on the other hand, probably leads to contraction of the gall-bladder.

5. *The Pressure of Adjacent Organs.*—The movements of the diaphragm help to express the contents of the gall-bladder. The fact that women tend to use their diaphragm less than men may therefore render them more liable to stasis of bile.

The Actions of Bile may be classified thus:

1. *On Digestion.*—Beyond the precipitation of acid albumen by neutralizing the gastric juice, bile does not appear to have much action on proteins, though Pavlov believed it assists trypsin. It certainly accelerates the action of amylopsin in digesting starches. The activity of pancreatic juice in splitting fats is trebled by the addition of bile, whether boiled or unboiled. This is due to (*a*) *the bile salts*, which lower surface tension and thus permit of closer contact between watery and oily fluids; (*b*) *cholesterol and lecithin*, which help to dissolve fatty acids and soaps, including even the otherwise insoluble calcium and magnesium soaps. Even in acid media this action continues because bile acids dissolve fatty acids.

2. *On Absorption.*—Here again it is the lowering of surface tension by the bile salts which promotes the absorption

of fats. It has recently been pointed out that the presence of at least a trace of bile salts is also necessary for the absorption of fat-soluble vitamins.

3. *On Peristalsis.*—Bile salts appear to increase the movements of the intestinal muscles and of the muscles of the villi. They are therefore natural laxatives.

4. *On Putrefactive Processes.*—Though bile acids are antiseptic, bile salts are not. They merely diminish putrefaction by promoting absorption.

It should be noted that only traces of bile salts are present in fæces. They are absorbed by the villi, presumably with the fats, and conveyed to the liver, where they are used over again. This is known as Schiff's biliary cycle. Copeman showed that when a biliary fistula permits the escape of bile on to the surface of the body, so that this cycle cannot occur, the amount of bile salts in the bile soon falls to one-tenth of its former figure.

If bile fails to enter the bowel, the ill-effects are principally due to the absence of bile salts. As they help in the emulsification and absorption of fats which have been previously split into fatty acid and glycerin by the pancreatic juice, the steatorrhœa which follows biliary obstruction is due to the increase of soaps and fatty acids in the stools, while in failure of the pancreatic secretion it will be the unsplit or neutral fat that will be in excess. Interference with absorption of proteins will lead to increased intestinal putrefaction, with a consequent increase in the indican of the urine. The absence of bile pigment from the stools causes the familiar clay colour, but as the excess of fat may mask the presence of bile we must not conclude from this colour alone that no bile is entering the intestine. Extraction of a clay-coloured fatty stool with acid alcohol or amyl alcohol may still show the presence of urobilin by the band in the blue of the spectrum or by green fluorescence on the addition of zinc chloride and ammonia. This would indicate incomplete

obstruction, such as is usual with gall-stones, while the entire absence of urobilin is suggestive of the more complete obstruction produced by new growth of the head of the pancreas. The presence of obvious bile pigment in the stools in a case of jaundice is, of course, against its being of obstructive origin.

Apart from hepatic colic, the presence of gall-stones may disturb digestion in several ways, as may cholecystitis. Flatulent dyspepsia is the rule. A test meal may show either hyperchlorhydria or achlorhydria.

Investigation of Biliary Function.

(*a*) *By Intubation.*—If 1 to 4 drachms of magnesium sulphate in concentrated solution be introduced into the duodenum by the Einhorn tube a sharp flow of bile is excited by reflex contraction of the gall-bladder. This can be removed from the duodenum for examination. It is clear that if there is complete obstruction of the bile ducts the method is not applicable. Lyon has extended the method by collecting three samples of bile by the duodenal tube. The first sample should be of transparent, yellow-golden colour from the common duct, the second darker and more viscid from the gall-bladder, and the third much thinner and lighter in colour from the hepatic and intrahepatic ducts. Microscopic examination of the fluid may also reveal the presence of pus.

(*b*) *By X-rays.*—The gall-bladder can be readily investigated, especially by the use of a radio-opaque substance such as tetra-iodo-phenolphthalein. Opacol is one of the trade names for such a preparation.

After a plain radiograph has been taken for comparison 4 grammes of the dye dissolved in a wineglass of water is given at night, and another radiograph is taken in the morning while the patient is fasting. If the gall-bladder is seen

only faintly or not at all a second dose of the dye should be given the next night.

When the gall-bladder has been visualized a fatty meal is taken and the radiograph repeated. This procedure empties the normal gall-bladder by causing contraction as soon as the fat enters the duodenum. Failure to fill properly or delayed filling indicates either a diseased gall-bladder, obstruction of the ducts or disease of the liver itself such as cirrhosis. A diseased gall-bladder may fail to concentrate the dye which reaches it because the walls cannot absorb water. Radiolucent gall-stones may be shown up in contrast to the surrounding shadow. Failure to fill may occur in certain diseases of the pancreas. It also occurs in late pregnancy, but the reason for this is unknown.

With the proper technique it is claimed that the percentage of errors by this method is very low.

Treatment of Cholecystitis.

A useful routine measure is to give 5 to 10 minims of belladonna to dilate the bile passages, and 10 grains of salicylate of soda to dilute the bile, together with 10 grains of hexamine as an antiseptic and 20 grains of bicarbonate of soda to prevent urinary irritation. Antiphlogistine is applied over the gall-bladder during this time, while the patient is directed to drink water freely so as to help the flow of bile. Formerly it was considered doubtful whether hexamine itself can liberate active formaldehyde in the alkaline medium of the gall-bladder. Specht states, however, that free formaldehyde can be demonstrated in the bile after administration of hexamine as such. Hurst gives very large doses of hexamine up to 100 grains for this purpose, together with sufficient bicarbonate of soda to render the urine alkaline. Even so, however, hæmaturia may be produced, and such large doses are seldom, if ever, advisable. One of us saw a case of a typhoid carrier (who had a gall-stone, as such

patients usually have) treated by helmitol after operation; for two hours after each dose the bile escaping by the fistula was colourless. Now reduced bile is almost colourless, and formaldehyde is a reducing agent. A patient who yielded pus from the gall-bladder by Einhorn's tube improved greatly under the belladonna and salicylate treatment and became free from symptoms, but still desired operation, as she was a stewardess on a liner and feared the risks of an acute attack while at sea. Mr. Harold Wilson accordingly operated, but found the gall-bladder normal. The evidence of the effectiveness of the treatment, at any rate in this case, appears to be complete. It should be followed up by a course of cholelith pills (P. D. and Co.) once or twice a day.

The dietetic principles underlying treatment are that meat extracts, purins, and condiments help to produce hyperchlorhydria; soft carbohydrates and green vegetables promote flatulence. The fats, while diminishing the secretion of acid in the gastric juice, depend on bile for their absorption, and if not absorbed they increase intestinal putrefaction by coating over the proteins; moreover, their influence in producing obesity must not be forgotten. The practical deductions from these considerations are: (1) White fish, eggs, cheese, mutton and chicken may be allowed, while soups, broths, liver, kidney, sweetbreads, and rump-steak should be forbidden until the hyperchlorhydria is checked. (2) Dry forms of carbohydrate such as biscuits, rusk, and toast are preferable to bread, ground-rice puddings and the like, because they demand thorough mastication before they can be swallowed, and therefore undergo a considerable degree of digestion by the saliva. (3) Sweets can be selected from jelly, egg custard, omelette, junket and stewed fruit. (4) At first vegetables had better be barred altogether, for, though cellulose is an aid to peristalsis, it promotes flatulence. As the patient's intestinal

condition improves, this rule may be gradually relaxed. (5) Fats in the form of butter or cream may be allowed, but only in small amounts for the reason given above.

It is important that water should be drunk freely to prevent inspissation of the bile. Patients do not care to be told to drink water from the tap, preferring, as of old, the waters of Abana and Pharpar. It is well, therefore, to select a spring which is mildly aperient, slightly alkaline, and not too highly mineralized.

Jaundice.

Jaundice is the classical example of a striking symptom of varying significance. Recent work has thrown new light on this. As with diabetes and nephritis, the centre of interest has shifted from the urine to the blood.

Slightly modifying McNee's conception of the structure of the liver, we may compare each lobule to a series of radiating tubular glands, shaped like test-tubes with the closed ends pointing to the centre of the lobule. The test-tube is lined with polygonal cells and its lumen represents the bile capillary. These test-tubes are packed in sawdust, which represents large endothelial Kupffer cells lining the wide capillaries of the portal vein. The polygonal glandular cells are not concerned with the manufacture of bile pigments, but merely transfer it from these vascular capillaries to the bile capillaries, modifying it in the process.

The Kupffer cells are a part of a much more widely distributed 'reticulo-endothelial' system, which is also found in the spleen, bone marrow, lymphatic glands, interstitial cells of the testes, reticular cells of the thymus and capillary endothelium of the adrenals. This system appears to be concerned in the metabolism of hæmoglobin and of fats, especially the lipoids. In excessive blood destruction its cells take up both intact and broken-down red corpuscles, as well as free hæmoglobin by phagocytosis. The iron-con-

taining part of the hæmoglobin molecule is broken off as hæmosiderin, which can be demonstrated by the Prussian blue reaction, while the hæmatoporphyrin becomes altered to form bile pigment. In health this work is largely done by the marrow, but when blood destruction is excessive other parts of this system may help. Now Van den Bergh has applied Ehrlich's diazo reaction to the detection of bile pigments in the blood serum, and has found that bilirubin may be present there in two different forms; while biliverdin does not give this reaction at all. Some sera would give a colour reaction at once—*the immediate direct reaction*; others would give only a *delayed reaction*, or no reaction until after precipitation with alcohol—the *indirect reaction*. Others again, as shown by Feigl and Querner, give a slight reaction at once, deepening later, or on the addition of alcohol—the *biphasic reaction*. It is found that bile from the gall-bladder, which has, of course, passed through the liver, always gives an immediate direct reaction, while bilirubin obtained from old hæmorrhagic effusions (which has been formed apart from the liver cells) gives a delayed or indirect reaction. The suggestion is that the liver gives the final touch to the manufacture of bilirubin, which normally is made from hæmochromogen, but which can also be made from hæmatoidin in old blood clot, and that it is only in this final form it can give the direct reaction. Hæmatoidin can only give a delayed or indirect reaction. When both forms are present the reaction is biphasic. Jaundice might therefore arise in several different ways, and we may adopt McNee's classification.

1. *Obstructive Hepatic Jaundice.*—Here the bile has been duly passed into the bile capillaries, but is obstructed in its outflow, and is therefore reabsorbed into the blood stream. Van den Bergh's test will give the immediate *direct reaction*. Moreover, such bilirubin being in its final state can be oxidized into biliverdin more easily than the other variety.

This is the condition found in the jaundice of gall-stones and new growth of the head of the pancreas, for instance. Van den Bergh adopted as his unit the presence of one part of bilirubin in 200,000 parts of serum. In this type of jaundice 50 units may be found. In gall-stones without jaundice the bile content of the serum is normal.

2. *Toxic and Infective Jaundice.*—Here the polygonal cells being diseased, some of the hæmatoidin from the Kupffer cells is unable to enter them, and therefore passes direct into the blood stream. The blood serum will therefore yield at first an *indirect reaction*, but as disintegration of the cells proceeds the bile capillaries become obstructed also and the reaction becomes *biphasic*, the direct portion of the reaction becoming intenser as obstruction becomes more marked. Such jaundice occurs—

(*a*) As a complication of acute fevers, such as pneumonia, typhoid, and spirochætal jaundice.

(*b*) After certain drugs, such as chloroform, phosphorus, and salvarsan.

(*c*) After damage of an unknown kind—acute and subacute yellow atrophy.

(*d*) After many general conditions of infection and toxæmia. Here the jaundice does not appear to be merely due to catarrh of the smaller bile ducts as was formerly thought, for a series of changes in the liver cells can be demonstrated, ranging from simply cloudy swelling (as in pneumonia), through fatty degeneration (as in chloroform poisoning), partial necrosis, and dislocation of the liver cells (as in spirochætal jaundice), to almost complete necrosis (acute yellow atrophy). In salvarsan poisoning any one of these stages may be met with.

3. *Hæmolytic Jaundice.*—When blood destruction is excessive more of its pigment is set free than the polygonal cells can deal with; some of the resulting bilirubin will be excreted normally, while some hæmatoidin remains unaltered

in the blood. The serum will, therefore, only yield the *indirect reaction*, and bile pigment will usually be absent from the urine, while constantly present in the fæces.

McNee suggests that as hæmolytic jaundice depends on excessive blood destruction, the cells of the reticulo-endothelial system, especially in the spleen, are thrown into increased activity, which may result in enlargement of the spleen. The blood serum comes to contain a greatly increased amount of pigment which is essentially of the same type as that arising from the physiological destruction of effete red corpuscles in health.

This conception would explain much which has been hitherto obscure. It has been recognized that 'splenic anæmia' is a consequence of several different conditions producing splenic enlargement. On removal the spleen may be found to be the seat of tuberculosis or endothelioma, among other conditions. Apparently we may now conclude that any disease of the spleen stimulating the formation or activity of the reticulo-endothelial cells sufficiently may produce splenic anæmia. It would also explain why splenic anæmia may go on to Banti's disease, in which cirrhosis of the liver and jaundice supervene, since the Kupffer cells of the liver are structurally and functionally an extension of the reticulo-endothelial system of the spleen. On the other hand, the occasion of occurrence of jaundice (without necessarily choluria) in Addisonian anæmia is apparently due to setting free of pigment which cannot be utilized because of the deficient formation of new corpuscles.

Van den Bergh has also shown that in some apparently healthy sallow individuals the bilirubin in the serum may reach nearly 3 units. Since the threshold for its excretion in the urine is 4 units, such individuals show no bile in the urine. The condition has been called 'simple familial cholæmia'; usually the spleen is not enlarged, while the fragility of the red corpuscles is only slightly increased. There would

appear to be all stages between this and the condition known as acholuric family jaundice. Here the patient may be born jaundiced or become so soon after birth. The jaundice persists with little or no variation for many years, but bile pigment is present in the stools as in health, while it is absent from the urine, in which any darkening present is due to excess of urobilin. Nevertheless, the indirect reaction is present in the serum. The spleen is always enlarged. There is considerable anæmia with a low colour index, poikilocytosis, nucleated red cells and reduction in the number of leucocytes. Yet the patient has good or fair health, and shows a normal resistance to intercurrent diseases. This condition tends to appear in more than one member of the family and in successive generations. Some of the patients are liable to attacks during which the colour deepens, when pain may be experienced over the spleen or liver, or both, and there may be slight pyrexia. Alcohol and syphilis do not appear to play any part in the ætiology. Enlarged abdominal veins, ascites, œdema of the legs, and hæmatemesis have never been recorded, and the liver does not appear to be cirrhotic, although it is sometimes fatty.

Attacks of hæmoglobinuria have been noted in this condition, which could be produced by exposure to cold, and in this connection it is interesting to note that in one family a cold bath would intensify the jaundice. All this points to hæmolysis as a cause of the jaundice. The serum from a patient agglutinates normal red corpuscles, but not his own red corpuscles or those from another individual suffering from the same disease. The most striking pathological feature of the condition is the undue fragility of the red corpuscles, for they are hæmolyzed by a dilute salt solution which has no effect on ordinary corpuscles. We may conclude that in acholuric family jaundice there is a chronic hæmolysis of unduly fragile corpuscles as a primary event, but that the threshold for the excretion of bile is not reached, while the

enlargement of the spleen and liver is secondary, to deal with the increased hæmolysis. What the cause of this undue fragility may be is still unknown, beyond the fact that as the corpuscles are more spherical than usual, any imbibition of extra fluid is likely to rupture them, since the sphere has the greatest surface compared with its cubical content.

Latent Jaundice is a term applied to conditions where the bilirubin content of the serum does not reach 4 units, so that the usual symptoms are missing. The hæmolytic type of this is seen in anæmias due to worms, and in all the newly born. Its occurrence is of prognostic value when salvarsan is being given, as it is evidence of the approach of poisoning by the drug. An obstructive type of latent jaundice occurs in cirrhosis. In this connection it is interesting to note that in the ordinary jaundice so common in the new-born (icterus neonatorum) the blood serum gives an indirect Van den Bergh's reaction, so that it is hæmolytic in origin. Before birth the fœtus has a polycythæmia reaching about 6½ millions per c.mm. This appears to be the direct result of the low oxygen pressure in the fœtal circulation, which stimulates the blood-forming organs to produce an excess of red corpuscles. By the second day after birth this excess has disappeared, and probably there will not be more than 4½ millions, due to hæmolysis, which may lead to obvious jaundice. The fact that latent jaundice is constant after birth supports this view. Severe jaundice in the new-born may be a familial tendency with a grave prognosis unless an intramuscular injection of 15 c.c. of maternal blood serum is given without delay and repeated for three to four days. It may also be due to suppurative pylephlebitis from septic infection through the umbilical cord or to congenital syphilis. Rarely it results from congenital atresia of the bile ducts.

Dissociated Jaundice has been described. If this merely implies that bile pigment may be found in the urine without

bile salts, it is comparatively common. Occasionally but rarely the converse occurs.

The effects of the failure of bile to enter the bowel have already been considered. We may now turn to the other effects on the body of the alteration in the course of the bile.

The Urine.—A rough guess may be made at the presence of bile pigment in the urine by merely shaking a specimen in a test tube, when the pigment colours the froth. This is much less marked with other colouring substances. The best test for bile pigments is Gmelin's: the play of colours obtained by successive stages of oxidation with fuming nitric acid, green being the most important thing to look for. Rosenbach's modification of dipping filter paper into the urine and then placing a drop of nitric acid on the paper is the easiest way of performing the test. The green colour given on pouring tincture of iodine on to the surface of the urine is not so sensitive a test, and usually succeeds when the jaundice is obvious. Huppert's test enables us to extract bile pigment from a urine containing other pigments. Ammonia and calcium chloride are added to urine, and the precipitate which forms is collected on a filter paper and washed. The precipitate is then boiled with alcohol acidified with sulphuric acid, when an emerald green solution results.

The only test of any value for bile salts in urine is Matthew Hay's test. Flowers of sulphur poured on to the urine sink if bile salts are present, owing to reduction of surface tension. No other test is sensitive enough to recognize the small quantity found in urine, but a control with normal urine should be made.

The Blood.—It has now been conclusively demonstrated that in jaundice the bile enters the blood stream rather than the lymphatics, appearing there within two hours after the experimental ligature of the bile duct. Bile salts *in vitro* have a marked hæmolytic action due to their solvent action on the lecithin and cholesterin of the red corpuscles. And

the serum of a jaundiced patient will hæmolyze foreign corpuscles readily, so that it may be impossible to carry out Wassermann's test, because hæmolysis occurs in all the tubes. But in the body the patient's own red corpuscles acquire a heightened resistance against bile salts, which increases with the intensity of the jaundice. This sharply differentiates ordinary jaundice from acholuric family jaundice, in which the red corpuscles are unduly fragile. Occasionally small subcutaneous hæmorrhages may occur, but more usually the hæmorrhagic marks on the skin are produced by scratching excited by the pruritus, or are really small telangiectases.

The Heart and Vessels.—One of the most definite results of jaundice is bradycardia. High tension usually accompanies a slow pulse, but in the bradycardia of jaundice the pressure is low and the pulse dicrotic. High tension stimulates the cardio-inhibitory centre in the medulla, and thus slows the heart through the vagus, but bile salts have a slightly depressing effect on the heart. Hence the slow pulse with low blood pressure. The action can be demonstrated easily on the isolated heart of a frog. As the effect can be abolished by atropine, bile salts probably act through the intracardiac endings of the vagus. The blood pressure is also kept low by the toxic action of bile salts on the smaller bloodvessels producing some degree of vaso-motor paralysis.

The Central Nervous System.—Any severe toxæmic jaundice will be accompanied by marked nervous symptoms—headache, delirium, and ultimately coma. But this is due to the hepatic inadequacy caused by the action of the toxins on the liver and not to the jaundice. Indeed, bile salts are probably not produced in this condition, the liver being too damaged to elaborate them. A mild degree of poisoning of the nervous system by bile salts is, however, common in ordinary jaundice, causing headache and depression. Bile pigments and bile salts are generally found in the cerebrospinal fluid removed by lumbar puncture.

The Skin.—Bile pigment usually appears in the skin soon after it does in the conjunctiva, but in the jaundice of pernicious anæmia the latter usually escapes. In obstructive jaundice the colour of the skin gives no indication whatever of the amount of bilirubin present in the serum. In the deep green jaundice of prolonged obstruction there may be less pigment in the serum than in early stages when the skin is just beginning to show a yellow tinge. This suggests that the skin is used as an alternative attempt at excretion, though, as will be pointed out later, it does not usually escape by the sweat. It is merely stored up in the skin, as if to free the more vital structures. Pruritus is a most troublesome symptom, but it is inconstant. It is due here, as pruritus always is, to currents of lymph set up between the prickle cells. Here the bile salts are responsible, as they cause alterations of surface tension which set up such currents. The patient indulges in much scratching, but without relief, for, as he often says truly, the itching is *beneath* the skin.

The Secretions.—Saliva, tears, and milk are not bile-stained in jaundice. It is frequently stated that the sweat is bile-stained, but this is exceptional. The copious diaphoresis induced by pilocarpin is, however, accompanied by bile pigment. Nasal and bronchial mucus is not tinged with bile. Inflammatory and passive exudates are, however, invariably bile-stained. Thus if mastitis occurs in jaundice the milk will be coloured with bile. The expectoration in bronchitis is not coloured; but if pneumonia occurs as a complication bile at once appears in the sputa. Again, should œdema of the lung ensue the sputa become bile-stained. In a case of jaundice without pneumonia, then, occurrence of bile-stained sputa is of serious import, being evidence of heart failure. Fluid in the pleural or abdominal cavity, being either the result of inflammation or of passive exudation, will, accordingly, be coloured by bile in a jaundiced patient.

The Fate of the Bile Pigment.—It will be gathered from

the above that the evidence in favour of the view that urobilin or its chromogen is formed in the intestine by reduction of bile pigment through bacterial agency is very strong, for when all bile escapes through a biliary fistula, or when complete obstruction prevents bile from entering the intestine, no urobilin is found. Again, it is absent from the fæces at birth, not appearing till bacteria have had time to establish themselves in the bowel, while if bilirubin is inoculated with intestinal bacteria urobilin is formed. Normally this urobilin colours the fæces, where it is often called 'stercobilin,' while a small amount is reabsorbed and appears in the urine. If there is polychromia from increased hæmolysis there will be increased formation of urobilin, while if there is partial or complete obstruction to the bowel there will be increased reabsorption of urobilin. In either case urobilinuria will occur, but it has most significance as evidence of hæmolysis. It may also be admitted, however, that when the gall-bladder becomes infected by fæcal bacteria, urobilin may be similarly formed by reduction of bilirubin, even before the bile has entered the bowel.

In conclusion it will be observed that apart from an unpleasant but harmless discoloration produced by bile pigments all the important symptoms in jaundice are due to bile salts. Their absence from the intestine causes steatorrhœa and wasting from deficient absorption of fats, increased intestinal putrefaction and constipation. Their presence in the blood causes bradycardia, headache, depression, pruritus, and sometimes subcutaneous hæmorrhages.

Treatment.—The treatment of jaundice must depend upon the cause, but the following general principles are usually applicable. During the initial stages the patient should be confined to bed. Although calomel is only indirectly a cholagogue, it may be given in doses of $\frac{1}{2}$ grain every hour for six doses; this often relieves the vomiting, and has the additional advantage of being aperient without causing drastic purga-

tion, which should be avoided. Ten hours after beginning the calomel treatment a Seidlitz powder should be given, for repeated doses of calomel, if not effective in opening the bowels, may set up mercurial stomatitis. Cholelith pills are useful here also. Alkalies are indicated as solvents of mucus in catarrhal cases, and, if the vomiting persists, may be combined with 10 grains of bismuth salicylate. As soon as the state of the stomach permits the more active sodium salicylate should be substituted as a diluent and disinfectant of the bile. In toxæmic cases the patient should be encouraged to drink large quantities of barley water and the like. With the onset of severe cases it is advisable to purge freely and to give an intravenous infusion of a pint of normal saline at body temperature. Venesection has the advantage of removing toxins while the infusion is diluting them. Theocin-sodium-acetate in 2-grain doses is a useful diuretic.

In even mild cases the diet will naturally be light. As dextrose is the most easily metabolized foodstuff in this state, it should be given by the mouth or rectum. Milk is usually regarded as the mainstay, but owing to its comparative richness in fat it is not really suitable, and is often much disliked by the patient. Barley water flavoured with lemon is preferable, with the white of an egg and a teaspoonful of Plasmon to each ½ pint. Tea is usually forbidden, though it is difficult to see on what grounds; jaundiced patients often crave for it, and if made in the Russian fashion without milk, but with a slice of lemon in it, seems free from objection. If the practitioner feels reluctant to abandon milk, it should be separated or thoroughly skimmed to get rid of as much fat as possible, and then a grain of sodium citrate added to each ounce of milk to diminish curdling. Benger's food made with water, calves'-foot jelly and lemon sponge can usually be taken without difficulty. Alkaline mineral waters may be given freely.

When the bile pigment has returned to the fæces in

obstructive cases, the patient feels much better, though still jaundiced; he can now get up and the diet should be cautiously increased. There is sometimes considerable depression during convalescence, for which strychnine and calumba may be given. Dilute nitro-hydrochloric acid in 10-minim doses is often recommended, but should not be given until all signs of obstruction have passed off.

For pruritus hot alkaline baths may be tried, or some of the following preparations: A lotion of 1 drachm of creolin and 1 ounce of glycerine made up with 10 ounces of water; an ointment of 20 grains of camphor, 30 grains of menthol and 1 ounce of vaseline; a dusting powder of $1\frac{1}{2}$ drachms of camphor, $\frac{1}{2}$ drachm of zinc oxide, and 1 ounce of starch powder; a paint or inunction of $2\frac{1}{2}$ drachms of ichthyol, 3 drachms of absolute alcohol and ether to 2 ounces. Other preparations which may help are superfatted ichthyol salicylic acid soap, or 10 per cent. of anæsthesine in olive oil. As explained in Chapter I, thyroideum siccum in $\frac{1}{2}$-grain doses may help by diminishing the formation of bile salts.

CHAPTER VI

URIC ACID AND RENAL CALCULI

Purin Metabolism.

We can only form an opinion as to the part that uric acid and allied substances play in disease by studying their normal behaviour in the body. Uric acid is a subject which has a peculiar fascination for the lay mind, and our patients often seek or wish to impart information concerning it. Again there is something about uric acid, as there is about alcohol, which seems to turn the mildest-mannered man into a heated partisan. The widest differences of opinion formerly prevailed, but most authorities now regard purins as by-products of metabolism which are harmless to the majority of individuals.

What are Purin Bodies?—Fischer gave the general name of purins to bodies containing the nucleus C_5N_4, which will yield two urea molecules on oxidation. Only twelve different purins are known to exist in nature, though 146 have been prepared in the laboratory. The most important ones are:

Oxy-purins	Hypoxanthin ...	$C_5N_4H_4O$
	Xanthin	$C_5N_4H_4O_2$
	Uric acid	$C_5N_4H_4O_3$
Amino-purins	Adenin	$C_5N_4H_4NH$
	Guanin	$C_5N_4H_4O.NH$
Methyl-purins	Theobromine ...	$C_5N_4H_2(CH_3)_2O_2$
	Caffein and thein ...	$C_5N_4H(CH_3)_3O_2$

The source of urinary purins is partly from the food (exogenous), and partly from the tissues (endogenous).

1. *Exogenous Purins.*—We take these substances in, as:

(*a*) Methyl-purins in tea, coffee, and cocoa.

(*b*) Free purins, such as xanthin and hypoxanthin, in meat extracts.

(*c*) Bound purins. Nuclei yield purins in their decomposition. The more cells a food contains the more nuclei it has, and therefore the more purins it yields. Accordingly, cellular organs, such as liver and sweetbread, are a great source of purin intake. Ordinary meat contains much less, with the exception of rump-steak; while fish, with the exception of salmon, contains but little. The amount in other articles of food is almost negligible.

It will be seen, therefore, that the practice of distinguishing between red and white meats in dieting a gouty patient is apparently unsound if it is regarded as a method of regulating his purin intake. To cut a patient off mutton and give him chicken and sweetbread hardly achieves the object that is presumably in view.

Adler claims, however, that white meats lose their extractives more readily on cooking than do red; thus, veal loses four-fifths of its extractives, while beef loses hardly any. Incidentally, the result of this must be that veal broth is laden with purins.

2. *Endogenous Purins.*—Even on a purin-free diet the urine contains purin bodies, so that some must come from the body tissues. Though the form of the purins may vary, the total remains fairly constant for the same person living under the same conditions, and amounts to about 0·2 gramme of purin nitrogen daily. An important source seems to be the leucocytes and the muscles. During exercise less uric acid and more xanthin and hypoxanthin are exerted. But after exercise, especially of an unaccustomed form, there is a considerable rise in the uric acid excretion. Graham and Poulton believe that purins are synthesized from proteins and carbohydrates, for a diminished intake of either leads to diminished formation of endogenous purins.

This accords with the clinical experience that excess of carbohydrate is bad for gouty subjects.

The Effect of Ingestion of Purin Bodies.—Although uric acid was formerly regarded in many quarters as definitely poisonous, it is a normal constituent of our bodies, and in leukæmia as much as 5 grammes of uric acid may be excreted in a day from the leucocytes. If uric acid is a direct poison, why does it not produce symptoms in leukæmia similar to those of 'uric acid diseases'? Again, in chronic nephritis uric acid is retained in the circulation but need not produce gout.

History of Purins after Ingestion.—After excision of a dog's kidneys, no uric acid or other purins can be found in the blood even on a diet rich in purins. This seems fatal to the hypothesis of 'retention' of uric acid as a factor in gout. Something must be able to destroy purins, probably intracellular ferments in the liver, since extracts of that organ cause uricolysis both *in vitro* and *in vivo*; while if the liver be excluded from the circulation, the uric acid in the blood and urine is increased. Such food purins as appear in the urine must have escaped by the kidneys before they could be destroyed in the liver. The more rapidly excretion is going on the more purins are removed before they can be oxidized. An example of this is seen on comparing the urine in a case of failing heart with that of subacute nephritis. In both the urine is concentrated, but in the former it is loaded with urates, while in the latter the urates are diminished, because, the excretory cells being damaged, and not merely congested, the liver can destroy purins more completely before the kidney can excrete them. But, further, in heart failure the basal metabolic rate is increased and hence more urates are formed, while in renal disease, on the other hand, their excretion is interfered with.

Purins and Gout.—The upholders of the uric acid theory of disease assume that the body can deal with its endogenous

purins, but is poisoned by ingested purins. There is little in the history of purin metabolism to support this view. We have seen that there may be a great increase in uric acid production without gouty symptoms, and that a healthy liver has a great power of destroying purins. Moreover, a vigorous reaction of the body to infection is marked by an increased production of purins, and it is probable that the increased output of purins after giving meat extract is simply due to the leucocytic reaction it induces. The excretion of uric acid is greatest in the early waking hours of the day, and least during the night. In other words, its excretion runs parallel with bodily activity.

We may look upon a person who is readily poisoned by purins in the same light as those who have cystinuria, alkaptonuria, or pentosuria—*i.e.*, they all lack a link in the chain of protein katabolism, so that intermediate products appear in the urine instead of the usual end-products. The curious point about the man who cannot metabolize purins is his fixed belief that the rest of mankind suffers from a similar incapacity. Hence the elevation of the purin-free diet to the dignity of a cult.

If food purins lead either to a uratic deposit in the tissue or to a high purin output, it is a sign of hepatic insufficiency rather than the cause of disease. Amid all the confusion that reigns on the pathology of gout we can hold to the two definite facts established by Sir Alfred Garrod: in gout there is an excess of uric acid in the blood, and during the paroxysm a diminished output of uric acid in the urine. We may add that there is a retardation in the excretion of exogenous purins. The whole reveals a deficiency in the capacity of the body to katabolize purins. Mere retention of purins will not *cause* gout. Uric acid can always be demonstrated in normal blood or lymph; in gout the amount is increased, anything above 3·6 milligrammes per cent. being regarded as definitely pathological. Gouty individuals

seem to possess some acquired or inborn defect of nuclein metabolism which lowers the resistance of the tissues, permitting response to an irritant which scarcely affects ordinary mortals. Llewellyn made out a strong case for this irritant being an infection of low virulence. It is well known that gout is most likely to make its first appearance in an injured joint.

It is only reasonable in such cases to diminish the intake of substances which are not necessary as foods, and which tax the liver to metabolize them, and the kidney to excrete them. The modern conception of the source and history of purin bodies should diminish our ardour in trying to wash uric acid out of the system. 'Much therapy is directed against this necessary result of nuclein metabolism,' but, as a matter of fact, most drugs have an insignificant effect in increasing the elimination of uric acid and its allies.

Water, by producing diuresis, certainly increases the output. It is chemically impossible that *lithium salts* can have any such effect. We know that chemical action is determined both by the mass and the avidity of the various interacting bodies, but also that, if in any mixture of acids and bases an insoluble salt can be formed, it will be formed. In face of this, what can be the use of a few grains of lithia introduced into the body to combat an amount of sodium which, in addition to all the advantage of mass reaction, forms the less soluble salt?

The action of *alcohol* is complicated. With malt liquors there is an actual intake of purins, while in all cases alcohol leads to diminished solubility of purins.

Salicylates can cause a very markedly increased output—sometimes as much as 50 per cent. But it is not a little disturbing to find that this increase will occur even after a purin-free diet has been taken for years. There are three possible explanations:

1. That salicylate washes out retained uric acid. But

since the liver rapidly destroys uric acid, retention does not occur, and therefore washing out cannot be effected.

2. That the drug causes increased katabolism of the tissues. But the increase is too great, and no marked loss of weight occurs on administration of salicylates such as this hypothesis would necessitate.

3. That it causes synthetic production of purins in the kidney. This is the most probable explanation. It would appear ironical if, in their enthusiasm for 'washing out' uric acid, those to whom it is anathema are merely increasing its production.

Cinchophen, which is put up under the names of *atophan*, *quinophan*, or *phenoquin* (2. phenylchinolin, 4. carbonic acid), is a phenol derivative which definitely increases the output of uric acid. When it is taken by a healthy individual, the excretion of uric acid even on a purin-free diet rises at once, and then slowly falls, returning to normal by the third or fourth day. When uric acid is injected into a normal man, its excretion is spread over several days, and the total amount injected is not recovered. But if the injection is given during a course of cinchophen, the excretion of uric acid is completed within twenty-four hours, and the whole amount is recovered. In a gouty individual the same results are obtained (Walker Hall), so that under the influence of atophan the gouty and the healthy renal cell seem to excrete just the same amount of uric acid. Its administration appears to shorten the acute stage of gout, and is accompanied by increased uric acid output. So far as it goes, this might be held to support the retention theory. More probably, however, both retention and constitutional disturbances are due to the same unknown perversion of metabolism, and the drug affects the endogenous formation of purins. It is put up in tablets containing 7½ grains, three of which should be given in the day, broken up in plenty of water. Weintraud, who warmly recommended it, advised

full doses of sodium bicarbonate at the same time, such as ½ ounce on the first day, and 1½ drachms on subsequent days. The method is well worth a trial both in acute and chronic gout, but it should not be given for more than two or three consecutive days in each week. Toxic jaundice, even fatal, has followed its continued use. It is obviously contra-indicated in urinary calculus and gravel.

The use of *colchicum* in acute gout is purely empirical, but is undoubtedly often efficacious in the relief of pain. Dixon and Malden found that its active principle—colchicine—excited the nerve-endings of plain muscle, and that the number of leucocytes diminished at first, afterwards returning in increased numbers. It is probable that the exciting effect on plain muscle is responsible for the purgative action of colchicine, which may serve to eliminate some gastro-intestinal toxin, while the diminution of leucocytes, by diminishing the endogenous formation of uric acid at this juncture, may perhaps just tide over the metabolic difficulty. The return of the leucocytes in increased numbers would account for the failure of colchicum to exert a prolonged influence.

Prevention of Deposition of Uric Acid in Urine.—Though we can do comparatively little to increase the output of uric acid, we can and ought to check its deposit in the crystalline state in the urine causing symptoms of stone and gravel. Sir William Roberts showed the importance of high acidity and high percentage in causing this deposit.

Acidity is at its height during the fasting hours, and seldom is a marked feature during digestion, owing to the loss of acid by the gastric juice. It is usually sufficient to give 20 grains of *potassium citrate* night and morning to correct high acidity. There is, however, one precaution which seems important. If uric acid deposit has already occurred in the form of a calculus, rendering the urine strongly alkaline will cause growth of the calculus by accre-

tion of phosphates. The patient should therefore be told to put a piece of red litmus-paper into the morning urine. If it turns blue, the drug must be diminished in amount until this just does not occur. *Fresh fruit*, such as pears, green figs, dates, oranges, and grapes, have been shown by Smith Jerome to have a similar action in checking high acidity. Fresh fruit, however, does not seem to suit the gouty subject with a large formation of endogenous purins.

High percentage of uric acid may be absolute or relative —that is, the total output may be increased or the urine may be concentrated. Both may favour deposition. The former should be regulated by cutting off foods rich in purins, the latter by diluting the urine. Patients do not care to be ordered to drink plain water. *Potash water* is preferable to soda water, because of the relative insolubility of the sodium salts. But it is the water which is the chief therapeutic agent.

Certain waters, such as those of Contrexéville, have a high repute for washing out uric acid. It has been questioned, however, whether the treatment at Contrexéville does not increase the endogenous formation of uric acid; whether, in short, as Goodhart said, the gravel passed is not manufactured on the premises. But an alkaline mineral water will help to prevent deposit of gravel both by diluting the urine and by rendering it less acid.

Gee pointed out the extraordinary effect of *whey* in preventing uric acid deposits, and there is no doubt as to this fact. A breakfastcupful should be given twice or thrice a day.

To sum up, uric acid is merely one, and one of the less toxic purin bodies. The purins come mainly from the foods, but partly from the tissues. The food purins are largely destroyed by the liver in health. The tissue purins are increased by leucocytosis and muscular activity. Though we can control the intake of food purins, we have very little

control over the tissue purins. For the ordinary individual, purins have hardly any toxic action. The gouty subject seems unable to metabolize his purins properly, and his kidneys excrete them too slowly. The inadequate metabolism leads to toxic symptoms, and the inadequate excretion to uratic deposit. It is still unknown what causes this inadequacy. Most of the drugs supposed to wash out uric acid from the system are incapable of doing so. Cinchophen and salicylates, especially the former, will definitely increase the excretion of uric acid. It is reasonable to diminish the purin intake in individuals whose power of metabolizing purins is defective, but probably in many cases much of the good done is simply due to reducing the quantity of food eaten by making it monotonous. Deposit of uric acid in the urinary tract can be diminished or prevented by diluting the urine and rendering it less acid.

The Basis of Urinary Calculi.

Deposits of calcium salts, whether oxalates, phosphates, or carbonates, may occur in the urine under varying conditions, having a widely different significance. Physiological considerations may help us rightly to appraise these, and may point out a line of rational treatment.

Urinary calculi are mixtures of crystalloids and colloids. This fact seems to explain their comparative insolubility, since the colloidal precipitate, which forms an essential part, is 'irreversible'—*i.e.*, does not redissolve on being placed in non-saturated solutions. The ordinary colloids in the urine, such as urochrome and mucin, are reversible, but, according to Schade, in certain pathological, and especially inflammatory, conditions, fibrinogen or fibrin, typical irreversible colloids, appear. In these instances inflammatory reaction is a necessary precursor of a calculus. In hyperparathyroidism, however, large deposits of 'stag-horn' calculi

composed of calcium salts may occur in the pelvis of the kidney as the result of disordered metabolism.

Benjamin Moore maintained that the discrepancy between the expected and actual solubility of calculi is due to a misconception as to their composition. This has generally been assumed from their appearance or from a partial and qualitative examination only. In this way the tradition has grown up that calculi are most commonly composed in the main of uric acid and urates. The striking murexide reaction is easily obtained if there be present only a small quantity of these substances. But complete quantitative examination of a series of twenty-four calculi removed by operation showed calcium oxalate to be the most frequent constituent of their centres. This forms another useful warning against the tendency, so common in medicine, towards unquestioning acceptance of traditional statements, which are copied from one textbook into another.

It is of little consequence whether a degenerated kidney cell or micro-organism forms the nucleus around which a renal calculus grows, or whether it starts spontaneously, since it is only a certain type of disordered metabolism, producing insoluble salts of calcium, which can keep it growing.

Moore laid curiously little stress on the fact that oxalates were the most abundant of the calcium salts in the majority of his cases, regarding this as merely due to their greater insolubility. The treatment he suggested was to diminish the intake of calcium salts by forbidding milk, things made with milk, wholemeal bread and oatmeal. But the conditions leading to an increased excretion of oxalates are also worthy of consideration, since they probably play as important a part in the formation of calculi as the base with which they are combined.

Swift Joly has emphasized the great importance of diet and of the prophylactic value of vitamins therein contained,

especially of vitamin A in all types of calculus formation. An interesting comment on this is the change of incidence in the occurrence of renal calculi during the eighteenth century. Prior to this, owing to the authority of Galen, the upper classes took little fruit or vegetables and suffered from renal calculi in consequence. When they began to eat them the lower classes got less of such foods and a reversal of the class incidence of calculi followed.

Oxaluria.

The urine contains substances which have been introduced with the food (exogenous) and substances which have been formed within the body (endogenous).

The origin of oxalates from the food is clear; their formation within the body is not so easily proved.

Small quantities of oxalates are normally present in urine, but they only have any clinical significance when they are deposited as calcium oxalate in envelope or, less commonly, dumb-bell crystals.

Sources of Urinary Oxalates—(a) Ingestion of Oxalates in the Food.—Rhubarb (which contains 0·24 per cent. of oxalic acid), spinach (0·32 per cent.), sorrel (0·36 per cent.), and strawberries, in our experience, are most prone to produce oxaluria in sufficient amount to cause symptoms. But many other articles of diet contain oxalates—*e.g.*, figs, potatoes, beetroot, French beans, tomatoes, plums, tea, coffee, and cocoa.

On the other hand, peas, asparagus, mushrooms, onions, lettuce, rice, cauliflower, pears, peaches, grapes, melons, wheat, and oats contain little or no oxalates.

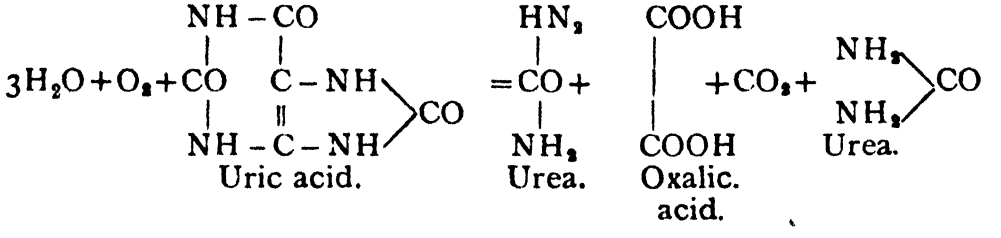
Helen Baldwin's *oxalate-free diet* is composed of meat, milk, eggs, sugar, butter, wheatmeal, rice, and biscuits.

The greater part of the oxalates in the food are in the form of the insoluble calcium oxalate. This can hardly be absorbed as such, but is decomposed by the acid of the

gastric juice, which accordingly seems to influence the absorption of alimentary oxalates. Thus, if there is no hydrochloric acid in the gastric juice, there may be no oxalates in the urine, even if spinach be eaten; but on giving hydrochloric acid by the mouth oxalates will appear. Similarly, we may reduce these alimentary oxalates by giving alkalies.

(*b*) *Dyspepsia.*—It is curious that oxalates will appear under precisely opposite conditions—when there is no hydrochloric acid. But as the oxalates are then presumably formed in the gastric contents, this amounts to ingestion as the source of the oxaluria. Thus Baldwin produced oxaluria in dogs by feeding on meat and excess of dextrose. A mucous gastritis with absence of free hydrochloric acid resulted, and oxalic acid was found in the gastric contents. The organic acid here provided for its own absorption. It also appears that oxaluria may similarly result from chronic pancreatitis.

(*c*) *Endogenous Formation.*—In the laboratory decomposition of uric acid results in the formation of oxalic acid.



A similar change has been assumed to occur in the body. Uric acid is extensively decomposed in the liver. If uric acid is perfused through an excised liver, oxalic acid is formed. If the metabolism of the liver is incomplete, it is easy to suppose the central carbon chain of the uric acid is not completely oxidized, when oxaluria would result.

However, several observers (Dunlop, Baldwin, Rendle Short) have been unable to find any oxalates in the urine on a milk diet, while others have found traces. We may con-

clude that endogenous formation does not occur in sufficient quantity to produce a deposit of oxalates, which is usually the result either of ingestion of food rich in oxalates or of fermentation resulting from excess of carbohydrate diet.

The body has considerable powers of dealing with oxalic acid. Esbach took as much as 6 grammes without inconvenience, and though it is almost certain that not all of this could have been absorbed, 0·181 gramme was found in the urine. Minkowski believed that, when once absorbed, oxalic acid does not undergo further oxidation.

Symptoms—(*a*) *Urinary Irritation*.—Most cases only show this. They are most frequent in the strawberry season, especially if the weather be very hot, so that the urine is also concentrated. We would suggest that there are several factors at work here. Strawberries contain oxalates, cream tends to dyspepsia, and the sugar by its fermentation produces more oxalates.

Micturition becomes painful, and is followed by prolonged smarting. Hæmaturia is not infrequent. Envelope crystals are found abundantly in the urine. In some people such symptoms may occur whenever they eat rhubarb.

Albuminuria is often associated with oxaluria, probably from mechanical irritation of the kidney by the calcium oxalate crystals. That actual hæmaturia occurs in the severer cases supports this idea.

(*b*) *Oxalate calculi* may form; they are hard mulberry-stones, usually mixed with uric acid.

(*c*) *Remoter Symptoms*.—It follows, from what has been said, that fermentative dyspepsia will lead to oxaluria. The so-called 'remoter symptoms' and the oxaluria must be referred to a common cause. We must not regard the oxaluria as causing them. The nervous symptoms do not resemble those seen in oxalic acid poisoning at all.

Such symptoms often occur in crises, sometimes precipitated by worry or overwork, sometimes by some intercurrent

disorder. They consist of attacks of depression and lassitude, headache, smarting pains on micturition, and sometimes hæmaturia, neuralgic pains in the back, chiefly referred to the kidney. The patient often becomes hypochondriacal. This oxaluria is the index of a very low state of health (Gee). The following is an example:

A nervous, delicate, hard-working youth suffered from paroxysms of pain in the left side. Physical examination and a skiagram revealed nothing. The urine contained abundant crystals of calcium oxalate, but no albumen. The paroxysms generally came on if he overworked or took much muscular exertion; they left him fatigued and much depressed. Subsequently he had two attacks of hæmaturia, the second rather severe, and accompanied by much pain. A stone was suspected, and his kidney was explored, but nothing was found to account for the symptoms. He had no more hæmaturia, but some occasional attacks of pain.

Treatment of Oxaluria.—The recognized treatment is abstention from oxalate-containing foods and administration of magnesia, since the oxalates are more soluble in the presence of magnesia. Peas should be taken when in season, as they are poor in oxalates and rich in magnesia. For Klemperer and Tritschler showed that when the amounts of CaO and MgO in the urine were about equal, as long as the urine contained 0·02 per cent. of magnesia, the calcium oxalate remained in solution, probably owing to the formation of a soluble double salt. And although the amount of oxalate deposited is no guide to the total oxalate excreted, it is only the deposit which causes the urinary symptoms.

Potassium citrate is of service in two ways—

1. As a diuretic it dilutes the urine.

2. By combining with the calcium it prevents the formation of calcium oxalate crystals. Martin showed that citrate threw calcium out of action by forming a non-ionizable soluble double salt. It is well known that citrate prevents

the curdling of milk and the clotting of blood for this reason, and it has therefore been extensively used in the treatment of gastro-intestinal conditions.

It has been employed in oxaluria with success. Some observers prefer to employ lemon juice to sodium or potassium citrate, and claim that in phlebitis, at any rate, it is much more effective. Now, if we can tell our patients that they need not give up strawberries altogether if they will also drink lemon squash, we shall effect the desired object while avoiding irksome restrictions. A caution against much sugar while on this treatment should also be given.

In the nervous cases we must treat the digestive disturbance also, and direct attention to preventing fermentation of the sugar. A holiday and change of air is generally required.

Phosphaturia.

Normally phosphates are present in the urine as—

(*a*) Acid phosphates of sodium and potassium.

(*b*) Earthy phosphates of calcium and magnesium.

It is only the earthy phosphates that can form a deposit. This may occur—

1. In the bladder, so that the last portion of the urine is milky. This is often mistaken for spermatorrhœa; the patient becomes needlessly depressed, and falls an easy prey to quacks.

2. As an iridescent pellicle on the surface of the urine when it has been passed.

3. Only on boiling the urine, when acidification is necessary to prevent confusing it with albumen.

Calcium phosphate forms a deposit of stellar crystals, magnesium phosphate appears as rectangular plates with bevelled edges, while ammonio-magnesium phosphate ('triple phosphate') forms 'knife-rest' or 'coffin-lid' crystals.

The term 'phosphaturia' is somewhat loosely applied to

any condition in which these various deposits occur. But it is clear that such deposit does not imply any increase in the total output of phosphates, since in no circumstances will the sodium and potassium phosphates be precipitated, while the earthy phosphates will be deposited on adding any alkali to any urine. Quantitative estimation would be necessary to prove an increase. But in considering the total metabolism of phosphates, their excretion by the blood must be taken into account.

Usually phosphaturia is merely a sign of diminished acidity of the urine, which is one of the ways in which the hydrogen-ion concentration is kept constant. Therefore phosphaturia almost inevitably occurs when sodium bicarbonate is given freely.

Many organic salts, such as citrates and tartrates, become bicarbonates in the blood, and thus reduce the acidity of the urine. Phosphaturia may therefore follow a diet rich in fruit and vegetables, while meat diet by increasing the acidity of the urine helps to keep phosphates in solution.

Again, if there be cystitis, ammoniacal decomposition will lead to a deposit of phosphates which will take the form of crystals of 'triple phosphates.' The occurrence of 'knife-rest' crystals at once suggests cystitis. In one case the passage of these crystals had occurred with hæmaturia at intervals for over a year. Between the attacks the urine was quite normal; but a stone was ultimately found. Particularly copious deposits of triple phosphates may occur in staphylococcal infections of the bladder.

There is, however, a residue of cases where the output is increased from the normal 2½ grammes of phosphoric acid to perhaps 7 or 9 grammes. Here the earthy phosphates will probably be in excess. The ratio of earthy to alkaline phosphates, which is normally 1 to 2, may rise to 5 to 2.

Wasting causes an increased excretion of phosphates, because the disintegration of nucleo-proteins yields phos-

phates. Conversely, phosphates are diminished in the urine in pregnancy and in convalescence after fevers, because they are required for building up. Phosphaturia may, therefore, be merely a symptom of wasting for which sometimes no organic cause can be found. It may be due to anxiety or change of habits and environment. In such cases attention should be mainly directed to the general health and psychological outlook.

Marked phosphaturia may occur in cases of multiple myeloid tumours leading to the excretion of the Bence-Jones protein. No doubt this is in consequence of the earthy salts being set free by the destruction of the bones.

Treatment.—We must remember that phosphaturia is a symptom and not a disease.

1. If triple phosphates be present, seek a cause for cystitis and treat that.

2. If phosphaturia is associated with dyspepsia, the digestive condition requires treatment.

3. If it be associated with wasting, the cause of the wasting calls for attention.

4. If it be associated with depression, the fundamental treatment must be directed to the underlying psychological cause, but the patient is usually symptomatically benefited by giving him acids, preferably combined with tonics.

Now, phosphoric acid usually suits these patients well. If their symptoms were really due to phosphatic loss, this would hardly be the case, because there would already be excess of circulating phosphate, and the tissues could not discriminate between this and the administered phosphate. Moreover, on a fish diet, rich in phosphates but not acid, the phosphaturia will probably be aggravated. Therefore it is simply because it is acid that phosphoric acid does good, and it does not matter whether phosphoric or nitro-hydrochloric acid is given. But an inorganic acid should be given, and with it tincture of nux vomica.

If the deposit of phosphates makes the patient anxious, as it is apt to do, Soetbeer's method of diminishing the calcium intake may be used. Milk, eggs, fish, fruit, which contain a good deal of lime, are not allowed, while food poor in lime, such as meat, potatoes, and cereals, is given. The phosphates are then excreted in more soluble forms. As always when strict dieting is enjoined, care must be taken to secure an adequate supply of vitamins, if necessary in the form of concentrates or the pure substances.

It is an interesting point of contrast that neurasthenics tend to oxaluria when the urine is very acid, but to phosphaturia if the urine is not very acid.

Cystinuria.

Cystin is only an occasional constituent of urinary calculus. Its presence in more than minute traces appears to be due to an inborn error of metabolism (Garrod). It is an amino-acid containing sulphur and is contained in many proteins, being especially abundant in hair. The tendency to deposit hexagonal crystals in the urine is lifelong in some persons, and runs in families, more commonly in the males. Exceptionally the deposit of crystals has occurred in the tissues, imitating gouty tophi. Cystinuria is little influenced by diet, and indeed the patient can usually deal with large quantities of cystin given by the mouth. It is the endogenous metabolism which is at fault, the sulphur-containing fractions of the tissue proteins being excreted as cystin instead of being further decomposed. The excretion of cystin is often accompanied by a variable amount of diamines, such as putrescin and cadaverin, which are not normally present in the urine and probably originate in the same way from incomplete breakdown of the tissue proteins. A cystin calculus is yellow, turning green on prolonged exposure to light, somewhat translucent, with a crystalline surface, rather soft and friable in structure.

Cystinuria may continue for years without producing calculi, and indeed an additional factor appears to be required before this occurs. The additional factor is an infection of the pelvis of the kidney, very generally due to *B. coli*; then the inflammatory colloids are provided, which glue the crystals together into a calculus. To render the urine aseptic is therefore the first indication in the treatment of cystin calculi, in order to prevent increase in size. The only other suggestion as to treatment is based on the hypothesis that endogenous cystin should normally become the taurin of the bile salts, and that its excretion as cystin is due to lack of cholalic acid with which it can conjugate. Cholalic acid may therefore be given in cystinuria as the prophylactic against calculus formation. On the other hand, alkalies help to dissolve cystin when formed, but cannot check the formation of fresh crystals.

CHAPTER VII

ALBUMINURIA AND THE TREATMENT OF NEPHRITIS

THE causes of renal albuminuria may be classified thus:

1. Without definite structural change of renal tissue—
   (*a*) Toxic—*e.g.*, in fevers and any slight infection.
   (*b*) Anoxæmic—*e.g.*, from failing heart, or anæmia.
   (*c*) 'Functional.'
2. With definite structural change of renal tissue.

'Functional' Albuminuria.

This has also been called alimentary, postural, cyclic, adolescent, to mention only a few of the names. Alimentary albuminuria is extremely difficult to produce. Certain experiments by D'Arcy Power upon himself are usually quoted as evidence of its existence. It is true that albumen appeared in his urine on the first day of the experiment, after twelve eggs had been eaten, but it disappeared in the evening, and did not reappear till the afternoon of the third day, after the consumption of forty-eight eggs. It was found again during the evening of this day, after which it disappeared again, and had not reappeared at the end of the experiment, by which time sixty-five eggs had been taken. Only once was the albumen present in sufficient amount to enable its coagulation-point to be determined, so that there was very little connection between the number of eggs consumed and the amount of albumen. A significant point, which seems to have escaped notice, is that at this time D'Arcy Power was aged twenty-two, and that the occurrence of the albuminuria was always observed after a considerable amount of exercise had been taken. Now, tran-

sient albuminuria after severe exercise is common in young men, without excess of albuminous diet.

Collier found albumen present in the urine of every one of the Oxford crew of 1906 after rowing a course. In the case of half of them the amount of albumen was quite large, and in men who went in for running races the albuminuria was even more pronounced. In all these cases he found the urine passed in the early morning to be free from albumen. Such albuminuria may fairly be called 'physiological.'

'Functional' albuminuria without violent exercise is not an uncommon condition in males between puberty and marriage. Dukes found it in 16 per cent. of all the boys entering Rugby School at the ages of thirteen or fourteen. The strain of examinations seems to be a factor. Thus a young man who was working for an examination in physiology happened to test his urine. To his alarm, it was loaded with albumen. He took a holiday, and the urine soon became free from albumen. Some years later the albumen returned during an intercurrent illness, again disappearing when he recovered from it. He had no further trouble of that kind. This should be a reminder, however, that some milder forms of toxæmic kidney may be taken for physiological albuminuria, so that a search should always be made for toxic foci, such as septic tonsils or tuberculous glands.

Dukes said that boys who faint in chapel are almost certain to be albuminurics. Their hearts are often excitable, and the condition vaguely diagnosed in them as 'weak heart' is frequently due to this.

Dukes divided them into three classes:

1. By far the largest class exhibit an increased arterial tension in consequence of irritability of the vasomotor nerves. The tension is, however, so unstable that it varies from hour to hour and day to day. This he regarded as pathognomonic of the disease.

2. The next most extensive class comprises those who have cold, clammy, congested extremities, accompanied by a large, feeble, compressible pulse, arising from deficient vasomotor control.

3. The remainder are the spare, highly-strung, over-sensitive neurotics.

Presumably his first and third groups overlap to some extent.

Cold bathing is another factor in inducing transient albuminuria, presumably by driving of blood from the periphery into the splanchnic area. The name 'proteinuria would be more exact, as a good deal of it is globulin.

In the cases where albumen readily occurs without some special strain hyaline casts may be seen, and often calcium oxalate crystals. Posture has an important influence. Albumen is absent from the urine passed first thing on rising, because this was secreted while recumbent; but it appears in urine secreted while in the upright position. Kneeling is said to produce albuminuria readily in some subjects, and if it is true that the albumen then comes from one kidney and not from both, a mechanical factor seems to enter into its causation. The fainting and variable tension suggest a vasomotor element. A lax condition of the vasomotor system failing to compensate for the effect of gravity would interfere with both cerebral and renal circulation, at least temporarily. Observations of the blood pressure confirm this; whereas change of posture has only a small effect on the blood pressure of a normal person, there may be a difference of 40 millimetres between the pressure in the upright and recumbent position in these patients.

Facts such as these place vasomotor insufficiency as a factor in this form of albuminuria, to which the name 'orthostatic' may therefore fairly be applied.

The subjects of functional albuminuria have often been growing rapidly, so that there is an extra demand for cal-

cium on the part of the tissues. This provides us with a convenient clinical test for functional albuminuria. Fifteen grains of calcium lactate three times a day in water should control it. A possible fallacy is that the albumen often disappears spontaneously or is only present at certain times in the day. More systematic observations are required.

Prognosis.—Dukes, who probably had a unique experience of this condition, entirely abandoned his earlier opinion that it tended to organic kidney disease, for he found that his patients even thirty years later were robust men. In fact, he only found albumen subsequently in one of these cases, and that was in a boy who had only recently left school.

The question is one of great importance in connection with life insurance. At present the attitude of some offices towards albuminuria is still one of rejection or of heavy loading. Is this fair? This has been justified by some on the ground that the expectation of life is so much lower in albuminurics. Of course it is, if post-scarlatinal nephritis and other organic cases are included. They would naturally bring down the average. But has any attempt been made in such tables to exclude obviously organic cases? We believe not. If the early morning specimen of a patient under thirty contains no albumen or casts and there are no cardiovascular changes, it is now usual to regard the case as one of functional albuminuria which can be accepted at ordinary rates. The general practitioner can also fortify his patient against the ordeal of examination by administering calcium lactate if he so desires, and there can be no objection to his doing so; for he will not be able to secure the acceptance of sufferers from organic nephritis, but only of those who will almost certainly be free from albuminuria when adolescence is past.

Treatment.—Having assured ourselves, by examining the early morning urine, by excluding the presence of casts other than hyaline, and by noting the effect of posture on the

blood pressure, that the case is one of orthostatic albuminuria, the first step in treatment is to reassure the patient. He usually comes before us, after the shock of rejection or postponement of his proposal for life insurance, believing himself to be the subject of an incurable disease, and is naturally apt to become hypochondriacal. Next a tonic line of treatment and a holiday are indicated, and usually that is all that is needed.

Organic Albuminuria.

A nephritic kidney not only lets things pass out which it should retain, it also retains things which it should excrete.

Now the function of the kidney is to keep the composition of the blood constant. There are three factors—the urine, the kidney, and the blood; if any two of these are known, the third can be determined. Until lately the last of these has not been sufficiently taken into account. The problem is simplified by the fact that the kidney effects very little change in the material it excretes. Ambard pointed out that the kidney passes material into the urine in three ways: (1) Blood and lymph only appear when there is actual solution of continuity. (2) Alcohol, acetone, and the like escape by diffusion, without concentration occurring. (3) Urea and other normal as well as some abnormal constituents are secreted in a higher concentration than that in which they are present in the blood.

Purely waste products are excreted according to their concentration in the blood, while the kidney interposes a threshold in the way of the excretion of substances which are of use, such as sugar, sodium chloride, and hæmoglobin.

The kidney is composed of a number of elements, each consisting of a glomerulus with its capsule and the tubule issuing from it. To this unit the name *nephron* has been given. Not all the nephrons are working all the time. The view of renal secretion now usually adopted is that of

Cushny, who regarded the glomeruli as simple filters, while the tubules secrete back into the blood enough of the filtered water and salts to keep the composition of the blood constant. In addition to this, special mechanisms probably exist for the synthesis of ammonia and hippuric acid.

Under normal conditions the activity of the kidney may be increased either by calling more nephrons into use, which Verney terms its *structural reserve*, or by increasing the pressure in the glomeruli, which he calls its *functional reserve*. The vascular arrangement of the kidneys permits of variations in glomerular as distinct from general blood pressure. If the glomerular pressure is raised, filtration is more rapid and there is less opportunity for reabsorption by the tubules, so that the urine is copious, dilute, and approximates to a simple filtrate of blood plasma with a specific gravity of 1,009. If the glomerular pressure is low, the output of water is diminished and more time is given for reabsorption. The resulting urine is scanty, concentrated, and of high specific gravity.

Platt suggests that the œdematous (or 'hydræmic') syndrome in nephritis results from a low glomerular pressure and the uræmic (or 'azotæmic') syndrome from a high one. A slower filtration resulting from a low glomerular pressure may be met for a time by using more glomeruli, but the reabsorption by each tubule into the blood stream is increased because of this slower flow. Thus more salt and water are returned into the blood and retained there as œdema unless the fluid can be excreted by other channels. The total volume of urine will be decreased, but it will contain more urea and similar substances than usual. Even under such conditions uræmia can occur if glomerular pressure falls so low that the whole reserve of nephrons cannot produce sufficient filtrate. Such a condition occurs in cases bordering on anuria. Evidently retention of salt with its consequent raising of osmotic pressure of the tissues is not, as Widal thought,

the only or even the main cause of dropsy in nephritis, and may be the necessary consequence of the retention of water.

Epstein showed that a feature peculiar to subacute nephritis was a great reduction in the protein content of the blood which almost entirely affected the albumen and not the globulin. The daily drain on the protein may even amount to 10 per cent. of the total quantity in the blood. The osmotic pressure of the blood falls in consequence, giving the tissues the power to absorb and retain fluid. This tissue starvation is also shown by the high lipoid content of the blood, just as in advanced diabetes. That the blood serum may be milky in nephritis was noted by Bright, and subsequent observers have called attention to a similar condition in the ascites of this disease. The abstraction of these lipoids from tissue cells may allow of imbibition of fluid, with consequent swelling of cells, thus increasing the œdema.

In the condition known as *nephrosis* (which often goes on to nephritis) Shaw Dunn has found an abnormal dilatation of the renal capillaries, which, as Verney had previously suggested, would contribute both to massive loss of proteins through the glomeruli and to scanty secretion of urine because of the free reabsorption from the tubules. The lowered osmotic pressure of the blood resulting from this loss of protein is undoubtedly an important factor in the production of œdema, as Epstein maintains.

In the uræmic syndrome the destruction of nephrons by disease is compensated for a time by the raised glomerular pressure in those which remain. But eventually there are too few nephrons left, even when working at full pressure, to produce sufficient filtration. Then nitrogen retention occurs, and uræmia may follow.

To sum up, salt retention and protein depletion with resulting dropsy and lipæmia are the principal features when glomerular pressure is low; nitrogen retention and cardiovascular changes when nephrons are being destroyed.

Formerly the orthodox, conventional treatment of chronic nephritis included the following principles:

1. Severe restriction of protein intake with exclusion of food rich in albumen, such as eggs; in bad cases absolute restriction to simple milk diet.

2. The estimation of the amount of urea in the urine as a guide to the capacity of the kidney.

3. Stimulation of the kidney to increased excretion by the use of diuretics.

4. Elimination by the skin by various diaphoretic measures.

5. Elimination by the bowel.

We venture to assert that each of these principles except possibly the third requires drastic revision in the light of recent work.

1. **Severe Restriction of Protein Intake.**—When we proceed to limit the protein diet rigidly in Bright's disease, are we not led away by false analogies with diabetes? Whereas there are the following essential differences:

(1) The sugar can be replaced by other things in a diet, while the protein cannot.

(2) The sugar excretion is preceded by an excess of sugar in the blood; albuminuria is not preceded by excess of albumen in the blood. The latter is due to a kidney lesion, the former is not.

(3) In Chapter V it is pointed out that there is a great breaking-down of the protein molecule into its constituent groups before it is absorbed into the body. The simple conception of Liebig, according to which the protein food is simply hydrolyzed into peptone, and then assimilated into the tissues with no further change than dehydration, is no longer held.

It has been well said that, just as a Gothic cathedral could not be built out of a classical temple without reducing it to its constituent stones, so the protein of the tissues cannot be

built out of the protein of the food without splitting it up into its simple constituent groups.

There is, therefore, no satisfactory proof that albumen is absorbed as such, and is able to run through the body; consequently, it is difficult to believe that the protein of the diet can directly influence the degree of albuminuria.

One of us tested this point several times by estimating the albuminuria on varying diets and comparing it with the urea and total nitrogen excreted. He found that the addition of three eggs to the diet did not really affect the albuminuria in cases of subacute nephritis.

We know now the physiological minimum of protein is much less than the 100 to 125 grammes formerly ordained. From observations on himself, his assistants, students, and a squad of soldiers, Chittenden concluded that weight and nitrogenous equilibrium could be kept up on 50 to 60 grammes protein a day or even less, with no diminution, but rather an increase, of physical and mental fitness.

He certainly proved a point of great interest and importance—that the minimum protein requirements of the body are much less than was supposed. But he went much further, and maintained that the minimum is also the optimum. To consume protein in excess of that required for the repair of the tissues he regarded as a physiological sin, the wages of which is migraine in earlier and cardiovascular degeneration in later life. He gave no evidence of this, but assumed that a liberal nitrogenous diet overtaxes the kidneys by which it has to be excreted. Why he assumed that the kidneys are unable to do more than the minimum necessary without damage to themselves is hard to see. It might as well be asserted that the deeper breathing necessitated by reasonable exercise dangerously overtaxes the capacity of the lung to excrete CO_2, and tends to asphyxia. He was, in fact, obsessed with the old idea that the body is unable to make any other use of protein food than to repair tissue

waste—an idea which other lines of work have rendered improbable. The physiological minimum is not necessarily the physiological optimum. Experience goes to show that when there live, side by side, a race living on a protein-rich diet and one on a protein-poor diet, such as Europeans and natives in India, the morbidity and mortality of an epidemic are much higher in the latter. The rapid rise of Japan corresponds to the adoption of a more liberal nitrogenous diet. To this Chittenden answered that prosperity causes an individual or a race to elaborate the menu, that the increased food is not the cause of the improvement.

Of our protein diet very little is used for direct repair of tissue waste, but doubtless much of the rest is used as a source of energy, and it is at least probable that the ammonia groups set free from this protein excess are useful in neutralizing acids which might otherwise lead to acid intoxication; moreover, protein in moderate excess of minimum requirements gives the tissues a wider choice of building material from which to select. In Hutchison's phrase, protein is one of those things of which it is necessary to have too much in order to have enough. Indeed, some 'first-class' protein is essential to life.

2. **Urea Estimations as a Guide to the Renal Capacity.**—When we give a normal individual an excess of protein food, he turns it into urea, and excretes it as quickly as possible. For this reason the amount of urea secreted in the day gives very little information as to the severity of a case of Bright's disease, unless the diet is carefully taken into consideration.

The procedure still adopted, especially at some foreign spas, is irrational. A man with chronic nephritis on a restricted diet has his urea estimated. Instead of the normal 30 grammes, he is found to be passing, say, only 16. The physician concludes that the capacity for urea excretion must be seriously decreased; the patient must take less nitrogenous food. This is done, and the next analysis

shows an even lower urea excretion. 'Worse and worse,' thinks the physician; 'this man is only fit for a milk diet.' Accordingly he is given 3 pints of milk a day and nothing else. He now bids fair to fulfil the gloomy prognosis formed; unless he fortunately rebels against this pitiful fare, and takes the law into his own hands. For, as the greater part of the urea comes direct from the food, the more the nitrogenous food is restricted the less urea will be excreted.

It is essential to know the amount of urea in the blood. This should normally lie between 20 and 50 milligrams per cent., although the latter figure would be rather high before middle life, and certainly too high in pregnancy. If the blood contains no excess of urea, we can safely permit a much greater variety in the diet than is allowed on orthodox lines. We should naturally avoid meat extracts and cellular foods, such as sweetbread, because they contain a large proportion of purins, which have to be excreted by the kidney, and this, when damaged, has difficulty in dealing with uric acid at any rate. If there is dropsy, the intake of salt should be somewhat restricted. Indeed, as Bryant found, even a healthy man with a healthy heart and kidneys may develop œdema as the result of taking excess of salt. The substitution of lemon juice will usually satisfy the patient. The amount of fat should also be cut down.

But Epstein would go much further than this. He would give a liberal protein diet in such cases in order to make good the drainage of albumen into the urine. His diet is selected from the following: lean veal, lean ham, whites of eggs, oysters, gelatine, Lima beans, lentils, split peas, green peas, mushrooms, rice, oatmeal, bananas, skimmed milk, tea and cocoa. He gives 120 to 240 grammes of protein, 20 to 40 of fat (unavoidably present in other foods), and 150 to 300 grammes of carbohydrate; with this 1,200 to 1,500 c.c. of fluid and enough salt to make the food palatable are allowed.

At St. Bartholomew's Hospital the following simple

modified diet to fulfil Epstein's indications has been used with benefit in suitable cases:

MODIFIED EPSTEIN DIET.

Solids.	*Fluids.*
Breakfast:	Tea, 250 c.c.
Egg, 1, boiled or poached.	Milk, 25 c.c.
Bread.	Sugar, *q.s.*
Jam.	
Lunch:	Tea, 250 c.c.
Bread and jam.	Milk, 25 c.c.
	Sugar, *q.s.*
Dinner:	
Lean meat, 50 to 100 grammes.	Lemonade, 250 c.c.
Potato.	
Greens.	
Fruit.	
Tea:	
Egg, 1, boiled or poached.	Tea, 250 c.c.
Bread.	Milk, 25 c.c.
Jam.	Sugar, *q.s.*
Supper:	
Lean meat, 50 to 100 grammes.	Lemonade, 250 c.c.
Bread.	
Tomato.	

Three times a day and once during night: Lemonade or Water, 250 c.c.

Although not prepared to agree with all Epstein's conclusions, we are convinced that he is right in saying that a salt-free diet is not always successful in abolishing œdema, and that a diet rich in protein is sometimes more successful. It is probable, indeed, that the disappearance of œdema may be due to the diuretic effect of the urea to which this diet gives rise as much as to its increasing the blood proteins, since there is no evidence that one can directly increase these by food proteins. And again, the œdema of acute nephritis can hardly be due to reduction of blood protein, since it comes on at a time when the total volume of the urine is too small to have affected this seriously.

Maclean and de Wesselow introduced a urea concentration test, which is of definite value. It is now carried out in a slightly modified form as follows: Fifteen grammes of urea dissolved in 100 c.c. of water and flavoured with a little tincture of orange are given to a patient first thing in the morning just after he has emptied his bladder. The urea in the urine passed two and three hours afterwards is estimated by the hypobromite method. If this amounts to more than 2 per cent. in the first specimen the kidney is efficient in concentrating power. Sometimes the diuretic action of the urea leads to dilution of the urine, but as this will have passed off by the end of the first hour, the specimens passed two and three hours after will give a more accurate estimate. Less than 2 per cent. of urea in these specimens connotes kidney damage. When serious nitrogen retention is suspected it is better to have the urea estimated in the blood before trying this test. Subject to these limitations it is a useful test, but Van Slyke's clearance test is regarded as an improvement. In principle it is based on the relation of the concentration of urea in the blood and urine respectively. The result is expressed as c.c. of blood cleared of urea per minute. A simple yet useful test is to take the specific gravity of every specimen of urine passed during 24 hours while the patient is on his normal diet, with no excess of fluids. Failure to excrete a specimen with a specific gravity of more than 1,012 suggests a failure of the concentrating power of the kidney.

When the concentrating power of the kidney is good, 45 to 60 grains of urea may be given three times a day in dropsical nephritis while the patient is on a diet which is not excessive in proteins, but is poor in fats. When urea retention is present a high protein diet is inadvisable, even if the patient can metabolize it, because he is getting the energy in a form that throws work on to the damaged excretory organs. What is the happy mean? We suggest that it can be arrived at thus:

Chittenden's diet gives us the physiological minimum of protein. As the amount of protein in the diet has no appreciable effect on the amount of albumen in the urine, a patient with nephritis would not be able to maintain his nitrogenous equilibrium on Chittenden's diet. We can add an amount of protein equal to the albumen lost in the urine,* when we shall be giving just enough to maintain equilibrium and yet not be taxing the kidney by calling upon it for any unnecessary work.

Von Noorden finds, clinically, that the chronic nephritic can easily excrete up to 15 grammes of nitrogen in the day, but above this elimination becomes irregular and uncertain. Fifteen grammes of nitrogen corresponds to 94 grammes of protein, and this is the maximum that should be allowed, while the minimum is about 60 plus the amount of albumen in the urine. Thus the theoretical and clinical results agree fairly closely.

In the epidemic of war nephritis one of us found the diets given below useful. The low nitrogen diet is for cases with nitrogen retention, while the moderate nitrogen diet is for the convalescent stage.

1. LOW NITROGEN DIET.

	Solids.		*Fluids.*	
Breakfast:				
Milk	4 ounces	Coffee	10 ounces	
Porridge	8 „	Milk	2½ „	
Bread	2 „			
Butter	¼ ounce			

* A convenient rule is this : When the reading of the albuminometer is 5 and the amount of urine is 2 pints, the patient is excreting as much protein as is contained in one egg. We take these figures because they admit of simple proportional calculation, and also because they represent the amount of albumen excreted in a case of nephrotic nephritis of average severity—*i.e.*, 6 grammes, which is the amount of protein in one egg.

Solids.		*Fluids.*	
Lunch:			
Bread	3 ounces	Milk	5 ounces
Butter	½ ounce	Barley water ...	10 ,,
Lettuce or tomato ...	1½ ounces		
Dinner:			
Potato	4 ounces	Lemonade, Imperial drink, or barley water	12 ounces
Greens	5 ,,		
Butter	¼ ounce		
Stewed fruit ...	4 ounces		
Boiled rice	4 ,,		
Tea:			
Bread	3 ounces	Weak tea	10 ounces
Butter	½ ounce	Milk	2½ ,,
Lettuce or tomato ...	1½ ounces		
Supper:			
Potato	4 ounces	Lemonade or barley water	12 ounces
Butter	¼ ounce		
Greens	5 ounces		
Stewed fruit ...	4 ,,		

This contains:—

Protein	49 grammes
Carbohydrate	358 ,,
Fat	35 ,,
Calorie value	1,992

2. MODERATE NITROGEN DIET.

Solids.		*Fluids.*
Breakfast:		
Egg	1 ounce	As No. 1.
Bread	2 ounces	
Butter	¼ ounce	
Lunch:		
Bread	4 ounces	As No. 1.
Butter	½ ounce	
Tomato or lettuce	1 ,,	
Dinner:		
Mutton or fish ...	3 ounces	As No. 1.
Bread ... ... (alternate days)	2 ,,	
Butter	½ ounce	
Stewed fruit ...	4 ounces	

	Solids.	*Fluids.*
Tea:		
Bread	4 ounces	As No. 1.
Butter	½ ounce	
Tomato or lettuce	1 ,,	
Supper:		
Greens	2 ounces	Milk ... ... 5 ounces
Potato	3 ,,	
Bread	4 ,,	
Butter	½ ounce	
Stewed fruit ...	4 ounces	

This contains (on average):

Protein	63 grammes
Carbohydrate	407 ,,
Fat	91 ,,
Calorie value	2,772

The rules which guide us in *acute nephritis* or in exacerbations of chronic nephritis are somewhat different, however.

As von Noorden pointed out, in the acute stage we concentrate our attention on the diseased organ, whilst in chronic cases we keep the general condition of the patient more in view. Nitrogen retention is a very prominent feature of acute nephritis, and a diet poor in nitrogen is strongly indicated. This period of retention is usually short; if it continues, it is very ominous. A few days' comparative nitrogen starvation will do no harm, and may avoid grave danger.

Von Noorden is of opinion that in acute and dangerous cases this is very necessary, and gives nothing but sugar, water, and fruit juice for from three to eight days.

3. **The Use of Diuretics in Bright's Disease.**—There has always been a tendency to regard 'flushing out' the kidney as a good line of treatment in Bright's disease; but before employing it we should consider what method of diuresis we mean to employ, how far such methods are desirable in the case before us, and how far they will achieve the end desired.

Routine and indiscriminate 'flushing out' is to be deprecated.

Methods of producing Diuresis.—The following are possible:

1. *By vaso-dilatation in the kidney,* as by the caffein group of drugs. These probably act as direct stimulants to the renal epithelium, the vascular changes being secondary. But the present feeling is against using such drugs as caffein, theocin and diuretin to stimulate a damaged structure. They were formerly used chiefly in subacute nephritis, and not infrequently hæmaturia followed. Therefore they should be only used where the kidneys are not organically diseased but diuresis is required.

2. *By vaso-constriction elsewhere,* in consequence of which the blood pressure is raised and more blood is forced through the kidneys. Digitalis was formerly held to act in this way, but it is now considered that its diuretic effect is purely secondary to its action on the heart, so that it can only be useful in nephritis when there is cardiac insufficiency as well.

3. *By increasing the quantity of circulating fluid*—(*a*) by absorption of water from the intestine, as by giving the patient large quantities of fluid to drink; (*b*) by increasing the osmotic pressure of the blood, thus attracting water from the tissues into the blood stream. The saline diuretics, citrates, acetates, etc., act in this way. This method is less open to objection in acute nephritis. Citrate of potassium renders the urine less acid and, therefore, less irritating to the kidney. As the extra water is drawn from the tissues it will tend to diminish, and cannot increase, the œdema. It has been shown that rendering the urine alkaline materially reduces the incidence of acute nephritis in scarlet fever. Though the reason for this is obscure, the fact is sufficiently proved to warrant that treatment as a routine.

4. *By diminishing reabsorption through the renal tubules.*

The newer diuretics such as salyrgan probably act in this way, and though there is some difference of opinion as to this, there is no doubt as to their efficacy. Their action is increased by giving 15 grains of chloride or nitrate of ammonium three times a day for 2 days prior to the injection of 1 c.c. of salyrgan, or the insertion of a suppository of novasural. Caution in their use is needed in nephritis.

It will be seen from this that the field of usefulness for diuretics in the treatment of nephritis is decidedly limited.

4. **Elimination by the Skin.**—This method of treatment is open to the following objections:

(*a*) Only 3 grammes of nitrogen can be got rid of through the skin in the day compared with 8 grammes that can be more easily eliminated by the bowel.

(*b*) Physiological rest for the kidney is not secured by giving it a highly concentrated urine to deal with, for defective adjustment of the kidney to varying concentration of the urine is a prominent feature of azotæmic nephritis.

(*c*) Diaphoresis is an exhausting process and may depress the heart. The use of drugs for this purpose such as pilocarpine is highly dangerous.

(*d*) The withdrawal of so much fluid without a corresponding removal of organic solids must increase the concentration of the toxins in the circulation.

If, therefore, it is decided to employ diaphoretic measures, it should be after fully weighing these objections as applied to the particular case. It has been urged in support of this method of treatment that, after a hot-air bath, the patient may be actually covered over with small crystals. These crystals, however, in the main, do not consist of urea but of sodium chloride; and here we have the clue to the kind of case in which diaphoresis will be of service—namely, that in which there is a retention of sodium chloride in the tissues with œdema, although chlorides may be diminished in the blood. The elimination of salt by the skin may therefore be

of indirect service by breaking a vicious circle. In cases thus treated diaphoresis may be actually followed by diuresis. We may conclude that the hot-air bath is only suitable when dropsy is present.

To sum up, the kidney, once damaged by chronic nephritis, cannot entirely recover, and the only thing which can be done is to attune the mode of life to a low key, subjecting the patient to as little strain as possible. He must be warmly clad and protected from fluctuations of temperature as far as possible. The bowels must be kept freely open, as the best alternative route for elimination of toxins. He may have a considerable variety of food, provided that the intake of protein does not fall below 60 or rise above 90 grammes in the day, and provided that he takes very little purins and salt. In constructing the dietary it will be convenient to remember that a pint of milk, one egg, ¼ pound of fish, and 2 ounces of meat contain altogether 72 grammes of protein. Allowing for the protein in bread and vegetables, it will be seen that the amount of nitrogen in this diet errs rather on the side of liberality. It will, however, serve as a rough guide. He can be helped by saline diuretics and unirritating preparations of iron. He will do all the better if his medical man realizes that many of the methods recommended in the treatment of this disease are impotent where not actually harmful.

Uræmia.

Uræmia is merely a clinical term to designate the final failure of the kidney to discharge its duties. No one today regards this as merely due to retention of urea. It is rather that renal failure alters metabolism so that abnormal toxic products are formed. While this is true in the main, not all uræmic symptoms can thus be explained. The vomiting and diarrhœa certainly appear to be attempts at vicarious elimination of such products as the diseased kidney

cannot accomplish. The rashes and intense pruritus which sometimes occur are probably symptomatic of an attempt to excrete toxins by the skin.

It is true that there may be urea retention in uræmia, and Canti showed that its degree is a measure of the prognosis. But if the hypobromite method is used this will evolve nitrogen from other substances besides urea. The urease method, on the other hand, only splits up urea. The difference between the two methods gives the amount of non-protein nitrogen other than urea. These figures from a case are striking and typical. The cerebro-spinal fluid yielded 0·69 per cent. by the hypobromite method and 0·45 per cent. by the urease method. The amount of 'unknown nitrogen' was therefore greatly raised both proportionately and absolutely, being 0·24 per cent. Expressed proportionately it was nearly 35 per cent. of the total instead of the normal 8 per cent. In our opinion this unknown nitrogen is a real toxic factor. Still the nitrogen yield by the hypobromite method from the blood or cerebro-spinal fluid gives a convenient index of nitrogen retention. When this, calculated as urea, is above 80 milligrams per cent., there is serious nitrogen retention, and Canti found that 300 milligrams or more was always a fatal portent. It should be noted that a high blood urea may also occur in cases of repeated vomiting, especially when the pylorus is obstructed or in any form of alkalosis. This is due to loss of chlorides in the hydrochloric acid, which is increased by lavage of the stomach or administration of sodium bicarbonate. The consequent reduction in blood chlorides impairs kidney function, even without organic change. The appropriate treatment is free administration of intravenous saline.

On analyzing the chief symptoms other than diarrhœa and vomiting which have been attributed to uræmia, we find that they have different meanings.

(1) *Epileptiform Convulsions and Amaurosis.*—The most

dramatic manifestation—namely, epileptiform convulsions—may develop, and recovery is possible not only from the uræmia, but from the nephritis. This has not been our experience with uræmic manifestations other than those in this group, which suggests that the toxins are not the same. Similar convulsions occur in eclampsia, which may also come on very suddenly, and from which recovery may be complete. Moreover, they occur in toxæmic kidney, in which the tubules are suffering from a degenerative but not an inflammatory change, the result of a chemical poison like mercurial salts or cantharides or the toxæmia of pregnancy. Although severely damaged for a time, such a kidney seems, as far as our tests of its efficiency go, to be capable of complete recovery.

Amaurosis may occur under similar conditions—*i.e.*, acute nephritis, toxæmic kidney, and eclampsia—and is also capable of complete recovery. We are therefore inclined to attribute both symptoms to the same cause. And that cause is not retention of nitrogen, nor, as far as we know, of any other toxin. Cerebral œdema is now established as the immediate cause, and for this reason such attacks are usually known as hypertensive crises. The best preventive treatment is an enema of a hypertonic solution of magnesium sulphate which withdraws fluid from the central nervous system by osmotic pressure.

(2) *Paroxysmal Dyspnœa* (*or Uræmic Asthma*).—It has been established that acidæmia may occur in nephritis from the failure of the kidney to excrete acid sodium phosphate. In health the kidney and the lung can ensure between them a fairly constant hydrogen-ion concentration in the blood; any change is soon compensated for. But when the kidney fails to excrete acid sodium phosphate the hydrogen-ion concentration of the blood must rise, and the respiratory centre will be stimulated to compensate for this by washing out more CO_2 from the lungs by increased respiratory effort.

Yet even the marked dyspnœa which constitutes uræmic asthma may prove inadequate to compensate for the acidæmia. The heart muscle is poisoned, cardiac failure ensues, and pulmonary œdema may follow. It is true that heart failure often excites dyspnœa in nephritis without acidæmia. But to-day it is generally felt to be impossible entirely to separate uræmic from cardiac asthma.

(3) *Headache, drowsiness, coma, hemiplegia, apoplectiform seizures, insomnia, and acute mental changes* usually occur in chronic lesions of the kidney, although they sometimes manifest themselves with great rapidity. This group of symptoms appears to be chiefly associated with kidney lesions when vascular changes are paramount. The association between chronic interstitial nephritis and cerebral hæmorrhage has been attributed to the occurrence of similar changes in the vessels of the kidney and the brain. But the association between vascular changes in these two organs is not limited to cerebral hæmorrhage. Although the endothelium of the healthy cerebral vessels is extraordinarily impermeable to toxins, its resistance may be lowered by disease. Frequently, however, actual vascular lesions, such as punctiform or grosser hæmorrhages, are found in the brain *post mortem*, when clinically the case appeared to be one of uræmia.

In uræmia the toxin may be diluted and acidæmia controlled by intravenous injection of 200 to 400 c.c. of 2 per cent. solution of sodium bicarbonate. Elimination by the bowel is important, but drastic purgation should be avoided. In such cases nitrogen retention undoubtedly plays an important part in the eventual disaster, but it is quite possible, as Canti showed, for the cardio-vascular changes to lead to heart failure without serious nitrogen retention. Then treatment directed towards combating this heart failure is the only thing which is of any avail, and it is capable of producing remarkable temporary benefit.

The clear-cut features of the different types are often blurred by the co-existence of several lesions. Thus, suppression of urine following retention of prostatic origin is very likely to be complicated by vascular changes as well, considering the age at which prostatic troubles occur, while the septic complications to which nephritics are so prone are apt to precipitate and to alter the manifestations of uræmia at any age.

It would appear, therefore, that even using the term in a restricted sense, the uræmic syndrome may be due to at least two different chemical substances, one nitrogenous and the other non-nitrogenous, in addition to cerebral œdema, vascular lesions and septic complications.

CHAPTER VIII

GLYCOSURIA, INSULIN, AND KETOSIS

A MEDICAL man is often faced with the problem of deciding whether a patient is suffering from diabetes when his urine reduces Benedict's solution.

This reagent has the advantage, unlike Fehling's solution, of not being reduced by uric acid, glycuronic acid, or creatinin. Other sugars, such as lactose, lævulose, or pentose, may occasionally be present in urine; but the only one likely to lead to confusion is lactose, which is commonly excreted during lactation. For Benedict's test 8 drops of urine are added to 5 c.c. of his solution and boiled for two minutes. If the solution remains clear there is less than 0·1 per cent. of sugar; a green opalescence or precipitate means 0·1 to 0·5 per cent. of sugar, a yellow precipitate 0·5 to 2 per cent., while a red precipitate indicates more than 2 per cent.

A normal man can deal with ingested sugar in the following ways:

1. He can store it as glycogen.
2. He can store it as fat.
3. He can use it at once for muscular energy.
4. Any excess that cannot be dealt with in these ways will pass out into the urine. Anyone may have glycosuria after taking enough *sugar* at one time. The limit of this assimilation for dextrose or cane sugar is 200 grammes or more, for lævulose 150 grammes, and for lactose 120 grammes. But glycosuria after any quantity of *starch* is not physiological. In Naunyn's phrase, a patient who passes sugar after the free ingestion of starch is virtually a diabetic.

Even in patients who do not ordinarily pass sugar there may be a lowered tolerance for carbohydrates, which may

precede the glycosuria and outlast it. As the kidney is capable of altering its threshold for the excretion of sugar,

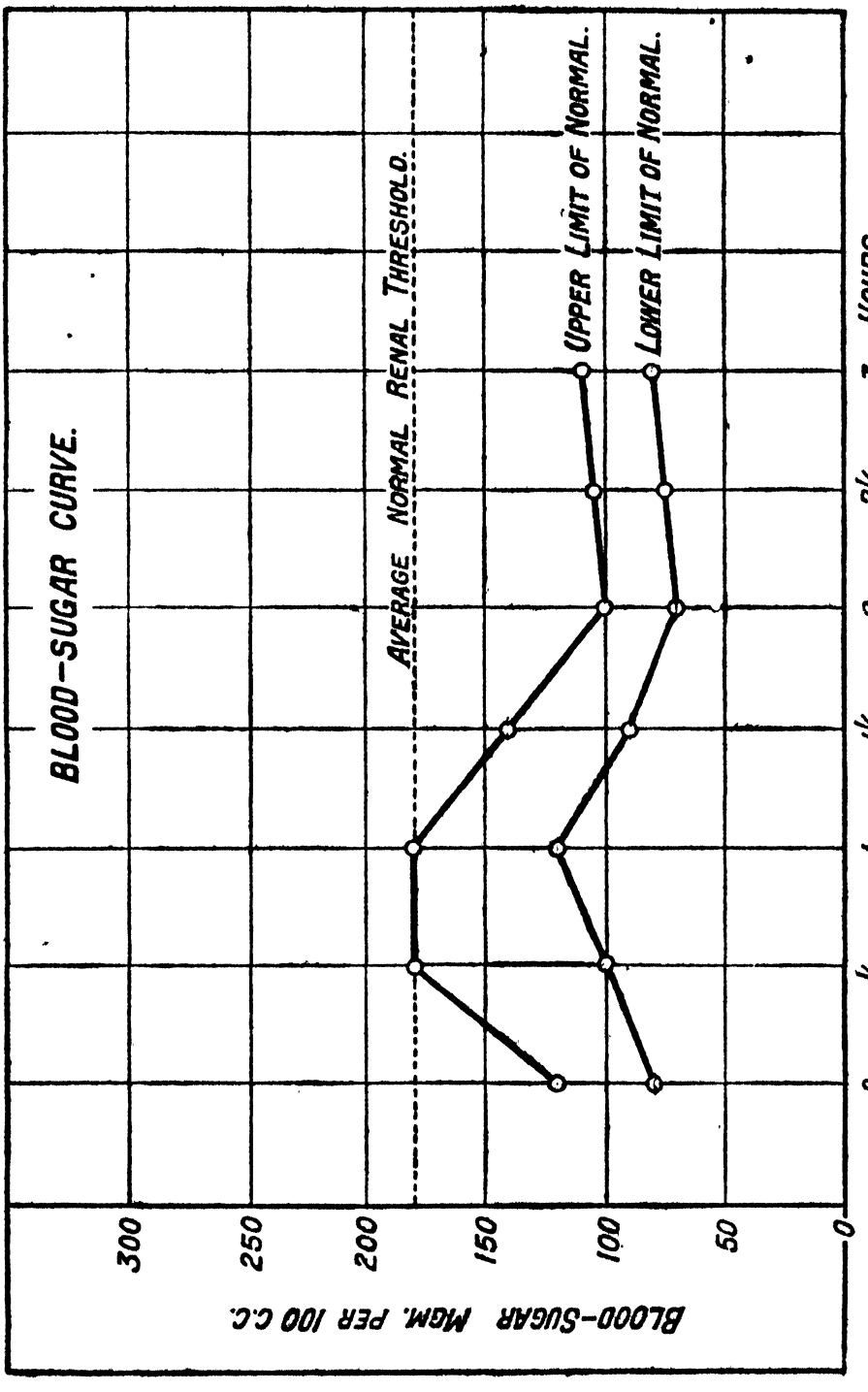


FIG. 2.—THE LIMITS OF NORMALITY IN VARIOUS NORMAL PEOPLE AFTER A 50-GRAMME DOSE OF DEXTROSE. No sugar should be excreted in the urine (Graham).

estimation of the urine alone does not give us adequate information as to the underlying condition. It may, however, be positively asserted that anyone passing both sugar

and diacetic acid on an ordinary diet is a diabetic. In other cases it becomes necessary to estimate the sugar in the blood. The normal response to 50 grammes of dextrose is shown in the accompanying curve. The blood sugar rises quickly to 0·16 to 0·18 per cent. and then falls again, returning to the original level in one and a half to two hours.

There are two essential points in the diabetic blood sugar curve. Firstly, it does not return to the fasting level within two hours, although the kidney excretes sugar. This is because the liver fails to store it and the tissues fail to use it. Secondly, the fasting level is raised. The absolute level depends upon the method of estimation, but over 0·12 gramme per cent. is usually regarded as pathological in the fasting subject.

The height to which the blood sugar rises after administration of sugar is of less importance in diagnosis than the delayed fall and high fasting level; indeed, in the opinion of some clinicians the 'lag curve' is of little or no pathological significance. It is expressed by a sharp rise above the normal threshold with a return to the normal resting level within an hour and a half. R. D. Lawrence finds that it so frequently occurs after gastro-enterostomy that it seems to be due to more rapid intestinal absorption and not to any defect of carbohydrate metabolism. He therefore regards it as a form of alimentary glycosuria, to which the name 'lag curve' is quite inappropriate. Others have attributed it to a delay in the action of the glycogen-storing mechanism of the liver.

In a well-marked case the diagnosis of diabetes can, of course, often be made on clinical grounds alone. In using the blood sugar estimation to decide a border-line case some possible fallacies must be borne in mind. Thus it is necessary that before the test the patient shall not have been starved of carbohydrate. Any individual who has been so fasted tends to show a blood-sugar curve approximating to

the diabetic curve. In Himsworth's opinion the curve rises whether the body is deprived of sugar or of the means of utilizing it.

Since insulin can make a diabetic curve become normal, it has naturally been thought that the cause of the altered metabolism in diabetes is a lack of insulin formation by the pancreas. This idea has been held in a more or less vague form since Lancereaux first called attention to the association between diabetes and pancreatic lesions in man, and Minkowski and Von Mering showed that excision of the pancreas produced diabetes in dogs. The discovery of insulin by Banting and Best in 1922 completed the evidence of the importance of the pancreas. They extracted it from a pancreas in which previous ligature of the duct had caused atrophy of the glandular tissue that produces the digestive ferments while leaving the cell islets unaltered. The existence of insulin, however, does not really prove that all cases of diabetes are primarily pancreatic in origin. On account of the deranged carbohydrate metabolism in other endocrine disorders, extra-pancreatic causes of diabetes have long been suspected. In this respect the pituitary body now takes a place second in importance only to the islets themselves. Houssay has shown that previous removal of the pituitary body prevents the appearance of diabetes when the pancreas is subsequently excised. The administration of anterior pituitary extract will then produce glycosuria. F. G. Young has shown that an animal with an intact pancreas can also be rendered permanently diabetic if given increasing doses of this extract. When this stage is reached structural changes will be found in the cell islets. The anterior pituitary seems to play an important part in regulating the manufacture of glycogen by the liver from non-carbohydrate sources.

In addition to this there are other endocrine influences on the level of the blood sugar; thus vasopressin, the secretion of the posterior lobe of the pituitary, was shown by J. H.

Burn to be antagonistic to insulin, as is adrenalin. Both these hormones appear to act on the liver in the opposite sense to insulin with regard to glycogen storage. Thyroxin can excite glycosuria; in Graves' disease sugar tolerance is lowered, and there may be actual glycosuria. Even in myxœdema the administration of thyroid extract may cause glycosuria. Garrod found it present in four out of eleven unselected cases. The antagonism between thyroxin and insulin can be expressed by saying that the former is a general katabolic agent, whereas the latter is anabolic. Any of these hormones—*i.e.*, adrenalin, thyroxin, vasopressin, and that from the anterior pituitary—by antagonizing insulin may therefore excite glycosuria.

It is well known that during the last war there was a considerable drop in the death-rate from diabetes, both in England and in Germany, the mortality rising again on the removal of food restrictions. An excessive carbohydrate diet calls for the secretion of more insulin to deal with it, and this, in time, may exhaust the pancreas.

It is a striking fact that the increased incidence of diabetes is almost confined to women of over thirty-five years of age. It is interesting to speculate whether the marked change of habit in regard to alcohol among women since the last war is in any way responsible for this. T. C. Hunt has shown that alcohol lowers the blood sugar, and Leyton suggested that this is due to its stimulating the pancreas. Given any inherent weakness in the pancreas, its powers might easily thus be overtaxed.

It will be noted that all the endocrine glands which tend to produce glycosuria are those which are controlled mainly by the sympathetic, while the production of insulin is under the control of the vagus.

A fall of blood sugar excites the pituitary to hasten the conversion of glycogen into sugar by the liver, while Le Barre's experiments show that a rise of blood sugar in

the cerebral circulation causes the vagus centre to stimulate the production of insulin by the pancreas, just as a fall of blood pressure excites the vasomotor centre, or a rise of hydrogen-ion concentration there stimulates the respiratory centre. It is clear, therefore, that anything which disturbs the balance of the autonomic nervous system in the direction of sympathetic overaction and para-sympathetic underaction may lead to glycosuria; this would explain the influence of nervous factors in the production of diabetes. Presumably the effect of Claude Bernard's 'diabetic puncture' of the floor of the fourth ventricle can be thus explained. The clinical equivalents of this process are seen in the glycosuria of concussion, cerebral tumours, cerebral hæmorrhage, pineal cysts, and the like. But there is another way in which these conditions might excite a temporary glycosuria, and that is by pressing on the pituitary body and thus increasing its secretion into the cerebro-spinal fluid. A mistake is very liable to occur in hospital practice when a patient is brought in already comatose and no clinical history can be obtained, but sugar is found in the urine. In such circumstances the test for diacetic acid becomes of paramount importance, for it will always be found positive in diabetic coma. Indeed, the smell of the breath may at once suggest the correct diagnosis.

In any asphyxial conditions glycosuria may occur; this is probably the cause of post-anæsthetic glycosuria and of the glycosuria of tuberculous meningitis, to which Garrod and Frew called attention. It appears when the respirations are shallow and grouped. The distribution of the meningitis does not support the idea that the glycosuria results from the pituitary body or the medulla being involved. It is more probably due to the stimulation of the sympathetic nervous system that occurs in asphyxia.

These newer views must modify our previous conceptions of diabetes and its treatment.

It has been recognized for many years that diabetes in the young is a much more severe disease than in older subjects. In the young it comes on with such a degree of acuteness that many people have been inclined to refer it to the result of some acute infection, though it must be admitted that the history of such an infection is often lacking. On the other hand, there is very strong evidence that a septic focus ordinarily has an immediate effect in lowering sugar tolerance, which may be persistent in a diabetic. If such an infection can so seriously aggravate diabetes, it is not illogical to think that it may also originate the condition. In the older group there has been an increasing recognition of the association between diabetes and arteriosclerosis, so much so that it might reasonably be suggested that in older subjects a local arteriosclerosis of the vessels of the pancreas may be the starting-point of the disease. The slow and insidious onset of this type of diabetes is compatible with the gradual progress of arteriosclerosis.

Although the immediate cause in the production of diabetes in the young and in the older patient is apparently so different, it is clear that a familial tendency to the disease is common to both. In a single family one may meet with both mild and severe types of the disease. Racial tendencies must also be considered. Diabetes is common in Jews and in Indians, but rare in negroes.

Treatment of Diabetes.—For some years after the discovery of insulin the tendency was to graft treatment by it on to the older methods of fasting and low calories. It is now recognized, however, that it may not always be necessary for the intake of protein and fat to be weighed, so that the patient may to a large extent be 'delivered from calories' in Lawrence's phrase. But at the outset it may be dogmatically stated that insulin should be given to all young patients and to those who cannot take at least 110 grammes of carbohydrate as starch without glycosuria.

Graham would add another class—patients over 60 if they are thin. The aim of treatment is to keep the patient's urine free from both sugar and ketones, especially the latter, and if possible to maintain a normal blood-sugar curve. But the maintenance of a good general condition is the prime consideration, to which more theoretical ones must give way. When the diagnosis has been made the patient should be put at rest for a time if the case is severe or there has been any recent infection. Otherwise the treatment can be ambulatory.

The Average Case. The patient should be weighed. Roughly speaking, every stone of adult body weight requires one line of Lawrence's line ration diet (p. 179). For a time the urine should be tested at 3-hourly intervals and the resulting colour given by Benedict's test recorded. The presence of ketones should also be looked for. If there is no glycosuria on this diet the amount of carbohydrate as starch should be gradually increased by, say, 5 grammes daily until 150 grammes is reached. If there is still no glycosuria an adult patient probably does not require insulin, unless he is dissatisfied with his ration of carbohydrate, for this can be only raised if he has insulin as well. Supposing, on the other hand, sugar appears, but only at certain times in the day, a redistribution of the amounts of carbohydrate taken at the different meals may correct this. But if sugar appears when only 100 grammes of carbohydrate is taken it is generally agreed that insulin is required; personally we prefer 125 grammes as the minimum. With insulin it is better to aim at 180-200 grammes of carbohydrate daily. For if carbohydrate is too severely limited there will be ketonuria, even if there is no glycosuria. If, on increasing the carbohydrate intake, sugar returns before the ketonuria is abolished, this is a clear indication for more insulin. Repeated blood sugar estimations are rarely feasible in general practice, though it is a great help to know the fasting level of the blood sugar at the

outset, as a guide not only to the severity of the case but also to give necessary information as to the height of the renal threshold.

It is always advisable to give insulin just before a meal. The rapid assimilation that follows may excite considerable hunger pain, which presumably means that the blood sugar is falling rapidly. It is a wise precaution to enjoin rest for six hours the first time insulin is given.

Hypoglycæmia.—The first signs of intolerance are sweating, faintness, and sometimes diplopia; but subjective discomforts, including headache, some mental confusion, a state of fear and of great irritability, are frequently complained of. More alarming signs are muscular inco-ordination, collapse, convulsions, and coma. If any such signs of hypoglycæmia occur, dextrose should be given, but with carefully controlled doses severe hypoglycæmic symptoms are not likely to occur. If the patient is unable to swallow dextrose it may be necessary to give a 5 per cent. solution intravenously. Usually, however, a subcutaneous injection of 5 minims of liquor adrenalin hydrochlor. will rapidly remove the symptoms by raising the blood sugar temporarily. The patient should be warned always to carry some barley sugar or dextrose with him to be taken at the first symptom of a reaction.

It would appear that hypoglycæmia from excessive insulin dosage acts in two stages, the first being characterized by overaction of the sympathetic, which increases the activity of those endocrine glands which can pour sugar into the blood. To this the fear, sweating, pallor, dilated pupils, and rapid pulse all bear witness. The later stage of coma is attributed to insufficiency of sugar for the metabolism of the moment in which the nerve cells suffer first—an intracellular asphyxia.

Indeed, the study of the effects of overdosage with insulin has led to the recognition of a new syndrome—hyper-

insulinism. Some cases of migraine and of hunger pain are associated with low blood sugar, and may be relieved by glucose. But severe symptoms may depend on a functional or an organic over-activity of the cell islets, and some cases have been relieved by the removal of an islet adenoma or even of the tail of the pancreas, in which islets are specially abundant. In the medical treatment of this condition the natural impulse would be to give large amounts of dextrose, but apparently this stimulates the production of more insulin. Some carbohydrate must be given, of course, but it should be remembered that an increase in the fat content of the diet is a method of damping down the activity of insulin.

Since exercise increases the combustion of carbohydrates, a diabetic should always be cautioned either to reduce his dose of insulin or to take some sugar prior to any strenuous exertion. Neglect of this precaution has occasionally led to alarming symptoms. Whatever the previous dose of insulin may have been, it is very important to increase it during any intercurrent infection, including even a common cold, for reasons already stated. Even the liability of the diabetic to tuberculosis seems somewhat diminished by insulin treatment. Should it occur, it should be regarded as an indication for increasing both the diet and the insulin dosage proportionately. Artificial pneumothorax is specially valuable in these cases.

The daily injection of rapidly acting insulin, even if repeated three times, cannot be a completely satisfactory substitute for the normal secretion poured out as required. Much research has, therefore, been directed towards modifications with a more prolonged though slower action. *Protamine zinc insulin* is the most satisfactory of these, and by its aid a single daily injection may be sufficient. Himsworth has compared the 'delayed' insulins to the basal anæsthetic whose effect is both mild and prolonged, while

ordinary insulin is comparable to the volatile anæsthetic which is superimposed at times when stronger control is required. Thus a dose of delayed insulin will not prevent glycosuria after breakfast, for it will not have had time to come into action. Accordingly it is often advisable to give some ordinary insulin in the same syringe. Lawrence and Archer recommend the following plan: a basal dose of delayed insulin is given amounting to three-quarters of the previous dose of ordinary insulin, but not exceeding 30 units, together with half the previous morning dose of ordinary insulin, which is gradually adjusted, reduced or omitted as the basal dose comes into full action. It is essential that if there is to be a change-over from ordinary insulin it should only be made under conditions permitting close observation. Allow at least a week for the transfer or, as Joslin remarks, you will rue it.

Lawrence, as the result of some years' experience of the protamine zinc compound, describes it as the practitioner's insulin for choice, but considers that in severe cases it is rarely able to keep the urine constantly sugar-free without risk of hypoglycæmia. He reduces the dose if all the urine tests are free for even one day, and certainly for two days. If a patient never passes sugar after supper or before breakfast the dose of delayed insulin is too high and should be reduced, perhaps by 4 units; if he never passes sugar after breakfast the ordinary insulin should be reduced.

Diabetes in Children.—As is well known, diabetes runs a particularly rapid and severe course in childhood. In pre-insulin days children contracting diabetes under the age of 10 hardly ever survived two years. They have especially benefited by the newer method of treatment in diabetes. There is a striking difference between the appearance of the children treated in the early days of insulin on a greatly restricted carbohydrate intake and those who have been

THE "LINE-RATION" DIET SCHEME

(One black portion added to one red portion = one Line ration)

Carbohydrate Foods (containing sugar or starch).

Black Portions (10 gm. C.).

	oz.
Flour, Rice, Sago, Tapioca (raw)	⅜
Biscuit, Toast or Breakfast Cereals; Oatmeal, Macaroni (all dry)	½
Bread (all kinds)	⅝
Potato, Peas or Beans (dried or tinned); Banana or Grapes; Dried Apricots (stewed)	2
Parsnips; Ripe Greengages; Prunes (stewed)	3
Raw Apple, Pear, Cherries, Gooseberries, Plums, Damsons, Orange (skinned); Young Peas or Beetroot	4
Peach or Apricot (ripe); Greengages (stewed); Broad Beans	5
Strawberries; Stewed Pears, Damsons or Plums	6
Milk; Raspberries or Melon (ripe)	7
*Apples or Cherries (stewed); Carrots or Leeks	8
*Jerusalem Artichokes; Loganberries; Blackberries (stewed)	10
*Grapefruit (in skin); Tomatoes; Red Currants or Black Currants (stewed)	12
*Onions, Turnips or Radishes	14

* Half portions of these are usually enough.

Negligible Starch Content in Average Helpings of—

Asparagus, Green Artichokes, French Beans, Brussels Sprouts, Cabbage, Cauliflower, Celery, Cranberries, Cress, Cucumber, Egg Plant, Endive, Stewing Gooseberries, Greens, Horseradish, Lemons, Lettuce, Marrow, Mushrooms, Radishes, Rhubarb, Salsify, Scarlet Runners, Sea Kale, Spinach.

Extras of no Food Value

Tea, Coffee, Soda-water, Bovril, Oxo, etc.; ordinary condiments and flavourings.

Red Portions (Protein and Fat).

7½ gm. Protein and 9 gm. Fat.

One Egg.

Bacon or Ham 1 oz. (lean only).

Kipper or Herring 1 oz. and Fat ¼ oz.

Lean Beef or Veal 1 oz. and Fat ¼ oz.

Lean Lamb or Mutton 1 oz. and Fat ¼ oz.

Lean Pork 1 oz.

Chicken or Pigeon 1 oz. and Fat ¼ oz.

Duck 1 oz.

Tongue (tinned or fresh) 1 oz.

Liver 1 oz. and Fat ¼ oz.

Kidney or Tripe 1¼ oz. and Fat ¼ oz.

Rabbit or Hare ½ oz. and Fat ¼ oz.

Cheese ¾ oz.

White Fish, Sweetbreads 1¼ oz. and Fat ¼ oz.

Sardines 1 oz.

Salmon 1 oz. and Fat ¼ oz.

Crab or Lobster 1½ oz. and Fat ¼ oz.

Pheasant, Grouse, Partridge ¾ oz. and Fat ¼ oz.

Fats are Meat Fats, Suet, Dripping, Butter, Margarine, Olive Oil; Thick Cream in twice the amount stated for other fats.

(*From* "The 'Line-Ration' Scheme," by R. D. Lawrence. By kind permission of the author. London: H. K. Lewis and Co., Ltd.)

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allowed 180 to 200 grammes with sufficient insulin to cover it. Nowadays they appear normal and healthy; formerly they were stunted and wizened, and the girls never achieved puberty at the proper time. If the choice lies between cutting down the carbohydrate below 180 grammes and allowing glycosuria to continue in a child, experience shows that the latter course is preferable. For coma, especially during an intercurrent infection, is their principal danger.

Treatment of Mild Cases.—In milder cases, where dietetic regimen appears to be adequate to keep the patient free from glycosuria, a balanced diet containing 30 calories per kilo of body weight in the proportion of 10 grammes of carbohydrate to every 7½ of protein and 9 of fat may be tried. Lawrence's line-ration scheme is an ingenious way of applying this principle, and allows of considerable variety in the dietary. To determine the number of rations allowed for each day it is only necessary to divide the body weight in pounds by 13·5. For practical purposes this means one line ration for every stone in body weight, as already stated.

It will be noted that the carbohydrate value of vegetables on this table are given at a lower figure than usual. Lawrence and McCance have recalculated these values, and have deducted the non-utilizable carbohydrate such as cellulose and inulin from them. It would appear that we have sometimes been giving less available carbohydrate than we thought, which would account for ketosis, which formerly was not anticipated in diets based on the older calculations. An occasional day of low diet, such as Graham's vegetable and egg diet, may assist such patients in maintaining their urine free from sugar.

VEGETABLE AND EGG DIET.

Breakfast.—Two eggs, scrambled with ¼ ounce of butter. Tea or coffee, with a little cream or milk; 2 ounces of lettuce, watercress, or tomato.

Lunch.—½ pint of Bovril, beef-tea, or clear soup; 1 poached egg on

spinach; any vegetables from list below with ¾ ounce of butter. The total amount of vegetables for the meal to be 6 to 8 ounces.

Tea.—Tea or coffee, with a little milk or cream; 2 ounces of lettuce, watercress, tomato, or celery.

Dinner.—½ pint of Bovril, beef-tea, or clear soup; 2 eggs, cooked as desired—*e.g.*, as savoury omelette; 6 to 8 ounces of green vegetables with 1 ounce of butter; water or lemonade as desired.

This diet has a calorie value of 820, and a carbohydrate intake of about 10 grammes.

LIST OF VEGETABLES WHICH MAY BE TAKEN.

Asparagus, broccoli, brussels sprouts, cabbage, cauliflower, celery, cucumber, endive, French beans, lettuce, leeks, radishes, sea-kale, spinach, tomato, vegetable marrow, watercress.

The modern treatment virtually abolishes the need for special breads. As Osler said: 'Most of the gluten breads are unpalatable, and the rest are frauds!' It is rash to trust to diabetic breads, for which, while it is admitted that they are not carbohydrate-free, it is claimed that they can be assimilated by the diabetic. Such claims are frequently unjustified, and the patient, believing that he can take such bread freely, often increases his glycosuria. Some of them contain very little less carbohydrate than ordinary bread, and are, of course, much more expensive. Others add unregulated amounts of protein and fat to the diet. Since every diabetic patient is now allowed to have at least 100 grammes of carbohydrate, this permits of the taking of a regulated amount of ordinary bread, as the effect of this can readily be controlled by insulin.

The patient should be taught to test his own urine with Benedict's solution for sugar and with a solution of ferric chloride for diacetic acid (see p. 182). Many patients can quickly learn to give themselves an injection of insulin, and syringes in metal cases containing an antiseptic solution are easily obtainable.

The treatment outlined above has rendered drugs obsolete. Pancreatic extracts given by the mouth are useless. Syn-

thalin can certainly lower blood sugar when given by the mouth, but as it acts by a toxic effect on the liver it is not a safe drug. The question of giving alkalis is discussed under Ketosis.

Insulin and the elimination of septic foci have vastly changed the prognosis in diabetes. It is, therefore, lamentable that prejudice has been deliberately roused against the use of such a life-saving remedy. The statement that if insulin is once given it must be continued for the rest of the patient's life has done untold harm. It is true that if insulin is abandoned the patient cannot continue such a generous diet, but this is not what is popularly understood by that statement. The layman supposes that if he gives up treatment by insulin his last state will be worse than the first. Some even believe that insulin creates a drug habit, like morphine or cocaine. It need hardly be said that both these ideas are quite erroneous. Patients who have once experienced the benefits of insulin are not likely to abandon them. It has been alleged that the death-rate from diabetes has not fallen since insulin was introduced; this is partly due to the increasing incidence of the disease already referred to, and as diabetes is a continuing disease it will naturally appear on death certificates, whatever the immediate cause of death. Thus the arteriosclerosis to which even the younger diabetics are prone does not appear to be influenced in its progress by insulin. The reason for this is unknown, though a high fat ration has been suggested. The death-rate from diabetes has fallen very definitely in the earlier years, but this is balanced by the increased number who now die after seventy-five. In other words, insulin is prolonging the lives of many diabetics until an age at which the normal expectation of life is practically nil.

Ketosis in General.

The terms 'ketosis' and 'ketonuria' are conveniently applied to the presence of certain ketones in the blood and urine respectively. They appear in many other conditions than diabetes, such as the recurrent vomiting of children, the pernicious vomiting of pregnancy, broncho-pneumonia, fevers, carcinoma of the digestive organs, rectal feeding, and after anæsthetics.

What general significance is to be attached to a symptom occurring under conditions apparently so diverse? Acetone comes from the decomposition of diacetic acid. The odour, variously compared with that of hay or of apples, is due to diacetic acid rather than to the acetone, which has a more penetrating smell.

It follows that the recognition of diacetic acid in the urine is of greater importance than the detection of acetone, its decomposition product. On the addition of ferric chloride a claret colour results, which (unlike the somewhat similar colour seen on addition of this reagent to the urine of patients taking salicylates or carbolic acid) does not appear if the urine has been previously boiled. This is a useful and practical test. A more sensitive one for diacetic acid is to add a few drops of a freshly prepared solution of sodium nitro-prusside to the urine and then pour some strong solution of ammonia on the top. A magenta-coloured ring appears at the line of contact, and diffuses upwards. As shown by Rothera, saturation with crystals of ammonium sulphate makes the reaction still more sensitive, perhaps too sensitive for practical guidance in diabetes. This test was formerly thought to show the presence of acetone till Rothera proved its real significance.

According to Hurtley, the liver converts some of this diacetic acid into the more saturated and less toxic β-oxybutyric

acid. The chemical relationship between these substances is expressed thus:

$CH_3CHOH\ CH_2COOH$ = β-oxybutyric acid.
$CH_3CO\ CH_2COOH$ = Diacetic acid.
$CH_3CO\ CH_3$ = Acetone.

The term 'ketone' is applied to any of these substances. What is their source? Clearly they do not come from carbohydrates, because carbohydrates diminish the amount of them in the urine. Do they come from protein or fat? Although some of the fatty groups in protein may increase ketosis, it is fat itself which is the main source.

Individuals differ in the ease with which they develop ketosis by a fatty diet. In some cases the ketonuria may be as intense as in severe diabetes, yet the toxic symptoms may be comparatively mild, and easily abolished.

The Element of Starvation.—Anyone can produce ketosis by starving himself. In some diseases associated with ketosis the element of starvation is obvious—for instance, in carcinoma of the digestive organs, certain febrile conditions, and rectal feeding. A wasting diabetic is being starved also from inability to metabolize carbohydrate.

Of all the tissues, the fat loses most in starvation, the more noble organs being fed at the expense of the less essential ones. To effect this the fat must be broken down, in the course of which fatty acids would be set free.

An easily assimilable carbohydrate, such as dextrose, leads to a prompt diminution or disappearance of the ketone bodies. That the acetonuria of febrile conditions could be largely inhibited by supplying the wasting tissues with carbohydrates was proved by von Noorden. Halpern recorded the case of a man with an œsophageal stricture, whose only food for twenty-six days was 30 grammes of dextrose *per rectum*, yet his urine contained no acetone or diacetic acid.

The rôle of carbohydrates in preventing ketosis is due to

their relative abundance in oxygen, which is drawn upon to complete the breakdown of the fats into CO_2 and water. In their absence the less completely oxidized fatty acids appear.

If fats are consumed in the fire of the carbohydrates, ketosis may be called the smoke from the fires of metabolism, which is due to the abnormal breakdown of fats necessitated by non-utilization of carbohydrates.

Ketosis in Diabetes.

In diabetes the incomplete oxidation of fat leads to the appearance of β-oxybutyric and diacetic acids in the blood. Adequate compensation for an increased hydrogen-ion concentration is normally effected by increased excretion of CO_2 through the deep breathing and by excretion of highly acid urine, together with increased ammonia formation by the kidney. The influence of diacetic acid in causing diabetic coma is, however, not dependent on its acidity, but on its containing the enolic group, which is directly toxic to nervous tissues.

Symptoms of Ketosis in Diabetes.—These are particularly apt to occur as the result of a septic focus, acute general infection, or constipation. Such symptoms as nausea and vomiting or vague and diffuse pains should lead to immediate examination for ketone bodies in the urine. As the condition becomes more severe, the respirations are seen to deepen and to become abdominal in type. Pain in the throat or epigastrium is not uncommon. The patient becomes steadily more drowsy. The blood becomes concentrated, as shown by the rise in hæmoglobin, partly because of the loss of additional fluid by the over-ventilation of the lungs. This is reflected in the smallness of the pulse, the collapsed condition of the veins, and the lowered tension of the eyeball. And thus the full picture of diabetic coma is quickly reached.

Treatment of Diabetic Coma.—The first essential in the treatment of diabetic coma is to give enough insulin, and if possible to deal with any precipitating cause of the coma, such as sepsis.

When coma threatens, as indicated by deeper breathing, headache, abdominal pain, and nausea, full doses of insulin should be given with dextrose, as the presence of an adequate amount of sugar is necessary to ensure the complete combustion of fat. Probably 50 units will be found a useful initial dose, repeating this as often as is necessary.

It is equally important to realize that the over-breathing which precedes and accompanies the coma, together with the large excretion of urine, invariably causes a severe loss of fluid from the body. If this fall in the volume of the circulating blood is not immediately combated by giving saline intravenously and otherwise, insulin may fail to avert a fatal issue. In severe cases 3 or 4 pints of saline intravenously may have to be given before consciousness returns. This treatment also benefits the renal and circulatory failure which accompanies coma.

Unfortunately, the patient, especially if a child, may sometimes pass from diabetic coma to hypoglycæmic coma without an intervening period of consciousness. This is an additional reason for the administration of dextrose. Severe and permanent effects on the central nervous system have been known to follow hypoglycæmic coma prolonged for many hours by large doses of insulin given without sugar. The differentiation of the two forms of coma is therefore of great importance. The following table (George Graham, slightly modified) shows the main points of each:

	Diabetic Coma.	*Hypoglycæmic Coma.*
Onset	Gradual.	Very sudden.
Skin	Usually flushed.	Usually very white, but may be normal.
Breath ...	Smells of acetone.	No smell of acetone.

	Diabetic Coma.	*Hypoglycæmic Coma.*
Respirations ...	Deep (especially the abdominal movements).	Shallow.
Eyeball tension	Low.	Normal or raised.
Urine	Contains sugar and diacetic acid.	Does not contain sugar or diacetic acid (unless bladder has not been emptied for some hours).
Blood sugar ...	Over 200 mg. per cent.; sometimes much higher.	Below 70 mg. per cent.; may be as low as 40.

At the onset of an acute infection, diabetic patients sometimes stop taking insulin because they cannot take food, thus increasing the risk of developing diabetic coma. They should be taught that even with a slight infection they need the guidance of a medical attendant; until one can be summoned they ought to take a full allowance of glucose in fluids and to continue their regular dose of insulin.

In cases of obvious septic infection the necessity for release of pus requires no emphasis. But certain cryptic infections, such as otitis media, may be overlooked unless a thorough examination is made.

Constipation, to which diabetics are prone, sometimes appears to precipitate coma. But it is at least as likely that it is the dehydration accompanying coma which renders the constipation so obstinate.

Non-Diabetic Ketosis.

To appreciate the significance of ketosis in general it is necessary to consider the equilibrium between acids and bases in the blood.

The Acid Base Equilibrium.—Claude Bernard first introduced the conception of constancy of the 'internal environment' of the body (*le milieu interne*) in spite of changes in the external environment. Increased knowledge of biochemistry has revealed remarkable instances of this, especi-

ally in the blood. None is more remarkable than the preservation of the reaction of the blood and body tissues. The reaction of blood, as of any other fluid, depends on the relative number of H-ions charged with positive electricity and OH-ions charged with negative electricity. When there is an excess of H-ions the solution is acid. When the two are equal the solution is neutral. The blood plasma as it exists in the circulation—that is, exposed to the normal CO_2 tension of arterial blood and in the presence of red blood corpuscles—is found to be kept slightly on the alkaline side of neutrality. It is measured colorimetrically by the use of indicators or by electrical methods, and is expressed numerically as *p*H.* These measurements show that the reaction is maintained in a healthy body with only slight deviations, though various factors are always tending to move it one way or the other, such as the secretion of acids and alkalis during digestion. The ingestion of large quantities of basic radicles, such as sodium and potassium, present chiefly in vegetables and fruit, would also tend to alkalinization, while the acids formed as a result of exercise or oxidation of carbon, phosphorus, and sulphur would tend in the opposite direction. The organs chiefly concerned in the regulation of the reaction are the lungs and kidneys and the blood itself. The blood contains what are known as 'buffer' salts, sodium bicarbonate and alkaline sodium phosphates; these buffers delay

* The concentration of hydrogen ions in a solution is expressed by *c*H.

The symbols H^+ and OH^- mean that the concentrations of hydrogen and OH ions are being expressed in terms of gramme equivalents of the ion per litre of the solution.

The product of the two is constant for all solutions and is 10^{-14}. A *c*H of 10^{-7} is a neutral solution; 10^{-14} is an alkaline solution.

To avoid the use of negative indices the letter *p* is used and the negative sign is changed. Instead of referring to a *c*H of 10^{-7} we say that the *p*H is 7—*i.e.*, neutral. Thus a *p*H of 6 is an acid solution and a *p*H of 8 is an alkaline solution; the reaction of the blood is on the alkaline side of neutrality and its *p*H is 7·4.

the changes in blood reaction, which would otherwise result in the addition or removal of acid or alkali.

The respiratory mechanism for regulation of the reaction of the blood is extremely sensitive, and works by alteration in the rate of elimination of CO_2. The kidney not only excretes acid or alkaline phosphates in a varying ratio, but also manufactures ammonia, which is available for the neutralization of acid. If this compensatory mechanism fails, either a potential alkalæmia or acidæmia results. *Alkalosis* can occur from taking excessive doses of sodium bicarbonate for dyspepsia. A similar effect is produced by the loss of large quantities of hydrochloric acid or of chlorides by repeated vomiting and diarrhœa. This lowering of the chlorides of the plasma necessitates the retention of bicarbonates, formed from CO_2 and the base liberated by the lost chloride, in order to maintain the osmotic pressure of the blood, which is even more important than the regulation of its H-ion concentration.

In severe degrees of alkalosis, non-protein nitrogen is also retained in the blood to keep up the osmotic pressure. This explains the high blood urea seen in certain cases of persistent vomiting, as in pyloric obstruction. The symptoms are general malaise, weakness, drowsiness, and sometimes tetany, the probable cause of the last being a change in the ionization of the blood calcium.

Chloride should be given (rectally or intravenously if necessary) in the form of ordinary salt, which causes a rapid excretion of the retained urea and of the extra alkali.

Acidæmia may also be brought about by medication. Ammonium chloride is used for this purpose when it is necessary to produce a highly acid urine in certain urinary infections.

Acid retention occurs in certain diseases, such as nephritis, where there is a definite rise in the H-ion concentration of the arterial blood. This is thought to be due to the retention

of acid phosphates, which may be a factor in 'uræmic asthma.' Yet, although the dyspnœa diminishes the CO_2 in the blood, administration of alkali in this condition gives disappointing results. Any benefit is only temporary. In some cases of cardiac failure it has been said that the blood is more acid because of its increased CO_2 content, but actual measurements usually show that this is more than compensated for by the accompanying dyspnœa resulting from oxygen lack.

In emphysema, as might be expected, the diminished alveolar surface results in a raised CO_2 tension in the blood, which is balanced by a higher bicarbonate level there, thus preventing acidæmia.

In disease, therefore, the clear-cut effects of any one lesion are seldom seen, and a study of the peripheral blood is not always adequate to reveal the condition of the circulation in the important nerve centres which control respiration and blood pressure. For example, in cardiac failure the poor circulation through the kidney impairs renal excretion, with consequent retention of acid, while the dyspnœa from oxygen lack in the respiratory centres leads to an increased excretion of volatile acids. The sum total of two opposing effects in cardio-renal disorder cannot always be predicted.

It must be confessed that non-diabetic ketosis is very seldom really toxic in its effect, though, of course, toxic symptoms may coexist with it. In some cases ketosis is evidently secondary to starvation, as already stated. Œsophageal or gastric carcinoma, cyclical vomiting in children, and pernicious vomiting in pregnancy are examples of this. In eclampsia and post-anæsthetic poisoning there are severe toxic symptoms, probably due to interference with the oxidases of the liver, but the ketosis is only one and probably not the most important manifestation of this.

Symptoms Associated with Non-Diabetic Types of Ketosis—(*a*) *In Recurrent Vomiting.*—In 1882, Gee described cases

of fitful and recurrent vomiting of unknown causation in children. Later observers noted acetone in the breath, urine, and vomit. Diacetic acid and oxybutyric acid have also been found when looked for. It usually occurs between three and eleven years of age, and the frequency of the attacks is very variable. There may be a prodromal period in which dyspnœa, sighing respirations, offensive breath, choreic movements, and general restlessness have been noted. The tongue is usually coated. Then vomiting begins, without nausea, and usually without gastric pain; all food is rejected, and towards the end of the attack bile appears, sometimes even blood. Constipation is common. The attacks may last only a few hours, but the average duration is five or six days. As a rule there is fever. On account of the loss of fluids, wasting is generally a very marked symptom. In later life these attacks are sometimes replaced by migraine, but they tend to disappear when puberty is reached. A mild degree of such a condition is quite common in children, and it is probable that 'biliousness,' which, as Gee said, is a real state, a very common state, but a state that is little understood, is also of this character. In some cases the tonsils or the appendix may be responsible; in others there may be bacilluria.

From one cause or another some functions of the liver appear to be temporarily suspended, possibly through some toxic action. There is evidence that the secretion of bile may cease for a time, hence the pale stools. At any rate, the prompt use of a mercurial purge may ward off an attack. When once the liver fails to do its work, abnormal products appear, including these acids. The vomiting accentuates the condition by increasing the starvation and the loss of saline bases.

(*b*) *In the Pernicious Vomiting of Pregnancy.*—Though the pernicious vomiting of pregnancy may be due in some cases to mechanical causes, such as the early enlargement of

the uterus, there is often a neurotic factor. A more serious group of toxæmic cases remains, however, in which it is thought that the chorionic villi provide the toxin. Whitridge Williams, noting the increased percentage of ammonia excreted in the urine of such patients, suggested that this might be due either to failure of urea formation in the liver or to the attempt to neutralize acid intoxication. But a very small proportion of the liver substance is sufficient to carry out the conversion of ammonia into urea.

In starvation from any cause the proportion of ammonia increases, mainly because of diminished urea excretion, which must occur since so much of the urea is derived directly from the nitrogenous food. Thus a high ammonia coefficient is then apt to acquire an undeserved significance.

Leathes puts it very fairly when he says: 'Before it can be safely maintained that these high figures are a sign in themselves of a toxæmia that is likely to prove fatal unless the most active measures be taken, it is necessary to prove that they are not sufficiently accounted for by some of the attendant circumstances of the patient's condition—the low nitrogen content of the absorbed food, the imperfect nutrition due to the incessant vomiting . . . aggravated possibly by the requirements of the fœtus.' In other words, the high ammonia coefficient may result from simple starvation rather than from an attempt to neutralize acids. Some cases reported by Gilliat and Kennaway appear to fulfil Leathes' requirements, for here the ammonia index showed a rapid increase which could not be accounted for by starvation.

(*c*) *In Gastro-Intestinal Ketosis.*—Here the ketosis merely results from starvation, and is not in itself responsible for symptoms, though it is naturally associated with rapid wasting.

(*d*) *In Broncho-Pneumonia.*—Garrod associated drowsiness, torpor, and vomiting with the presence of diacetic acid in the urine.

The principal symptoms, then, which seem to be commonly associated with the various forms of ketosis are dyspnœa, wasting, vomiting, drowsiness, and coma.

(*e*) *Post-Anæsthetic Ketosis*.—That death might follow the delayed action of chloroform was first suggested, so long ago as 1850, by Casper. Other anæsthetics besides chloroform have also been found to cause it.

Twelve hours or so after the anæsthetic the patient (usually a child) suffers from profuse and repeated vomiting, the vomiting eventually resembling the dregs of beef-tea. Sometimes there is a preliminary period of restless excitement and delirium.

This is followed by drowsiness, apathy, and unconsciousness, deepening to coma. Death usually occurs about the fifth day, but sometimes later, from gradual or sudden cardiac or respiratory failure. Pyrexia is not the rule, though the temperature may be very high just before death. The pulse becomes very rapid. Albuminuria with casts is common. Furthermore, there is a smell of acetone in the breath, while diacetic acid is found in the urine. It will be noted that these symptoms resemble in essentials the features of other ketoses; but the abnormal acid was only looked for at first where something went wrong after anæsthetics.

It is now generally agreed that diacetic acid is often present in the urine after anæsthetics, and not uncommonly before. Frew has shown that in children the mere change of diet accompanying admission to hospital is sufficient to induce ketosis. As the hospital diet is rich in carbohydrates, it is not due to starvation, but to the fact that the child apparently takes time to adapt its digestion to the change. Thus the majority of children that are admitted for operation receive their first anæsthetic while ketosis is already present. In addition to this tradition formerly demanded that the patient should be starved both before and after operation, and that an acute diarrhœa should be produced. In short, everything

was done to induce ketosis, and then a toxic vapour was given, and an operation was performed which still further lowered vitality. It is curious that toxic symptoms did not occur more frequently. Modern methods of preparation for operation, especially the administration of dextrose, avoid most of these pitfalls, and consequently post-anæsthetic ketosis is now comparatively rare. Incidentally, chloroform should never be used in operations on diabetics.

Although at operation the liver may have been seen to be normal, yet, in cases which terminate fatally shortly after the use of chloroform, post-mortem examination reveals a toxic hepatitis. It is reasonable, therefore, to assume that post-anæsthetic ketosis is a milder manifestation of the same condition.

It is relevant to note that the presence of bile salts can nearly always be demonstrated in the urine after administration of chloroform, and, as shown in the chapter on the work of the liver, the question of fatty changes in that organ is not a simple one. It is, however, clear that lack of glycogen materially increases the difficulty with which the liver does its work. Deprivation of readily assimilable carbohydrate is therefore the most effective way of inducing the catastrophe of post-anæsthetic poisoning.

Treatment of Ketosis.—The principles underlying treatment are:

(1) To prevent incomplete oxidation of fatty acids as far as possible.
(2) To combat dehydration.

By what methods can these principles be put into effect?

(*a*) *In the Recurrent Vomiting of Children.*—To ward off attacks, prodromal signs should be noted—white stools, offensive breath, some change in complexion, usually indicative of what are called 'bilious attacks,' and the presence of abnormal acids in the urine—then mild aperients and

easily digestible foods are indicated. Barley water is usually tolerated. Small doses of grey powder or calomel should be given. Normal salt solution *per rectum* is useful. When the condition is fully developed, the only treatment of real value is water, dextrose, and insulin. If the first two cannot be retained when given by the mouth, 4 per cent. of dextrose should be added to a pint of normal saline, and should be given every four hours, either by the rectum or intravenously if necessary. If the appendix or tonsils are involved, subsequent removal may be considered.

As emphasizing the association between this condition and migraine in later life, attention may be drawn to the cessation of the flow of bile, which has been observed by one of us immediately before an attack of migraine. Three grains of sodium taurocholate in a capsule is rational and helpful to ward it off.

(*b*) *In the Pernicious Vomiting of Pregnancy.*—In the nervous type remarkable results may be obtained by isolation from solicitous relatives and by emphatic encouragement by means of suggestion. Bromide, by the rectum if necessary, is generally helpful. Otherwise the treatment is the same as in other forms of ketosis. It may, however, become necessary to empty the uterus. Provided that it is not left too late, this is followed by rapid recovery. The condition may recur at subsequent pregnancies.

(*c*) *In Post-Anæsthetic Poisoning.*—Both starvation and fright cause ketosis. Four hours' fast before operation is too long for children. Ten grammes of dextrose freely diluted and flavoured with lemon juice should be given at hourly intervals. The effect of fright cannot be altogether controlled, but may be diminished by preventing starvation, and in the use of a basal anæsthetic *per rectum*. Should symptoms of ketosis occur despite these precautions, it must be treated as in other cases. Dextrose must be got into the system somehow, together with insulin to ensure its assimi-

lation. Today the tendency is to rely on the intravenous method, giving 5 to 10 per cent. of dextrose in saline by this route.

Ketosis as a Treatment for Bacilluria.

During observations on the value of a ketogenic diet in epilepsy it was noted that a high degree of ketosis inhibited the growth of organisms in the urine. This led to the use of such a diet in the treatment of *B. coli* infection of the urinary tract.

It was then discovered that a derivative of ketone, mandelic acid, passes through the body unchanged and exerts the same antibacterial action in the urine. Still more recently it has been found that sodium mandelate is even more effective and materially shortens the duration of the disease. Three and a half grammes are given four times a day. It is necessary to maintain a urinary *p*H of about 5·2. The drug will often do this by itself, but, if not, ½ gramme of ammonium chloride should be given twice a day in addition. Some observers prefer ammonium mandelate, finding that this does away with the need for the disagreeably tasting ammonium chloride. There is no need to diet the patient, but the care of the intestinal tract and the exclusion of surgical complications, such as stone or obstruction to the urinary outflow, remain as necessary as before.

This method is free from the drawbacks of the ketogenic diet, and was distinctly the best treatment known for such infections, until the introduction of sulphonamides, which is now preferred by most observers.

CHAPTER IX

SOME ASPECTS OF HEART DISEASE

THE early years of this century saw a revolution in cardiology by the introduction of the electrocardiograph only comparable with that effected by the stethoscope at the beginning of the nineteenth. The electrocardiograph* has focussed attention on the muscle of the heart as inevitably as the stethoscope did on its valves. And this is an advance, for the chief value of a murmur is to help us to form an opinion as to the probable effect of a valvular lesion on the heart muscle. Increasing knowledge of cardiac physiology in general has also enabled us to obtain a more balanced view of the various factors involved in heart failure.

In this revolution three names stand out pre-eminently: Gaskell was the forerunner to whom we owe our fundamental conceptions of cardiac rhythm; James Mackenzie taught us the classification and significance of various clinical disturbances of that rhythm; Thomas Lewis has not only given us accurate knowledge concerning the central mechanism by direct observation, but has also enabled us to view the circulation from the periphery.

The Genesis of Cardiac Rhythm.

Prior to Gaskell, physiologists had referred the rhythm of the heart to the intracardiac ganglia. In the first place he showed that the ventricle of the frog's heart, 'physiologic-

* It is impossible to overestimate the value of the electrocardiograph for the investigation of the disturbed action of the heart muscle, but our present aim is to show how far this can be recognized even without its aid. For the interpretation of electrocardiograms, readers are referred to such books as Sir Thomas Lewis's *Clinical Disorders of the Heart Beat.*

ally disconnected' from all such ganglia, would beat with an independent rhythm if only the intracardiac pressure were raised. Further experiments on the tortoise's heart enabled him to reach the conclusion that rhythm was an inherent property of the cardiac muscle, and did not depend on the intracardiac ganglia. The beat normally began at the sinus, because here the muscle was of a more embryonic character, while the ventricular muscle was the most differentiated.

He also showed a point which has now become of great practical importance. If the bridge of auricular muscle be made too narrow by cutting, a 'block' is established on the course of the muscle wave, so that not every beat can pass over into the ventricle, but only alternate waves, or one out of every three, according to the width of the bridge. An adequate strand of conducting tissue is essential to the due propagation of the wave of contraction along the cardiac tube.

Stanley Kent, in 1893, was the first to apply these results to the mammalian heart by proving the existence of muscular continuity between auricle and ventricle. His, and then Tawara, worked out the nature of the connecting band or 'auriculo-ventricular bundle,' as it is now called, in much greater detail. It begins near the anterior edge of the right coronary vein. Just below the insertion of the median flap of the tricuspid valve this bundle forms a knot-like thickening, the auriculo-ventricular node. From this knot a process arises which penetrates the fibrous septum, and divides into two main branches, which pass obliquely downwards. When they reach the papillary muscles they divide into a large number of branches, some of which enter the papillary muscles, while others pass on beyond them to mingle everywhere with the ordinary cardiac muscle fibres.

The node is made up of fine, pale, branching fibres with faint striation, which in some respects resemble embryonic

muscle fibres. The fibres interlace and fuse with one another, thus contrasting with the elongated parallel arrangement of the rest of the cardiac muscle. Morphologically and histologically these fibres represent the invaginated portion of the primitive tube from which the complex heart of the mammal is built up.

Then Keith and Flack found a remnant of primitive fibres persisting at the sino-auricular junction, in close connection with the vagus and sympathetic nerves, and having a special arterial supply. This is called the 'sino-auricular node.' Here the dominating rhythm of the heart normally arises, and here it may readily be modified by those extrinsic nerves which are known to influence it.

Between the sino-auricular node and auriculo-ventricular bundle there appears to be no strand of specialized tissue. As we pass from the lower to the higher vertebrates, the primitive tissue becomes reduced in amount and more concentrated in position; a single strand of communicating muscle fibre is peculiar to the mammalian heart. With this reduction the heart becomes less automatic in its action, and more in subjection to the central nervous system. Indeed, the nodes are extremely intimate neuro-muscular contacts. They would appear to be symmetrical structures originally—a view which is supported by the fact that the right vagus and sympathetic act chiefly on the sino-auricular node, while the left sympathetic nerve acts specially on the auriculo-ventricular node. We may regard the bundle as a co-ordinating mechanism which conducts the stimulus rapidly to all parts of both ventricles.

The anatomical and experimental evidence is in favour of extending Gaskell's conceptions, slightly modified, to the mammalian heart. Hering was able to produce a complete stoppage of the supraventricular parts of the heart by a cut made at the sino-auricular junction; while Erlanger has shown experimentally that it is possible, by interfering with

the auriculo-ventricular bundle, to reproduce many of the forms of irregularity met with clinically.

The Properties of Cardiac Muscle.

Before discussing the clinical equivalents of these phenomena, it will be well to consider a little more closely certain physiological properties of cardiac muscle. When the heart responds to a stimulus by a contraction, the ventricle contracts as one whole unit. This implies a need for co-ordination by some conducting mechanism. This *conductivity* is most highly developed in the bundle of His, in which the rate of conduction is 4 metres a second.

If the stimulus is strong enough to produce any response at all, the contraction is the best of which the heart is capable at that moment. This is the so-called *all or none* law. The force of contraction depends on the initial length of the muscle fibre. It will be diminished if the oxygen or food supply is impaired, or if one beat follows too closely on another. As we shall see, the latter occurs in the case of 'premature' beats or extra-systoles.

If a stimulus occurs during the period of contraction the muscle is 'absolutely refractory' and the stimulus is without effect. It is 'relatively refractory' for a short period after the contraction is over. That is to say, only very strong stimuli are effective in producing a response. As we shall see, this *refractory period* is of importance in the understanding of disorders of rhythm such as auricular fibrillation and flutter. Quinidine and digitalis owe part of their action in these disorders to the effect they have of lengthening the refractory period.

The rate of the heart is regulated both by intrinsic and extrinsic factors. A rise in venous pressure increases the diastolic filling of the heart, and by stretching the cardiac muscle not only automatically increases the force of contraction, but also the rate of the heart beat. This is known

as the Bainbridge reflex. For the same reason a fall of venous pressure slows the heart. A rise or fall of pressure on the arterial side, however, has precisely the opposite effect, for the nerve endings in the carotid sinus excite a reflex slowing of the heart when the pressure rises, and an acceleration when it falls. This extrinsic regulation is controlled by the vagus and sympathetic, the mutually opposing action of which is comparable to the 'reciprocal innervation' of skeletal muscle.

Quite apart from these cardiac reflexes, there is a controlling influence exerted by the higher centres through the vagus and sympathetic on the rate of the heart. Exercise, emotion, fever, and dyspnœa in their several ways accelerate the heart through the sympathetic. The acceleration accompanying the increased metabolism which follows an increased supply of thyroxin, whether from spontaneous hyperthyroidism or by direct administration, is of sufficient clinical importance to merit special mention.

The Coronary Circulation.

The main factor which determines the coronary flow is the pressure at the root of the aorta. When the blood pressure is raised and the work of the heart thereby increased, the blood supply to the heart muscle is increased at the same time. As pointed out elsewhere, the sympathetic nerves which constrict the bloodvessels in other parts of the body dilate portions of the coronary arteries. An increase of CO_2 or of acidity in the blood also dilates these vessels. But more powerful than either is arterial anoxæmia; when the oxygen of the arterial blood is diminished, such extreme dilatation of these vessels occurs that even in severe asphyxia the oxygen consumption of the heart remains as near normal as possible.

Within certain limits the coronary flow is unaltered by the rate of the heart, but with very high rates it is possible for

the filling of the coronary arteries to be impeded to some extent, for occasionally very rapid rates, such as in paroxysmal tachycardia, are associated with pain of an anginal nature. More commonly such pain occurs after exercise in severely anæmic subjects, even in early life, and ceases when the anæmia is suitably treated.

Heart Failure.

The commonest causes of heart failure are degenerative changes in the muscle due to impaired nutrition from coronary sclerosis, and the changes wrought on the heart by infections such as rheumatic fever.

Although it is the condition of the cardiac muscle which matters most, the stenosis of a valve has an additional effect by diminishing the output per minute. Thus in mitral stenosis there may be a fall of 40 or 50 per cent. in the circulation rate.

When for any reason the heart muscle is unable to maintain its normal output, the slower circulation leads to the accumulation of metabolites which stimulate the respiratory centre, causing shortness of breath. This centre is so sensitive that undue dyspnœa on exertion is the earliest sign of heart failure. Examination of the peripheral blood under such conditions merely shows the diminished CO_2 content resulting from the increased respirations; our present methods cannot detect the actual nature of the metabolites.

It is to be noted that even a pathological slowing of the circulation rate does not diminish the amount of oxygen supplied to the body, because the slower circulation allows the venous blood to become more deoxygenated than normal. Indeed, in congestive heart failure the oxygen consumption of the whole body may actually rise.

Dyspnœa, then, is the most valuable symptom of early heart failure. The most valuable sign is a rise of venous

pressure, which can be observed in the veins of the neck, and which is due to the delay in the handing on of the blood by the weakened heart muscle. Not only does this delay result in an increased diastolic volume of the heart, constituting dilatation, but the consequent venous congestion leads to enlargement of the liver, scanty albuminous urine, and œdema of the extremities.

Certain physiological principles will help to a comprehension of the factors in heart failure.

How great is the reserve force of the heart is seen by the experiment in which a ligature is placed round the pulmonary artery and slowly tightened. The lumen of the artery may be reduced to one-third of its normal size without perceptibly diminishing the output of blood, though the intracardiac pressure will have to rise three- or four-fold. The same thing is observed if the work of the heart be augmented by increasing the diastolic inflow, either by pressure on the veins of the abdomen, or by injection of large quantities of fluid into the circulation, or by damaging the aortic valves. Within very wide limits the output of the denervated heart is independent of the resistance (Starling), but depends on the diastolic filling.

Now, A. V. Hill proved that the energy set free from a muscle varied with its initial length. In other words, the strongest stimulus to a muscular contraction is the previous stretching to which it has been subjected. Starling applied this principle to the heart, and showed that an increased peripheral resistance caused the heart to dilate until diastolic stretching developed sufficient energy to enable the heart to put out an amount of blood equal to that entering it. A new point of equilibrium is reached almost immediately, so that this dilatation is essentially a useful adaptation. Now, a physiological dilatation of this sort should be temporary, but if the maximum elongation obtainable is not enough to develop sufficient energy, the heart remains dilated. This is

unlikely to occur if the nutrition of the muscle is unimpaired. The reserve force of the normal heart is enormous. But if the muscle is diseased its contractility is diminished.

It is often a surprise to find a high blood pressure in association with a failing heart and a feeble pulse. It is not that the heart is failing behind the high pressure, for lowering the pressure does not relieve the heart. Indeed, such lowering will diminish the coronary flow when it is most needed. There is also an increased risk of coronary thrombosis. Neither can it be that, as the output of the heart falls, vaso-constriction occurs to diminish the size of the bed to be filled, for this would only account for pressure being maintained at its normal level. Such rise of pressure is due to partial asphyxia, which stimulates the vasomotor centre to produce vaso-constriction. The normal effect of the consequent rise of blood pressure would be to stimulate the heart to renewed effort by stretching its muscle, an attempt which, in this case, is unsuccessful, as the myocardium cannot respond.

In the same way a rise of venous pressure causes the blood entering the heart to stretch the auricle more thoroughly and stimulate it to a better beat. The short, sharp auricular contraction suddenly squirting blood into the already partly filled ventricle is the best possible stimulus to its contraction. But this rise of venous pressure has drawbacks: it tells directly on the thin-walled capillaries, unlike raised arterial pressure, which is shut off from the capillaries by the constriction of the arterioles. Their thin walls allow transudation of fluid to occur into the surrounding tissues; hence congested liver, albuminuria, and dropsy.

For continued additional work to be performed, hypertrophy of the cardiac muscle must occur, but its method of production is still doubtful. It may be asked, In what respect is the hypertrophied heart inferior to an ordinary one? It is as powerful, and it can meet the demands made upon it. The answer is that its testing time comes with

increasing arteriosclerosis. The hypertrophied heart needs more blood supply, but it is precisely in the arteriosclerotic type of case that the coronary arteries are more likely to be narrowed.

We can understand why the heart, though it can adjust itself so well to increased resistance to its systolic output, is very intolerant of interference with its diastolic filling. One important factor in this filling is the aspiration of blood into the chest by the respiratory movements. When persons are crushed to death in a crowd they die of syncope, not of asphyxia. Yet it is the compression of the thorax that kills, and children, with their comparatively yielding chests, suffer first. The rapidity of their death is largely due to the fact that the heart cannot be properly filled. Again, rupture of an aneurism of the first part of the aorta into the pericardial sac may be immediately fatal, though only 8 to 10 ounces of blood are extravasated in some cases. No one dies from such a small loss of blood as that; death is not from hæmorrhage, but from the sudden rise of intrapericardial pressure, which prevents the diastolic filling of the heart. In pericardial effusion the accumulation of fluid is not so rapid, so that the heart has time to accommodate itself to some extent; but here, too, its action is seriously embarrassed. Interference with the diastolic filling strikes a serious blow by depriving the heart walls of that stretching which is so powerful a stimulus to contraction. In other words, the heart cannot give out if it does not receive.

It follows from what has been said that it is quite possible for heart failure to occur in the presence of a normal rhythm; when this happens the prognosis is worse because it implies a poorer heart muscle. More commonly, however, it is precipitated by a change of rhythm which puts the heart at a serious mechanical disadvantage. In paroxysmal tachycardia, for instance, the muscle itself may be quite sound and yet circulatory failure may arise within a few

hours. We will therefore proceed to consider types of disturbed rhythm and their influence on the competence of the heart.

Types of Disturbed Cardiac Rhythm.

We can classify the principal types of cardiac irregularity in terms of disturbed function of the primitive cardiac tube. If the rhythm be initiated irregularly at the sinus venosus, we have the type known as *sinus arrhythmia*; an abnormal stimulation of the tube at some point below the sinus results in a smaller premature contraction or *extra-systole*. These may originate in either auricle or ventricle. *Paroxysmal tachycardia* is a series of such extra-systoles originating usually in the auricle. If the contraction of the muscle fibres between the sino-auricular node and the auriculo-ventricular bundle is disorganized, we have *auricular fibrillation*. A diminution in the conducting power of the bundle or one of its main branches delays or prevents each contraction of the auricles from being followed at the proper interval by one or both ventricles (*heart block*). Finally, owing to exhaustion of contractility, the beats may vary in strength (*pulsus alternans*). Most forms of irregularity can be explained as due to one or more of these conditions.

1. **Sinus Arrhythmia.**—The remains of the sinus venosus at the entrance of the great veins is the normal 'pacemaker' of the heart and sets the rhythm. In sinus arrhythmia *the rhythm is initiated at the normal place, but not at evenly spaced intervals*. Once the wave of contraction is started it is propagated quite normally. The duration of systole remains constant, but the diastolic intervals vary. As the pulse quickens it is the diastolic intervals that are encroached on, so that this type of irregularity tends to disappear as the heart quickens—as, for instance, in fever or exercise. On the other hand, it is apt to be noticed for the first time as the heart slows down after a febrile attack. The dog shows

this form of irregularity very obviously, which disappears after section of the vagus or the administration of atropin. It is therefore due to vagal stimulation. Sinus irregularity can also be induced reflexly by swallowing or by deep respirations—two acts in which the sensory branches of the vagus are stimulated.

Sinus irregularity can be recognized by the fact that the pulse rate varies with respiration, quickening during inspiration, and slowing during expiration. It is common in children and is also met with in healthy adults. Its recognition is important, simply that undue significance may not be attached to it. In short, an irregularity that disappears with exercise need not trouble us.

2. **Premature Beats or Extra-Systoles** have been defined as *premature contractions of the auricle, or more usually of the ventricle, in response to a stimulus from some other portion of the heart than the sino-auricular node, but where otherwise the fundamental rhythm is maintained.*

When a stimulus is initiated at some other part of the heart than the sino-auricular node a premature contraction will occur, and as the heart has not had time to accumulate enough contractile material, this beat will be smaller than normal, and, for a similar reason, it will be followed by a longer ventricular pause. This disturbance of rhythm constitutes the extra-systole, and usually involves the ventricle alone, though it may implicate the auricle. It had been produced experimentally many years before its clinical counterpart was known. As was shown experimentally by Marey, and clinically by Lewis, the fundamental heart rhythm is not disturbed by an occasional extra-systole; the next beat after it occurs at the proper time. It can be detected by the premature cardiac impulse followed by an abnormally long pause. If the premature beat occurs very soon after the normal beat, the heart is not full enough nor the beat strong enough to open the aortic valves. In this

case only the first heart sound will be audible and no corresponding pulse will be felt at the wrist. When every alternate beat is premature and yet reaches the wrist, 'coupling' of the pulse is felt. This is an important phenomenon of digitalis poisoning which should be carefully watched for.

The chief sensation of which the patient may complain is the long pause after an extra-systole, as if the heart had 'stopped,' or a 'thud' which accompanies the beat following

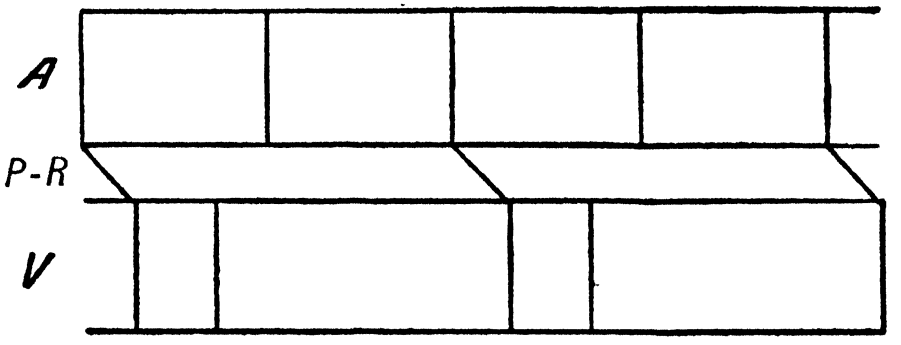


FIG. 3.—EXTRA-SYSTOLES.

A represents the auricular beat and *V* the ventricular. *P-R* represents the interval occupied by the passage of the impulse along the auriculo-ventricular bundle. Note that the auricular beats are regular, but that a premature ventricular beat occurs after the normal one. The next auricular beat, therefore, reaches the ventricle during the refractory period, and consequently is not followed by a ventricular contraction.

the pause. What patients term 'palpitations' are usually extra-systoles.

The prognosis of premature beats is simply that of the associated cardiac lesion when one is to be found. If there is no evidence of cardiovascular disease they may usually be disregarded. Coffee, tea, tobacco, oral sepsis, and digestive disturbances may all excite extra-systoles. They are more frequent, or, at any rate, the patient is more conscious of them, after food. Bromides in a digestive mixture may afford considerable relief.

3. **Paroxysmal Tachycardia,** *a series of regularly and frequently repeated extra-systoles arising from an abnormal*

focus instead of from the sinus. That is to say, the beat originates abnormally, although the pulse is not itself irregular. According to Lewis, a simple tachycardia such as occurs in exophthalmic goitre, pulmonary tuberculosis, infective conditions, and alcoholism, can be distinguished from the paroxysmal type as follows: The pulse rate falls during rest or recumbency, rising to the original rate on standing up again; it is enhanced by exercise, emotion, and the like; the electrocardiogram is of the normal type, and the rapidity is gradual in onset and termination. This simple tachycardia should never, in the absence of other signs, suggest a cardiac lesion. Paroxysmal tachycardia, on the other hand, appears and disappears abruptly, and is uninfluenced by posture and exercise. In this the electrocardiogram shows a decided departure from the normal. This is usually due to an abnormal focus in the auricle, and the auricular extra-systoles are initiated there, passing onwards to the ventricle as usual, but *backwards* to the entrance of the great veins, thus inverting the auricular wave in the electrocardiogram. Paroxysmal tachycardia usually produces contractions at about the rate of 180 times a minute.

Attacks may be precipitated by exertion, emotion, flatulence, and the assumption of certain postures. If the paroxysm is brief, the only symptom is the rapid fluttering action of the heart, but in the more prolonged cases all the classical signs of heart failure may develop and anginal symptoms may occur. Usually these abate quickly on cessation of the tachycardia, but fatal heart exhaustion has occasionally followed. Venesection is therefore indicated when congestion is severe. It is also important to ensure sleep, by hypnotics if necessary. The spontaneous ending of paroxysmal tachycardia has led to various forms of treatment being credited, without justification, with producing the desired effect. A careful search should be made for any septic focus,

a firm abdominal binder should be worn, and the application of an ice-bag to the precordium should be tried; compression of the vagus in the neck is sometimes helpful. Some patients have found for themselves that deep respirations or the adoption of a certain attitude, such as lying supine, affords relief. The most useful drug in preventing or diminishing the frequency of attacks is quinidine, which may be given in doses of 3 grains three times a day. Mecholin has also been advocated.

4. **Auricular Flutter.**—The importance of the refractory period of cardiac muscle has already been emphasized. If this is shortened in the muscle around the mouths of the great veins, a continuous excitation wave is enabled to travel in a regular circle in this region. This is termed 'circus movement' and leads to auricular flutter, in which the auricular rate is about 300 a minute, but, as may be imagined, the ventricle cannot follow such a pace. It usually responds to every second auricular beat or it may respond unevenly, producing obvious irregularity. The ventricular rate is therefore about 150 a minute and is usually not affected by exertion. It will be noted that this rate is definitely lower than that characteristic of paroxysmal tachycardia; the duration of flutter is also much more prolonged. Indeed, when a tachycardia persists for weeks or months, it is probably due to flutter. This condition is not apt to lead to congestive failure in the way in which paroxysmal tachycardia is liable to do, probably because of the lower ventricular rate. The treatment is to convert flutter into fibrillation by digitalis; as soon as this occurs the drug is stopped immediately. This is often followed by the resumption of a normal rhythm.

5. **Auricular Fibrillation.**—*The regular contractions of the auricle are replaced by very rapid, irregular, and ineffective twitchings of all the auricular musculature.*

Fibrillation, like flutter, results from circus movements,

but the contractile wave follows an irregular and varying course, unlike the regular wave of flutter. This irregular circus movement sets up a number of very fine waves with a frequency of 500 or more a minute. These reach the auriculo-ventricular bundle in a rapid and highly irregular rhythm, to which the ventricle can respond only in an irregular manner.

Auricular fibrillation principally occurs in (1) mitral stenosis, when the damaged muscle of the auricle with its obstructed outflow has become incapable of orderly contraction; (2) hyperthyroidism, particularly when of long standing; here the carbohydrate metabolism of the fibres of the primitive tube is probably at fault; (3) arteriosclerosis, involving the coronary blood supply to the auricular muscle.

Auricular fibrillation can generally be recognized by the following clinical points: the pulse is completely irregular; there is no relation between the size and the strength of the beats and the preceding diastolic pauses, such as is found, for instance, with extra-systoles.

This irregularity becomes more obvious after the patient has exerted himself slightly, as by sitting up and down three or four times. Multiple premature beats, on the other hand, usually disappear after this procedure. When the veins of the neck are full it can sometimes be seen that the only large wave is synchronous with ventricular systole.

In cases of mitral stenosis, which is the commonest associated heart lesion, the presystolic murmur disappears with the onset of fibrillation, while the mid-diastolic rumble persists, but the latter is only audible in advanced stenosis. The crescendo presystolic murmur is due to auricular contraction, while the diastolic murmur, diminuendo in character, is due to the blood which has been stored up in the auricle during ventricular systole flowing through a constricted orifice as soon as the ventricle passes into diastole. The former is an active process, the latter is passive.

In cases of hyperthyroidism in which auricular fibrillation is common there are no such murmurs audible. The differential diagnosis between these two conditions is particularly important because their treatment differs.

With the onset of auricular fibrillation the subjective symptoms may increase. Precordial pain, a fluttering sensation, faintness, and dyspnœa with orthopnœa are common. If they occur suddenly with an irregular pulse, they are always due to fibrillation.

It must be remembered that the pulse rate, although usually frequent, is not always so. There may be a natural degree of block in the bundle with a heart rate as low as 60 a minute, or digitalis may have been given previously and may have caused a partial block. When this occurs it is more than ordinarily difficult to detect the type of irregularity.

In consequence of the disorderly rhythm imposed on them, the ventricles are placed at a great mechanical disadvantage, and it is to this that the serious symptoms are due. Fibrillation plays an important part in the ultimate breakdown of the heart. If the ventricular rhythm can be made slower and more regular, enough blood will pass from the auricles into the ventricles for the purposes of the circulation, even though the former remain in their state of paralytic distension. The action of digitalis is more successful in auricular fibrillation than in any other class of case, and a few doses may change the condition from one of acute distress to one of comparative comfort. This is due to its depressing effect on conductivity, producing, in fact, a mild degree of heart block, so that the auriculo-ventricular bundle ignores a large number of the irregular stimuli it receives from the fibrillating auricle.

Treatment of congestive failure with auricular fibrillation is an urgent matter, and digitalis must be given in quantities sufficient to ensure an adequate concentration in the body.

A milligram of digoxin should be given by mouth, followed by ½ milligramme four hours later. When the patient is under constant observation, even 1½ milligrammes may be given for the first dose. It will act within three hours by this route. The appearance of coupled beats is a sign to stop digitalis altogether for a time.

When the desired effect is obtained, ¼ milligramme should be continued twice daily, or, better, ⅛ milligramme four times a day. This is the maintenance dose, and may usually be continued indefinitely. If the pulse rate is satisfactory and there is no coupling of beats, some nausea and occasional vomiting may safely be ignored.

When there is no need for rapid digitalization 2 grains of digitalis folia should be given three times a day until the desired effect is obtained; after this a maintenance dose should be continued. This will usually prove to be 1 grain twice or thrice daily.

The influence of the drug is less if there is fever. Its action is also less marked in the arteriosclerotic cases.

If there is much œdema or free fluid in the abdominal cavity, the diuretic action of digitalis is aided by an injection of salyrgan on alternate days for a week. A suppository of novasurit may do equally well, but in some patients this is apt to irritate the rectum.

It is quite possible that diuretics also help by diminishing œdema of the heart muscle itself.

It will be noted that digitalis does not strike at the root of the mischief; it merely checks its effects. In quinidine, however, we have a drug which can frequently control the circus movements by lengthening the refractory period and slowing the conduction of the excitation wave from point to point in the muscle. Thus it restores a normal auricular rhythm. It is of great value in hyperthyroidism, whereas in mitral stenosis it is unsafe, because of the risk of loosening a thrombus from the wall of the auricle as a result

of restoring auricular contractions. Careful enquiry should be made for any previous history indicating stenosis, such as hæmoptysis. Quinidine is also contra-indicated in the presence of any gross cardiac disease where the heart may be unable to maintain a normal rhythm. But in other forms of auricular fibrillation, whether associated with arterio-sclerosis or toxæmia, or even when no definite ætiological agent can be found, it is always worth a trial. While hyper-thyroidism persists auricular fibrillation may recur. If a normal rhythm is obtained following its use, quinidine in small doses may be continued for a few weeks. But this should only be regarded as a temporary measure until the thyroid condition can be treated surgically. After surgical treatment, normal rhythm is often resumed spontaneously. If this does not occur after three weeks quinidine should then be given. It is best to begin with a dose of 2½ grains three times a day, and indeed this may prove adequate. Some patients have an idiosyncrasy for quinidine, which may show itself by faintness, giddiness, vomiting and diarrhœa or skin rashes. If these symptoms do not occur, the drug can be gradually increased if necessary up to 7 grains thrice daily, and then reduced to 1 grain three times a day for one week as soon as normal rhythm returns.

6. **Heart Block.**—*Every auricular contraction is not followed by a ventricular contraction.*

Heart block may be: (1) *Complete*. The rhythms of the auricle and ventricle are then entirely independent. (2) *In-complete*. Then the conductivity of the auriculo-ventricular bundle is so impaired that one out of every two or three auricular beats is unable to initiate a ventricular beat. (3) *Latent*. No beats fail to come through, but the P-R interval is consistently longer than usual.

The features of complete heart block are: (*a*) Slow pulse, at first paroxysmal, but tending to become permanent. The commonest rate is 30 a minute, but 20 or even as low as 6

have been observed. (*b*) The auricular contractions, as evidenced by the wave in the jugular vein, remain approximately normal, however, and even by inspection of the neck it may be possible to make out that every contraction of the auricle is not followed by a ventricular contraction. (*c*) Attacks of vertigo, syncope, or epileptiform convulsions in the severer cases. The last is most likely to occur during a change from incomplete to complete block.

The combination of slow pulse and epileptiform convulsions has been known since the middle of last century

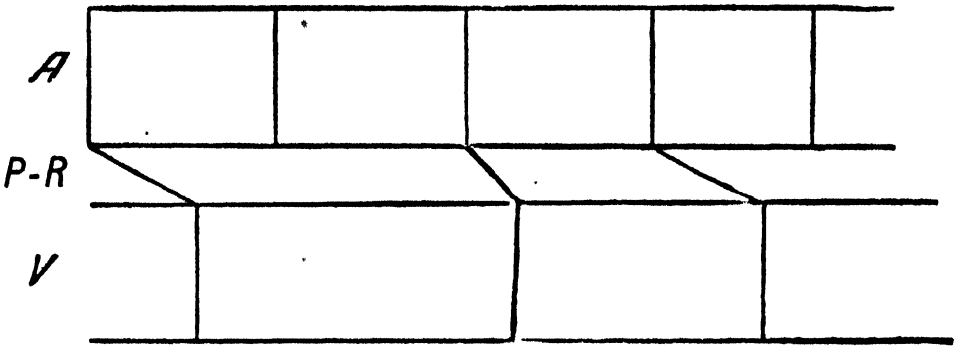


FIG. 4.—HEART BLOCK.

Note the lengthened *P-R* interval, also that each auricular beat is not followed by a ventricular contraction. The short *P-R* interval appears after each dropped ventricular beat.

as Stokes-Adams disease, but its significance and the method of its production were not recognized for many years. The cause is a lesion of the auriculo-ventricular bundle, the cerebral symptoms being due to anæmia of the brain resulting from the defective circulation.

The bundle may be involved in fibrosis, gumma, atheroma, thrombosis, or fatty infiltration; new growth is occasionally responsible.

Temporary heart block occurs in acute rheumatism and influenza. This is an indication, especially in young people, of myocardial damage and should be treated by complete

rest. Recovery may be complete, or fibrosis may follow, producing organic changes in the bundle in later life.

Heart block has also been observed in asphyxial conditions.

The action of digitalis in producing heart block has already been mentioned. It is indeed chiefly due to this property that digitalis enjoys the reputation it does in the treatment of cardiac failure.

In complete heart block the ventricles continue to beat slowly and independently of the auricles, for they have a rhythmical power of their own. This, however, is usually not adequate to maintain the circulation efficiently.

As a large proportion of cases of heart block are due to syphilis, Wassermann's reaction should be tried in every case, and if it is positive, vigorous antisyphilitic treatment must be carried out, for, though often disappointing, it affords the best chance of relief. Atropin is indicated on theoretical grounds, as it paralyzes the inhibitory action of the vagus, but it does not appear to give good results when the block is complete. Barium chloride in doses of $\frac{2}{3}$ grain three times a day over a long period may be useful in warding off attacks. Injections of 5 minims of liquor adrenalin hydrochlor. may be very useful as an emergency measure, and ephedrin hydrochloride in half-grain doses by the mouth is sometimes beneficial. It might be thought that digitalis is contra-indicated, since it depresses the conductivity of the bundle. But it may improve the contractions of the independently acting ventricle, and there seems to be an actual advantage in converting an incomplete into a complete heart block, since it is the alterations from one to the other that induce convulsions.

Complete heart block of long standing usually terminates in congestive failure whatever treatment is adopted. It must be borne in mind, however, that the condition is a relatively rare one.

Vaso-vagal Attacks.—The influence of the vagus—especially the left—in producing heart block and in slowing the heart has already been mentioned.

An overaction of this mechanism, combined with excessive dilatation of bloodvessels elsewhere, is seen in the so-called *vaso-vagal syncope*.

This is the commonest form of fainting attacks, especially in young persons, and is thought to be due to an exaggeration of reflexes originating in the carotid sinus and aorta.

The attacks occur in healthy persons as a result of fatigue, or after pain or sudden emotion. They come on most commonly when the subject has been standing or kneeling in a fasting condition; for example, at early service. They occur also in chronic heart disease, as in aortic regurgitation. An attack may commonly be prevented by lying down. Unconsciousness lasts a few minutes only and is accompanied by pallor and sweating. Vaso-vagal attacks may be accompanied by much mental distress, the so-called 'angor animi.'

The important point about this condition is to differentiate it from true cardiac syncope, which is rare. The prognosis in the former is entirely favourable, whereas in the latter it is very bad.

7. **Pulsus Alternans.**—*A regular succession of small and large beats.* Whereas deficient conductivity will lead to heart block, impaired contractility will lead to pulsus alternans. The latter is generally attributed to variation in the number of the ventricular fibres which contract during systole. But if this were so, there might be cardiographic evidence of its existence which is not forthcoming. Another view is that the heart, as a whole, is defective in contractile power. This rather contradicts the 'all or nothing' principle of cardiac contraction. Pulsus alternans is usually associated with high blood pressure, because it is caused by myocardial degeneration consequent on the coronary arteries sharing in the general arterial disease. It may be

brought out only on exertion, and it is well to try the effect of exercise in suspected cases. It is difficult to recognize the condition by the finger even when the pulse tracing shows obvious alternation. As the systolic pressure of the larger beats is higher than that of the small beats, the condition may be recognized by applying the sphygmomanometer and just raising the pressure in the armlet sufficiently to halve the pulse rate at the wrist. This alternation implies a grave condition, for it is the expression of an exhausted heart, with great impairment of its reserve force. In Lewis's graphic phrase, 'it is the faint cry of an anguished and fast-failing muscle, which, when it comes, all should strain to hear, for it is not long repeated.'

Apart from angina, the dominant symptom is apparently causeless breathlessness. The dyspnœa is sometimes paroxysmal, or there may be Cheyne-Stokes respiration. The gravity of pulsus alternans may be gathered from the fact that in Windle's series of seventeen cases no patient lived longer than seventeen months after he first observed pulsus alternans. Its diagnosis from the bigeminal pulse of ventricular extra-systoles is important, for the latter means no more than increased excitability of the heart; it is in no sense an index of the degree of myocardial degeneration, and does not afford any indication as to the expectation of life. The distinguishing point is that in extra-systole the long pause follows the small beat, while with an alternating pulse the intervals are equal. On auscultation the characteristic rhythm of the extra-systole will be recognized.

CHAPTER X

THE VASOMOTOR SYSTEM IN DISEASE

THE introduction of precise methods of registering blood pressure in clinical work has naturally directed much more attention to the part played by the vasomotor system in disease.

Briefly, the functions of the vasomotor system are two—to regulate the general blood pressure, and to regulate the local blood supply. These functions are carried out by the following structures:

1. **The Vasomotor Centre,** which begins 1 or 2 millimetres below the corpora quadrigemina and ends 4 millimetres above the calamus scriptorius. But there must also be secondary centres in the cord, since asphyxia can still produce a rise of blood pressure after the medullary centre has been cut off, though not after the spinal cord has been destroyed. There is, further, some degree of local vasomotor control, since some recovery of tone may occur after complete separation of the vascular area from the central nervous system. This is probably due to the usual effect of stretching plain muscle—namely, that it contracts more forcibly.

2. **Efferent Nerves,** which can either constrict or dilate the vessels.

(*a*) *Constrictors.*—These are much the most numerous, and are confined to the sympathetic. Leaving the spinal cord in the anterior roots of the second thoracic to the second lumbar nerves, they pass into the sympathetic chain by the white rami communicantes, and end around a nerve cell in the first ganglion they reach. Here a new non-medullated 'post-ganglionic' fibre starts, which is distributed to its appropriate destination. This is the method of distribution, whatever the part of the body to be supplied.

(*b*) *Dilators.*—These are not nearly so numerous. The muscular coats of the bloodvessels being always partly contracted, it is possible for dilatation to be produced by inhibition of a constrictor. Pure dilator nerves will, therefore, only be found where there is a special need for marked and rapid dilatation. Thus the chorda tympani nerve carries dilator fibres to the submaxillary gland, and the auriculo-temporal nerve to the parotid. The nervi erigentes form part of the pelvic visceral nerve springing from the second and third sacral roots. All these belong to the *parasympathetic* system—*i.e.*, those fibres with visceral functions which leave the central nervous system above the cervical or below the lumbar plexus. Unlike the constrictors, they have their ganglionic station close to their destination.

The existence of dilator fibres, also, in mixed nerve trunks has been proved by taking advantage of the fact that constrictors degenerate more quickly after section, and are more readily affected by cooling than dilators; on using slow, rhythmically repeated shocks (one per second) a dilator effect can be obtained, whereas rapidly interrupted shocks would excite the constrictors.

Dilator nerves to the limbs appeared in a new aspect when Bayliss showed that they seem to be in every way identical with the sensory nerves. Under experimental conditions, at any rate, these fibres are able to carry ' antidromic ' impulses —that is to say, the same fibre is able to convey sensory impulses towards the brain and dilator impulses towards the periphery. Apparently some fibres passing by the posterior roots have been actually traced to the peripheral vessels. The stimulation of these antidromic fibres appears to set free a histamine-like substance which has a local vaso-dilator action.

3. **Afferent Nerves.**—Impulses may pass to the vasomotor centre, calling for a general rise or fall of blood pressure. While the efferent nerves may produce either a local or a

general effect, the afferent can only produce the latter. They are of two kinds:

(*a*) *Pressor*, producing a rise of blood pressure. All sensory nerves are pressor in their action, causing the vasomotor centre to throw out increased constrictor impulses, particularly to the splanchnic area. This explains the rise of pressure which may be seen in any painful condition. It has the effect of increasing the blood supply to the brain; at the same time vaso-dilatation occurs at the site of the painful stimulus through the antidromic fibres. In this way the blood supply is simultaneously increased at the point where the painful stimulus is *received* and where it is *perceived*, thus facilitating the appropriate reaction in each case.

(*b*) *Depressor*, producing a fall of blood pressure by causing the vasomotor centre to relax the normal constrictor tone in the splanchnic area, which thereby becomes flushed with blood. The only pure depressor nerve is the depressor branch of the vagus. This may be regarded as a way of escape for the heart, if it be labouring against too high a blood pressure, since its nerve endings are in the aortic wall.

The existence of depressor fibres in sensory nerves may also be demonstrated, since on regeneration after section they recover before the pressors, and on cooling they retain their function longer. Stimulation of the mucous membrane of the rectum and vagina may also produce a depressor effect, especially under light anæsthesia.

The Carotid Sinus Reflexes are now recognized as important. The carotid sinus is a dilatation of the bifurcation of the common carotid artery and is richly supplied with sensory endings of the same type as those between tendon fibres; these are 'presso-receptors' and are exquisitely sensitive to minute internal changes of pressure. An undue rise in pressure in either the aorta or carotid sinus produces a reflex dilatation of arterioles, which at once causes the general arterial blood pressure to return to a lower level. This is also

brought about by a slowing of the heart through the vagus. The sensory nerve endings in the wall of the carotid sinus are also able to initiate a reflex in the opposite direction—*i.e.*, undue fall of pressure locally will lead to a rise of general blood pressure through the action of the vasomotor centre. Changes in sino-aortic pressure may also have widespread effects, particularly on respiration.

In addition to this, Heymans has shown that there are also chemo-receptors in the neighbouring carotid body which are sensitive to chemical changes in the blood. Various drugs producing hyperpnœa and circulatory changes act through these chemo-receptors, again underlining the close interaction between nervous and chemical stimuli.

The section of the sino-aortic nerves in animals is followed by a very striking condition of permanently raised blood pressure, which is eventually followed by arterial degeneration.

Vasomotor Disturbances.

Failure of the vasomotor system to respond adequately to the needs of the body may result either in insufficient regulation of the general blood pressure or of the local blood supply. We will take examples of each.

It is not uncommon to be told by a patient that one of his first symptoms was that, on getting out of bed in the morning to pass water, he fainted. Normally a change of posture should not produce a considerable effect on the blood pressure, the slightest degree of cerebral anæmia at once inducing the vasomotor centre to throw out increased constrictor impulses, which, by tightening up the splanchnic bloodvessels, forces more blood to the head again. In this way the effect of gravity is counterbalanced. But if the vasomotor response is inadequate, the erect posture will lead to cerebral anæmia, and hence to fainting. If the intra-abdominal pressure is lowered at the same time by the emptying of the bladder, this is still more likely to happen.

Fainting following the tapping of ascites is due to the same cause, and, as is well known, it may be prevented by tightening up a binder round the abdomen as the fluid escapes, thus avoiding splanchnic engorgement.

During prolonged recumbency the vasomotor centre will lose its promptitude in responding to changes of posture, which explains the faintness that any patient is liable to on first getting out of bed after a long illness.

Insomnia may be due to inadequate control of the general blood pressure by the vasomotor system. Ordinarily a certain degree of cerebral anæmia plays an important part in inducing sleep. The hypnotic effect of taking some warm fluid or a little food is due to the vaso-dilatation it induces in the splanchnic area, thus drawing away blood from the head. Cold feet may help in causing insomnia by keeping too much blood at the opposite end of the body. The cold extremities which so commonly accompany heart failure are apparently due to the shutting off of the blood supply from less vital structures in order to maintain the cerebral and coronary circulation at all costs.

Insomnia is often troublesome in conditions of high arterial tension. Apart from measures directed towards the cause of the high tension, we should treat this symptom by propping the head up on fairly high pillows, by flushing the abdominal vessels by a drink of hot fluids, and by preventing the feet from getting cold.

In 'functional' or orthostatic albuminuria, inadequate vasomotor control, as we have seen, plays an important part. Albumen, therefore, is present in the urine secreted in the day, but absent from that secreted while in bed.

Examples of failure in the regulation of the local blood supply are seen in Raynaud's disease and in erythromelalgia.

At first sight it is not a little surprising that the organs composing the 'tripod of life'—the brain, the lungs, and the heart—do not conform to these general laws. Yet on con-

sideration it will be clear that it is just because they are so important that they cannot be subservient. For we must remember that the vasomotor system can override the local needs for the general demands. The efferent path in a reflex arc is open to impulses coming from many quarters, although the afferent channel is reserved for impulses coming from the particular organ it supplies.

The organs composing the 'tripod of life' cannot allow their local needs to be subordinated in this way. This may cause them in disease to override the interests of the general economy for their own advantage, though it is merely an example of the survival of the fittest, the most vital organs being protected at all costs.

It is for just such reasons that we find the spleen, a comparatively leisured organ, has its blood supply most subordinated to the vasomotor system. The splanchnic area plays the largest part in vasomotor effects. Now, it may well be that the stomach or intestines cannot spare their extra blood at a time when vaso-constriction is called for in the general interests of the economy. The spleen is a portal reservoir which will not suffer vitally from a vaso-constriction, and so it is called upon. Indeed, Barcroft has shown that this property of the spleen is an important factor in the regulation of the volume of the circulating blood. Thus after hæmorrhage the spleen contracts in order to maintain the blood volume. It is because of its subordination to the general interests that diseases of the spleen are accompanied by so few definite physiological features. As Frederick Taylor tersely put it, the spleen is more sinned against than sinning.

The way in which the local needs may be overridden by the vasomotor system is seen in the blanched condition of the skin in the cold stage of fever and in the slowing of digestion that may be produced by severe effort soon after food.

We may consider some of the results of the special conditions of the vasomotor system obtaining in the 'tripod' of brain, lungs, and heart.

Brain.—Munro, in 1783, enunciated the dictum that the quantity of blood in the cranium is constant, since the brain substance is incompressible and enclosed in a rigid box. Allowing for variations in the quantity of cerebro-spinal fluid, this is true.

The first effect of a rise of arterial pressure will be to express the cerebro-spinal fluid from the cranium, and then to compress the cerebral sinuses until the pressure in them rises to that which the brain substance exerts against them. Thus the conditions approximate to those obtaining in a system of rigid tubes.

Now, the one part of the brain that must keep up its supply of arterial blood is the medulla, for here are the centres that are essential to life. If the blood supplied be too rich in carbon dioxide, the respiratory centre is excited to increase the respiratory rhythm; if the quantity of blood be not adequate, the vasomotor centre is excited by the slightest degree of cerebral anæmia to contract the vessels in the great splanchnic pool, and thus force more blood up to the head. There are two ways in which the blood supply to a part may be increased—local vaso-dilatation, or vaso-constriction elsewhere. In a rigid box a local relaxation of muscular tone would not be very effective, for it might be overridden easily by the intracranial pressure already existing. To force the blood in by a general rise of blood pressure is to employ a much more powerful mechanism. Thus it is we find that the blood supply to the brain is mainly controlled by means of the splanchnic area, which, in its turn, is controlled by the vasomotor centre within the cranium.

This does not mean that there are no vasomotor nerves in the cerebral vessels—such have been found by Morison, Gulland, and others—and perfusion of adrenalin will cause a

slight contraction of these vessels. But it is safe to assert that they must play an entirely subsidiary part, and that all the vasomotor effects ordinarily observed can be adequately explained without reference to them.

To avoid cerebral anæmia, the general blood pressure must be kept at a point above the intracranial pressure. This was clearly proved by Cushing, who adopted the method of varying the intracranial pressure by introducing normal saline solution into the cranial cavity from a pressure bottle. The effect on the general blood pressure was observed by means of a tracing taken from the femoral artery. Until the intracranial pressure exceeded the blood pressure, nothing more than a slight quickening of pulse and respiration occurred, and even this could be avoided if the fluid did not interfere with the sensitive dura. But when that point was reached, the blood pressure was at once raised until it was again greater than the intracranial pressure. This was repeated with each increase of intracranial pressure until the blood pressure was forced to a level considerably over 200 millimetres of mercury. Then the vasomotor centre began to show signs of giving way. The splanchnic vessels could be seen to contract every time the brain was compressed, and to dilate again as the pressure fell. If the pressure were raised too rapidly, the so-called major symptoms of compression might be produced—convulsions, evacuation of the bladder and rectum, cessation of the respiration and pronounced vagus effect upon the heart, often causing its complete arrest for from ten to twenty seconds. Then followed a release from this extreme vagus inhibition, and the vasomotor centre began to exert its striking influence.

If the vagi were divided before the compression was applied, the blood pressure could be seen to correspond even more closely than before to the degree of intracranial tension, always remaining slightly higher. If both vagi and spinal cord were thus divided, an increase in intracranial tension

did not affect the level of the blood pressure in the slightest degree, showing that the adjustment is brought about by constriction of the bloodvessels in the rest of the body.

The absolute necessity of maintaining the blood pressure at a higher level than the intracranial establishes a vicious circle, for the hæmorrhage produces a rise of pressure, and the rise of pressure increases the hæmorrhage. For this reason some authorities consider that cerebral hæmorrhage is inevitably fatal, and that recovery from a vascular lesion in the brain proves it was thrombotic or embolic in nature. This seems an extreme view, but it may be admitted that a rising blood pressure in cerebral hæmorrhage is of a very grave prognosis, as it shows the bleeding is still continuing.

Is there any way of lowering intracranial pressure directly? Then the vasomotor centre would allow the blood pressure to fall; this would assist the arrest of hæmorrhage, and the vicious circle would be broken. Lumbar puncture will diminish intracranial tension, and has, therefore, been recommended in such cases. It has been thought to be risky, in that it will leave the arteries less supported, and therefore more liable to bleed, while it may allow the cerebellum to be pushed down into the foramen magnum, thus pressing on the medulla. But as soon as the intracranial pressure is reduced the blood pressure will fall, and therefore the liability to hæmorrhage is diminished, though, one must admit, not abolished. That the blood pressure can be reduced in this way has been frequently observed. Another useful method of reducing intracranial pressure is the administration of hypertonic saline solution intravenously or, more simply, *per rectum*. This abstracts fluid from the circulation.

Cushing's experiments also explain why we so frequently find more than one hæmorrhage into the brain substance, if the initial one be at all large. If looked for, small hæmorrhages into the pons will be found very commonly in cases

of ordinary lenticulo-striate hæmorrhage. It was formerly a puzzle to decide how these were produced, and whether they occurred simultaneously with, before, or after the large hæmorrhage. It is now clear that the large hæmorrhage is responsible for driving up the general blood pressure so much that diseased arteries in other parts of the brain are unable to withstand the strain.

The effect of changes in the venous circulation must also be considered, for anything interfering with the return of blood from the head to the heart must raise the venous and consequently the capillary pressure on the brain. Hence the vascular accidents which may occur during defæcation or violent paroxysms of coughing, as in whooping cough.

Lungs.—The absence of direct vasomotor effects in the pulmonary vessels has some interesting bearings on the treatment of hæmoptysis, which have already been touched upon in the first chapter. It must be remembered, however, that the lung receives blood by another channel also, the bronchial arteries, springing from the aorta. In the hæmoptysis of mitral stenosis the pulmonary vessels alone are involved; adrenalin and other constrictors will therefore do harm by forcing blood from the systemic into the pulmonary vessels. But amyl nitrite may do good, because it will relieve the engorged lung by dilating the systemic vessels. In the hæmoptysis of phthisis, either pulmonary or bronchial vessels may be eroded, though the former are more likely to be implicated, since they are more numerous. But styptic drugs would be inadvisable even if we could be sure that a bronchial artery were the source of the hæmorrhage, for any benefit derived from their local action would be outweighed by the general rise of pressure and by the pulmonary turgescence, which might cause other weak spots to rupture. Nitrite of amyl might still be useful, as the widespread dilatation would draw blood away from the lungs, and thus more than counterbalance the risks of reopening the bleeding-

point. Also the lowered pressure would favour the sealing of this point by blood clot. The same principles would therefore guide us, whichever set of vessels were involved. Artificial pneumothorax, by allowing the lung to retract, may promptly arrest hæmorrhage, and should be considered in severe hæmoptysis.

Œdema of the lungs is a common terminal event. This form of œdema may develop very acutely. It is held to indicate a somewhat rapid failure of the left ventricle, such as occurs in thrombosis of the left coronary artery, while the right ventricle continues to beat forcibly. As there is no vaso-constrictor action in the pulmonary vessels, there is nothing to prevent engorgement of the lung capillaries, and an effusion must occur into the alveoli.

A patient, usually with high blood pressure and often with aortic disease or (in women) with mitral stenosis, is seized, generally while recumbent, with sudden dyspnœa and cyanosis. He becomes greatly distressed, throwing himself about or coughing incessantly. A quantity of froth, which has been compared to that of beer, only finer and thinner and sometimes blood-stained, begins to issue continuously from nose and mouth. Death may occur within a few minutes, and will not be delayed beyond a few hours, if the condition cannot be relieved.

As the heart continues to beat strongly after the patient is apparently suffocated, it might be urged that death could not be from syncope. But it seems likely that the forcible sounds are produced by the right heart. The most probable sequence of events is this: The normal exact balance between the output of each ventricle is upset; if the output of the left ventricle is reduced even temporarily while that of the right continues unchanged, the surplus blood must be accommodated in the lungs until they become engorged, since they are unable to shut off any of the blood supply by vaso-constriction. An outpouring of serum occurs into the

alveoli in such quantities that the patient is drowned in his own secretion. The dramatic effect of venesection supports this view. It temporarily lowers the pulmonary blood pressure and probably improves the coronary circulation by facilitating the coronary venous return. An immediate injection of $\frac{1}{4}$ grain of morphia should always be given. Indeed this is often effective even without venesection. Its sedative effect on the respiratory pump presumably diminishes the return of blood to the right heart. By these means a remarkable recovery may be achieved. The addition of $\frac{1}{100}$ grain of atropin sulphate, formerly advised, is no longer recommended by most authorities.

Heart.—The way in which the supply to the heart muscle is made proportional to its requirements has already been explained in the chapter on some aspects of heart diseases.

On Blood Pressure.

The vasomotor system is, of course, only one factor in determining the blood pressure. Its importance lies in its sensitiveness to the needs of the organism; like all nervous mechanisms, it is characterized by the rapidity of its reactions.

The pressure, by which the whole of the vascular system is kept distended with blood, is the product of:

1. The beat of the heart.
2. The peripheral resistance.
3. The elasticity of the vessel wall.
4. The volume of the blood.

1. **The Beat of the Heart.**—While the energy of the heart necessarily originates the pressure in the vessels, an increase in its output will cause a rise in pressure only so long as the size of the arterioles remains the same. When there is a large amount of blood in the great veins awaiting entrance

into the heart, this stretches the right side of the heart reflexly, causing acceleration of the rate, but not necessarily a rise of pressure. Indeed, the nervous mechanisms provide that when the body is at rest the pulse rate will vary almost inversely with the arterial blood pressure. If the pressure rises to a point at which the cardio-inhibitory centre in the medulla is stimulated, the heart is slowed through the vagus by means of the nerve endings in the carotid sinus and aorta.

2. **The Effective Peripheral Resistance** is provided mainly by the constriction of the muscular coats of the small arteries, which are chiefly controlled by the vasomotor nerves. That the capillaries can change their calibre under the influence of chemical stimuli is, however, now proven, and the arterioles themselves are not unresponsive to such. Thus Gaskell showed that the acid products of metabolism would dilate the peripheral vessels, and thus provide for their own removal. Moreover, marked dilatation of the coronary vessels occurs in anoxæmia, thus ensuring an immediate increase in blood supply. In the first stage of high blood pressure in disease there need be no structural change in the vessel wall, but the muscular coat contracts, possibly under the influence of toxic agents. This is in accordance with the general principle that the important functions are subserved by both a chemical and a nervous mechanism. How essential the nervous factor is in maintaining the pressure is seen on destruction of the cord, when the vessels lose their tone so completely that the circulation cannot proceed. It is the splanchnic area which has in this way by far the greatest influence on the general blood pressure.

3. **The Elasticity of the Vessel Wall** tends to diminish variations of pressure between systole and diastole. With each heart beat the vessel distends, retracting again when systole is ended; thus during diastole the pressure remains higher than it otherwise would do. With loss of elasticity comes a more violent fluctuation. Indeed in the absence of

hyperthyroidism and of aortic regurgitation, a pulse pressure of over 60 mm. is a valuable early sign of rigidity in the blood vessels. Mark the tendency to a vicious circle. If the work is too much for the heart it dilates and later, probably in consequence of overstretching, hypertrophies. With increasing arteriosclerosis, and consequently greater work, the hypertrophy continues. A hypertrophied heart needs a larger blood supply, but the arterial thickening is especially apt to involve the mouths of the coronary vessels, thus diminishing their supply of blood to the cardiac muscles.

4. **The Volume of the Circulating Blood** has within wide limits in the normal animal only a subordinate and temporary influence on mean blood pressure (Janeway). Its variations can be easily compensated for when at rest by the vasomotor system. This limits the usefulness of venesection as a treatment for hypertension to those cases where this compensating mechanism has become damaged by arteriosclerosis or chemical agents. In the treatment of an engorged pulmonary circulation venesection as already explained may restore the balance.

The blood pressure in health reflects the various physical and mental states; a cold bath, a meal, the smoking of a cigar, an animated discussion, all affect it. Irrespective of such disturbances, there are also small diurnal variations. It might be questioned whether this does not destroy the value of a blood pressure record. But no one questions the value of a temperature chart which also shows fluctuations not produced by disease, and no one doubts the importance of a pulse record, though this can also be affected by nervousness. It is, however, important that the patient should be assured that the process is quite painless. If the pressure is raised through nervousness, the pulse rate may also be increased. A high pressure with a slow pulse cannot usually be attributed to nerves. It is well to take three readings at

intervals in doubtful cases. Examination in the recumbent posture yields the most reliable results.

The standard method of estimating blood pressure involves circular compression of the upper arm by an air pad, adjusted by an armlet not less than 12 centimetres wide, to which a mercurial manometer is attached. Spring manometers are much less reliable unless frequently tested against a mercurial one. Air is pumped in until no pulse can be heard by the stethoscope placed over the artery immediately below the armlet; as the pressure in the armlet is slowly released, the point at which the sound first reappears is taken to indicate the systolic pressure. The radial pulse should also be felt as a control. On further releasing the pressure in the armlet loud thumps are heard; as the pressure is still gradually lowered a point is reached where this is replaced by a muffled sound. Indeed, the disappearance of the thump can not only be heard, but felt by light palpation over the brachial artery. This is taken as the diastolic pressure, which is important as being the charge which the arteries must constantly bear and from which they cannot escape. A high diastolic pressure wears an artery out more quickly than a high systolic with a low diastolic pressure.

It is usual to regard the average systolic pressure as 120 millimetres and the diastolic as 80 millimetres for a person aged twenty. It is normally lower in childhood, and the systolic pressure tends to rise at the rate of about half a degree a year after twenty. But no rigid rule can be laid down, and a systolic pressure of 120 to 140 in an elderly person suggests a good expectation of life. A diastolic pressure of more than 90 in the recumbent position should be regarded with suspicion.

Pulse pressure is the difference between systolic and diastolic pressures, and is normally about 50 per cent. of the latter. It is greatly increased in aortic regurgitation, because of back-flow from the aorta into the heart and of the

change of tone in the peripheral vessels; and in hyperthyroidism when the basal metabolic rate is increased. It is diminished in certain cases of cardiac weakness.

It is impossible to discuss the whole question of blood pressure in disease within the limits at our disposal, but we may take examples of the way in which its study has enlarged our ideas, cleared up difficulties in diagnosis, and helped in prognosis. This has naturally reacted on treatment.

It has enlarged our ideas on the subject of the heart failure in acute infections and shock. Work on wound shock seems to show that the capillaries are the vessels chiefly concerned. And Dale and Richards have shown that capillary dilatation may occur as the result of toxic action. The term 'exæmia' has been suggested for this condition.

In the light of the knowledge we have thus obtained, it would appear that many of the stimulants employed are quite unsuitable for a condition of vasomotor paralysis. Strychnine acts on the centres, which are already exhausted or intoxicated, and therefore unresponsive. Ether has little or no effect; while brandy, which is a vaso-dilator, can hardly benefit vessels that are already relaxed. Barium salts—*e.g.*, $\frac{2}{3}$ grain of the chloride—and pituitrin, which act directly on the muscle fibre, and not on nerve endings, may sometimes help. An abdominal binder should be applied firmly to prevent accumulation of blood in the now stagnant splanchnic pool. But the main point is to keep up the volume of circulating blood. During the last war Bayliss introduced the method of infusing a solution of gum arabic, in the hope that this, approximating more to the osmotic pressure of blood, would not transude so quickly into the tissues. But improvements in the technique of blood transfusion have now made it the best method of dealing with all conditions of exæmia.

As an example of the help which has been given in diagnosis in a hemiplegia which is due to hæmorrhage, the

blood pressure must be high for reasons already stated, while if it is due to thrombosis this need not be the case. Grainger Stewart has shown that the fatal issue in cerebral thrombosis is often due to a rise of pressure in the stage of reaction, or as a result of stimulant treatment, which bursts the now-softened vessel. In the treatment of cerebral thrombosis, then, we must be careful when we use any stimulant not to raise the blood pressure excessively. Thyroid extract, on the other hand, helps to increase circulation without raising the pressure.

The fact that perforation in typhoid fever causes a rise of pressure, while hæmorrhage produces a fall, is one that will often be of great value in diagnosis.

In albuminuria, again, the blood pressure will be an aid to diagnosis. In all forms of nephritis it is usually raised. Mahomed found that in acute nephritis the arterial tension rose even before albumen appeared in the urine. This is perhaps due to cerebral œdema, which would otherwise starve the medulla of blood. But in 'functional' orthostatic albuminuria, though the pressure fluctuates, it does not rise above normal. As the treatment demanded in the two conditions is quite different, it is essential to be clear which we are dealing with; and the manometer will help us.

As to prognosis, the grave import of a continued rise in pressure in cerebral hæmorrhage has already been insisted on. In pneumonia a continued but gradual fall of pressure is the rule. A rise of pressure may be due to the onset of some complication or merely to increased anoxæmia, which, together with its attendant delirium, may be promptly relieved by oxygen. In Addison's disease a steady fall of pressure may foretell the imminence of a fatal issue. A rise of blood pressure in pregnancy is a valuable prognostic sign of the approach of toxæmia.

Hypertension.—It is now generally conceded that there is

a stage in which the blood pressure is raised before the structural changes of arteriosclerosis occur, and the manometer will help us to detect it. To take an example: A busy man nearing fifty years of age, and leading the active life of his time, on walking rather smartly to catch his morning train, finds himself out of breath for some little time afterwards. On arrival at his office he has a difficulty in concentrating his mind on his work, and on rising quickly from his chair at the end of the morning he feels very giddy, and reels a little. Now, a little anxious about himself, he becomes introspective—a rare thing with him—and recalls that small worries have upset him more than they need, that responsibility has been more irksome, and that he has not felt so sure of his judgment. He tells his partner that he thinks he has been out of sorts lately, and is met with the frank reply that it is very likely, for, at any rate, his temper has been shocking. He goes to lunch, and thinks that a whisky-and-soda will put him straight. But it doesn't; it only makes him feel more uncomfortable. He lights a good cigar, and is rewarded by palpitations, instead of the blissful sensations that smoking used to evoke. He remembers now that alcohol and tobacco do not seem to have agreed with him as they used. By the end of the day his head is aching, and he feels thoroughly worn out. He manages to eat a very good dinner as usual, however, and begins to shake off some of his fears. But his night's rest is disturbed, and next morning he feels very 'bilious,' or perhaps he has a return of the neuralgia that has been troubling him of late. It will be a good thing for him now if a violent attack of epistaxis occurs, if only to send him to his doctor. The doctor takes a heavy responsibility upon himself if he simply reassures him, tells him he is run down, prescribes some strychnine, advises a good piece of steak for lunch, and some fine old port after dinner. A more careful examination would certainly have revealed an accentuated second sound at the aortic base, and a blood

pressure of 180 to 200 millimetres; possibly also a trace of albumen, with granular casts in the urine.

The responsibility is all the greater because this man is still in the stage when treatment may be effective; and he is more likely to abide by it than the lower type of patient, 'full of coarse strength, butcher's meat, and sound sleep, who will suspect any philosophical insinuation, or any hint for the conduct of his life which reflects upon this animal existence.'

Perhaps it is even better for him if the danger-signal takes the form of an attack of hæmaturia, for he is not likely to try home remedies for this, as he may for epistaxis; nor is there much fear of the doctor treating it so lightly.

This may be simply the stage of increased blood pressure, without structural change, produced by toxic agents. If in this stage the patient takes less meat and no alcohol, gets more fresh air and a better evacuation from his bowels, reduces his weight if this is at all excessive, and leads a simpler and less strenuous life, an improvement in his blood pressure and his general condition will follow. But if this high pressure continues, a structural change will probably ensue.

An association between nephritis and hypertension has been recognized for a long time—certainly since the days of Bright. Its explanation was generally thought to be an accumulation in the blood of pressor substances of undetermined nature.

The majority of cases of high blood pressure, however, were considered to originate from extra-renal causes, and the common condition, 'essential' hypertension, had received no explanation.

That renal and non-renal hypertension may be linked together is now shown by the illuminating experiments of Goldblatt and other American workers. By artificial narrowing of a renal artery in animals, it was shown that hypertension

can be produced at will. The animals so treated may go on to develop a picture similar to that seen in essential hypertension in man, but its development could be prevented by removal of the ischæmic kidney. This experimental hypertension occurs before there is evidence of renal failure. Further evidence that renal failure to excrete pressor substances is not responsible for hypertension was produced by Harrison and others, who showed that bilateral nephrectomy leads to no rise of blood pressure; though ligature of the ureters causes a slight rise. Subsequent experiments have shown that, in the ischæmic kidney, a pressor substance is formed which can be extracted: to this the name of 'renin' has been given.

The idea that the kidney itself contains a pressor substance is not new; it was demonstrated by Tijerstedt and Bergman at the end of the last century. But the new work has given a great impetus to the study of the question, leading to the isolation of the substance apparently responsible, and to a fresh attack on the treatment of hypertension.

One method (used by Wakerlin and Johnson on animals) appears to depend on the production of some anti-substance by injections of renin prepared from another species. Thus hog renin injected into dogs with experimental hypertension produced striking reductions in blood pressure; it also prevented its development if used early.

The other method is of more physiological interest. Merrill, Williams and Harrison observed that the increased sensitivity in nephrectomized animals to this pressor action of renin only occurred a number of hours after removal of the kidneys. They therefore suggested that normal kidney tissue may contain an anti-pressor substance. It has also been shown that removal of the healthy kidney in an animal with one-sided experimental ischæmia results in a marked increase in blood pressure. Later experiments of Katz and others seemed to indicate that the degree of experimental hypertension caused

by obstruction of the renal arteries depended on the ratio of normal to ischæmic kidney.

During the latter part of pregnancy, an animal with experimental hypertension shows a definite fall in blood pressure, which returns to its normal height after delivery: this can be explained by the loss of the healthy fœtal kidney tissue.

Grollman, Page and other workers have extracted an anti-pressor substance from healthy kidneys which, when administered by mouth or by injection, causes a prolonged fall of blood pressure in animals with experimental hypertension, and even in man with 'essential' hypertension.

There can be no doubt about the great importance of this work, but it is not yet possible to evaluate its results or to say what part these findings play in causing renal disease in man. It is claimed that modern methods reveal a high percentage of renal disorders in essential hypertension, and a few cases of unilateral disorder in man, with raised blood pressure, have been reported, which have been cured by nephrectomy. The opposite, however, is also true, and there is ample evidence that similar renal disorders may have no apparent influence on the blood pressure. For instance, the contracted kidneys of renal dwarfs do not lead to hypertension.

As far as one can see at present, it appears that in the normal subject, in addition to the numerous factors previously well known to influence blood pressure, there is a humoral mechanism in the kidney itself consisting of a pressor and an anti-pressor substance which normally maintain a balance. As yet we only know of one mechanism—ischæmia—which can liberate the pressor factor. We are ignorant of factors which can liberate the opposing substance.

In looking at the question of hypertension as a whole, it would be a mistake to exaggerate the significance of the newer work, at the expense of earlier observations. For example, the effect on blood pressure of some types of obesity,

which is reversible by treatment, and more important still the preponderating influence of heredity in hypertension—not to mention the rarer but well known disturbances of the blood pressure in various ductless gland disorders—must make us critical in accepting any minor renal abnormality as the only essential cause. It is difficult to see how such minor disorders could operate in some cases and not in others.

Also awaiting further investigation in the light of recent work is the question of fluctuation in blood pressure in so-called 'labile' types of subject who appear to be candidates for permanent hypertension later. Until renin and its opposite can be identified and measured, we shall not know the full answer to these questions. In the meanwhile this field can be regarded as one of the most promising in medical research.

The cardiac hypertrophy is purely secondary. Allbutt protested 'against the accusation of these striving hearts of complicity in the arterial disease. . . . They are stout and faithful, even in defeat.'

We are likewise impelled to protest against the tendency to regard the rise of blood pressure in later life as merely a physiological event. A result of this tendency is to regard a systolic blood pressure of 120 to 140 in people over fifty as pathological, whereas such persons are really candidates for longevity. If this were generally recognized, patients would be spared much needless anxiety. It is true that a loss of elasticity may occur in the middle coat of the arteries as it does elsewhere with advancing years. But this is not necessarily accompanied by any rise of blood pressure. It is an involutionary change, which is followed in extreme cases by a calcareous degeneration of the arterial wall, which, in Allbutt's words, 'results rather in the contraction of the spheres of mental and bodily activity than, as with hyperpiesis, in the imminence of the fell sergeant Death—death by apoplexy, by cardiac defeat, or by intercurrent acute pneumonia.'

Treatment of High Blood Pressure.

It must be borne in mind that when there are organic changes in the arteries or kidneys, the blood pressure must be higher than normal for an adequate circulation to be maintained. In the 'pre-sclerotic' stage we should pay more attention, as Osler urged, to the peripheral field of the circulation. 'Obstruction in the fields can be overcome to a certain point, but it is cheaper and safer to clear out the weeds. . . . We too often tinker at the pump and the mains, instead of looking at the seat of trouble in the fields.' The abiding difficulty in the treatment is that we do not know what degree of raised pressure is necessary for any degree of arteriosclerosis, but we do know that the problem has to be met by putting the patient into the way of physiological righteousness rather than by depressor remedies.

The diet should be regulated; the bulk and number of the meals should be reduced; roasted meats, soups, and gravies should be avoided, while fruits, green vegetables, and non-nitrogenous foods may be given freely, though farinaceous and fatty diet should be limited in the case of the obese. The salt usually added at table should be limited. A pure milk diet is most useful in high-pressure cases when combined with rest. It should be tried for a few days during periods of increments of pressure. Coffee, tea, tobacco, and alcohol should be limited, and in certain cases excluded. It is best to separate fluids from the solids, or to allow them only at the end of meals.

A warm bath taken daily on rising is a valuable adjunct to treatment, but very hot or quite cold baths should be avoided. Artificial Nauheim baths, the material for which can now be readily obtained, will lower pressure, but we are not satisfied as to their advisability, as they act by vaso-dilatation. Balneological treatment is often useful. These

patients generally do best in a warm, equable climate for the winter. A life of undue rest should be avoided, but half an hour's complete repose after the midday and evening meals should be enjoined.

These patients are apt to become unduly anxious, and their fears should be allayed as far as possible. As a rule, they should not be told the pressure reading. Particularly they should not read the index themselves, as this alone will send it up.

A free action of the bowels is, of course, important. It is usual to give potassium iodide or 10 to 20 drops of liquor iodi simplex in milk for a time. There is still too great a tendency to employ nitrites, which simply lower pressure by vaso-dilatation. This is, perhaps, not to be wondered at. In the early days of antipyretic drugs there was a similar tendency to indiscriminate lowering of the temperature. It is so pleasant to see some objective result from our treatment. But the rise of pressure is a symptom just as surely as a rise of temperature, and to lower either without due consideration is to side with the toxin rather than with the patient.

Sometimes hyperpiesis has to be treated, however, just as hyperpyrexia has, irrespective of the cause. Then we should select those vaso-dilators whose action is slow and prolonged. Matthew found that the fall produced by amyl nitrite was too brief to enable him to register it with the manometer. Nitro-glycerine only lowers the pressure for forty minutes, but is of proved value both as a prophylactic against and a treatment for anginal attacks. Erythrol tetranitrate in $\frac{1}{2}$-grain doses produces a fall lasting six hours. The great drawback to its use is, however, its liability to induce severe headache in some patients. Mannitol produces a prolonged effect also. Oliver recommended a tabloid prepared for him by Burroughs and Wellcome, having the following composition: Sodii nitrit., gr. $\frac{1}{2}$; erythrol tetranitrat., gr. $\frac{1}{8}$; mannitol hexanitrat., gr. $\frac{1}{4}$; ammon. hippurate, gr. 1. One or two of these

tabloids (designated 'tabloid sodii nitrit. co.') may be taken for lengthened periods, if omitted for a few days or a week in each month. From the early appearance of atheroma in myxœdema, thyroideum siccum is often prescribed with advantage in doses of $\frac{1}{10}$ to $\frac{1}{5}$ grain three times a day in cases of arteriosclerosis with high pressure. Indeed, according to some authorities, iodide merely acts in arteriosclerosis by stimulating the secretion of the thyroid gland.

There is a great difference in the response to treatment. In some cases the results are remarkably good, and patients have been restored to years of useful and active life if they come under treatment before arteriosclerosis is established.

CHAPTER XI

THE LIFE-HISTORY OF THE RED BLOOD CORPUSCLE

On few subjects have our views been so fundamentally altered and expanded during the last few years as on anæmia. The newer conceptions illustrate physiological principles remarkably well, for we can now visualize many forms of anæmia as due to a failure at some point in the life-cycle of the red corpuscle.

On the analogy of the neuron, Boycott introduced the term *erythron* for the blood and the blood-forming organs. This entity regarded as an organ is considerably larger than the liver. As the sinusoids in the red bone marrow are lined with endothelium and only communicate with capillaries, the whole erythron is intravascular, unlike the leucocytic apparatus that originates outside the bloodvessels, into which the white corpuscles subsequently migrate. Like other organs, it can hypertrophy; anoxæmia is the great stimulus to this. It can also atrophy and does so under increased oxygen tension. It can suffer from trauma by toxins or by direct hæmorrhage. It can undergo repair according to the rules governing repair in other tissues, but after birth regeneration of red corpuscles is confined to the red marrow.

The most primitive cells in the erythron are the erythroblasts which line the sinusoids in the bone marrow. They give rise to large nucleated cells containing hæmoglobin, the megaloblasts. We are at present ignorant of the active agent in this stage of development, but we do know that it can be interfered with by certain poisons such as benzol and by radio-active substances. Heavy metals such as lead tend

to be stored up in bone, and the same is true of radium and thorium. Once this has happened, the erythron is bombarded by gamma rays, megaloblasts fail to develop, and aplastic anæmia results. As its name implies, aplastic anæmia is characterized by a failure of blood formation; it is inevitably fatal once it has really developed, and the patient is merely kept alive for a time by transfusion. He is living on borrowed blood, for the transfusion fails to stimulate any formation of his blood, as it may in other forms of anæmia.

The megaloblast gives rise to normoblasts, smaller cells, but still nucleated. For this it requires the aid of hæmopoietin, formed in the pyloric end of the stomach and in the duodenum and stored in the liver. If this is lacking, further development is checked, and Addisonian or pernicious anæmia, megalocytic in type, results. The next step in the healthy subject is for the nucleus to disappear from the normoblast, leaving a network behind characteristic of the reticulocyte, whose appearance is evidence that blood formation is proceeding. The reticulocyte becomes the ordinary red corpuscle. For these later changes iron is essential, aided by thyroxin and perhaps by a trace of copper. In their absence a microcytic anæmia results.

Immature cells stick together, the formation of rouleaux in shed blood being a survival of this tendency. As the corpuscles multiply they distend the narrow communication between the sinusoid and the blood capillary, and as they become less sticky they are swept by the accumulating plasma into that capillary, thus embarking on their adult life. That life lasts about thirty days, by which time they have been threshed to bits in the circulation. Their remains are scavenged by the spleen, the colouring matter going to form bile, the iron to be stored up in the liver, spleen, and, to a lesser extent, in the kidney.

Such, in brief, is the life-history of the red corpuscle.

Normally immature cells will not appear in the circulating blood, but may do so when the normal process of maturation is interfered with. The sequence of events may be held up at any point, like a cinema film; indeed, as a blood disease increases in gravity, the film may be actually reversed, and cells of increasing immaturity appear. Thus the anæmia of sprue may be first microcytic, then megalocytic, and finally aplastic in type.

Clearly anæmia may result either from diminished blood formation or from increased blood destruction. The new work principally relates to the types due to failure of formation. Of these types, it would appear logical to deal first with megalocytic and then with microcytic anæmias, since the former implies a defect in maturation at an earlier stage in the cycle.

Megalocytic Anæmias.

For many years the pernicious anæmia described by Addison was attributed to something which caused excessive blood destruction. In 1912 Minot was struck with the idea that it might be due to some dietary deficiency, especially in view of its constant association with achlorhydria. He recalled Samuel Fenwick's suggestion in 1880 that the primary defect was in the stomach. In 1919 a study of the relapses of pernicious anæmia convinced him that there was something lacking that was needed to convert the primitive red cells which crowded the bone marrow into normal cells, rather than that there was excessive blood destruction going on. In 1922 Whipple's work on hæmoglobin regeneration by means of liver and other foods gave Minot the clue he needed. He started to feed patients suffering from pernicious anæmia with relatively small doses of liver with some benefit, and early in 1926, in conjunction with Murphy, gave large weighed amounts daily with striking success. The preparation of liver extracts soon followed, and then Castle

in 1929 discovered that when beef is incubated with gastric juice something is formed which is equally effective. In this process apparently two factors are concerned—the intrinsic one, possibly an enzyme, contained in the mucosa of stomach and duodenum; the extrinsic one contained in food rich in the vitamin B complex, with which, however, it does not seem to be identical. It would appear, therefore, that the substance required to convert the primitive cells in the marrow into the normal cells is manufactured in the stomach and stored in the liver.

This is a good example of the way in which scientific discovery is made. Chance only visits the mind that is prepared, as Pasteur said. An intuitive idea is submitted to criticism based on experiment and the collection of facts until it takes shape as a working hypothesis. In the present instance it is of particular interest that at one stage attention was deflected from the stomach to the liver before the real sequence of events was recognized. Achlorhydria is now seen in the proper perspective: a gastric lesion may destroy the cells producing hydrochloric acid, with or without destruction of the intrinsic factor; the converse—loss of the intrinsic factor without loss of the secretion of hydrochloric acid—is extremely rare, although different areas of the stomach are responsible for the production of each. Subacute combined degeneration of the cord is, as we know, closely associated with pernicious anæmia, but on the whole opinion inclines to the view that another closely similar intrinsic factor is lacking, for there is no correspondence between the degree of anæmia and the intensity of the cord changes. Much larger doses of liver extract are needed to remedy the latter than the former.

The purest form of the potent substance extracted from the liver at present known is Dakin and West's anahæmin, which appears to be a complex of a number of amino-bodies.

Theoretically a megalocytic anæmia could result from a

failure of the stomach to manufacture the required material, or from the defective absorption of this, or from a failure in its transport from the liver to the bone marrow. Clinically each of these types can be recognized. In the first group come Addisonian anæmia, the pernicious anæmia of pregnancy (where a latent partial deficiency may become manifest because of the demands of the fœtus for blood-forming material), the anæmia resulting from an extensive gastrectomy or new growth from the stomach, and the tropical anæmia in women, which appears to be due to the absence of the extrinsic factor from the diet and which yields to administration of such a yeast preparation as marmite. In the second group come anæmias following sprue, cœliac disease, intestinal stenoses, or multiple anastomoses. In the third group comes the 'achresthic' anæmia of Wilkinson, where there is satisfactory production and storage, yet the bone marrow fails to respond. This last condition has an interesting analogy in von Gierke's disease, where mobilization and utilization of glycogen similarly fails to occur.

Davidson distinguishes between these anæmias, dependent on a deficiency of the factor necessary to normal maturation of the red corpuscle, and a group of relatively rare macrocytic anæmias usually secondary to prolonged stimulation or irritation of the bone marrow. In this latter category he mentions acholuric jaundice, leukæmia, lymphadenoma, and metastatic malignant deposits in bone marrow as causes.

The most striking feature of the blood picture in Addisonian anæmia is the raised colour index, the deficiency in hæmoglobin not being so severe as in the number of corpuscles. By plotting out the diameters of a number of corpuscles in a curve, Price-Jones was able to show that their average size was larger than normal, which is intelligible now that they are known to represent a more primitive type of cell. This increase in size is the sole reason for their

higher content in hæmoglobin. The imperfection of their manufacture is shown by their variability in size (anisocytosis), in shape (poikilocytosis), and in staining reactions (polychromasia, punctate basophilia). Nucleated cells may be seen, of which the most characteristic are the megaloblasts. Van den Bergh's indirect reaction is positive, which has been attributed to failure on the part of the bone marrow to utilize the free circulating pigment. The white corpuscles are also reduced in number, which is due to the failure of the bone marrow to produce polymorphs.

We do not propose to describe the clinical features of Addison's anæmia beyond calling attention to the raw glazed condition of the tongue which William Hunter described; it is an indication of the atrophic state of the alimentary mucosa and is not infrequently seen in other conditions associated with achlorhydria. Indeed Magnus has now shown that the gastric mucosa in Addisonian anæmia is atrophic.

Treatment of Addisonian Anæmia.—There is such a variability in the response of the patient to treatment that there can be no standard dosage. Very severe cases may require transfusion at the outset; a pint of blood from a suitable donor should be given very slowly, together with 5 c.c. of a liver extract suitable for intravenous use. But today a patient ought not to be allowed to get into such a condition as to need this. If the blood count is under 2 million, intramuscular injections of 2 to 5 c.c. of a liver extract (such as hepastab, campolon, or pernæmon forte) should be given on four consecutive days deeply into the gluteal region. It is well to alternate from side to side each day and to massage firmly at the site of injection afterwards, to diminish pain and stiffness. Afterwards weekly injections of 5 c.c. will probably be sufficient, but only a blood count can decide this. Both on the grounds of efficacy and expense this is far preferable to oral administration of liver extract, or giving cooked liver.

It is generally advisable to combat the achlorhydria by giving a drachm of dilute hydrochloric acid in a tumbler of orangeade with meals.

Some patients respond better to stomach extracts than to liver preparations, and in any case which fails to improve this method should be tried. We have seen ventriculin succeed where liver extract had failed. Other preparations are pepsac and ektomak. The usual initial dose is a tablespoonful three times a day given in milk, orange juice, or water, but this can usually be reduced as the patient improves. The unpleasant smell of these preparations can be mitigated by exposing them to the air for twelve hours.

As reticulocytes are evidence of new blood formation, an increase in their number is the best indication of a patient's response to treatment. There are usually less than 2 per cent. present before treatment, and they begin to increase rapidly after four days of giving liver preparations, reaching a maximum on the seventh to tenth day, after which their numbers fall again. Ungley states that the height of the curve is inversely proportional to the initial red cell count; with a count of one million, the reticulocytes may reach 40 per cent., but with a level of $2\frac{1}{2}$ millions not more than 15 per cent. may be expected.

Once the blood picture has returned to normal, a maintenance dose must be continued, which may vary greatly in individual cases. Two to five c.c. of campolon intramuscularly once every two or three weeks or 4 ounces of stomach extract weekly may be regarded as average doses. Hydrochloric acid is thereafter only required if indigestion or diarrhœa is present.

With regard to iron, it may be said that the demand for this during the rapid manufacture of new red corpuscles is so great that 30 grains of ferri et ammon. citr. or 3 grains of ferrous sulphate in a pill should be given three times a day

until a normal blood picture is obtained. After that it can be discontinued.

In the anæmia of sprue and cœliac disease vitamin B (in the form of marmite) and calcium salts should also be given, while fats should be reduced to a minimum, since they only increase the diarrhœa. In tropical anæmia marmite is sometimes quite effective in conjunction with a good mixed diet without any drugs, since it is the extrinsic food factor which is missing in this condition.

Microcytic Anæmias.

The almost complete disappearance of a disease formerly as common as chlorosis may be, as Parkes Weber believes, entirely due to changes in the fashion of women's clothes, but the recent observations of Stanley Davidson and his colleagues on the blood counts of 3,500 individuals of the poorest class in Aberdeen and the neighbourhood also throws light on the subject. The high incidence of anæmia in women, and in the infants they bear, in contrast with its absence in men of the same social status, is striking, and justifies the conclusion that the physiological demands for iron made by menstruation and pregnancy are not satisfactorily supplied by the diets of many women of the poorest class. Iron is necessary for the maturation of the normoblast into the erythrocyte, and too many women are on the border-line of iron shortage. If they also have achlorhydria, which perhaps interferes with the assimilation of iron, anæmia is more likely to occur. Changing conditions may have postponed its onset, and Witts' simple microcytic achlorhydric type may find its victims among those who formerly would have developed chlorosis earlier in life. And so we are led back to Lloyd Jones's view, expressed more than forty years ago, of the association of anæmia with the reproductive function.

Chlorosis yielded to treatment by iron, but now that we know that thyroxin also plays a part in the maturation of the normoblast, it does seem probable in the retrospect that some chlorotics were the subjects of a mild degree of hypothyroidism which was unsuspected.

Simple achlorhydric anæmia is the commonest of the primary anæmias, and usually occurs in women between the ages of twenty and fifty. It generally improves after the menopause. It appears to be directly associated with achlorhydria, which interferes with the absorption of iron and other mineral substances. Glossitis is present in about half the cases, and the inflammation of the mucosa, of which this is evidence, may involve the pharynx sufficiently to cause dysphagia, the so-called Plummer-Vinson syndrome. The spleen is slightly enlarged in about a quarter of the cases. The hæmoglobin is reduced more than the number of red corpuscles, and a Price-Jones curve shows that this is due to a diminution in the average diameter of the corpuscles—*i.e.*, less than the normal 7·2 microns. This is expressed by saying that, whereas in pernicious anæmia the curve has a shift to the right, in simple achlorhydric anæmia the shift is to the left. The colour index is therefore low. The leucocyte count is normal and Van den Bergh's indirect reaction is negative. A curious feature, to which Witts called attention, is the brittle condition of the nails, which are occasionally hollow and spoon-shaped. The disease is chronic, but rarely fatal, and there is a strong tendency to relapse.

Treatment.—Large doses of iron by the mouth is the only successful treatment. It has now been clearly demonstrated that the amount of iron which can be given by injection is ineffective, and if sufficient were given by this route it would be toxic. This method should therefore be abandoned. Ferrous salts should be given rather than the ferric. Thirty grains of ferri et ammon. citr. with some

glycerine, and well diluted, should be given three times a day. A smaller dose (2 to 3 grains t.d.s.) of ferrous sulphate is effective, and is unlikely to irritate the stomach if given as a pill after food. Hydrochloric acid relieves the dyspepsia, and naturally septic foci call for treatment. It is unnecessary and useless to give liver and stomach extracts, while transfusion is seldom, if ever, required.

Hæmolytic Anæmias.

It is now recognized that hæmolysis is not such an important factor in causing anæmia as was formerly thought. Symptomatic anæmia may result from hæmolysis by bacterial toxins and other poisons. Primary hæmolytic anæmias such as acholuric jaundice, sickle-celled anæmia, and the grave familial jaundice of infants are rare and are due to some congenital abnormality of the erythron. The typical features of these anæmias include jaundice, which may be quite slight in the chronic cases, but more intense and accompanied by hæmoglobinuria in the acute, if the breakdown of red corpuscles is rapid. The colour index is usually about normal. As the bone marrow is reacting vigorously, the reticulocyte count is high, and nucleated red cells, even including megaloblasts, may appear in the circulating blood. The treatment of acholuric jaundice has already been discussed, and there is no known treatment of any value for sickle-celled anæmia (which has only been observed in negroes). Hampson showed that the grave familial jaundice of infants, formerly always fatal, can be cured by daily intramuscular injections of 5 to 10 c.c. of the mother's blood serum as already mentioned.

The nature of the acute febrile hæmolytic anæmia of Lederer is quite unknown, but transfusion may be extraordinarily successful.

To sum up, anæmias associated with defective blood

formation—the anhæmopoietic anæmias—are due to arrest of the normal process of maturation of the red corpuscle at some stage, while anæmias associated with increased blood destruction—the hæmolytic anæmias—are due to a congenital abnormality of the erythron. Symptomatic anæmias may result from (*a*) depression of the function of the blood-forming tissues by infections and cachexias, or (*b*) losses of blood, either frank or occult.

CHAPTER XII

ON CYANOSIS AND DYSPNŒA

THE essential cause of cyanosis is an abnormally large amount of reduced hæmoglobin in the capillary blood, while the essential cause of dyspnœa is excess of carbon dioxide or some other abnormal acid in the respiratory centre. It will follow that, although these two conditions are often associated, this is not necessarily the case. Thus in uræmia we may see dyspnœa without cyanosis, whereas in congenital heart disease cyanosis occurs without dyspnœa. As Lewis points out, if a patient is urgently breathless and an equivalent cyanosis is not found, the dyspnœa is not wholly due to deficient aeration of the blood. Non-cyanotic dyspnœa is produced by the presence of abnormal acids in the blood, such as diacetic acid in diabetic coma, acid sodium phosphate in uræmia, and lactic acid in various conditions. Pulmonary reflexes through the vagus can also produce dyspnœa.

Mere diminution in the amount of oxyhæmoglobin is not sufficient to cause cyanosis. Thus in coal-gas poisoning the corpuscle contains less oxygen, and yet there is no cyanosis, for the new compound, carboxyhæmoglobin, is a bright cherry-red.

But if enough of the hæmoglobin is reduced or is in the form of methæmoglobin or sulphæmoglobin, there is cyanosis. In an earlier chapter it was shown that nitrite-producing microbes in the intestine may cause methæmoglobinæmia or sulphæmoglobinæmia, which may lead to a striking degree of cyanosis. Certain coal-tar drugs may also be responsible for the former condition. Either can readily be detected by the spectroscope. It is needless to repeat what has already been said, beyond urging the necessity of diagnosing these toxic conditions from ordinary cyanosis.

Ordinary cyanosis becomes perceptible as soon as there is about 5 grammes of reduced hæmoglobin per 100 c.c. of blood. It depends on the absolute concentration of reduced hæmoglobin rather than on its ratio to oxyhæmoglobin. Thus anæmic individuals with less than 5 grammes of hæmoglobin per cent. cannot become cyanotic. Cyanosis is also influenced by the thickness of the epidermis and the amount of pigmentation, but still more by variations in the number, width, and length of blood-filled capillaries per unit of surface; thus it is increased by stasis.

Lundsgaard and Van Slyke classify the causes of true cyanosis somewhat as follows:

1. Although all the air traverses lung tissue which is anatomically accessible to inspired air, diffusion of oxygen is hindered by (1) low oxygen tension in the alveoli occurring at high altitudes, (2) decreased permeability of the alveoli due to physical conditions such as the exudation of fluid into them.

2. Part of the blood passing from the right heart to the arteries traverses a path to which access of air is anatomically impossible, as, for instance, when there is a patent foramen ovale in the heart.

About one-third of the venous blood may be shunted through an unaerated path before sufficient unsaturation results to cause cyanosis. In collapse of one whole lung by artificial pneumothorax the arterial blood is still nearly saturated with oxygen. This is because the pulmonary capillaries are closed and circulation prevented through the collapsed areas.

3. There may be increased reduction of the oxygen in the capillary blood, either from decreased rate of flow or from increased rate of oxygen consumption by the tissues.

The principal causes of cyanosis, therefore, appear to be interference with diffusion in the lungs, shunting of un-

aerated blood into the arteries without passing through normal lung, and slowing of the capillary flow.

Nature's method of compensating for defective oxygenation of existing corpuscles is by adding to their number. Thus prolonged residence at high altitudes, such as Quito in Ecuador, results in polycythæmia. The diminished oxygen tension at that height necessitates an increase in the number of oxygen carriers, so that, though each is capable of carrying less, the total amount of oxygen carried to the tissues remains the same. On the other hand, there is a reduction in the amount of hæmoglobin in animals kept under increased oxygen pressure. Applying this to diseases associated with chronic cyanosis, we should expect to find polycythæmia also. Conversely, polycythæmia in itself tends to produce cyanosis, for, as we shall see, by slowing the capillary circulation it increases the reduction of hæmoglobin. And when there is excess of hæmoglobin the limit of 5 grammes in the reduced state will be reached more easily.

Erythræmia (Splenomegalic Polycythæmia).—The most striking example of increase in the red corpuscles occurs in the condition first described by Vaquez in 1892. Our knowledge of this disease has been added to by the observations of Osler, Saundby and Russell, and Parkes Weber. The patient is usually in the middle period of life. He is generally, though not invariably, cyanosed, but there is no respiratory distress. The eyes may be prominent and the conjunctivæ suffused. Examination of the blood shows that the red corpuscles are increased from the normal 5,000,000 to a figure varying between 8,500,000 and 12,000,000 per cubic millimetre, while the hæmoglobin is raised to 120 or 150 per cent. The white corpuscles are usually increased from the normal 8,000 to 20,000 per cubic millimetre, but in some cases are actually diminished. The viscosity of the blood is naturally considerably increased. The spleen is usually enlarged; sometimes it is greatly en-

larged, but then infarcts or tubercles have usually been found. Even intravascular clotting often occurs. The urine frequently contains a trace of albumen. Pigmentation of the skin has been noted. The most prominent symptoms are torpor, both mental and physical; a sensation of fulness in the head, with headache and vertigo; and in some cases nausea and vomiting. As Osler pointed out, these symptoms remind us of those to which mountain-climbers and aeronauts are liable. There are also certain vasomotor symptoms. If any part be rubbed it goes red, and if the patient gets hot the general cyanosis is apt to be replaced by a general flushing. A dependent part becomes blue, but if it be held up it may become pale. The vessels must be very full, for the volume of the blood is increased. Now the capacity of the vessels may be increased by relaxation of the vasomotor tone, and this loss of tone causes the effect of gravity on the circulation to become more pronounced. By the relaxed state of the vessels we can also explain the fact that the blood pressure is not necessarily raised, although the vessels are so turgid.

The increased viscosity of the blood is a necessary result of its concentration by excess of red corpuscles. Gustav Mann calculated that the maximum number of corpuscles which the blood is capable of holding in each cubic millimetre is 13·9 millions. A blood count of 12,000,000 implies, then, a very great increase in the viscosity of the blood, and therefore a considerable delay in the circulation time through the capillaries. This has been experimentally demonstrated. Anything which increases the stay of the blood in the capillaries allows of the abstraction of more oxygen from it. We should therefore expect that this cause of cyanosis would be diminished in part by stimulating the rate of the circulation by warmth and friction, as is actually the case.

The polycythæmia remains to be explained. There is

certainly an increase in the erythroblastic tissues in the red marrow. This could arise in two ways. Either it is compensatory or it may be of the same nature as a new growth. This latter view has been put forward by Parkes Weber, who considers that the change in the red bone marrow is primary; that there is an over-production of red cells, just as in myelogenic leukæmia there is an over-production of white cells. There is no evidence that this change is compensatory.

The cyanosis is not due to an abnormal reducing agent in the blood, nor is there any reason to suppose that it is other than the result of slowing of the circulation by increased viscosity of the blood.

Treatment.—There is at present no effective treatment for the disease. That oxygen inhalations are no good is only to be expected, as there is no deficiency of oxygen in the blood. Temporary benefit may be derived from repeated bleedings combined with X-rays. Phenyl hydrazine has been advocated, starting with 0·1 gramme daily, a careful watch being kept not only on the blood count, but also on the general condition of the patient. It has been suggested that there may be an excessive production of hæmopoietic hormone, the condition being the antithesis of pernicious anæmia. For this reason liver should be avoided in the diet, and the intake of animal proteins restricted.

Cyanosis in Congenital Heart Disease.—During fœtal life the circulation is so arranged that the purest blood from the placenta is sent as quickly as possible to the head. To achieve this the liver is short-circuited by the ductus venosus, and the blood entering the right auricle is directed by the Eustachian valve through the foramen ovale into the left auricle. In this process the limbic bands of the auricle assist by drawing the inferior vena cava towards the foramen. From this point the adult course of the circulation is followed to the head. The returning stream enters the heart by the superior vena cava, and passes down into the right ventricle,

being largely shut off from the other stream in the right auricle by the Eustachian valve and the limbic bands. It leaves the right auricle by the pulmonary artery, but as it is unnecessary for all this volume of blood to go to the lungs, it is diverted by the ductus arteriosus into the aorta beyond the origin of the carotids.

It is not correct to attribute the child's first breath to the stimulating effect of exposure to the lower temperature of the outside world, for interference with the placental circulation while the child is still *in utero* will cause it to breathe; and if the child be received into a bath at body temperature, respiratory movements will occur as usual. When the placental circulation is interfered with, carbon dioxide accumulates in the respiratory centre, and produces its usual effect—a stimulus to respiratory movements.

These movements aspirate a large volume of blood into the lungs, which returns by the pulmonary veins to the left auricle. A fall of pressure, therefore, occurs in the right auricle, and a rise of pressure in the left, which helps to close the oblique opening in the foramen ovale. The downward movement of the diaphragm alters the plane in which the limbic bands act, so that they no longer draw the inferior vena cava towards the foramen ovale.

The alterations in pressure also help to close the ductus arteriosus, as the distended aorta now projects within its lumen, and stops the flow through it.

In this way the ordinary post-natal condition is arrived at. But if there be stenosis at or below the pulmonary valves, the mechanism of this change is fundamentally disturbed, though the fœtal circulation will not have been embarrassed in any way. The pressure in the right side of the heart will be too great to allow of closure of the septum between the two sides, so that it remains patent either in its auricular or its ventricular portions. In the latter case there is probably a true congenital defect, a reversion to the type of reptilian

heart; while the former is commonly the necessary result of a fœtal endocarditis.

The deficiency in the exit of blood from the right ventricle will be made good to some extent by the ductus arteriosus remaining open. There may be complete atresia of the pulmonary valves, in which case the whole of the blood to the lungs reaches them by this route.

The only way in which the body can compensate for this obstruction of the pulmonary artery is by charging the blood more highly with corpuscles, so that the oxygen capacity of that portion which does reach the lungs will be increased. Polycythæmia is therefore always met with in such cases, and may amount to 8,000,000 or more per cubic millimetre. This, by slowing capillary circulation, adds to the cyanosis.

It has been contended that the polycythæmia and cyanosis are alike due to general congestion of the venous system from obstruction; but it has probably been the lot of everyone to see cases of congenital heart disease with marked cyanosis and a high degree of polycythæmia in which signs of such congestion were entirely lacking.

Other causes of chronic cyanosis call for only brief consideration. A startling degree of cyanosis is produced by a syphilitic endarteritis of branches of the pulmonary artery (Ayerza's disease), in which condition the patient may appear almost black. The acquired cardiac lesions typically associated with cyanosis are diseases of the tricuspid and mitral valves. Here the distribution to the lungs is not at fault, and oxygenation is normal; at the same time, venous congestion causes a certain degree of stasis in the capillaries, so that the blood there is more reduced than normal. If œdema be present also, this might increase the concentration of the blood. In this way a moderate degree of polycythæmia is found in the blood obtained from the peripheral circulation. This is spoken of as a relative polycythæmia, since there is

not an absolute increase in the number of corpuscles, but only an alteration in their distribution with respect to the fluid constituents.

Mediastinal inflammation and growths act in very much the same way by producing venous stasis.

According to Osler, cyanosis of an extreme grade is more common in emphysema than in any other affection, except congenital heart disease. 'So far as I know,' he said, 'it is the only disease in which a patient may be able to go about, and even to walk into the hospital or consulting-room, with a lividity of startling intensity. The contrast between the extreme cyanosis and the comparative comfort of the patient is very striking. In other affections of the heart and lungs, associated with a similar degree of cyanosis, the patient is invariably in bed, and usually in a state of orthopnœa.' He made another exception in favour of toxic cyanosis.

In emphysema there is such a gradual diminution of the oxygenating surface of the lung that the discomfort to the patient is reduced to a minimum. There is only a moderate polycythæmia, however. After emphysema, fibroid change in the lung is, perhaps, the most important cause of marked chronic cyanosis. Here again the diminished surface available for respiratory interchange is responsible.

When, in these conditions, the right heart begins to fail, cardiac causes for cyanosis are superadded, and the dyspnœa becomes marked. Until then the right heart has an extraordinary power of compensating for increased resistance in the pulmonary circulation.

In pneumonia, cyanosis was generally attributed to failure of the right heart rather than to the consolidation of the lung, with consequent insufficient oxygenation. But the 1918 epidemic of influenza showed many striking examples of cyanosis before heart failure occurred, which led to reconsideration of the problem. It was noted that in such cases very little air distends the affected lung. Kline and Winter-

nitz showed by injecting the lung through the pulmonary artery that only a very scanty colour was produced in the consolidated portion, whereas the normal parts were deeply stained. By means of X-ray examinations of human lungs injected with barium emulsion Gross found that the vessels in the region of grey hepatization were almost impassable. Arterial anoxæmia in pneumonia is therefore due, not to the consolidated portion of the lung, but to insufficient interchange in the areas which are merely congested. Adequate oxygen administration will remove this important factor in the cyanosis.

Oxygen can produce a striking alleviation of cyanosis in emphysema with failing heart. This contrasts with its failure in congenital heart disease, and provides a further argument against explaining the cyanosis in that condition as due to venous congestion.

Local cyanosis, such as occurs in Raynaud's disease and other vasomotor diseases, appears to be due partly to increased capillary distension and partly to stasis, allowing of increased absorption of oxygen by the tissue. Traumatic cyanosis, which is seen in the rare condition of pressure stasis following severe crushes of the chest, has been shown by Beach to be due to mechanical over-distension of the veins and capillaries. True extravasations of blood may occur as well, however, especially in the lax tissues around the eye, where the ordinary changes of colour in bruises will follow.

Conclusions.—Cyanosis may be due to:

(*a*) *Arterial anoxæmia,* which in its turn is caused by—

(i.) A low pressure of oxygen in the inspired air, as at high altitudes.

(ii.) Interference with pulmonary ventilation.

(iii.) Short-circuiting of venous blood, as through a patent foramen ovale or through unventilated lung tissue. A short circuit may also occur in the lung simply because diseased alveolar walls interfere with the passage of oxygen through

it. It is in the last condition, which occurs in pneumonia and pulmonary œdema, that oxygen is specially indicated.

(*b*) *Peripheral stasis*, where, although the arterial blood is fully oxygenated, the slowing of the peripheral circulation allows of more complete reduction of oxyhæmoglobin. This occurs in polycythæmia and in mitral stenosis.

(*c*) *Toxins*.—Toxic cyanosis is due to a chemical change in the hæmoglobin molecule, produced by drugs or intestinal intoxication, and leading to the formation of methæmoglobin or sulphæmoglobin. It is not associated with polycythæmia, and there may be marked oligocythæmia.

We would emphasize, in conclusion, the assistance that the blood count and the spectroscope will give in making the diagnosis on which alone correct treatment can be based.

Dyspnœa.—A healthy man may become short of breath from two different causes—by taking strenuous exercise or by going to a high altitude. Now these two ways illustrate the two main types of dyspnœa in disease. We may say that an athlete who is 'breathless' has incurred an oxygen debt. Muscular contraction can take place in the entire absence of oxygen, for this is only needed for the recovery process. Glycogen supplies the requisite energy for contraction by breaking down into lactic acid; hexose diphosphate and pyruvic acid being intermediate stages for the accomplishment of which vitamin B_1 is necessary (R. A. Peters). But oxygen is immediately needed to rebuild the lactic acid into glycogen, oxidizing one-quarter of it in the process. When exertion does not produce dyspnœa, it means that the intake of oxygen balances the production of acid; but if muscle were unable to run into debt for oxygen, our capacity for exertion would be limited indeed. As long as this debt is unpaid, lactic acid is present in the blood stream, increasing its hydrogen-ion concentration; in other words, there is acidæmia, which stimulates the respiratory centre to

renewed effort. If the debt piles up enough there is fatigue sufficient to stop the exertion, which is protective in that it allows of recovery taking place without incurring fresh expenditure. Rigor mortis is oxygen bankruptcy. The continuance of dyspnœa after exercise indicates that the oxygen debt is not paid off (A. V. Hill, Meyerhof). In the corresponding type of breathlessness in disease there is increased hydrogen-ion concentration in the blood, due to lactic acid or some other substance. Thus we have seen that in uræmic dyspnœa there may be retention of acid sodium phosphate. Even when in the ketosis of diabetes there is no acidæmia, a chemical substance is present which similarly stimulates the respiratory centre. There will be no cyanosis until the heart begins to fail.

On the other hand, at high altitudes the mere lack of oxygen due to its low tension in the atmosphere directly stimulates the respiratory centre, nervous tissues being more sensitive to this lack than any other tissues. The resulting hyperpnœa washes out CO_2 from the lungs, so that the blood tends to be more alkaline, a condition which the kidney tries to rectify by excreting more alkali. The dyspnœa of heart disease is due to oxygen lack, largely the result of capillary stasis, which allows of more complete reduction of hæmoglobin. It is therefore usually associated with cyanosis; but there need be no increased production of acid. Indeed, the increased pulmonary ventilation may actually produce alkalæmia.

'This broad distinction between cause and effect may be recognized: when acidæmia is associated with breathlessness, the acidæmia is the cause of the breathlessness; when alkalæmia is associated with breathlessness, the breathlessness is the cause of the alkalæmia. . . . Just as the dyspnœa of exercise is the type to which acidæmic forms of dyspnœa may be referred, so the dyspnœa of high altitudes is the prototype shown in normal individuals of the alkalæmic forms.'

Treatment.—It follows that if dyspnœa is associated with acidæmia, administration of alkali to increase the alkaline reserve of the blood may be helpful. Its limitations in the case of diabetic ketosis have already been considered. But when dyspnœa is associated with alkalæmia, as it usually is in simple cardiac cases, it is clearly futile to give alkalies. If digitalis is not contra-indicated on other grounds, it should be tried in such cases, because a cardiac tonic will help to relieve capillary stasis and the consequent anoxæmia.

Naturally both in cyanosis and dyspnœa treatment by oxygen seems the rational procedure. But, as already pointed out, when the cyanosis is due to the shunting of unaerated blood from the right to the left side of the heart, as in congenital heart disease, oxygen will be of no avail. In failing heart it will not be effective when capillary stasis is responsible for the oxygen lack, but when pulmonary complications, such as congestion and œdema, are present it will be very helpful. In coal-gas poisoning and pneumonia it is particularly indicated. Perhaps it is of most help in post-operative thyroid crises, though these are fortunately rare. The failure of oxygen inhalations is often due to the method of administration. As formerly given, it had no effect in increasing the inadequate oxygen content of the blood. When the funnel of an oxygen cylinder is 10 centimetres distant from the mouth, oxygen has no advantage over the ordinary air. But when the funnel is placed right over the mouth and nose, the effect on the alveolar oxygen is almost identical with that obtained by the nasal catheter, and is more comfortable (Hilton). By this latter method a rubber catheter is introduced through the nose into the naso-pharynx, the catheter being retained in position by the Tudor Edwards spectacle frame. The catheter is attached to a Wolff bottle containing warm water, through which oxygen is bubbled as fast as the patient can comfortably bear. This does not usually exceed 2 litres a minute. The Haldane

mask and oxygen bag is far more efficient, but patients as a rule cannot tolerate it for long. Campbell's box-mask respirator is equally effective and more comfortable. The B.-L.-B. mask is of value, but still leaves something to be desired. The ideal method theoretically is the oxygen tent or chamber, in which an atmosphere of 60 per cent. of oxygen is maintained. Largely owing to the enterprise of E. P. Poulton, these oxygen tents have been made available for hire with skilled service.

That oxygen given in this way does definitely benefit the oxygen desaturation of the blood has now been proved by arterial puncture. This allows of direct measurement of the percentage of oxygen in the blood before and after treatment. Injecting oxygen subcutaneously is a practice which is useless, since there is plenty of evidence to show that it is absorbed far too slowly to be of any service.

CHAPTER XIII

ON ALLERGY AND SOME ALLERGIC DISEASES

A STUDY of allergy is a step towards a scientific doctrine of diathesis. It exemplifies particularly well the variation in the response of different individuals to similar stimuli. Rolleston has succinctly defined idiosyncrasy as an unusual physiological personal equation. Allergy is a chemical idiosyncrasy, and in Jonathan Hutchinson's phrase 'idiosyncrasy is individuality run mad.' This expresses what may be regarded as the salient feature of allergy—a fierce and frightened attempt on the part of the cell to conserve its chemical identity. It is characterized by two essential features: spasm of involuntary muscles and increased capillary permeability (Bray).

The sufferer from allergy demands our sympathy, for in the stress of life it must be a tremendous handicap to feel uncertain whether one's physical frame is going to let one down at a critical moment by an attack of asthma, a crippling headache, a disfiguring eruption, or an undignified and rapid retreat in order to vomit. Well might Sir Thomas Browne congratulate himself on having 'no antipathy or rather Idiosyncrasy in dyet, humour, ayre, anything.'

Every known protein contains histidine as one of its fractions. Break off a single CO_2 molecule from this histidine, and it becomes a powerfully toxic substance, histamine. This substance when liberated from the tissue cells can produce all the phenomena of allergy. The chemical basis of allergy is therefore simple, like the chemical basis of life, but the factors which lead to the liberation of this substance are almost as varied as life itself.

Histamine was originally isolated by Barger and Dale

from ergot in 1910, and then from the intestines. If it is applied to the human skin it promptly raises an urticarial wheal; if injected intravenously into animals it produces a condition like anaphylactic shock, accompanied by contraction of plain muscle, thus exciting bronchial spasm among other things. The problem is, How does a substance which is toxic to everybody become liberated only in the tissues of certain people, in answer to stimuli which are quite harmless to everyone else?

At first no attempt was made to distinguish between allergy and anaphylaxis. There is still some difference of opinion on this, but we may agree with those who regard anaphylaxis as an acquired sensitivity, whereas the tendency to allergy is inborn. Anaphylaxis of short duration may be passively transmitted to the offspring by the placenta or the milk for the same substance towards which the mother has been sensitized, but this soon fades away. It cannot be transmitted at all by the father. Allergy shows a definite familial tendency in two out of every three cases. It can be transmitted by either father or mother, it is manifested towards various substances which may be different from those to which the parents are sensitive, and it is of long duration.

Of late there has been a tendency to confine the term anaphylaxis to experimentally produced hypersensitiveness in animals, but there is hardly adequate reason for this. We know that though the first injection of horse serum into a guinea-pig produces no untoward effects, a second injection after an interval of nine to fourteen days is generally fatal. The temperature, blood pressure, and white blood count all fall, the coagulability of the blood is diminished, and a bronchial spasm occurs. A similar condition, though usually not so severe, may be produced by the injection of the blood of a sensitized animal into another one, after a latent period of fifteen to eighteen hours. But we know that a second injection of diphtheria antitoxin, which, of course, has horse

serum as its vehicle, more than eight days after the first may similarly be fatal to a child, and that severe symptoms of shock are not uncommon. Many theories have been put forward to account for this. It seems most probable that the effect of the first injection is upon the liver, which produces proteolytic ferments in large quantities to deal with the foreign protein that has been injected. When the second dose is injected, these ferments speedily break histamine off from the injected protein and this produces its usual toxic effect. That this effect is on the tissue cell is shown by Dale's reaction, in which the uterus of the sensitized animal is carefully freed from blood and suspended in a bath of Ringer's solution; the addition of a minute trace of the substance to which the animal is sensitized will cause an immediate contraction of the uterine muscle.

Desensitization can be effected either by giving a second fairly large dose of the same antigen before the eighth day or by repeated doses so minute as not to produce shock. In this way the animal or individual acquires an immunity against further injections. As we know, it is sometimes possible to desensitize non-specifically, and injections of peptone are often used to this end.

Clearly, anaphylaxis is the opposite of immunity. Morley Roberts made the profound remark that 'immunity is assimilation.' There is one flesh of birds and another of beasts. From the welter of amino-acids which result from the disintegration of food proteins each animal has to build up its own characteristic and specific tissues. Specificity is chemical as well as morphological. To some foreign proteins we are naturally immune—*i.e.*, we can assimilate them automatically; to others we acquire immunity—*i.e.*, we learn to assimilate them. But to some foreign proteins immunity is neither congenital nor acquired. The tissues continue to resent the intrusion of such. They will not assimilate them. Such proteins excite anaphylaxis in varying degrees. Richet

defined anaphylaxis as the last stand of the cell against adulteration of its protoplasm. In extreme degrees anaphylactic shock is fatal because assimilation would mean too profound an alteration of bodily structure. In less degrees anaphylaxis declares itself in violent attempts to get rid of the foreign invader.

From this point of view allergy may be an inborn resentment, while anaphylaxis is an acquired one. Richet introduced the term anaphylaxis about 1900 to signify its antithesis to prophylaxis. Von Pirquet introduced the term allergy in 1906 to include all conditions of altered reactivity. All anaphylaxis is therefore allergic, but not all allergy is anaphylactic.

As already stated, the chemical foundations of the study of allergy were laid by Dale in 1910 by his work on histamine. Fourteen years later, Thomas Lewis began his classical studies on the local reactions in the human skin. He showed that there are three components in this: (1) the primary dilatation of capillaries—the *red line*; (2) an increased permeability of these capillaries, producing the *wheal* which is independent of the nerve supply; and (3) a widespread dilatation of the surrounding arterioles, the *flare*, which depends on the integrity of the sensory nerve fibres in the neighbourhood. He then showed that all these phenomena could be produced by intradermal injections of histamine. As he was not convinced that such responses were always due to histamine, he designated the causal agent the H-substance, implying that it was either histamine or a histamine-like body.

In 1929 Dale added a second observation of paramount importance—namely, that adrenalin directly antagonizes histamine. This explains why adrenalin is by far the most effective treatment in an allergic crisis, for it both neutralizes histamine and stimulates the sympathetic (*i.e.*, inhibitory) nerves to plain muscles, such as those of the bronchi, in-

testines, and uterus. But these observations further show how it is that the psychical state can modify allergic manifestations. It is clear that the individual who is liable to asthma may be much more sensitive to his particular allergen when he is worried or overworked. On the other hand, a sudden shock may lead to an equally sudden additional secretion of adrenalin.

Thus a doctor, in pre-motoring days, was driving his gig down a steep hill when he began to have an attack of asthma. The horse, realizing the failure of control, began to bolt. The sudden fright of this checked the paroxysm.

Another instance of the profound influence of the psychical state on allergy may be seen in angio-neurotic œdema. It is amazing that Osler should have said in 1915 that he had notes of only 18 cases in private practice and that during twenty years there had been only 16 cases at Johns Hopkins Hospital out of 23,000 medical cases. For in the later stages of the last war it was fairly common, and in the distressful peace that followed it was by no means rare. Nervous worries bulk large in exciting an attack, although the underlying allergic tendency must be continuously present.

But can we push the chemical problem a little nearer home? What precisely causes the liberation of the H-substance? Dale and Lewis both agree that the union of antigen and antibody acts like any other injurious stimulus by releasing it from the local tissue cells or, in the grave cases, from a large organ like the liver. It is of interest in this connection to recall that it has been found that the most profound shock resulted from those wounds which led to the most extensive crushing of muscles, and the histamine theory was invoked to explain this.

There is another destroyer of histamine besides adrenalin, and this is a special ferment, histaminase, discovered by Best and McHenry in 1930. Each of the manifold constituent groups in the protein molecule has its own

specific ferment. Garrod showed that many of the inborn errors of metabolism are due to the lack of some one or other of these specific ferments, and that this lack can often be shown to be transmitted along Mendelian lines of inheritance.

It is therefore plausible to attribute, at any rate in part, familial and hereditary allergic sensitivity to a lack of histaminase, which in the ordinary individual destroys histamine as soon as it is set free. In anaphylaxis there appears to be a slowly reacting substance set free from its combination in the tissue cell by a mechanism which is comparable with that by which snake venom produces its effects.

This is about as far as we can take the general biochemistry of allergy, and we may put the emphasis on a congenital lack of histaminase aggravated by an intermittent deficiency in adrenalin. As to general clinical features, sensitivity may be shown to a number of different substances by the same individual, and not always to the same substances. A general sensitivity which may have various manifestations is more often transmitted than a specific sensibility towards any single substance. As to age, Bray, in his 'Recent Advances in Allergy,' which is a veritable storehouse of information, states that most allergic conditions begin early in life and, with the exception of hay fever, tend to originate less frequently with advancing years. With regard to sex, he finds eczema commoner in males and migraine in females, while hay fever attacks either sex equally. Asthma, though twice as frequent in boys as in girls till puberty, is unfavourably affected by the catamenia, so that female cases are slightly more prevalent until the time of the menopause, when the male cases again predominate, though now more slightly.

Most allergic manifestations are worse at night, because of the predominance of vagus activity then, so that there is a relative insufficiency of the sympathetic nervous system. It seems a general rule that if a patient is sensitive to one

emanation from an animal he will be to all the others. Thus, if he gets asthma from horse dandruff, which, by the way, has quite recently been shown to contain histamine, he will get serum sickness from an injection of horse serum, or urticaria from rubbing either the dandruff or the serum into his skin. This is, of course, the rationale of the skin tests, which have, however, proved of less diagnostic value than was at one time hoped, because if a man is sensitive to one he may be sensitive to a large number of substances, and his sensitivity may vary from time to time.

Thus in one case where the patient was shown to be sensitive to cereals, excluding them from his diet was followed by a dramatic improvement. Some months later, however, the attacks recurred, and the tests were repeated. He was now no longer sensitive to cereals, though he was to a number of other substances that had previously produced no reaction. In his case it is interesting to note that there was (*a*) a familial factor; one brother had giant urticaria, and another had attacks of intestinal colic and diarrhœa of otherwise unexplained causation. And there was (*b*) a nervous factor. He had attempted suicide, and his brother was almost 'mental.'

We may take it that allergy expresses itself chiefly (*a*) in the respiratory system—*e.g.*, asthma, vasomotor rhinitis, hay fever, recurrent catarrhs; (*b*) by skin rashes; (*c*) by effusion into joints; and (*d*) in the alimentary canal by diarrhœa and vomiting or spastic colon, though there are many others which, with more or less show of reason, may be referred to the same origin.

Purpura and Urticaria.

In dealing with some allergic diseases, we shall start with urticaria and its relations to purpura. Purpura may be symptomatic of many conditions, including infections.

These do not concern us here beyond noting that, as it is held that an allergic factor is present in certain infections, it may be that such purpura is sometimes a manifestation of this.

Then there is thrombocytopenic purpura accompanied by a low platelet count, which is greatly benefited by splenectomy; it does not appear to belong to the group we are to discuss, that of the arthritic purpuras, such as Schönlein's and Henoch's, which have been called anaphylactoid. The former used to be regarded as truly rheumatic, as was erythema nodosum, merely because the patients developed swellings of the joints as they do in so many toxic states. Indeed, Poynton and Schlesinger have recently advanced the view that even in rheumatic fever the synovitis is not so much the direct result of the infection by bacteria as a sensitization to their products of disintegration.

These arthritic purpuras may be compared with urticaria, especially the giant form of urticaria, to which the somewhat cumbrous name of 'angio-neurotic œdema' is often given. In purpura the blood, as a whole, passes through the capillary wall, thus causing the eruption, whereas in urticaria the exudation through the capillary wall is merely serous fluid and leucocytes. A patient may have purpura in one attack and urticaria in another. In giant urticaria, organisms may be found in the stools similar to those found in Henoch's purpura.

Apparently *B. Welchii* can produce a series of events ranging from intense hæmolysis to recurrent attacks of giant urticaria. Sir Thomas Lewis has shown that two different lysins may be produced which determine the form that the reaction takes—a hæmolysin which may cause hæmoglobinuria, and a dermolysin which causes urticaria. *B. Welchii* is a recognized cause of hæmolytic anæmia, and so is paroxysmal hæmoglobinuria. In this latter condition we know that a hæmolytic agent is continuously present in the

blood, but it is only activated by exposure to cold. Now, Bray recently reported a striking example of allergy induced by cold. Here again we have examples of the close association between hæmolytic processes and allergy, illustrating Lewis's contention. Again, there is a rare condition known in Italy as fabismus—an acute hæmolytic anæmia which follows a meal of beans some time after the first and innocuous meal of this kind. Here we have an example of a hæmolysin produced by an anaphylactic reaction, but recalling an ordinary food allergy. Clearly the association between anaphylactoid purpuras and other allergic reactions is a very close one.

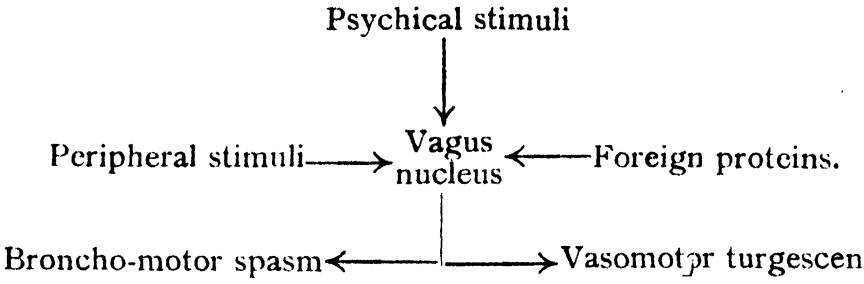
As to the ætiology of angio-neurotic œdema, the nervous factor bulks large, and next in importance are familial and hereditary tendencies. Intestinal infections and foreign proteins must always be considered. It is the 'local expression of the presence of a circulating toxin to which persons of a nervous temperament are prone.' The attacks may be excited by emotion, exposure to cold or slight trauma; they may coincide with menstruation.

Treatment.—The principal points in treatment are: (*a*) Investigate the toxic factor by (i.) inquiring as to the influence of any special food, and by (ii.) a bacteriological examination of the stools for pathogenic organisms—do what is possible to remove or raise resistance against such factors. (*b*) Try general desensitization by giving a capsule containing $7\frac{1}{2}$ grains of peptone before meals. This is sometimes quite helpful, but if it appears necessary to resort to intravenous injection of peptone, one should begin with minute doses, for fatal results have occasionally been reported. Old tuberculin is of value as a general antigen, 1 minim of a 1 in 100,000 solution being the usual initial dose. (*c*) Damp down the over-active parasympathetic with bromide and belladonna. (*d*) Increase the antagonistic effect of the sympathetic by injections of adrenalin (say, 5 minims

of the 1 in 1,000 solution), or by routine administration of ½ grain ephedrine three times a day. (*e*) Calcium salts are only likely to be useful when there is definite evidence of calcium deficiency in the blood. (*f*) As in purpura, autohæmotherapy is of definite value, 10 c.c. of whole blood being given on three occasions, the first of which should be during an attack. (*g*) The recent isolation of vitamin P_1—known as citrin or hesperidin, prepared from paprika, hips or lemons—gives promise of another line of treatment for purpura when associated with increased capillary permeability.

Asthma.

Asthma is generally taken as the typical example of an allergic disease, but it cannot be completely explained by biochemistry. In many allergic conditions the nervous system plays an important part, but in none more than in asthma. It is always a dangerous thing to try to express a disease in a formula. Nevertheless, one of us attempted to do so for asthma in 1920, which Hurst improved upon in 1923. He has defined asthma as due to an unstable or irritable condition of the bronchomotor portion of the vagus nucleus, which causes it to react unduly to psychical or peripheral stimuli, or to foreign proteins in the circulating blood. This could still be modified with advantage—first, by allowing that the foreign protein may act on nerve endings in the nose or bronchi; and, secondly, by including the obvious vasomotor turgescence which accompanies the bronchomotor spasm, as this is generally present, and is sometimes the most striking feature of an attack, just as it is in the closely allied condition of hay fever. Moreover, it is carried out by the same vagal mechanism. Thus modified, the formula can be expressed diagrammatically as follows:



We will first consider the stimuli acting on the centre, and then some features of its response.

1. **Psychical Stimuli.**—That asthma often occurs in neuropathic families and that asthmatics are unduly suggestible are well-known facts. The paroxysm excited by an artificial flower figures in every textbook. But it is extraordinary to witness the almost instantaneous relief that may follow a hypodermic injection of distilled water into a patient who is anticipating one of adrenalin, when this is known to be efficacious. This explains why the asthma curer who has profound belief in the efficacy of his treatment finds increasing justification for that belief. For his confidence arouses responsive confidence in his patient. But what is not so clearly recognized is that the effective stimulus often arises from a psychic conflict. Naturally, other influences will help to decide in which of these ways the psychic trauma reveals itself. Thus, one sufferer from a psychic conflict who has to face a hostile environment may escape through an hysterical paralysis, but another who has to face the internal disorder produced by sensitiveness to foreign proteins is more likely to develop asthma.

2. **Foreign Proteins.**—Much of what has already been said about allergy in general will apply here. But we must distinguish between the cases where the foreign protein is particulate and acts locally, and those where it gets into the circulation and acts on the vagus nucleus. Van Leeuwen called attention to the effect of a wheat parasite in producing epidemics of asthma in Holland. On removal of the

sufferers to a higher altitude the attacks ceased. While there they could breathe air through a tube in which this parasite was placed as long as a filter of cotton-wool was inserted so as to prevent any particle of it reaching the air passages. If this filter was removed, inhalation of the parasitic particles would produce an asthmatic paroxysm, even in the Swiss mountains. Feather pillows and horsehair probably act in the same way. But when asthma is produced by some food, then we must assume that the respiratory effect is produced centrally. In either event we generally find that the patient has an hereditary tendency to asthma and hypochlorhydria. Not infrequently the blood sugar is low, and administration of glucose helps by increasing the store of glycogen in the liver, which increases its antitoxic power also. This diminishes the liability of an allergen to liberate histamine from the liver. It is well recognized that repeated bronchial infections may lead to asthma even in people with no hereditary tendency to it, and with a normal gastric juice. The repeatedly irritated bronchial mucosa develops a sensitivity which probably results in the local liberation of histamine, just as will happen in an irritated skin. Probably in this local liberation of histamine we may find the explanation of the occurrence of asthma and eczema in the same person or same families.

3. **Peripheral Stimuli.**—Of all sources for peripheral stimulation, the nasal mucosa is well known to be the most effective in producing an asthmatic paroxysm. Indeed, some rhinologists speak of a 'trigger area' in the upper part of the nose. But if the nose can fire off an allergic reaction, it can also suffer from an allergic response. Bray has called attention to the frequency with which the allergic state produces a boggy condition of the nasal mucous membrane, which clears up as the allergic reaction passes off. This fact probably explains the wide differences of opinion as to the value of treatment of the nose in asthma. Obviously

it is no use treating the nasal results of allergy. Tilley was of opinion that light cauterization of the nose would often stop paroxysms by destroying the sensitive surface, but that no permanent benefit is conferred by this. Many rhinologists are sceptical as to the help given to the asthmatic by operations on the nose. It is not much use destroying the trigger if the gunpowder is still there. There are many other, if less effective, triggers available—eye-strain, gastric and intestinal disturbances, enlarged bronchial glands, and uterine disorders. Stimulation of the pleura by paracentesis may excite an attack. Reviewing these peripheral excitants, one may remark that while the scent of a rose is accepted as a cause of genuine asthma, the sight of an artificial rose as a cause is sometimes regarded as indicative of hysteria, whatever may be implied by this. In other words, if the peripheral stimulus starts in the first cranial nerve, the response is considered genuine, but if it starts in the second nerve it is not. Surely this is not very logical. On the scheme here suggested one afferent impulse is direct, while the other acts through psychical associations; both are equally genuine.

The Influence of the Parasympathetic.—The great function of the parasympathetic or extended vagus may be defined as promoting the assimilation of suitable and the rejection of unsuitable material. Thus it starts the secretory and muscular processes of digestion, while it empties the rectum and bladder, and can reject food by vomiting. The excitation of bronchial catarrh and cough is similarly a method of ridding the body of unsuitable material, and it is interesting to recall in this connection that drugs which are expectorant in small doses are emetic in larger ones. The similarity of the parasympathetic action on the alimentary and respiratory tracts is not surprising when we remember that the latter tract develops as an outgrowth from the former.

Without accepting the whole of Eppinger's and Hess's

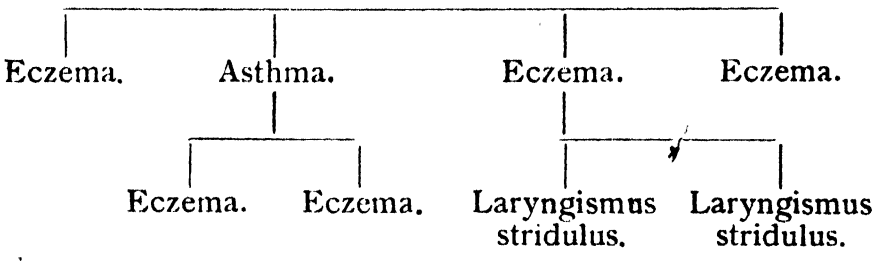
theories we may agree that the asthmatic is a vagotonic, and is liable to other manifestations of vagotonia. There was a curious instance of this in a man who suffered from both asthma and gastric ulcer, and who had found out for himself that he could relieve the pain of his ulcer by smoking a stramonium cigarette. And a form of mucous colitis with colonic spasm has been termed 'asthma of the colon.' Fibrinous bronchitis is closely comparable with muco-membranous colitis.

The Sympathetic and Endocrine Balance.—But vagotonia may be relative as well as absolute. In other words, it may well be that an overactive vagus is due to diminished action of the antagonizing sympathetic. The reinforcement of the adrenalin effect by pituitrin may be held to point in the same direction. The glands which co-operate with the sympathetic appear generally to help in checking the asthmatic paroxysm. The stimulating effect of the gonads on the sympathetic-endocrine group may account for the influence of uterine disease in exciting asthma.

In general terms, it would appear that when the endocrine balance sways in the direction of the vagus, asthma is likely to occur in susceptible subjects; when the balance is redressed in favour of the sympathetic, attacks may be cut short or prevented.

Asthma, Anaphylaxis and the Skin.—The skin undoubtedly has excretory functions. Uræmia may first manifest itself by a rash in the form of a marked toxic erythema. The rashes of the exanthemata have often been compared with that produced by serum in anaphylactic subjects. This conception of an excretory mechanism is expressed in the popular idea of the benefit derived by 'getting the rash out.' The toxin which cannot be assimilated —*i.e.*, to which the body is not immune—must be got rid of somehow, and at any rate from the vital structures. In this connection it is interesting to note the occasional alterna-

tion of attacks of eczema and asthma. The following family tree is a striking example of this alternation:



Other skin diseases, such as prurigo, dermatitis herpetiformis, and erythema multiforme, are also regarded as allergic manifestations by many authorities. In this connection it is relevant to point out that the presence of histamine has been demonstrated in herpetic vesicles. It is further of interest to recall that both in skin diseases and in asthma eosinophilia is a usual feature of the blood picture. As an attack of asthma goes on and expectoration becomes more abundant, the eosinophils pass into the sputa. The skin reaction of an asthmatic to foreign proteins may be an attempt to wash out the offending non-assimilable material from the skin. Mackenzie Wallis reported the occurrence of eosinophilia also in the urticarial wheals produced by the skin test. This accords with the observations of Kanthack and Hardy fifty years ago on the rôle of eosinophilia in bacterial infections and intestinal digestion, which have passed into undeserved oblivion. An eosinophilic reaction appears to be a method of dealing with foreign proteins, whether in skin, bowel, or bronchi.

Treatment.—These considerations help to provide a rational explanation for some methods of treatment which have been empirically used in the past. We hope also that they may help to emphasize the necessity for an all-round assault on every case of asthma from these various aspects. For some, asthma is merely a psychological problem; but that is to close one's eyes to the toxic factor. For others the

toxic element is the primary thing, the nervous factor being merely the failure of the nervous system to co-operate successfully in getting rid of the toxin. But this view is not capable of explaining the influence of suggestion in actually producing a paroxysm in the absence of the exciting toxin. The suggestibility of the patient should be utilized to help him confidently to expect a cure. The effect of climate may often be due to suggestion. An asthmatic goes to a place and has an attack; therefore each time he goes there he expects to have one, and has it. The converse is also true. To point this out in the former instance may help him to avoid repetition. But quite apart from suggestive influences, altitude has a definite effect on asthma. Very few asthmatics can achieve a paroxysm at much more than 3,000 feet above sea-level. Mont Dore is 3,500 feet above the sea and owes much of its effectiveness in the treatment of asthma to this fact.

Search must be made for deeper-seated psychological troubles. Naturally, sources of peripheral irritation must be eliminated; this includes avoidance of late suppers and cold bedrooms. The skin reactions may be tried in determining the foreign proteins to which the patient is sensitive. Where ordinary preparations fail to elicit a response, it is sometimes advisable to try an extract prepared from the dust present in the patient's house. According to Bray, the earlier in life an allergic condition develops, the more likely is a positive diagnosis to be reached by this method. Methods of desensitization should be considered, whether by a general or a specific antigen. For the former, injection of 2 c.c. of 1 per cent. sulphur in olive oil is recommended. The patient should be kept in bed for twenty-four hours afterwards, because the febrile response which is aimed at may be quite sharp.

The universal belief in the efficacy of the belladonna group in asthma finds its justification in the paralyzing action of such drugs on the parasympathetic endings, just as the fillip given to the sympathetic by adrenalin or ephedrine helps to

redress the balance in another way. According to some, the influence of iodide is mainly to activate the thyroid; if this is so, the benefit of this drug in asthma is comprehensible, since the thyroid secretion lowers the threshold to sympathetic stimulation. But so far we have no explanation of the way in which arsenic acts in this disease, though it has been used since the days of the Romans, and certainly it often seems to help. It is also important to do everything we can to restore an impaired endocrine balance.

This all-round attack on the problems of asthma affords the best chance of relief, especially if carried out before structural changes, such as emphysema, have occurred. After that a vicious circle is set up which is hard to break.

Respiratory Manifestations of Allergy in Childhood.

The alternation of asthma with laryngismus stridulus in members of the same family has already been mentioned. But a more frequent respiratory manifestation of allergy in infancy and childhood, the true nature of which is apt to be overlooked, takes the form of a simple bronchitis. Such children, colloquially known as 'chesty,' sometimes have one catarrhal attack after another. If they contract measles the respiratory complications are apt to be particularly severe. Removal of the offending allergen, or desensitization against it, is usually followed by good results.

Hay Fever.

Although an association between a paroxysmal rhinorrhœa and hay or certain flowers has been suspected since the sixteenth century, it was Elliotson, in 1831, who maintained that the condition was produced by pollen. It is, of course, the wind-borne pollen which is chiefly responsible, though close contact with other pollens can have a similar effect. Timothy grass is apparently the chief offender. Here is a good example of a local allergic reaction, though, as Elliot-

son pointed out, pollen may also produce a dermatitis. Noon and Freeman were the first to prepare a pollen antigen in 1911. This, which is entirely innocuous to non-allergic subjects, can be highly toxic to sensitized individuals. Fifty times the dose which would be lethal for such an individual has no effect on a rabbit, even when given intravenously. Indeed, one can hardly imagine that a grass-sensitized race of rabbits would survive. Even the most sceptical as to the value of vaccines would admit that scientific use of pollen vaccine may be very helpful. Freeman's method of 'rush inoculation' has improved the prognosis. He gives subcutaneous injections of the specific pollen extract every one and a half to two hours throughout a fourteen-hour day. This treatment lasts two to four days, and he maintains that if it is done at the beginning of the pollen season immunity can be guaranteed for that year. Unfortunately, it will very likely have to be repeated in subsequent years. Obviously the analogy between asthma and hay fever is close. In each we have a trigger reaction and a vasomotor turgescence followed by an exudate, which is, however, much more abundant in the case of hay fever.

Food Sensitivity.

All of us must have come across extraordinary instances of sensitiveness to some special form of food. Allergy provides a scientific explanation of the adage, 'One man's meat is another man's poison.' The factor of suggestion seems to come less into this than into other allergic reactions, for the patient is usually very careful to avoid the article of food which causes such distressing symptoms, and only takes it unwittingly.

It is clear that molluscs and arthropods are more often responsible for such severe symptoms than vertebrate fish. Their liability to excite urticaria is also well known. It was observing a friend's nettlerash which followed the eating of

some crab that interested Heidenhain in lymph formation. Presumably their wider morphological divergence from us is accompanied by a wider chemical divergence. In this connection it is interesting that whereas anyone sensitive to such reactions is apt to get one from horse serum, he is not likely to get one from ox serum. It has been supposed that this is due to our habit of eating beef, so that its proteins are no longer foreign to us. At any rate, it suggests interesting experiments on the effect of ox serum on vegetarians, and horse serum on the inhabitants of countries where horse-flesh is a normal diet.

Rowe has compiled some convenient 'elimination diets' for the diagnosis and treatment of cases of food allergy, by which one can fairly quickly arrive at the responsible factor. They exclude foods to which the patients are most commonly sensitive, which Bray regards as wheat, milk, eggs, apple, banana, orange, celery, cabbage, cauliflower, potato, chocolate, fish, and nuts. Another method is that of Cunningham, who, after preliminary treatment by calomel and Epsom salts, places the patient on one article of food, usually meat, for three days. Then every day one other food is added, until the one responsible is detected by the production of a reaction.

Rowe described the occasional occurrence of 'allergic toxæmia' in rather less sensitive individuals. It is characterized by a sense of fatigue and the onset of nervous symptoms, if the food responsible for exciting the allergic reaction is repeatedly ingested.

We do not propose to deal with the drug allergies further than to point out the not infrequent production of asthma and angio-neurotic œdema by aspirin, and of the danger of attempting to desensitize against it; nor shall we deal with the vexed question of the influence of allergy in aggravating infections such as tuberculosis, scarlet fever, and acute rheumatism. Much interesting work has been done

and many ingenious suggestions have been made on this subject, but we must concentrate our attention on the simpler issues first. That many joint conditions may be allergic is probable in view of the way that recognized allergic states so often involve swelling of the joints. But we must beware of explaining too much by a convenient and fashionable hypothesis.

Enuresis.

We should, however, like to call attention to Bray's ingenious suggestion that some cases of enuresis are due to allergy. He was led to this view by noting that on getting rid of some recognized allergic symptoms a previously troublesome enuresis would disappear. Consequently he began to investigate and treat cases where enuresis was the sole symptom on similar lines. The idea is attractive because it fits in with what one knows of the visceral nervous system. The pelvic visceral nerve stimulates the emptying mechanism of the bladder and, like the vagus which stimulates contraction of the bronchial muscles in asthma, belongs to the parasympathetic. The sympathetic nerve supply to the bladder, on the other hand, while closing the sphincter vesicæ, inhibits the detrusor muscle. Here, as elsewhere, we see the clear-cut antagonism between the sympathetic and the parasympathetic. Ephedrine, by stimulating the sympathetic, may check enuresis more efficiently than belladonna, which, of course, paralyzes the parasympathetic. Indeed, several observers have recorded instances where ephedrine caused retention of urine. It is interesting to find that an allergic state may, by upsetting the balance between the sympathetic and parasympathetic, produce the opposite condition of enuresis.

We will try to draw the threads together by giving this brief description of allergy. It is an unusual response to an ordinary stimulus, which, though innate and familial, is yet

modified by conditioned reflexes. On the chemical side it is possibly due to an inborn error of metabolism characterized by a lack or shortage of a particular intracellular ferment—histaminase; on the nervous side by a relative overaction of the parasympathetic. The response of the organism ordinarily takes the form of trying to evict the invading foreign protein by every means in its power, but if this is inadequate the cell will die rather than surrender its chemical individuality.

CHAPTER XIV

HOW DO DRUGS ACT?

IT is probable that originally drugs were given as a form of sympathetic magic. The Hindoos treated jaundice by painting the patient a still brighter yellow with turmeric, and in parts of Suffolk if a man cuts himself with a scythe he will oil the scythe to prevent the wound from festering. Sympathetic magic was responsible for much ancient polypharmacy with animal extracts often of a disgusting nature, to which may be due the lingering prejudice against any animal extracts in therapy. The ascent from magic through empiricism to rational therapeutics has proved slow and arduous, as can be seen from the history of the vegetable alkaloids. Originally herbs were gathered at certain phases of the moon, with mystic incantations, then certain of them were found effective apart from such ritual, and finally their active principles were isolated in a pure state. We may well marvel at the apparent ease with which plants can manufacture potent alkaloids, only some of which have been imitated, and those laboriously, by the pharmacologist. Nor do we know what use the plant makes of such alkaloids in its own metabolism.

The use of some drugs is still entirely empirical and the scientific explanation of their action has not yet been reached —colchicum for gout and salicylates for rheumatism, for example. In other instances the rationale has only been discovered after a long interval—such as emetine for amœbic dysentery and quinine for malaria. One is constrained, therefore, to utter a plea for empiricism, especially when one recalls the scorn of the pharmacologist for the clinical belief in cod-liver oil before vitamins were discovered. As Timme reminds us, 'the abysmally ignorant South American

savages who gave us cinchona bark for malaria did not even know the formula for quinine.' After the researches of Laveran and of Ronald Ross had explained its mode of action, it was observed that quinine was not fatal to every phase of the life-history of the parasite, and the next stage was an attempt to synthesize its essential quinoline nucleus with other substances to overcome these difficulties, resulting in the making of plasmoquin and atebrin. Yet no one knows how the quinoline nucleus destroys the malarial parasite, or why it needs different associates to deal with different stages of its life-history.

Here we are dealing, however, with the action of a drug on an invader. If we want to get an idea of the way drugs can influence our own tissues we shall probably do this best by studying the behaviour of those substances which the body forms for its own purposes, such as hormones and antibodies, as well as those highly active catalysts the vitamins it obtains from food. In the case of the hormones, the old problem which came first, the hen or the egg, can be answered. Some hormones at least existed before a mammal was there to make use of them. Thus œstrogenic substances are to be found in the coal measures, and ma-huang trees in China and India manufacture ephedrine, so closely allied to adrenalin, independently of the adrenals. As evolution proceeded the increasingly complex organisms found such substances advantageous and at last learned to make them. Vitamins being so much more widely distributed in foods, the animal body has not had to go to the trouble of making them. Vitamins for the most part are acquired needs, acquired as structure and function became more complex, though even lowly forms of life make use of vitamin D. This acquiring of a need explains quite simply what on the face of it appears a mystery. How is it that the germ of rice which is removed by polishing contains just the amount of vitamin B_1 which is necessary to

the proper utilization of the grain? It was because rice in its natural state was found such a useful food that it was eaten and therefore cultivated, and it was so useful precisely because it contained both the food and the catalyst. Not until man polished the rice for æsthetic reasons did he remove the catalyst and get punished by suffering from beri-beri. For we must remember that the vitamin was placed there for the good of the plant and not for us. When the germ begins to shoot it starts to live on the grain, and its vitamin enables it to oxidize that grain so that the germ can make use of that ample store of food. We use the vitamin in precisely the same way as the growing shoot.

When we come to apply the principles deduced from the study of hormones and vitamins to the actions of drugs in general we are confronted with a number of problems; for that reason this chapter is headed by a query. We may classify the principal ways in which drugs act thus:

(1) They increase or diminish the effects of stimuli reaching the cell from without.
(2) They modify the chemical changes occurring within the cell itself.
(3) They may themselves be so altered in chemical constitution by the cell as to be capable of fresh activity, yet with diminished toxicity.

It may be observed that some of the best illustrations of the first group can be obtained from hormones, of the second from vitamins, and of the third from chemotherapy.

1. We little realized at the beginning of this century that a new era in pharmacology had dawned when Langley showed that the effect of adrenalin on any part is the same as if the sympathetic nerve to it had been stimulated; it merely seemed an extraordinarily interesting example of a chemical substance imitating a nervous stimulus. But it was much more important than that. From a study of adrenalin Langley

and Elliott independently put forward the theory of a receptive substance beyond the nerve ending, on which it acted, an idea which has borne much fruit.

Cholinergic and Adrenergic Nerve-Endings.—In 1907 W. E. Dixon showed that, after stimulating the vagus to the heart, a muscarine-like substance could be extracted from the heart muscle which was inhibitory in its action on other heart muscle, and could be antagonized by atropine, just as atropine antagonizes vagus stimulation. This accords with the well-known effect of atropine in checking other secretions. Unfortunately, this work of Dixon's met with so much scepticism that he dropped the subject. It was subsequently revived and greatly extended by Dale, and in 1921 by Loewi. The substance produced was proved to be acetylcholine, which was liberated not only when the vagus to the heart was stimulated, but whenever any parasympathetic fibres came into action. There seems to be an inert precursor of acetylcholine present in the receptive substance which, on the arrival of the nervous impulse, is activated by some oxygen set free from glucose by tissue respiration, and then this, having done its work of, say, making a muscle contract or a gland secrete, is as promptly destroyed in its turn by a ferment—a special esterase.

Now, it is known that physostigmine—or eserine, as it is often called in clinical work—imitates the effect of parasympathetic stimulation. Thus, either stimulating the third cranial nerve or instilling eserine will contract the pupil. Loewi has shown that this is because eserine prevents the esterase from destroying the acetylcholine produced. Apparently, then, atropine and eserine act respectively by interfering with and expediting the normal chemical results of parasympathetic stimulation. It is important to note that if atropine be given and the vagus subsequently stimulated, just as much acetylcholine is produced as before, but the atropine prevents it from getting into the receptive substance.

In the same way sympathetic stimulation has been found to produce adrenalin at the post-ganglionic nerve-endings. This is in addition to the adrenalin always stored up in the medulla of the adrenal gland, which can be drawn upon as an emergency ration when there is a sudden demand for widespread action of the sympathetic for purposes of defence.

We can therefore divide the nerve-endings of the involuntary nervous system into cholinergic and adrenergic, according as they liberate acetylcholine or adrenalin.

Just as the appropriate chemical material may get into this receptive substance so may a toxin. G. N. Myers has shown that a therapeutic drug may seize on the receptive substance, and thus bar the way to the ingress of the toxin. He found, for instance, that the diphtheria toxin could be prevented from attacking the heart if digitalis were given first. This resolves a clinical and pharmacological conflict. The pharmacologist has maintained that digitalis cannot exert its usual effect on the toxic heart, but the clinician still continues to administer it, and claims good results. Now we see that, though digitalis would have to be given prophylactically to produce its full effect, if it is got in early it can still bar the way to the toxin swamping the heart. The pharmacology of the future will have to concern itself with the natural history of these receptive substances, and find out in what way they can be helped by drugs both positively, by facilitating their reactions, and negatively, by blocking the way against the entrance of toxins.

Naturally a good many attempts have been made to use acetylcholine therapeutically where increased action of the vagus or other parasympathetic nerve is required. It must be admitted that the results have been disappointing. When it is given intravenously, the effects are too brief, when given by intramuscular or subcutaneous injection too uncertain. The acetylcholine is destroyed too quickly by the esterase.

We can see how necessary it is for the activity of the acetylcholine normally to be so brief. Otherwise the effect on a tissue cell would last longer than the brain commanded. But knowing, as we do now, what kind of actions it can produce, the way is pointed out to possible therapeutic uses if more stable substances with the same or similar actions should be available. Research in this direction was much encouraged by the work of E. C. Dodds on synthetic hormones, by which he showed that simpler compounds could have the same effect either to a less or even a greater extent than the natural hormone. It seemed possible that by varying the composition of such synthetic compounds more selective responses might be produced, enabling us to subtract from or add to the pharmacological action of the native substance.

On the cholinergic side two such attempts have been made. One is called Doryl, and is the urethane of choline; compared with acetylcholine it has more effect on the gastro-intestinal tract and bladder, and less on the cardiovascular system. It has therefore been found useful in post-operative atony. It can be given by intramuscular or subcutaneous injection, by instillation on to the surface of the eye in glaucoma, or even by ionization through the skin. Given by the mouth its action is uncertain, and it may cause some discomfort and headache. The other is a methyl compound of acetylcholine called Mecholin, which acts on the cardiovascular system and less on the gastro-intestinal tract; just the opposite of Doryl. It has been useful in paroxysmal tachycardia, while ionizing it through the skin has relieved the pain of various conditions associated with constriction of the arteries or with phlebitis. This may not be considered a very large harvest for so much toil, but it illustrates a point of great interest—namely, that drugs can be prepared synthetically which will have the same effect as a substance prepared by the body for its own use, though to a varying degree.

F. R. Fraser has made a useful classification of the acetyl-

choline substitutes into those with an action like muscarine and those acting like nicotine.

On the adrenergic side of the sympathomimetic drugs ephedrine and benzedrine (amphetamine) are well known. Less well known are cobefrin, neosynephrin and propadrine. Of these five cobefrin has the greatest pressor effect and propadrine the least. As an aid to local anæsthesia cobefrin is 5 times and neosynephrin 20 times more powerful than adrenalin. As a decongestive adrenalin is too constrictive and is followed by too much secondary vasodilatation and irritation, so that ephedrine is more popular for this purpose, though benzedrine is also effective; the elaborate preparations of this and of neosynephrin and propadrine have no advantage over their solution in normal saline. For the relaxation of bronchial spasm none of these synthetic drugs are as powerful as adrenalin. Nor have they any advantage as mydriatics, while they relax gastro-intestinal musculature only in such doses as to affect the circulation.

A study of the absorption and fate of this group of drugs has led to some interesting conclusions. A very efficient vasoconstrictor naturally limits its own absorption, while if a preparation is chemically unstable it is destroyed by the digestive juices or in the liver; therefore oral administration can only be effective if the drug is chemically stable and not too vasoconstrictive. Ephedrine, benzedrine and propadrine fulfil those conditions, while neosynephrin is much less effective by that route. Those with a catechol or phenolic nucleus —*i.e.*, adrenalin, its modification adrenalone, and cobefrin— are almost completely inactive by the mouth; together with neosynephrin they are mainly destroyed in the body by whatever route administered. On the other hand, those without a hydroxyl linkage on the benzene ring—*e.g.*, ephedrine, propadrine and benzedrine—resist decomposition more completely and are to be found in the urine. As the duration of action depends on the ease with which the body

can destroy or eliminate them the former group should be used when brief action is required, the latter for more prolonged effects.

Turning to the other side of such reactions, we find, for instance in eumydrin and prostigmin, synthetic drugs which have a more selective action than their native congeners on blocking and facilitating the action of acetylcholine. As pointed out in Chapter III eumydrin, which is the methyl nitrate of atropine, acts specially in the relaxation of pyloric spasm. Prostigmin, like physostigmine, prevents the destruction of acetylcholine at the end plate but does so for a longer period. The muscular weakness of myasthenia gravis resembles that seen in poisoning by curare, when, as is well known, the junction between muscle and nerve is blocked at the end plate. Physostigmine can remove that block, so in 1934 it occurred to Dr. Mary Walker to see if it would help a patient with myasthenia gravis. The effect was striking and dramatic. Then in the next year she tried the synthetic prostigmin and found it still more efficacious without any of the toxic drawbacks of the natural product. It will also completely relieve the artificial myasthenia experimentally induced by thymus extracts. Now thymus tissue is lymphatic, and in myasthenia there are little collections of lymphatic tissue (lymphorrhages) to be found in the muscles. It would appear that in some circumstances lymphatic tissue forms a curare-like poison which can be overcome by prostigmin, thus allowing acetylcholine once more to enter the end plate and restore the power of the muscle to contract. In view of the tendency to use quinine rather indiscriminately as a tonic it is important to observe that it increases the block at the end plate in this particular form of muscular weakness.

So here we have a fairly complete series of observations showing how the normal transmission of the nervous stimulus is effected, and of the ways in which it may be interfered with or assisted by certain drugs. The action of strychnine

presents some interesting considerations in this connection. Normally a reflex action finds its way through one particular path in the abundant nervous network, because the other paths offer greater resistance to its passage. Now strychnine lowers the resistance to the passage of a nervous impulse—hence its use as a stimulant or tonic. But if given in larger doses this resistance is reduced so much that even the slightest sensory impulse finds all the pathways equally open and all the muscles are thrown into action. In normal muscular action the contraction of one group naturally has to be accompanied by a relaxation of its opposing group; but under the influence of strychnine this relaxation is converted into contraction also, so that the whole body is thrown into rigid contraction, in which the strongest group of muscles wins. Very much the same happens in tetanus infection. So here we have an example of a drug doing something which might be considered helpful—namely, facilitating the passage of nervous impulses—but which may have a disastrous effect by throwing open all the pathways for it at once.

The barbiturates offer a good example of the way in which a drug may bar the entrance of stimuli into the cell by being adsorbed on to the cell envelope as already explained under Hyperthyroidism. These examples will serve to illustrate ways in which drugs act by increasing or diminishing the effects of stimuli reaching the cell from without.

2. **Drugs may act by modifying the chemical changes within the cell itself.** Although vitamins provide the best illustration of this, some of the activities of thyroid extract provide a good starting point for the discussion. Note that it speeds up metabolism in the direction it is normally going. Thus, if a little thyroid extract is added to water containing some tadpoles they quickly metamorphose into tiny frogs. Now in that change the gills shrink to nothing and the limbs begin to grow, and it is possible to see under the same field of the microscope the cells of the gills rapidly breaking down

and the cells that are going to form the front legs multiplying with equal rapidity under the influence of thyroid.

Thyroxine, the active principle of the gland, is the only animal substance that contains any notable amount of iodine. Our marine ancestors obtained their iodine from sea water, and their rudimentary thyroids were placed close to the gills so as to fix that iodine. The first effect of iodine shortage is thyroid enlargement. The gland 'gasps' for it. Giving iodine helps it to return to a more resting state.

From the obvious effects of iodine on the thyroid it has been claimed that the therapeutic effect of iodine or iodides is entirely due to their altering the stage of activity of the thyroid gland. This is probably too narrow an interpretation. One thing about thyroxine is certain—that it causes the consumption of more oxygen because of the increased rate of combustion. This leads to the question of the influence of drugs on oxidation within the cell. As explained in Chapter XII, we remain out of breath for some time after violent exertion because we have incurred an oxygen debt, which has to be repaid by inspiring increased amounts of air afterwards. Sugar is the fuel used by the muscles, and if this is not completely oxidized some of it remains in the circulation as lactic acid, which irritates the respiratory centre to increased activity. Since the burning of a piece of sugar is a simple matter, one might suppose that to oxidize it within the body would also be simple. But the body has to carry out the process without alterations of temperature, osmotic pressure, etc., which renders it a highly complicated procedure. A whole series of enzymes are required, and vitamin B_1 is an essential partner in this series. The more sugar, or starch, which becomes sugar, that we eat the more vitamin B_1 we need to oxidize it. We have already pointed out that alcoholic neuritis is not due to the alcohol itself, but to the alcohol capturing the vitamin before it can get to the nervous system, where it is needed if the nerve cells are to utilize their

oxygen. Alcoholic neuritis is therefore a deficiency disease in exactly the same way as beri-beri. Clearly oxidation within the cell cannot proceed without both sugar and vitamin B_1. An overdose of insulin locks up so much sugar in the form of muscle glycogen that the brain cells cannot get enough, and the patient rapidly goes through all the stages of asphyxiation even though freely supplied with oxygen. Give him sugar, however, and he speedily recovers.

As is well known, cyanide is a deadly protoplasmic poison; while a considerable dose is immediately fatal, a weaker dose reproduces the symptoms of asphyxia. This at once suggests that the brain cells are being starved of oxygen. Yet the patient gets plenty of air, but, like the insulin-poisoned patient, he cannot use it, though for a different reason. His trouble is that the cyanide combines with one of three catalyst enzymes that link the oxygen to the tissue cell. To a certain extent this can be corrected by methylene blue, which helps to oxidize the sugar in the cell.

Then take coal-gas poisoning. Here the carbon monoxide, having a stronger affinity for the hæmoglobin of the blood than has oxygen, seizes upon it and holds it, so that it cannot convey oxygen to the tissues. Thus we see that the brain cell can be internally suffocated, as it were, either because oxygen is not being carried to it by the blood, as in coal-gas poisoning, or because the fuel, *i.e.*, sugar, has been locked up, as by an overdose of insulin, or because the oxidation changes cannot be carried out through lack of vitamin B_1, or because a similar catalyst has been annexed as in cyanide poisoning. Obviously these interferences vary considerably in the speed and gravity of their ill-effects, but fundamentally they all act by checking oxidation within the brain cell.

Naturally oxidation of sugar is necessary not only for the brain but also for the muscles. When our voluntary muscles are diseased or fatigued we rest them. But there is one muscle that can never rest, and that is the heart. Therefore its need

of vitamin B_1 is more urgent. Heart failure is by no means uncommon in chronic alcoholics, and can often be remedied quite quickly by large doses of this vitamin. Thus the case of a policeman is recorded whose ordinary consumption of beer was fourteen pints daily, with some extra on occasions (he explained he did not pay for it; it came to him in the course of his work). His heart had failed so much that he was highly dropsical, yet in three days the dropsy all cleared up simply through large doses of vitamin B_1.

That iron plays an important part in oxidation has long been known. Its tendency to rust, which is one of its disadvantages in industry, is its great physiological merit, for by its alternate oxidation and reduction in hæmoglobin oxygen is carried all over the body. We have now learned in addition that ferrous iron contains one more electron than the ferric, and that the handing over of this electron is the activator of the series of oxidative changes in the cell already referred to. We have also learned the exact stage in the manufacture of red blood corpuscles that iron is required.

Now our daily requirement of iron is only about 3 grains, less than is contained in any ordinary good mixed diet. Yet we know that 90 grains of iron and ammonium citrate a day are required for the cure of ordinary anæmia, and even though 6 grains of ferrous sulphate a day may be sufficient, that is double the physiological demand. It seems that in disease it is sometimes necessary to 'swamp' the body with a drug before it can produce its effect, as if there were some obstacle to its absorption which has to be overcome by mass action. Possibly one such obstacle in the case of iron is the absence of hydrochloric acid in the gastric juice which is so common in anæmias, but it is doubtful whether this is the whole story. Certainly the iron salts are more soluble in its presence, but that argument does not apply to all the instances in which minerals have to be given in large doses to meet a comparatively small demand by the body. Other factors

come in; thus we know that vitamin D is necessary for the absorption of calcium from the bowel and parathormone from the parathyroids is required to keep an adequate quantity of it in the circulation; also that sodium cannot be sufficiently retained in the body in the absence of adrenal cortical secretion. It has also been maintained that thyroid secretion is needed before iron can be built up into hæmoglobin. So it would appear that hormones and vitamins play an important part in enabling mineral salts to produce their proper effect on the tissues, but that when they are deficient absorption and utilization can sometimes be forced on the body by mass reaction. Nevertheless it is obviously more physiological to assist our mineral drugs by the appropriate hormone or vitamin if we know what it is.

Antitoxins and allied substances illustrate another way in which material usually of a protein nature can modify the chemical processes of the cell. In 1907 Ehrlich produced a highly elaborate explanation of such phenomena; it is rather fashionable today to scoff at this explanation as being far too mechanical. But it should be remembered that his theory led him three years later to the production of salvarsan and thus to the foundation of chemotherapy, which is now one of the most active developments in therapy.

3. **Chemotherapy** also illustrates the third topic—the alteration of a drug by the cell so that it assumes fresh activity, yet with diminished toxicity. This last great triumph of therapeutics may at first sight seem a departure from the biological approach on the importance of which we have insisted. But it will be found to be not so remote as it appears. Strictly speaking, the treatment of any malady with a chemical agent of known composition might be included in the term 'chemotherapy'; actually, however, it is almost universally limited to the treatment of parasitic diseases by chemical disinfection or control of the causative agent without producing marked toxic effects in the patient.

Now, just as vaccines apparently cause a reaction on living tissues leading to the formation of a new effective substance, so do some drugs—for instance, emetine in amœbic dysentery and salvarsan (arsphenamine) in syphilis. Both of these are, however, ineffective against the appropriate parasite in the test-tube. Therefore the specific effect of such a drug depends upon its chemical interaction with some constituent of the living cell. It is necessary that the drug should be presented to the tissues in such a form as not to poison them. Thus arsenic in its inorganic form is highly poisonous; linked to a benzene ring compound, it can be tolerated by the patient in much larger doses, while the active arsenic is set free at the appropriate point; it appears to be changed by the cell from pentavalent to trivalent arsenic in the process.

Chemotherapy has its disappointments, however; one such was optochin (ethylhydrocupreine). Although it has a powerful action in destroying pneumococci, which in the test-tube considerably exceeds that of the very successful sulphapyridine (M. and B. 693), it failed when put to the clinical test. Henry Moore attributed this to two main causes—it cannot penetrate into the solidified pneumonic lesion, and it is so toxic that the safe dose is hardly effective. The most dramatic success of chemotherapy has been with the sulphonamides. They have the great advantage of being readily absorbed when given by the mouth except sulphaguanide, which should therefore be the choice for intestinal therapy. As Fleming has pointed out, we have for the first time in the sulphonamide group antiseptics which are more lethal to bacteria than to leucocytes. Sulphanilamide, which is the most generally useful drug of the group, only interferes with leucocytes in concentrations twenty-five times greater than can be obtained therapeutically in the body, while it inhibits the growth of *Streptococcus pyogenes* in concentrations only $\frac{1}{50}$ of such therapeutic concentrations. By paralyzing the microbes in the circulation as it were it allows the natural

defensive mechanisms to complete their destruction. The last two years have seen a great extension in the local use of sulphonamide compounds. No advantage seems to be obtained by substituting any other of the compounds for the cheaper sulphanilamide, with the possible exception of sulphathiazole, which is the least toxic used thus. The danger of sulphur-containing foods while on such treatments has been exaggerated, but drugs such as sulphur and sulphates should be avoided.

It is a very interesting fact that just as the body can be educated by small doses of a toxin to resist larger doses, so a microbe can be educated by small doses of these drugs to resist larger doses of them. In the earlier days of salvarsan treatment it was found that inadequate dosage made the spirochæte resistant to any further administration of arsenic. The same is true of sulphonamides. This shows that in chemotherapy a biochemical reaction is excited in the invading parasite. A further suggestion of a biological relationship is indicated by the fact that the latest example of the sulphonamide group to be synthesized, sulphathiazole, contains a group similar to that in the molecule of vitamin B_1.

Another example of increased therapeutic and diminished toxic action resulting from the combination of a metallic drug with an organic vehicle is mersalyl (salyrgran), even though its action lies outside the rigid definition of chemotherapy. Mercury particularly affects the re-absorbing tubules of the kidney, and if a poisonous dose of, say, corrosive sublimate is taken they are gravely damaged. Yet if we give mersalyl, their action is merely inhibited, so that concentration by re-absorption does not occur. For that reason mersalyl acts as a powerful diuretic by interfering with a normal process. In this way the mercury is rendered more therapeutic but less toxic. The pituitary gland apparently exerts some control over this re-absorption, and in some cases of gross obesity associated with pituitary disorders the real cause of the

increase of weight is retention of water, or perhaps more accurately increased re-absorption by the kidney tubules. This is confirmed by the dramatic reduction of weight which has followed the injection of 1 mil. of mersalyl in this type of case. In two patients a single injection was followed by the loss of a stone in weight; in one of them this occurred within twelve hours. Of course, they put a good deal of it on again; curiously enough the one that lost weight most quickly regained it more slowly than the other, but in neither case was the original weight regained, and some patients have kept much better with an occasional repetition of the dose. Here the drug appears to over-ride the antidiuretic effect of pituitary extract by simply diminishing re-absorption by the kidney tubules.

An extension of the biological approach in therapy is exemplified by the method of giving one disease to cure another. Of this the most outstanding example is the treatment of general paralysis of the insane by malaria. This is after all the same plan as that adopted in certain tropical areas of ridding a district of an insect pest by the introduction of some other insect or animal. A recent application of a similar principle in medicine has been made by Alexander Fleming, who found that the well-known mould Penicillium could inhibit the growth of certain bacteria, and who made an extract containing the active principle penicillin. It can now be prepared as a strong aqueous extract which, when saturated with ether, is quite stable, and it appears to be many times more powerful than the most potent of the sulphonamide compounds. Although its action is similar, penicillin does not appear to belong to this group, however. If the pure active principle can be isolated it may well lead to the production of another series of chemotherapeutic agents.

Chemical Structure and Physiological Action.

As the specific effect of a drug usually depends upon its chemical interaction with some constituent of the living cell, it was hoped that it might be possible to correlate physiological action and chemical constitution, but to a great extent the attempt yielded disappointing results at first. In one instance, however, a definite relationship between physical state and physiological action was made out. Certain hypnotics are relatively inert substances, and may differ widely chemically, but they have this in common, that they are soluble in fat and other lipoid compounds, and so tend to collect especially where such compounds exist—that is, the central nervous system—thus interfering with the normal working of the nerve cells. However, the investigation was one-sided, and should have involved consideration of the structure of the cell as well as that of the drug. For it is clear that the nature of the receptive substance in the cell influences the reaction profoundly. How otherwise can we account for the fact that the pituitary growth hormone will still further elongate the already long backbone of a dachshund, while it increases the length of a collie's legs? Evidently the success or failure of such natural drugs depends on some innate or acquired capacity of the individual to respond. And herein may lie the explanation of idiosyncrasy to drugs. But of the nature of this receptive and selective capacity we know practically nothing.

A few years ago a fresh start was made on the relation between structure and action when a striking instance was demonstrated, largely through the work of Dodds. Œstrin, vitamin D, and the carcinogenetic substances to be found in tar, all contain the condensed carbon rings called phenanthrene. Thus it appears that normal reproductive activity, normal growth of bone, and that irregular, disorderly, unrestrained growth which constitutes malignancy are alike

conditioned by this condensed ring, chemical alterations in it, apparently merely of hydrogenation, leading to extraordinarily different types of growth. The whole subject assumes fresh interest when we recall that phenanthrene was first derived from coal-tar and was therefore originally formed under the influence of sunlight ages ago, just as calciferol is formed in our own subcutaneous tissues by bright sunlight every summer.

As stated earlier, Dodds found that simpler compounds than those prepared by the body can have the same effect as the natural hormones either to a less or even a greater extent. It may be asked why should the body trouble to make a more elaborate and no more effective hormone than can be made in the laboratory? To this the answer has already been given in another connection; it is because the body has to carry out the reactions at a temperature of 98·4° F. and with severe limitations as to acidity or alkalinity. Many of the laboratory procedures would be incompatible with the life of the cell.

It is obvious that this new approach in pharmacology is an outstanding example of physiological principles in treatment. We can therefore draw to a close on an optimistic note, for herein we may trace the foreshadowing of an accurate and rational system such as therapeutics has not hitherto achieved.

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