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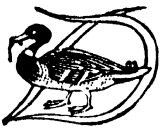
A HUNDRED YEARS OF BIOLOGY

A HUNDRED YEARS OF BIOLOGY

BY

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To
J. B. D.

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PREFACE

IN some academic circles there exists a belief that a science of biology can be established only on the basis of researches in cytology and cell physiology. In writing this book for "intelligent amateurs as well as specialist students" I have not adopted this point of view; instead I have accepted as biological all those matters which relate to living organisms.

The reader will not find in my book the usual fragments of botany and zoology out of which writers often compound "courses" of biology. I have omitted much information which can readily be found in text-books, and I have tried to provide a readable picture by sketching a historical background and the main trends of biological development and including a filling of biological facts and ideas. Botanists will hardly be satisfied with the topics I have elected to discuss, for my standpoint has been that of the animal biologist, and zoologists may consider my treatment of certain topics too sketchy and elementary. If I have not dug deeply, I have at any rate covered a fair amount of ground. If I have overstressed the historical background of biology it is because many facts and ideas which may seem to be recent acquisitions go far back into the past, and if I have dealt too methodically with the perfection of the instruments of biology it is only because such developments often tend to be taken for granted. My final chapter serves to show how individualistic effort has given way to concerted action in biological research—team-work in which the biochemist and biophysicist now play their parts. I am conscious of many sins of omission, but every effort has been made to avoid possible sins of commission. I have also tried to show the specialist student where he can find much more information than can be dealt with in my book. I make no apology in respect of technical terms; it is surprising how many of those used may be found in a *Chambers's Dictionary*!

It is a pleasure to acknowledge the valuable assistance which many persons have given me in my quest for information. I am grateful especially to Professor Adrien Albert (Australian National University), L. Fasken (Agricultural Research Council), D. L. Gunn (Anti-Locust Research Centre), L. L. Lachat (Armour Laboratory, Chicago), Sir

W. G. Ogg (Director, Rothamsted Experimental Station), D. Purdie (Armour Laboratory), Professor H. E. Shortt (London School of Tropical Medicine and Hygiene), and B. P. Uvarov (Director, Anti-Locust Research Centre). I only hope the information which they have given me has been satisfactorily passed on to the reader. To many writers and publishers who have given me permission to reproduce figures and matter which has already been published, I am also truly grateful; I have indicated elsewhere the original sources of the figures which have been reproduced in my book.

To many others I would also like to express my gratitude and crave their indulgence of my use of information gleaned from the original literature of biology, as well as from many books. To many writers I am especially indebted. In such a work as this it is obvious and inevitable that the writer owes much to many writers and publishers who are not specifically named. I have tried faithfully to give the sources of my information so that there shall be no ambiguity on this score, and throughout I have made every effort to give the credit for biological discoveries to those who deserve it. My book has been made possible only by the efforts of many scientific workers and writers, and in presenting it humbly to the reader attempting to grasp the fringe of biology as it is understood by researchers in various fields of study, I accept the responsibility for any errors of fact which may arise from understatement. The credit for my book really belongs to many workers who have created the modern science of biology.

classifying them, except as trees, shrubs and herbs—wild and cultivated —and groups such as oaks, willows, etc. The Italian Andrea Caesalpino made the first determined effort to classify plants (*De plantis libri*, 1583), but the first formal scheme was devised in 1623 by Gaspard Bauhin, who named about 6,000 species according to the first binomial system, the tentative forerunner of the system perfected by Linnaeus. The seventeenth century produced the work of Joachim Jung, John Ray and Joseph Pitton de Tournefort. Jung was an ardent student of structure and he gave names which are still used to leaves of various shapes, and to such floral parts as stamens, style and perianth. He failed to recognise the sexuality of flowers, but he took over Bauhin's binomial system and named what were in effect genera and species. His unpublished work came into the hands of Ray, who carried this system through to Linnaeus. Ray was at first a cataloguer of plants, and he classified nearly 19,000 species, making about 125 groups, many of which persist to-day as Natural Orders. He had the ambition to classify all known living things, however, and when his friend Francis Willughby died he embarked on zoological classification and left his mark on that. Tournefort was a field botanist who travelled widely in quest of new plants. His schemes were inferior to those of Ray. The important distinction of the seed-leaves in plants was neglected and flowering and flowerless plants were grouped together.

The great Swedish naturalist Carl Linnaeus has been called the "reformer of descriptive natural science". He gathered up old and new knowledge and he was tireless in the field, both at home and abroad, but his work owes much to Caesalpino, Camerarius, Jung and others. The first edition of his famous *Systema Naturae* in 1735 was a small pamphlet, but in it living organisms were classified into species, genera, orders and classes. Plants were arranged according to the characters of the sexual organs, so that his scheme came to be known as the "sexual system", though it had little to do with sex. By 1758, when the first volume of the tenth edition appeared, Linnaeus had named and described about 4,370 species of animals, which formed six classes, distinguished mainly by external characters: Quadrupedia, Aves, Amphibia, Pisces, Insecta and Vermes. Little attention was paid to the backboneless animals, insects apart, and the group of fishes was dealt with according to the system of Peter Artedi.

A more satisfactory scheme was produced by Lamarck (1809) and in this vertebrate and invertebrate forms were separated as such. Many of the arrangements suggested could not stand, but ideas con-

cerning evolution led Lamarck to propound a branching scheme in which worm-like animals led on to jointed-limbed forms (Arthropoda) by one branch and through other groups to fishes and vertebrates generally by another. His was the first suggestion of a tree-like classification indicating relationships, a phylogenetic scheme which became popular during the late nineteenth century. Many systematists amended the schemes, and Baron Cuvier, so-called "Dictator of Science", formulated a great scheme of his own in 1817. This was not surpassed till 1864, when Thomas Henry Huxley's *Elements of Comparative Anatomy* was published. Students interested in the evolution of botanical classification up till the time of Linnaeus should see the article by T. A. Sprague (1950). For a similar outline in regard to animal classification see A. Tindell Hopwood (1950 *a*).

The improvement of botanical classification after Linnaeus was largely due to the efforts of A. L. de Jussieu (1789), who divided the plant kingdom into 15 classes, all but one of them seed plants. These were in turn divided into orders, some of which roughly corresponded to families of the present day. It is notable that the classification of plants in three broad groups on the basis of the seed-leaves was a modification of Ray's scheme. Lamarck's standard *French Flora* was published in 1778, and the next improvement of note after de Jussieu was made by A. P. de Candolle (1819), who recognised the vascular elements of plants as taxonomic characters. Endlicher's scheme came later (1846–50) and was followed by the still more elaborate schemes of G. Bentham and J. D. Hooker (1862–83), A. W. Eichler (1875, 1878), A. Engler and K. Prandtl (1887–98) as the nineteenth century was bringing improvement in our knowledge of structure or morphology. A. J. Wilmott (1950) has outlined the progress of systematic botany from Linnaeus to Darwin; H. K. Airy Shaw (1950) has dealt with post-Darwinian developments of taxonomy.

Early Study of Structure and Function

The sixteenth century brought many notable attempts to draw knowledge straight from nature. The artistic anatomical studies of Leonardo de Vinci were of this character, and so were the illustrated *Herbals* of Gerard, Brunfels, Boch and Fuchs. Early during that century, however, Paracelsus was striving to interpret the phenomena of life in chemical terms, passing on ideas that inspired van Helmont and Sylvius during the seventeenth century. Equally remarkable were Pierre Belon's books on birds and fishes, and his extraordinary

essay in comparative anatomy (1555), an almost bone-for-bone comparison of the avian and human skeletons, which lacked only recognition of the significance of homologous parts. Then followed the work of the encyclopaedic naturalists, notably Conrad Gesner, whose *Historiae animalium* (1551–58)—a large four-volume work of 4,500 folio pages—dealt with the minute structure of many animals. From this source Topsel in 1607 compiled his *Histories of Foure-Footed Beastes.* Some of Gesner's illustrations of fabulous things showed, however, that the study of animals was not based entirely on nature. There was a great tendency also to accept authority blindly, but in the study of anatomy Andreas Vesalius cut across traditional methods of teaching by using demonstrations and produced a comparatively modern book based on dissections and what they revealed, going far beyond the teachings of Galen.

In dealing with the early history of physiology, the study of function, K. J. Franklin (1949) remarked: "with the seventeenth century one feels that one has stepped from the ancient into the modern world". William Harvey was inspired by a great determination to study actual structure and to determine facts by experiments on living animals. His efforts not only led him to the discovery of the circulation of the blood in 1628; they inspired biologists who came after him to use similar methods, to test deductions based on structure by experimental investigation and to use hypothesis as a means of extending knowledge. Philosophical considerations and the application to physiology of knowledge gained in physics and chemistry also promoted new advances, and in 1614 Santorio applied physical theory to the study of biology. Fifty years afterwards, in 1662 and 1664, came the legacy of René Descartes' work, the earliest treatise on physiology. By 1679 the Italian Borelli had tried to explain the locomotory movements of man and animals with the help of mechanical science, and Perrault in 1680 studied the action of muscles. About the same time, and with little optical aid, Malpighi and Mariotta were investigating the functions of plants. When lenses and microscopes were invented and pressed into service the boundaries of biology were widely extended and its provinces more thoroughly mapped out. Details hitherto unknown were coming into focus.

The Classical Microscopists

The first pictures of magnified objects (insects) were drawn by the son of Hofnagel and published in 1592, though the naturalist Moeffet

probably used lenses when this work was in progress (see Locy, 1925). The Dutch brothers Hans and Zacharias Jansen have been credited with the discovery of the microscope some time between 1591 and 1608, when Cornelius Drebbell also was making serviceable instruments. Soon afterwards (about 1610) Galileo was observing insects and other small animals by means of an "optic glass". Illustrations of some of the early microscopes are represented in the appendix "*Dioptrique*" to Descartes' *Discourse on Method* (1637). The first to use the new instruments in Italy was Francesco Stelluti, who, before 1630, investigated the structure of bees. Many microscopic observations were published soon afterwards. Kircher in 1646 wrote notices on microscopic forms of life, and the first treatise on such forms appeared in Robert Hooke's *Micrographia* (1665). Minute things destined to become important in the future were becoming visible for the first time, and the classical microscopists were magnifying them and revealing new paths in biology. Versatile Marcello Malpighi of Bologna was interested in the development of plant seeds, the structure of plant stems and roots and the function of leaves, and also in the anatomy of the silkworm, the development of the chick embryo and the microscopic structure of glands and tissues. His demonstration of capillaries in the lungs of animals completed the story of the circulation of the blood as told by Harvey. Nehemiah Grew was an ardent student of plant structure and, like Hooke, he worked in London. Jan Swammerdam of Amsterdam was an expert dissector of insects and other small creatures and a tireless observer of the intricacies of structure in animals previously regarded as "simple". The tribute of Cole (1944) is worth noting: "If Swammerdam could have commanded a modern binocular dissecting microscope he would doubtless have done so, and thereby saved himself much toil and strain, but whether he would have discovered more is not so certain." Anthony van Leeuwenhoek of Delft observed nearly everything on which he could bring his lenses to bear; he saw spermatozoa in 1677 and made drawings of bacteria in 1683. Pictures of various Protozoa began to appear in the biological literature about 1693, though many years were to elapse before the Dane Otto Frederik Müller published the first standard work on microbiology in 1786.

Spontaneous Generation

For many centuries naturalists believed that some living things arise from inanimate objects, eels from the hairs of horses and worms

from the mud and slime of ponds. The idea of "spontaneous generation" arose from imponderable evidence, yet the evidence of the eyes led some to believe that barnacles grow out of a rotten log floating on the sea, or that maggots are formed by the rotting of flesh. One of the first serious sceptics of such ideas was Francesco Redi who, in 1668, proved that maggots do not appear in putrescent meat that has been covered with gauze; they arise from the eggs of flies which have access to uncovered meat. Prejudice was so strong, however, that Redi himself believed certain plant galls to arise by spontaneous generation, and it was left for Vallisnieri in 1700 to prove that they are caused by larval insects arising from eggs deposited in the plants by their parent. The coming of the microscope did not dispel the idea of spontaneous generation and even falsely favoured it, for Leeuwenhoek's hay infusions became cloudy with teeming organisms in just a few days. The experiments of John Turberville Needham (1748) and Lazzaro Spallanzani (1765) on heated and sealed nutrient broths revived the controversy, and although Spallanzani later (1786) proved the fertilising power of the sperm in animals, thus showing the fallacy of the idea, a fresh belief in spontaneous generation sprang up at the beginning of the nineteenth century. This was not dispelled till Louis Pasteur in 1861 demonstrated that if a broth be heated sufficiently to kill all the organisms contained in it, and if precautions be taken to prevent the ingress of organisms, the broth will remain free of living things for periods of many months and even years. By this time it was evident that living forms can arise only from pre-existing living things by a process of reproduction, or by what Thomas Henry Huxley in 1870 called *biogenesis.*

Germ Theories of Disease

During the seventeenth and eighteenth centuries the idea arose that living organisms may cause disease. In 1658 the imaginative Jesuit Athanatius Kircher saw worm-like organisms in liquids such as water, milk and vinegar, in decaying vegetation, and in the blood of persons suffering from the plague. His germ theory of disease was ill-founded —with the simple lenses at his disposal he could hardly have seen bacteria—but it inaugurated a new field of biological study. By 1685 Leeuwenhoek had described indubitable micro-organisms and had provided Kircher's speculations with a foundation of fact. Using these discoveries Nicolas Andry in 1701 propounded a genuine theory linking the origin of disease with infection, by germs. This caused

some excitement but it also invoked strong disapproval, and for fifteen decades the theory was seriously neglected. It received some support from Linnaeus, who classified Leeuwenhoek's animalcules with *contagia vera* under the heading of "*Chaos*", and it was revived in 1762 by M. A. Plenciz of Vienna. In 1794 Reimarus identified living things with the *materia morbi* of infectious diseases. Microbiology had benefited also from the experiments on spontaneous generation and it was further advanced by O. F. Müller in 1786. In 1810 Appert applied Spallanzani's method of sealing off and heating nutrient broths to the problem of the preservation of foodstuffs. The first actual demonstration of a bacterium as the causal agent of disease was due, however, to the influence of Pasteur's work, which persuaded C. Davaine in 1861 to reinvestigate the microbe of anthrax already discovered by Davaine and Rayer in 1850. Biology was now being applied to human affairs in the field of bacteriology. About 1854 Schroeder and Dusch used cotton wool to filter or to trap micro-organisms and to keep them out of experimental cultures, and about 1881 these were first isolated on plated media by Koch. Microbiology was established.

Mycology.

The early history of mycology, the study of fungi, has been described in detail by J. Ramsbottom (1941). Fungi were well known to the classical writers, largely because some of them are edible (their uses are many: see J. Ramsbottom, 1936), and to the early writers on plants. Caesalpino in 1583 likened fungi to zoophytes and considered them to be intermediate between animals and plants. R. Hooke (1665) examined the structure of some of them, including blue moulds and white, and the first of Leeuwenhoek's famous letters to the Royal Society of London (1673) began with reference to a mould, while his discovery of yeast was described in a letter in 1680. M. Malpighi in 1679 dealt with the moulds found on cheese, citrus fruits, wood and bread. During the seventeenth century the art of raising mushrooms from the mycelium, or "spawn", began in Paris, probably before 1678, and in 1707 Tournefort gave the first account of the growth of this plant. Linnaeus (*Flora Lapponica*, 1737) divided the genus *Agaricus* into a number of sections and gave brief diagnoses of forty-seven species. Fungi also entered into the discussions on spontaneous generation. P. A. Micheli (1729) was one of the first to cultivate fungi from the spores, with which L. Spallanzani also carried out many experiments. Nevertheless, there was a widespread belief which persisted well into

the nineteenth century that some fungi reproduce without the need for spore formation.

The economic importance of fungi was established in 1836 when C. Cagniard-Latour described the yeast cells of beer and demonstrated the importance of living cells to the process of fermentation. The chemical as distinct from the organic theory of fermentation persisted for some time, however, until it was finally demolished in 1859 by L. Pasteur. During the course of E. C. Hansen's experiments, which began in the Carlsberg Laboratory about twenty years afterwards, yeasts soon came to be the best known of all the fungi. But fungi parasitic in animals had long been known. They were first studied in 1726 by C. A. F. Réaumur, who investigated *Cordyceps sinensis*, a Chinese relative of the European form, *C. militaris*. So intimate was the relationship between parasite and host that the parasitised individual was believed to be a plant in summer and a worm in the winter! The true nature was first deciphered by James Hill during the second half of the eighteenth century. J. T. Needham wrote in 1769 about the "vegetable fly" of the West Indies. There was much controversy about the nature of parasitic fungi. "Time and again," stated Ramsbottom, "all seems to be getting into something like order, and time and again there is a throw-back to mediaeval mysticism." G. R. Treviranus in 1803 saw no possibility of fungi arising from "seed", and some writers accepted alleged proofs that they do not. In 1836, however, M. J. Berkeley, the Father of British mycology, described sporulae, and two years later he dealt with "fructification" in some fungi. Some time before this, C. H. Persoon's *Synopsis* (1807) contained a useful account of the fungi, and Fries in 1821 published his *Systema Mycologicum*, and this was followed by a number of works leading on to the *Hymenomycetes Europaei* (1874); these "are the bed-rock of mycological taxonomy" (Ramsbottom).

The first recognition of the sexual process in fungi was due to C. G. Ehrenberg who in 1818 described conjugation in *Syzygites megalocarpus*, which is better known as *Sporodinia grandis*. Other notable works are those of N. Pringsheim in 1851 on Saprolegniaceae and A. de Bary in 1852 on Peronsporaceae. The discovery by W. F. B. Hofmeister in 1852 that the sexual organs of the fern exist on the prothallus, not on the fronds of the sporophyte, led to a search for the sexual organs of fungi, and in 1860 P. A. Karsten showed how an egg-shaped and short-stalked female cell gives rise to the fruit body of *Agaricus campestris*. The first attempt to trace out the entire life-history by a method

free from objections was made in 1827, when J. Schilling cultivated *Aspergillus glaucus* in a culture-chamber under the microscope. In 1868 O. Brefeld proposed that culture media used in such experiments should be sterilised and that single spore cultures should be made. He used gelatine as a culture medium, and Koch in 1881 introduced "nutrient gelatine", while the wife of W. Hesse in 1882 made the suggestion of using agar-agar. The methods adopted by bacteriologists—*e.g.* J. Lister's dilution method (devised in 1878) for isolating bacteria, and R. Koch's poured plate method—were adopted by mycologists and great benefits were soon forthcoming.

The benefits were not all on one side. Ramsbottom has remarked: "The common knowledge of bacterial diseases of man nowadays makes it seem strange that it was not until the work of Pasteur, Lister and Koch that the importance of bacteria in this connexion was understood. Indeed, in the first half of last century fungi were regarded as far more important as human and animal pathogens". Plant diseases were classified in 1705 by J. P. de Tournefort, who attached no significance to the fungi, and at the beginning of the nineteenth century F. J. A. N. Unger (1833) considered that parasitic fungi arose from the diseased tissues of plants. The potato famine of the eighteen-forties brought much new research fostered by scientific bodies and governments, which offered rewards for methods of preventing and eradicating fungal diseases. J. Berkeley in 1846 was the first definitely to lay down the statement that "the decay is the consequence of the presence of the mould, and not the mould of the decay". Within another ten years the researches of L. and C. R. Tulasne, A. de Bary and others had so much improved knowledge that Berkeley (1860) wrote: "Fungi were long regarded as the mere creatures of putrescence and therefore as the consequence, not the cause of disease . . . almost everyone is now ready to acknowledge what a weighty influence they have in inducing diseased condition, both in the animal and vegetable world." Henceforth, the rôle of fungi in causing plant diseases was clear, and studies of the factors influencing infection and immunity, and also remedial measures, were soon building up a formidable new biological discipline —which now attracts many biologists.

Eighteenth-century Anatomy and Physiology

F. J. Cole (1944) summarised the progress of knowledge in comparative anatomy to the eighteenth century as (1) a recognition that minute animals and the minutiae of anatomy are not *ipso facto* con-

temptible but repay study, (2) the development of skill and technique necessary for the study of fine details and the accumulation of a body of comparative data, and (3) the integration of data into logical patterns or co-ordinate principles, giving new impetus and direction to inquiry. During the eighteenth century the Dutchman Peter Camper made comparative studies of the ear in fishes, reptiles and mammals, discovered the significance of the air sacs in the bones of birds, compared the skeletal and muscular systems of the orang-utan and man, and pondered over his collections of fossil bones. At a time when fossils were interpreted fancifully, he correctly regarded them as the preserved remains of animals long since dead. At about the same time John Hunter was making precise and accurate comparative studies of various organ systems of animals and, with the assistance of his brother William, was assembling his famous collection of anatomical specimens. The celebrated Frenchman Vicq d'Azyr was led by similar studies to enunciate the important principle of serial homology and Compte de Buffon was producing his *Histoire Naturelle*, attempting to survey the entire realm of nature. This ambitious work consisted of 44 volumes and took fifty-five years to produce (1749–1804). In it Buffon adopted the Aristotelean idea of a Ladder of Nature, which C. Bonnet formally applied to non-living as well as living things, arranging man, birds, fishes, molluscs and insects in a linear series, and beneath these plants, various inorganic things, and finally water, air and fire, a scheme based on the idea of unity of plan which was believed to indicate "community of origin". According to Buffon, nature is made up of individuals and groups of individuals which breed with one another to produce other and similar individuals, and he was reluctant to believe in any systematic units above the level of the species.

Advances in physiology may be found in the work of G. E. Stahl, German vitalist and opponent of Descartes' mechanistic theories, Herman Boerhaave's efforts in 1708 to explain the functions of the animal body in terms of blood and vital spirits, F. Hoffmann's *Fundamenta physiologiae* and other works. In 1727 Stephen Hales published his *Vegetable Staticks*, giving accounts of transpiration, root pressure and other plant functions. Malpighi in 1675 believed that food synthesis takes place in the leaves of plants, and Hales showed that the leaves take something from the atmosphere. Hales also made determinations of the blood pressure and blood flow in animals. Soon afterwards Albrecht von Haller's *Elementa physiologiae corporis humani* appeared (1757–66), presenting physiological facts and theories up to

its time and giving enlightened accounts of the mechanics of respiration, digestive action, the action of the nervous system in animals and other subjects. The conception of tropistic behaviour in plants arose from the experiments of Andrew Knight, who used centrifugal force to override the effect of gravity. The demonstration by J. Priestley in 1774 that plants immersed in water evolve oxygen revealed a new aspect of respiration. The discovery by A. Lavoisier that combustion is a process of oxidation, and that it takes place in living organisms, led on to the discovery of J. Ingenhousz in 1779 that in darkness plants behave like animals, "fouling" the air, and that green plants have the power to "purify" air that has been breathed by animals. N. T. de Saussure in 1804 proved that when carbon dioxide is absorbed by a plant an equal volume of gas is given off and yet the dry weight of the plant increases, also that plants grown in wet sand devoid of organic materials nevertheless increase their carbon content. Little notice was taken of these discoveries, however, and it was left for J. Liebig in 1840 to prove that plants gain their carbon from the carbon dioxide of the atmosphere, and not from materials in the soil which forms their anchorage, and for H. J. Dutrochet in 1837 to prove that only cells containing green pigment can absorb CO_2.

Amino-acids and Proteins

The significance of nitrogen-containing animal and vegetable substances, proteins, was realised during the eighteenth century. Nitrogen was discovered independently by Daniel Rutherford in 1772 and Cavendish in 1774, and the fact that ammonia contains both nitrogen and hydrogen was revealed by C. L. Berthollet in 1785. The name protein was invented by G. J. Mulder in 1838 two years after J. B. J. D. Boussingault published his work on plant proteins (see M. V. Tracey, 1948). Mulder analysed substances such as fibrin, albumin and silk, and later (1839) he suggested that they contain sulphur and phosphorus, as well as carbon, hydrogen and nitrogen. In the meantime, several amino-acids had been discovered, asparagine by L. N. Vauquelin and Robiquet (1806), cystine by W. H. Wollaston (1810) and both glycine and leucine by H. Braconnot (1820). Before the middle of the century Bopp (1849) discovered tyrosine, and before the end of the century at least ten more amino-acids had been discovered. Tracey (*loc. cit.*) has given a list of them and their discoverers and also of other amino-acids found during the twentieth century.

During the early part of the nineteenth century Liebig and others

believed that the proteins of an animal's body and those of its food were identical. In 1842, however, Dumas and Cahours showed that plant and animal proteins differ in composition, and henceforth, thanks largely to the pioneer efforts of Johnson in America, the truth gradually emerged that the animal remakes its proteins from amino-acids in the food. When during the early part of the twentieth century the peptide linkage was discovered—by E. Fischer and F. Hofmeister independently in 1902—it became clear that from a few amino-acids (20–30) an almost infinite variety of synthetic proteins can be formed. Only a few of these theoretically possible proteins are used by animals and plants, however, though their number can be increased at the will of the biochemist by the simple expedient of injecting a foreign protein into the animal's body, for this results in the formation of an antibody which is itself a protein (see p. 330). This has led to new conceptions regarding the structure of proteins; see I. Langmuir (1939) and J. D. Bernal (1939).

Development

Notable attempts were made during the sixteenth and seventeenth centuries to unravel the tangled threads of animal development, one of the earliest being that of Volcher Coiter, who opened hens' eggs from day to day in order to watch the progress made by the embryo. But the founder of modern embryology was Fabricius, whose valuable works in 1600 and 1621 on the formation of the foetus and embryo were marred by errors of observation and belief in the false doctrine of *preformation*, according to which the embryo was supposed to exist in miniature inside the ovum. William Harvey (1651) did not support this theory, but M. Malpighi (1673, 1689) imagined that what lay just beyond his powers of discernment could be explained by the theory of *emboîtement*. Such ideas stood in the way of progress for nearly a century, till C. F. Wolff published his *Theoria generationis* in 1759 and his observations on the development of the chick in 1768. The truth gradually emerged that plant organs such as roots and leaves arise from apparently homogeneous regions in the growing points, and that the organs of a chick likewise appear by a true development or *epigenesis*. Controversy on the topic preformation *versus* epigenesis thus persisted long after the discovery of the male gamete or spermatozoon (which A. von Leeuwenhoek figured in 1679). C. Bonnet in 1762 held on to the idea that the individual existed in miniature either in the ovum or in the sperm, and famous personages in biology took opposite sides in what

now seems to be the ridiculous controversy between the ovists and the spermatists, or animalculists.

During the nineteenth century the study of development was rapidly advanced by the work of H. C. Pander, K. E. von Baer and others, who used dissecting needles and simple microscopes to good effect. Pander (1817, 1818) discovered germ-layer formation in the chick, and invented the terms "blastoderm" and "germ-layer". The three layers which develop in order from the outside were called the "serous," "vessel" and "mucous" layers, but Remak in 1845 popularised the now familiar names used for them, namely *ectoderm*, *mesoderm* and *endoderm*. Baer began to study embryology in 1819, two years after the publication of Pander's work on the chick. In 1828 the first volume of his great book, *Ueber Entwicklungsgeschichte der Thiere, Beobachtung und Reflexion*, was published. It contained the first full account of chick development and much information on the laws of development in general (see E. S. Russell, 1916). A few years earlier, probably in 1824, Prévost and Dumas had described segmentation in the egg of the frog, and in 1836 Rusconi published a similar investigation of the newt's egg. The same year K. E. von Baer published a detailed study of frog development, and segmentation was realised to be a widespread phenomenon. In 1837 segmentation in flatworms was described by C. T. von Siebold, in a hydroid (*Campanularia*) by S. L. Lovén, and in starfish and nudibranch molluscs by M. Sars. One year later T. L. W. Bischoff described the segmentation of the egg in a mammal, and in 1839 M. Barry gave an account of the development of the rabbit from the division of the ovum to the morula stage. In 1842 C. Vogt described segmentation in the piscine egg (*Coregonus*), and in 1847 Bergmann described the process in the avian egg, Coste confirming the general features in 1850. Segmentation had then been studied in many kinds of animals—the hydra and various hydroids, starfish, Polyzoa, rotifers, nematodes, earthworms, bristleworms and leeches, many molluscs and arthropods, and representatives of all classes of vertebrates (see Leydig, 1848). T. H. Huxley (1849) meanwhile had discovered that the body of coelenterates is composed of two embryonic layers, which correspond to the ectoderm and endoderm. Animal structure of three grades then became recognised; the protozoan type, the coelenterate type and the type shown by all other multicellular animals. For these three types E. Ray Lankester in 1873 invented the names Holoblastica, Diploblastica and Triploblastica.

Biologists generally have acclaimed Wolff as the founder of the

germ-layer theory, but Baer gave the credit for it to his friend and associate Pander. Another friend was M. H. Rathke, who in 1829 confirmed the germ-layer theory in respect of the crayfish, in which he noted the close resemblance between the developing legs and the jaws. He had previously (in 1825) described the four gill-slits (visceral clefts, as we now call them) in a mammalian embryo (pig) and also the three similar clefts in an embryo bird. Subsequently Rathke investigated the homologies of the visceral arches in vertebrates, though the terms "homologue" and "analogue" were not clearly defined till Owen's *Lectures on Invertebrate Animals* appeared in 1843. A *homologous* organ than came to be recognised as essentially the same organ in all its varieties of form and function in different animals; and *analogous* organs as organs which have the same function in different animals but not the same origin in the individual.

Protoplasm

The living materials of animals and plants came under close scrutiny long before the modern idea of the cell emerged. A. Trembley in 1744 pictured the living hydra as a mass of "grains" bound together by a "glairy" substance, Duhamel du Monceau in 1758 noted that the living substance of plants is a web-like "substance vesiculaire, ou cellulaire", and B. Corti in 1774 observed the circulation of granules (cyclosis) in the living stuff of some fresh-water plants. Various protozoan animals had first come under observation long before this, *Vorticella* in 1677, *Paramecium* in 1702 and *Amoeba* in 1755. In 1835 F. Dujardin came to doubt what he regarded as far-fetched opinions concerning the internal structure of certain ciliates. What others regarded as a living "jelly", Dujardin called "sarcode", the properties of which he carefully defined. (For an account of Dujardin's ideas regarding protoplasm see E. Fauré-Fremiet, 1935.) The name "protoplasm" which is now used to denote the living substance dates back to January 1839, when, at a meeting of the Silesian Society for National Culture, J. E. Purkinje used the word *Protoplasma* for the first time in a scientific sense. The name came into general use when H. von Mohl in 1846 preferred it to Schleiden's term "Schleim", which was too easily applicable to mucus and other slimy substances to be free from ambiguity. Von Mohl was unaware that Purkinje had used the term a few years before. Not long afterwards, in 1850, F. Cohn came to the conclusion that "the protoplasm of botanists and the contractile substance and sarcode of the zoologists, if not identical,

must then indeed be in a high degree similar formations" (see J. R. Baker, 1949 *a*).

The Cell Theory

The importance of cells in the structure of organisms gradually became obvious during the early part of the nineteenth century. Robert Hooke in 1665 had used the term "cells" to denote the porous, honeycomb-like texture of cork; Marcello Malpighi in 1675 had used the terms "utriculi" and "sacculi" to denote microscopic units in the structure of various plants such as the chestnut, pine and fig; and Nehemiah Grew in 1682 went further and showed that such units, "bladders" or "cells", exist in the actively growing parenchyma of plants. The true importance of cell structure was not made obvious to all biologists, however, till 1831, when Robert Brown discovered the cell organ known as the nucleus which was first identified in 1775 by Roffredi (see J. R. Baker, 1949 *b*). Theodor Schwann, invented the term "cell theory" and also defined it in his *Mikroskopische Untersuchungen* (1839) (see J. R. Baker, 1948), and it is generally attributed to M. J. Schleiden and T. Schwann and dated 1839.

The late Lieutenant-Colonel J. Stephenson, speaking at the Centenary Celebration of Brown's discovery of the nucleus in 1931 (*Proc. Linn. Soc. London, Session 1931–32*, Part II, p. 49), believed that the cell-theory "owes its existence to no single man; many workers combined to build it up; but if any names are to be specially associated with it, it certainly should not be anyone who appeared on the scene for the first time in 1838". Stephenson sketched a brief history of the cell theory from about 1830 to 1850, and ended with Max Schultze's definition in 1861 of a cell as a particle of protoplasm containing a nucleus. He remarked that F. J. F. Meyen's *Phytotomie* (1830) contains many references to cells; about one-third of the book being devoted to a discussion of them. In 1834 R. Brown recognised the nucleus in various plant tissues, and one year later Johannes Evangelista Purkinje, professor of physiology at Breslau, obtained a microscope and, with the help of students and assistants, began systematically to study animal tissues. The Breslau school developed its studies rapidly. In 1833 Wendt described epidermal scales, in 1834 Purkinje and Deutsch investigated sections of decalcified bone, discovering bone cells and the canaliculi in which their outgrowths lie. In G. Valentin's handbook of embryology (1835) the term "Körnschen" is applied to cells. J. E. Purkinje and G. Valentin published a monograph on ciliary activity in

1835, and Raschkow wrote about the epithelium of the mammalian tooth germ, likening it to plant parenchyma and applying to its elements the term "cellula". In 1836 Purkinje described nerve cells and the epithelium lining the central canal of the nerve cord, and about this time or a little earlier (1835) Valentin wrote his prize-winning essay *Histogenia comparata* for the French Academy, a large and valuable work that remained unpublished.

Johannes Müller led a rival school in Berlin. His monograph on the hagfishes (1835) contains references to the cells of the notochord and to various types of cartilage. Not long afterwards (1837–38) J. Henle described epithelia of various kinds from the conjunctiva, intestines, stomach, glands and other organs, using the term "cell" and giving to various kinds of epithelia names that are still used. The youngest member of Müller's school was in fact Theodor Schwann, who published his first scientific paper in 1838. The division of cells had been observed already by several biologists: by Dumortier (1832) and H. von Mohl (1835) in species of *Conferva*, by Morren (1836) in *Closterium* and by F. J. F. Meyen (1838) in the shoots and roots of various Phanerogams. By 1838 Purkinje and Valentin were aware of the origin of cellular tissues in adults from similar tissues in the embryo, were familiar with the use of the term "cell" in relation to both plants and animal structure, could recognise both the nucleus and its nucleolus, and knew about the production of new cells by the division of pre-existing cells. The building up of the cell theory was indeed the work of many biologists.

E. B. Wilson (1925) referred to the cell theory as a turning-point in biology, a source of fruitful researches, and one of the commanding landmarks of the nineteenth century. He suggested that the key to every biological problem must be sought in the cell, because every living organism is, or at some time has been, a cell. Once the theory had been applied to the analysis of organic functions it led to progress in physiology and pathology, and to the development of the new science of cytology. It inspired Remak, Nägeli, Kölliker and others to demonstrate the fundamental importance of cell division in the reproduction of both plants and animals. It solved the riddle of the origin of individual life and led to the detailed study of heredity. According to Wilson, it took about thirty years (1840–70) to define the outlines of the theory and to establish the principles of genetic continuity. After this developments proceeded in the direction of specialised cytology and cytophysiology.

The rise of the cell theory tended to disconnect more and more the morphological and physiological aspects of biology, which began to separate during the seventeenth century. Turpin in 1828 considered the plant cell to be an elementary primary organism and the plant to be a sort of community of cells. C. Vogt in 1842 also regarded the cell as an entity having its own separate life, a sort of "organism in its own rights". R. Virchow in 1859 modified this into a colonial theory of organism, the cells of the individual working together for the common good, or in disease for the common ill. This view was popular for some time and persisted into our period, but not all biologists regard favourably the "atomic" picture of organism, and Johannes Müller and his pupil C. B. Reichert in 1855 doubted the dominance of the cell. J. Gray (1931) has stressed the difficulties of regarding the cell as a physiological unit in the metazoan animal; it is an opinion which "nearly every experimental biologist has declined to accept". He regarded the cell as the unit of mechanical stability which is necessary in large and varied forms of life, but in his view the "real unit of life must be of a protoplasmic nature irrespective of whether it is subdivided to form a mechanically stable system or not; in other words, cellular structure is not in itself of primary significance". Nevertheless the study of cells has, during the past one hundred years, become the fundamental biological discipline.

CHAPTER TWO

SOME TECHNICAL ADVANCES

ADVANCES in knowledge often come about when new ways are found of tackling old problems, either by modifying existing methods of observation or else by devising new techniques. In much less than one hundred years the biological outlook has been transformed, partly as a result of physiological developments, which have been outlined carefully by H. J. Franklin (1949), but largely by improvements in microscopic technique, which implies better methods of observing things under the microscope and also better ways of preparing them for microscopic examination. The special research methods of biophysics have been dealt with in detail by a group of specialists (see F. M. Uber (Ed.), 1950).

Improvements in the Microscope

During the early part of the nineteenth century the microscope was more a recreational toy than an instrument of discovery, but at this time notable improvements were being made in lens systems. The first achromatic lenses were made by the English mechanic Dolland, but the Italian Amici (about 1812) and the Frenchman Chevalier (about 1820) greatly improved achromatic objectives, which appeared in Britain in 1824. In 1830 Joseph Jackson Lister—father of Lord Lister and one of the founders of the Royal Microscopical Society—showed how to correct spherical aberration in microscope objectives by arranging two achromatic lenses in such a way that positive aberration of one cancelled out the negative aberration of the other, a device still used in some low-power objectives. Lister also improved the adjustment slide and other parts of the microscope, and soon after 1830 much better models were being put into the hands of biologists all over Europe. By 1840 Amici had produced the first water-immersion objectives, and during the next thirty-five years further improvements were made in the optical systems of microscopes and many new accessories appeared. The binocular microscope was invented by Riddell in 1853, but not for another sixty years were good high-power models becoming available.

Up till 1875 the microscopist called first and foremost for high

magnification, and then for crisp definition, freedom from chromatic effects, and a good, flat field of vision. Magnification was soon found to be a fetish, for it can be obtained simply by projecting the image of an object on to a screen, and microscopists soon realised that they had a lot of "empty magnification" and faulty definition. A more worthy aim was good "resolution", which in practice is the closeness with which two points can be situated in an object and yet remain discrete in the eye of an observer. In microscopy this depends on two factors —the numerical aperture (N.A.) of the objective, and the wave-length of the light that is used. The N.A. determines how close the front lens of the objective can be brought to the object and still give an image. The shorter wave-lengths of light are important, because very minute particles below a certain size set up in them disturbances which would not arise in the longer ones. Ernst Abbe was one of the first to attach more importance to resolving power than to mere magnification. He did not publish much work himself, but accounts of his work began to appear in 1875, and his colleagues perfected his theory of image-formation which, for some time, gave microscopists a fairly simple conception of resolving power (see H. Moore, 1940). By 1878 much improved Abbe microscopes were coming into use. According to Sir R. Hadfield (1920), oil-immersion objectives first appeared in England in June 1870 when, at a meeting of the Royal Microscopical Society, Mr Wenham exhibited one which required cedar oil. In 1886 the compensating ocular was introduced, and in 1887 Bausch and Lomb invented the iris diaphragm. One year later substage illumination was brought into use. Microscopy was becoming less and less a pastime for the amateur and more and more a serious biological discipline, and with the coming of better substage condensers and apochromatic objectives biologists could place much more reliance in what they saw under the microscope.

The biologist is never fully satisfied with the "resolving power" of the microscope, concerned as he is with fine and still finer details of cell-structure. Under the best conditions, and when white light is used, the practical limit of resolution is reached when two particles are situated about 0·20 μ (1/5,000 mm.) apart. A microscope magnifying 1,000 diameters will enlarge this limiting resolution of particles up to 0·2 mm., which is about twice the resolving power of the unaided eye at the distance of clearest vision. This result can be achieved by the use of an objective that magnifies fifty times if the eyepiece will magnify the image twenty times, or, better, if the object is enlarged one hundred

times and the image ten times, for an eyepiece cannot improve resolution though an objective can. Apochromatic lenses, if perfect, would give full resolution, good definition, a perfectly flat field, and freedom from chromatic aberration. Achromatic lenses often give good definition and a flatter field than apochromats, but resolution may be inferior and correction for colour imperfect, which implies that they are less suited to photographic work.

The "Ultra-Microscope"

The illumination of microscopic objects was improved when Siedentopf (1903) for the first time applied the Tyndall effect to problems of microscopy and introduced dark-ground illumination, a method previously known but not popularised. Sir R. Hadfield (1920), quoting an article (*Scientific American*, October 2, 1915), gave the size of particles visible by this method as 0·004–0·006 μ, magnitudes closely approaching the dimensions of the molecules in some biological substances—for instance, starch (0·005 μ, according to Lobry de Bruyn). This, the method of the "ultra-microscope", can be illustrated by what is seen when a ray of sunlight enters a darkened room through a narrow slit. Innumerable particles of dust which are too small to be seen in full light are illuminated by the ray and become visible when viewed laterally. The smallest particles that can be observed are about as large as the particles of gold colloid—0·005 μ diameter. The greatest value of the ultra-microscope lies in its application to the study of colloidal matter.

The Use of Ultra-Violet Light

August Köhler (1904) was the first to show that animal cells can be photographed by means of ultra-violet light, to which the human eye is insensitive. His pictures of dividing nuclei in certain tissues of the larval salamander show chromosomes darkly, as if stained, and the same appearance of dark and opaque nuclei was evident in cartilage cells from a newt. His methods were elaborated by J. E. Barnard, who developed ultra-violet photo-microscopy at the National Institute for Medical Research in London, and who described (1941) how profoundly his outlook was altered by Köhler's discovery. His method of illumination doubled resolution at one step, extending the range down to a particle size of 0·1 μ. This made possible the photographing of things unseen—for instance, the larger viruses of animals. In practice, magnifications of 3,000 diameters can be obtained, but the expensive

lenses used must be made of quartz because glass is opaque to ultra-violet radiations.

The advantages of ultra-violet microscopy were extended by the discovery and application of fluorescence. Fluorescence has been defined (A. Pijper, 1942) as the capacity that some substances have when irradiated with light of a particular wave-length of emitting light of a longer wave-length. In practice, irradiation by ultra-violet light causes fluorescent particles to emit visible light, the colour of which may be highly characteristic of their chemical nature. Substances which do not themselves fluoresce can be treated with weak solutions of certain dyes (fluorochromes) which do. By this means the pathologist has been easily able to identify tubercle bacilli in masses of sputum, and many other discoveries have been made. Vitamins and carcinogenic cells fluoresce characteristically, and the fluorochromes have been used for mapping the routes by which dissolved substances penetrate and travel through the tissues of animals and plants. Readers interested in the history of the technique and results of fluorescent microscopy should consult the review by P. Ellinger (1940).

The Use of Polarised Light

Physicists and geologists have long been familiar with the use of polarised light in the microscopic study of mineral crystals, a method which has also been of benefit to biology. G. Valentin (1861) was the first to use polarised light in the study of plant and animal tissues. About the same time, Carl Nägeli—who gave the name *micellae* to certain colloidal aggregates in protoplasm—also used this method to study the structure of cell walls and starch-grains in plants. Like crystals, some tissues and other biological structures can split a ray of polarised light into two components, so that they seem to have two refractive indices. The emergent rays are slightly "out-of-step", but when combined (by means of an "analyser") they produce a characteristic interference pattern. Such structures—and they include the calcified skeletal parts of Protozoa and other animals, tissues such as muscle and nerve, and various kinds of cell inclusions—are said to be *birefringent.* In the dark field of the polarising microscope birefringent particles show up as brilliant objects which might otherwise remain invisible.

C. Nägeli (in C. Nägeli and S. Schwendener, 1877) was the first to suggest that birefringence is evidence of orderliness of molecular arrangement, whether in biological structures or in mineral crystals.

His belief was substantiated by O. Wiener (1912), who claimed that birefringence is an indication that particles are small in one dimension by comparison with the wave-length of light. A detailed analysis of plant tissues along these lines was later carried out by H. Ambronn (1916) and his pupil A. Frey-Wyssling (1935 onwards), while W. J. Schmidt and his pupils (1924 onwards) studied animal cells and tissues. The subsequent discovery by Laue of the diffraction of X-rays by crystals (see W. Friedrich, 1922) led to the extension of many of Nägeli's ideas and justified the technique of birefringent microscopy (see L. E. R. Picken, 1940).

Phase-contrast Microscopy

Living cells and tissues reveal little of their structure when viewed in the bright field of a microscope. To see more detail one must stop down the diaphragm of the condenser, and as this is done beyond a certain point, light deficiency more and more obscures detail, until in the end resolving power is completely lost. The finer details may never be seen, for resolving power may be lost before sufficient contrast is obtained to make them visible. Some early experiments on image-formation produced data which showed how the contrast of a microscope image could be altered and even reversed. Abbe (1892) reversed this contrast by means of glass wedges placed in the back focal plane of his objectives, and K. Bratuscheck (1892) used this apparatus on a grating of alternating clear and translucently dark strips and was the first to study phase relations within the microscope.

Colourless living cells and tissues contain regions of different particle size and refractive index which result in differences of optical path. In passing through such regions light is speeded up or slowed down, with decrease or increase in "optical path" (distance traversed by light × refractive index) and the phase-relations of the light are altered. The human eye is insensitive to such alterations, but not to differences of intensity, and the phase-contrast microscope controls the light traversing it so that phase-differences established in the light passing through the object are converted into differences of intensity. Phase-contrast is therefore a method for increasing or decreasing contrast in the images formed by the microscope. J. Rhineberg (1904, 1905) and A. E. Conrady (1905) obtained photographs of a fine grating with a phase-contrast microscope, and F. Zernicke (1934, 1935) discussed the implications of the method in microscopy. Zeisswerke, who took out German patents in 1932, then produced equipment which

came to be used in various parts of Europe, and this was described by A. Köhler and W. Loos (1941).

The methods and principles of phase-contrast microscopy were described subsequently by a number of workers, Zernicke (1942), C. R. Burch and J. P. P. Stock (1942)—the first description in English, E. H. Linfoot (1945), O. W. Richards (1944, 1946, 1947) and others. Richards (1946) made a report on more than sixty kinds of materials observed with the help of fifty-six different phase-plates, and (1947) dealt with such applications as counts and measurements of bacteria, yeasts, algae, diatoms and protozoa, the phenomenon of cyclosis in *Elodea*, cytological work on gametes, salivary gland chromosomes and blood cells, the study of textile fibres and photomicrography. Phase-contrast microscopy has also been used for the study of malignant cells by W. M. Firor and G. O. Gey (1947) and by R. J. Ludford, J. Smiles and F. W. Welsh (1948). Some workers have used the slit type of Zernicke plate—Burch and Stock (1942), for instance—but most workers seem to prefer the annular diaphragm and diffraction plate. Using phase-contrast methods, J. J. Angulo, O. W. Richards and A. L. Roque (1949) were able to demonstrate virus inclusion bodies in unstained sections of tissue taken from cases of yellow fever, herpes simplex, fowl-pox and distemper. The phase-contrast microscope has improved the conditions for observing unstained living materials, but it is not as valuable as that much more elaborate and costly instrument, the electron microscope.

The Burch Microscope

Entirely new principles of microscope construction are employed in the Burch reflecting microscope (Burch, 1947), which forms an image by reflection from complex, curved and mirrored surfaces. Refraction phenomena are eliminated, so that light rays of various colours come to the same focus, giving a perfect achromatic image. Light of different wave-lengths can be used with such a microscope without changing the focus of the instrument, which has been associated with ultra-violet and infra-red spectrometers. In biological research of the future this instrument will be used to identify intracellular structures and protoplasmic constituents.

The Electron Microscope

This instrument was invented about 1931, or a little later. About five years before this, de Broglie had indicated that electrons might

behave like light-waves, and in 1927 this was substantiated by G. P. Thompson in England and Davisson and Germer in the U.S.A. The first instrument of magnetic type was constructed in 1931 by Knoll and Ruska in Berlin. Three years later they produced a model with a magnification of 10,000 diameters and a resolving power of 0·05 μ. Improved models with five times this resolving power were constructed at the Siemens Works just before the War, when construction was also proceeding in both England and America. In 1936–37 Metropolitan-Vickers built a magnetic electron microscope for L. C. Martin at the Imperial College, London, and in Toronto Hillier and Prebus (1938) constructed an instrument having several new features.

Various types of electron microscope are now available, but they are complex and costly and more suited to a biophysics laboratory than to a biologist's room. V. E. Cosslett (1947 *a*) has described them and (1947 *b*) has also discussed their place in biological research. G. E. Donovan (1944) has dealt with the difficult technique of mounting specimens, and with the practical applications, disadvantages and future possibilities of electron microscopy. Minute objects can be mounted whole, but larger objects must be cut into very thin sections and then mounted on films of collodion, for glass is opaque to electrons. By such methods, fine details of structure have been revealed for the first time in viruses, bacteriophages and bacteria. Bacteriophages, once regarded as macromolecular structures, were for the first time seen as sperm-like bodies with definite head and tail portions. Bacteria can now be classified according to the number and arrangement of their flagella, as are some Protozoa.

Dark-ground illumination has been used in conjunction with the electron microscope by M. von Ardenne (1939), giving such fine resolution that he contemplated the possibility of viewing single atoms and studying their distribution. This prospect also promises severe technical difficulties, but when these have been overcome the biologist will come to know very much more about the internal structure of genes, macrophages, bacteria and viruses, about which the ordinary methods of microscopy tell him nothing. Physiologists may be interested in the electron-microscope studies of muscle made by Farrant, Mercer and Rees (1947), and perhaps also in investigations on the localisation of minerals in muscle determined by micro-incineration within the electron microscope (see M. H. Draper and A. J. Hodge, 1949). The technical treatises edited by D. G. Drummond (1950) deals with most aspects of electron microscopy—optical matters, basic techniques,

films and surface replicas, viruses and micro-organisms, tissues, etc., and also with photographic considerations.

Spectroscopy

About the middle of the eighteenth century Melvill (1752) noticed that flames coloured by metals or their salts give spectra with characteristic bright lines when passed through a prism of glass. During the early nineteenth century Herschel (1823) suggested that the analysis of such lines might serve to determine the presence of certain metals. About twenty years previously Wollaston (1802) noted that dark bands cross the luminous solar spectrum. These were mapped out by Joseph Fraunhofer—eleventh and last son of a master glazier, and the Father of spectroscopy—who also studied the optical properties of glass with great success. Fraunhofer could not have guessed that his discoveries would be of use to future biologists studying the chemical nature of cells. Spectrographic analyses of the tissues of animals and plants and of soils have been carried out frequently, as is shown by the well-documented review of Mitchell (*Biol. Rev.*, **22**, 1947, 1–29). More than ninety chemical elements are known to exist in protoplasm, and the spectroscope reveals many which exist only in minute amounts. Without the spectroscope to help him, the physiologist would be handicapped in the identification of blood-pigments, but haemoglobins, haemocyanins and rarer pigments can now be recognised by the elementary student because of their characteristic spectra. In research, the spectroscope has been coupled profitably with the microscope, as was shown in the notable discovery of cytochrome by D. Keilin in 1925 (see Chapter Ten). It can also be coupled with other biological techniques—with micro-incineration for instance, to determine the nature of the ashed remains of biological structures.

Microtomes

Cutting hand-sections of tissues must have been an irksome task to botanists of one hundred years ago, but to the zoologist it often meant hopelessly imperfect preparations and faulty observations where accuracy was essential. The distinguished embryologist von Baer studied the extremely fragile embryos of birds solely by means of dissections. Microtomy would have been a great boon to him. Beset with such difficulties, Valentin and Purkinje improved the section-cutting technique by means of two parallel knives clamped together but having their edges slightly apart, so as to cut between them a slice of tissue—a kind of double-edged scalpel. Significant progress was made

about 1866, when Wilhelm His first experimented with his sliding microtome.[1] His well-known paper, *Beschriebung eines Mikrotoms*, appeared in 1870, but for several years afterwards he worked on improvements for it. About the same time (1874) Leon Ranvier was using a somewhat similar but more practical model at the Collège de France, and soon afterwards this was developed by the French botanist Rivet. In 1870 Alexander Brandt, working with a Rivet microtome in Leuckart's laboratory at Leipzig, was dissatisfied with his results. With the help of a laboratory technician named Leyser he developed yet another type, a sledge microtome which came to be known as the Leyser-Brandt. In the models of His and Ranvier the object to be cut was moved mechanically. In Rivet's microtomes there was mechanical movement of the knife. The Leyser-Brandt microtome introduced movement of both knife and object (see *The Educational Focus*, Bausch & Lomb Optical Co., New York, **9**, 1938). Automatic machines came into use after Threlfall submitted his model in 1883. About this time, perhaps a little earlier, sliding and rocking microtomes were in use in America, and the Pfeifer rotary model came into use there, earlier models possibly in 1879. The Minot rotary microtome was designed in 1886, and in this case also trial models appeared somewhat earlier (see R. P. Cowles and O. W. Richards, 1947).

Imbedding Methods

The introduction of microtomes brought new methods of preparing microscopic objects, which must be imbedded in paraffin wax or some other medium for the support of delicate parts during the cutting process. Klebs introduced paraffin imbedding in 1869, and the method became popular in Britain after A. G. Bourne (1882) described how it was carried out at the *Stazione Zoologica*, Naples. Paul Meyer (1883) was the first person to use egg-albumin for attaching sections to microscope slides. Celloidin imbedding was first used by Latteux when sectioning hair, but this method was modified for soft tissues by Duval (1879). The frozen-section technique, which has come to be essential in cytochemistry, is a much older technique, which was introduced by F. V. Raspail (1825) and used also by Stilling (1842) (see J. R. Baker, 1945).

[1] D'Arcy Thompson (1942) remarked that "Old Stirling", right-hand man of John Goodsir, "brought into use, or re-invented, Sir John Hill's forgotten microtome," indicating an eighteenth-century origin. F. J. Cole (*Nature, London*, **167**, 1951, p. 1042) put the date of Hill's "cutting machine" at 1770 and mentioned also an instrument made by G. Adams Jr. in 1787.

Special methods are used for preparing specimens viewed in the electron microscope, and Coslett (1947 *a*, *b*) has outlined some of them. An electron beam has poor penetrating powers, and sections must be ten to one hundred times thinner than paraffin sections. The specially devised "super-microtomes" cut at the knife-like rim of a wheel which revolves several thousand times per minute. Another method is to cut wedge-like sections and confine observation to the thinner portions, and a third is to cut somewhat thicker sections and hollow them out to a suitable degree of thinness. All specimens must be viewed *in vacuo*, so that movements can be studied only by photographing selected phases of it as "stills". The technique of making surface impressions is useful for the study of surface structure in viruses and other biological entities. Minute particles or topographical irregularities can be shown by "shadowing" them with gold and other elements. Various other and still more technical methods are practised.

Fixation

Whenever possible, cells should be studied alive, but for most purposes they are killed first and studied afterwards. The instantaneous death of a sizable animal does not imply the death of its tissues. These may die a lingering death and alter by decomposition before they can be studied properly. The killing of cells and tissues is called "fixation", which was introduced in the early days of microscopy and is still in process of refinement. The needs of biologists vary. The fixation of cells for the study of their arrangements in tissues (histology) does not require the same refinements as the fixation of cells for study as such (cytology), but many blunders have been made in the past in the use of chemicals for both purposes. The discerning biologist chooses his fixatives with discrimination, testing effects one against another and relating all of them to the appearance of the living cell.

The idea of preserving animal tissues probably first occurred to Robert Boyle, who experimented with alcohols before 1662 and who introduced ethyl alcohol as a preservative for anatomical specimens in 1663 (see R. T. Gunther, 1925). One of the first records of this process goes back to May 1662 when Mr Croune (Croone) exhibited to the Royal Society of London two embryo dogs sealed up in a vessel containing spirits of wine (see F. J. Cole, 1944). The early microscopists made use of crude preservatives for the small animals they studied, H. Baker (1774) using vinegar to preserve the hydra. During the early part of the nineteenth century methods were refined somewhat.

Chromic acid was used by Hannover (1840) and by A. Corti (1851), who also found that acetic acid preserves nuclei well, so that it came to be used by R. Remak (1854) and Auerbach (1874), and by W. Flemming (1884) in his well-known mixture. Potassium dichromate was introduced as a cytological fixative by H. Müller (1859), and mercuric chloride was used in "Goadby's liquid" (see Quekett, 1848) and later by Corti (1851) and Remak (1854) before it came to be used in Lang's mixtures in 1878. Mixtures of compounds came into use about this time, Zenker's and Altmann's in 1894, Helly's in 1903. F. Blum (1893) noted the hardening properties of formalin by its action on his own fingers. During the twentieth century many new fixatives have been introduced and to select one for a specific purpose is not an easy matter, even though various books are available for reference. In recent years a much more critical attitude has been taken up, largely as a result of the work of W. B. Hardy (1899) and A. Fischer (1899) on the fixation of proteins. Using various biological substances—peptone, haemoglobin, albumin, nuclein, globulin, etc.—in solution, Fischer showed that fixation with Flemming's and Altmann's mixtures and with simple solutions such as osmium tetroxide and chromic acid will produce precipitates of varying appearance—finely or coarsely granular and reticular. Even the same protein gives very different microscopic pictures after different fixatives have been applied to it. Hardy reached similar conclusions, and in 1900, after studying gelatin and egg-albumin fixed in various ways, he formed the opinion that fixation separates solids from liquid in protoplasm and produces a structure which was not there before. Hardy's criticisms of alveolar theories of protoplasmic structures have been deemed unjust, but his work has instilled in cytologists a healthy caution regarding appearances in fixed tissues and this has been of great service to biology.

A novel procedure, dehydration at low temperatures, was introduced by Altmann in 1894 and has been revived recently by I. Gersh (*Anat. Rec.*, **53**, 1932) under the name of "freeze-drying". Altmann knew that a fragment of tissue becomes hard and brittle, its cells much distorted, by drying at ordinary temperature, but may instead be dried over phosphorus pentoxide *in vacuo* and then thawed out without losing its characteristic features. At low temperatures ($-40°$ to $-30°$ C.) the salts of tissues freeze out together with water, forming an eutectic, so that cells are never exposed to the action of concentrated salt solutions as they are when drying follows the more usual course. Tissues dried in this way can be passed directly into paraffin wax, and so long as the

temperature does not rise above about 40° C. *in vacuo*, they cut well. I. Gersh developed this method, first of all freezing the tissue in liquid air and then drying it *in vacuo*. R. R. Bensley and I. Gersh (*Anat. Rec.*, **57**, 1933, 205) fixed tissues in this way and then passed them into a chamber cooled to −20° C. and subjected to a high degree vacuum, which is increased as water evaporates and is maintained for about twelve hours, and until drying is presumed to be complete. The tissues can then be imbedded in paraffin wax in just a few minutes and mounted after sectioning without treatment with the usual dehydrating agents such as alcohol. One advantage of this method is that cell inclusions are less likely to be lost during the preparation of cellular specimens than they are by the ordinary methods, for the liquids which leach them out are reduced to a minimum. G. H. Scott (*Protoplasma*, **20**, 1933, 133) allied the methods of freeze-drying and micro-incineration. He preferred alcohol cooled to −177° C. to liquid air for the cooling or "quenching". N. L. Hoerr (*Anat. Rec.*, **65**, 1936, 293) stressed that swiftness in this part of the process improves fixation. He used pentane cooled to −131° C. or iso-pentane at −195° C. (these substances are less viscous than alcohol at low temperatures and freeze more rapidly), followed by dehydration at −30° C. Readers may be interested in the detailed description of the technique given in the recent book by E. W. Flosdorf, *Freeze-drying* (Chapman & Hall, 1950).

Staining Methods

Some of the classical microscopists stained small objects to make them more clearly visible. Leeuwenhoek discovered the method of staining and wrote to the Royal Society of London in 1714 describing the use of Crocus (saffron?) macerated in wine to stain muscle fibres, but his letter was not published for five years. Five years later still (in 1724) a pupil of Swammerdam named Ruysch injected cinnabar in tallow and wax into the blood vessels of human anatomical specimens, to aid identification. A. Trembley (1744) fed living hydra on various pigmented organisms and was able to see in the coloured animal hitherto unknown extensions of the digestive cavity (enteron) in the tentacles. Botanists also experimented with coloured liquids about this time. Sarrabat (1733) put the stems of plants in the coloured juices of plants (*Phytolacca*) and watched the colour rising in the vessels. Reichel (1758) used an unspecified red liquid for the same purpose and examined the coloured parts under a simple microscope. John Hill (1770) stained the vessels of plants with alcoholic solutions of

cochineal and other substances. A long pause followed these desultory practices of staining. Not until well into the nineteenth century was the staining technique rediscovered and developed, but with the establishment of the cell-theory progress was assured.

In his enormous book *Die Infusionsthierchen* Ehrenberg (1838) described the use of indigo and carmine to reveal the "stomachs" (food vacuoles) of infusorians. Wagner had used this method in 1832 and it was an improvement on that used by von Gleichen (1778). Göppert and Cohn (1849) coloured the granular cell contents of *Nitella flexilis* by means of carmine and madder as an aid to the study of cyclosis, and A. Corti (1851) used stains to colour the cochlear epithelium in his dissections of the inner ear. It was seen that nuclei become darker than the cytoplasm when cells were treated with compound watery solutions of alcohol, sugar and carmine. Three years later the botanist T. Hartig (1854) independently discovered that carminate solutions affect the nuclei of plant cells in the same way.

An influence far greater than any so far mentioned was that of J. von Gerlach (1858), who has often been credited with the discovery of the staining technique but who was, according to J. R. Baker (1945), its last rediscoverer one hundred years after the chance discovery of Reichel. Gerlach may be regarded as the originator of controlled and standardised methods of using stains in histology. Such methods were for some time detrimental to the development of histochemical methods and may have retarded progress in that aspect of cytology which deals with the chemistry of cells and their products. Soon after the discovery of an aniline dye by William Perkin (1854) stains of various sorts became essential to histological investigation (see H. J. Conn, 1948). Basic fuchsin was first manufactured in 1856, and other dyes were discovered in the swift succession—safranin 1859, methyl violet 1861, aniline blue 1862, eosin and methyl green 1871, thionin and methylene blue 1876, acid fuchsin 1877, orange G 1878 and crystal violet 1883. Beneke (1862) first used an aniline dye, "lilac aniline", in acetic acid and his example was soon followed by Waldeyer (1863), Onimus (1865), Frey (1868), Böttcher (1869) and others. According to Quekett (1848) extracts of logwood became popular after 1840, and in 1865 Böhmer used pure crystalline haematoxylin in histopathology. The method of regressive staining—overstaining followed by de-staining, or differentiation, with alcohol—was introduced by Böttcher in 1869, adopted by Hermann (1875) and developed by Flemming (1881). Schwartz (1867) introduced double staining, using a carminate solution and then picric

acid, and Ranvier (1868) simplified matters by combining the two stains in one solution of picro-carmine.

Ehrlich (1877–79) systematically studied the staining action of various aniline dyes, and he was the first to use safranin. In 1886 he introduced his well-known acid haematoxylin, stabilising the stain and the mordant (alum) with the acid. He also came to recognise the different actions of basic (nuclear) and acidic (cytoplasmic) stains, and in dealing with blood he worked with neutral stains. The development of cytology brought other stains into use, and mixtures and methods alike became more elaborate. Flemming (1891) introduced triple staining, and Mayer (1892) brought haemalum into use. During this period Canada balsam was first used for making permanent mounts of microscopic objects. Histologists were now coming to need help with the problem of choosing suitable techniques, and in 1885 the first edition of Bolles-Lee's now well-known *Microtomist's Vade-Mecum* was published. Histological and cytological matters were at this time attracting the attention of biologists everywhere, and much futility must have been felt as inferior methods were tested and found wanting, but out of a welter of effort practicable methods were evolved to satisfy the needs of histologists. The development of methods for the more critical work of the cytologist was slower, and indeed is still going on. It has been outlined by H. J. Conn (1948). For the details of these methods the reader will need to consult the standard works on cytology.

Histochemical Tests

When Link (1807) placed twigs and leaves of plants in a solution of iron sulphate and saw the blackening of cells near the spiral vessels he made the first histochemical test for tannins. There are now many methods of identifying cell constituents, and only the briefest references to them can be made here. Colin and de Claubry (1814) first noted the blue colour which starch gives when treated with iodine, but the French botanist François Vincent Raspail, who has been recognised as the founder of histochemistry, introduced the test into microscopic technique in 1825. A glowing tribute has been paid to this pioneer by J. R. Baker (1945). He interested himself in the flowering and fruiting of grasses, and with very limited resources closely studied this iodine reaction with starch. In 1828 Raspail also noted that plant proteins and sugars together give a purplish-red colour when treated with strong sulphuric acid, thus providing the basis of the aldehyde test for the amino-acid tryptophane nearly fifty years before it was intro-

duced by Adamkiewcz (1875). One year later Raspail applied chemical tests to the protoplasm of *Chara* which form the bases of three reactions that are still widely used in the laboratory for the identification of proteins, the xanthoproteic reaction, Liebermann's test and the aldehyde reaction. Baker has affirmed that "Raspail's careful chemical investigation of the protoplasm of *Chara* would be an eye-opener to anyone who thinks that the microchemical analysis of the contents of a cell is a product of modern times".

Raspail's example was followed by other biologists. In 1850 Franz Schulze of Rostock first demonstrated the chlor-zinc-iodine test for cellulose, and Fürnrohr recorded the fact in the same year. In 1859 Sachs used alkaline copper sulphate to demonstrate carbohydrates in plant preparations and potassium hydroxide to reveal tannic acid. Müller (1866–67) determined that resins and ethereal oils take up the red pigment of alcanna root much more avidly than do watery or alcoholic mixtures. Max Schultze used osmium tetroxide at the suggestion of Franz Schulze, first for the study of luminous organs in the glowworm but in the same year (1865) for the purpose of staining fatty substances in animal and plant tissues. Ten years later L. Ranvier used quinoleine blue for colouring fats, and in 1882 Dippel used alcanna for staining fatty substances in animals and plants. In 1896 L. Daddi included fats stained with Sudan III in the diet of birds and discovered that the fatty tissues of their bodies become coloured with the dye, thereby extending the list of vital stains. Vital staining with methylene blue was first used on living nervous tissue by P. Ehrlich (1886), who displayed the nervelets in the intestine of the mouse and who came to believe that dyes have a specific affinity for certain side-chains of protoplasmic molecules. Others have shown, however, that many factors must be considered—solubility, electrical conditions, diffusibility and others (see W. M. Bayliss, 1927). One of the least toxic intravital stains is neutral red, which is quickly taken up by cytoplasm and becomes concentrated in granules of various sorts. The stain may seem to be harmless to an organism, but it is known that granules swell by exposure to it, so that its use may give a distorted picture of cell inclusions. The reader will find a summary of the methods used in histo- and cytochemistry in the book by D. Glick (1949).

Micro-incineration

This remarkable method of analysis was first practised by F. V. Raspail (1833), who demonstrated that leaves and other parts of plants

can be calcined and reduced to ashes, losing all traces of organic matter, without the loss of general structural characters. The next notable advance was made when Liesegang (1910) modified the technique to deal with sections of animal tissues, which were calcined on slides for the purpose of microchemical analysis. Even delicate structures such as the retina of the eye and nerve cells can be studied by this method. These researches were extended by Herrera (1913), E. Neumann (1915), M. Prenant (1919) and Molisch (1920), but it was the Frenchman A. Policard who improved the technique and established its use in cytology. In 1918 he studied the repair of fractures in bony tissues and found that a faithful image of the "mineral skeleton" of cells and tissues remained after micro-incineration. About five years later (1923) he devised methods for carrying out micro-incineration in an electric quartz furnace after suitable fixation. G. H. Scott (1930 onwards) improved the technique further and applied the method of the ultra-microscope to calcined specimens. The method has become a useful biological tool. In practice, tissues are generally fixed by means of alcohol-formol mixtures and if the ashed residues are intended to show cell-detail sections should not be more than 5 μ thick. Details of later work along these lines can be found in the review by Hintzsche (1938) and much information is given by E. S. Horning in the book edited by G. Bourne (1942).

Microdissection and Micromanipulation

Dissection has been practised by anatomists for many centuries, and the classical microscopists were familiar with rough-and-ready dissection of minute organisms. Out of these efforts has arisen a more or less standardised technique of microdissection. This may involve only freehand manipulation, or it may call for methods of a mechanical kind performed under the microscope.

Freehand microdissection does not require elaborate apparatus, often not more than fine scalpels and needles, but much has been achieved with small resources and the historical developments are worth mentioning. The methods have been described fully by H. Spemann (1923) and O. Mangold (1928) and in brief by Hörstadius (in C. E. McClung, 1937, p. 43). They have been used in particular by embryologists. Using fine scalpels and needles, R. Zoja (1895) was able to separate the cells (blastomeres) of the segmenting egg, and Y. Delage (1899) succeeded in dissecting the unsegmented egg of sea-urchins. H. Driesch (1893) evolved a technique for shaking blastomeres apart,

and C. Herbst (1900) separated them by chemical means, using calcium-free sea-water. A delicate technique was devised for dissecting the eggs of echinoderms and Amphibia by Spemann (1906), who used hair ligatures and exceedingly fine glass needles, a method which led to the introduction of mechanical microdissection. Like Ross G. Harrison (1904), Spemann was one of the pioneers of tissue transplantation with the eggs of amphibians and other animals. Early experiments were carried out with hosts and donors having cells of different size and colour, so that the transplants from the donors could be recognised and their fate studied in the recipients or hosts. Such methods were succeeded by the use of vitally stained explants (S. R. Detwiler, 1917; S. Hörstadius, 1928, 1935), which in turn gave way to local vital staining of particular cells or sets of cells in developing embryos (W. Vogt, 1925). All these methods have been modified in various ways by the many biologists who have since used them.

By using fine pipettes instead of needles freehand micro-injection can be carried out on small animals and embryos. In the early work of H. Hoyer (1908) and Mozejko (1911) the pressure necessary for injection was controlled by the foot operating a special valve, so that the hands were free for actual manipulation. H. M. Evans (1909) used modifications of a method devised by Popoff (1894), injecting liquids into the capillaries of bird and mammal embryos through a pipette drawn out and then redrawn in a microflame about as large as a match-head. The apparatus was filled with the liquid and injected by regulated blowing through a mouthpiece. H. McE. Knower (1908) obtained the necessary pressure by heating the air in a glass bulb, the expanding gas driving the liquid through a glass tube and into the micropipette. He has described his method with illustrations (see C. E. McClung, 1937, p. 54, Fig. 3) and gave a list of special precautions and suggestions for micro-injectors.

The more refined methods of micromanipulation, which may be carried out on isolated cells, require more elaborate and costly apparatus, and a lot of manual skill. Results obtained by such methods were described by R. Chambers (in E. V. Cowdry, 1924), who has also written (1940) an account of recent developments. A full account of methods applied to the study of cellular phenomena has been written by R. Chambers and M. J. Kopac (McClung, 1937, p. 62). Some objections have been raised to the technique on the grounds that operated cells immediately become abnormal. But the expert usually takes great care not to damage cells too much and the slight injury

produced is often soon repaired. Any kind of experimenting with living cells has its drawbacks, and microdissection is not the worst thing that can happen to a living cell.

Micromanipulators are mechanically controlled instruments for accurately moving microneedles and micropipettes in three planes under the microscope. Several elaborate types now available compete with one another for ease and precision of movement in the needle-points. The type devised by P. de Fonbrune (1939) has a hand-rest and a universal level which operates three pumps that move the needles in three planes by hydraulic action. Particulars and pictures of various models are given in the articles by Chambers (1940) and McClung (1937). The fine needles are drawn out in a special machine (D. du Bois, 1931), which heats the tips electrically by means of a platinum loop, and ground, polished, or etched to microscopic points. One needle may be bent into a hook for holding the cell to be dissected, while the other is more nearly straight and does the cutting. Perfection of micro-injection methods has been by accurate mechanical control of the pressure required for injection and the fluids (mercury and air) used for propelling the injection liquid. Such refinements are applied more particularly to the study of Protozoa and Algae and to the fields of tissue culture, cellular physiology, cytology and embryology, but modifications serve for such tasks as the isolation of micro-organisms in the preparation of pure cultures, the study of colloids and fibres, and research on enzymes.

The Centrifuge and Ultra-Centrifuge

The force of gravity is well known to exert an influence on living organisms. J. B. Denis (1672) first showed that this force induces the stems of plants to grow upwards and their main roots to grow downwards. By means of forces greater than gravity, generated by means of a kind of water-wheel, T. A. Knight (1806) showed that the roots and shoots of seedlings orient themselves to centrifugal force, just as they do to gravity. Later on, biologists found many other uses for the centrifuge, one modification used by J. Sachs (1875) and other botanists for the study of geotropic movements in plants being the now familiar klinostat. By comparatively gentle centrifugation C. Dehnecke (1880) watched starch-grains glide through the cytoplasm of plant cells. By more vigorous centrifugation D. Mottier (1899) was able to show that the inclusions of the centrifuged cell may become stratified according to their relative densities. Many names famous in embryology have

been associated with the use of the centrifuge, studying the eggs of animals and the effect of centrifugation on development. W. Roux (1884), T. H. Morgan (1903) and J. W. Jenkinson (1914) used the eggs of the frog, Lillie (1909) the eggs of the annelid worms, and T. Boveri (1910) the eggs of *Ascaris*. Morgan (1927) gave a list of eighty-two references to biological researches of this kind as an appendix to his account of the possible effect on subsequent development of redistributing the visible materials of the egg by centrifuging.

Various methods have been used to generate a centrifugal force, but the details are too specialised to be mentioned here. Hand-driven instruments gave place to water- and electrically-driven ones, and these to various types of super-centrifuge, such as the Sharples instrument, which developed forces up to 62,000 G, and the Svedberg, which took this figure up to 800,000 G. Svedberg spent many years from 1923 developing his instrument, an account of which is given by T. Svedberg and K. O. Pedersen (1940). J. W. Beams likewise spent many years from 1930 onwards developing his air-driven ultra-centrifuge, which generates a force up to 7,000,000 G. H. W. Beams and King (1940) have given a short list of general problems which can be profitably tackled by means of the centrifuge in its various forms, with some salient references. The work has an extremely varied character. It includes effects on developing plants and animals (geotropism and polarity), the study of the subsequent history of redistributed materials in the cell and the effect of redistribution on development in the embryo, the determination of the viscosity of protoplasm and of membrane strengths in cells, the determination of molecular weights and concentration of bacteria and virus particles, the separation and purification of hormones and enzymes, studies on cell division and cell components which play a vital part in cell division, and studies on the structure of Protozoa and other microscopic organisms. With some of the results which have accrued from such studies we shall be concerned in later chapters.

Tissue Culture

Perhaps the first step towards a technique for the cultivation of tissues outside the body of an organism was a realisation by Claude Bernard (1878) of the importance of the "internal environment" not merely as something produced in metabolism but also as a kind of medium in which the activities of the tissues can be regulated. The first obvious step, however, was made by W. Roux (1885) when he removed a fragment of the neural plate of a chick embryo and cultivated

it in a warm salt solution. Some time later C. A. Ljunggren (1898) attempted the culture of human skin, and G. Haberlandt (1902) isolated groups of cells of certain plants. L. Loeb (1902) placed small fragments of guinea-pig skin in a clot of serum and introduced this under the skin of another animal, a method later adopted by many embryologists studying the development of the eye and other organs. J. Joly (1902), working with the white blood corpuscles of *Triton*, made cultures by what came to be known as the "hanging-drop" method and kept them alive for several weeks. S. P. Beebe and J. Ewing (1906) modified Loeb's method and kept cultures of cancerous tissue from the dog in various animals.

These tentative methods gave way to a more definite and reliable technique after Ross G. Harrison (1907) devised methods of cultivating fragments of living nerve, and biologists owe much to A. Carrell, who greatly improved the technique. The first demonstration of cultivated cells outside the body of an organism were somewhat sensational. Carrell, who demonstrated his cultures in Paris on December 10, 1910, must have been disappointed, to say the least, when well-known biologists declared his tissue fragments to show marked signs of necrosis. It did not deter him, however, and with the help of Burrows and later Ebeling and others he further developed Harrison's technique of explantation, which is said by those who practise it to be more arduous and difficult than the technique of the bacteriologist. Strains of connective tissue cells from the embryo chick have now been kept alive and normal for more than a quarter of a century, which is far in excess of the life of the animal from which they were taken.

Improvements in the technique have also been made by W. H. and M. R. Lewis (1924) and much information can be found by the reader in the works of E. N. Willmer (1928, 1935), T. S. P. Strangeways (1924), W. Bloom (1937), R. C. Parker (1938) and A. Fischer (1946). The use which has been made of the technique can be realised from the list of 753 references cited by Parker on such subjects as the cultivation of the main cell types, experimental morphology, physico-chemical constitution of the medium, biological test materials, growth measurements, the cultivation of cells for grafting, the cultivation of tumour cells, the propagation of viruses, tissue culture in relation to diseases, hypersensitivity and immunity, and effects of irradiation. Some work with cultures also fits in the category of what E. Mayer called "causal pro-morphology".

The technique calls for the use of sterilised glassware and instru-

ments, and much of the necessary apparatus has been described and figured by Parker, who also dealt in a general way with the handling of saline solutions, preparations of plasma and serum and tissue extracts, with the preparation of synthetic media and the various kinds of culture themselves. These last are usually of the "hanging-drop" or the "Carrel flask" type, which call for different methods of observation and photography, which are also dealt with.

For an account of an allied technique—the culture of whole organs—see the article by H. Okkels (1942).

Radioactive Tracers in Biological Research

The first tracer experiment was carried out in 1913 at the Vienna Radium Institute. The first use of a radioactive indicator in biological research came about ten years later when G. de Hevesy studied the distribution of lead in a plant. When in 1934 artificial radioactivity was discovered a useful source of materials became available and the tracer technique developed along with the production of active isotopes of many lighter elements. To-day biologists can select from a considerable list of possible tracers (see the table in Paneth's article, *Nature*, London, **163**, No. 4141, 1949, 388–390).

The use of radioactive tracers is anything but simple and the investigator must always bear in mind the possible effects of tracers on account of their radiations, which may vitiate the apparent distribution of certain elements in living materials. Paneth has enumerated a few outstanding kinds out of many possible kinds of research with radioactive tracers—the use of radioactive H (tritium) and carbon-11 and -14 in the study of photosynthesis, radioactive sodium, potassium and chlorine in the study of cell permeability, radioactive iron in investigations of the life of red blood cells, and radioactive phosphorus in the study of fertility of the soil and the metabolism of teeth. One of the best-studied tracers is radio-iodine, which has led to better understanding of thyroid function and the functional relationship between thyroid and pituitary glands. The metabolism of bone salts has been studied with the help of radioactive calcium, strontium and plutonium. But Nature has carried out her own experiments on a vast scale, particularly with carbon, which is "labelled" because mixed with carbon-14 everywhere in biological processes. This isotope can be produced in uranium piles by the impact of neutrons on nitrogenous substances, a process which ensues naturally in the upper layers of the atmosphere under the influence of cosmic rays, the carbon atoms there

uniting with oxygen atoms to yield the gas carbon dioxide. Plants assimilate atmospheric carbon dioxide and they must take in and incorporate in their structure a small amount of carbon-14, whence it passes to the bodies of animals and man. Its lifetime is limited, however—the half-life being about 5,000 years—and it has consequently disappeared from carbonaceous materials such as coal- and oil-fields, but remains active in existent organisms and their waste products as found, for instance, in sewage deposits, which have the standard amount of C-14 (Paneth, 1949).

Several recent books and articles on tracer research which are likely to interest the student can be mentioned. The book by G. Hevesy (1948) contains a rather advanced account of the biological applications, the article by W. V. Mayneord (1950) deals with some applications in medicine, and the article by R. H. Burris (1950) is concerned with isotopes as tracers in plants. Perhaps the best general account of radioactive tracers in biological research is to be found in the book by M. D. Kamen (1950), and the best popular account in the article by J. E. Harris (1951).

Cinematography

It has been said that the true function of cinematograph films is scientific research, not entertainment. A considerable set of historical developments certainly shows that the cine-camera has become an effective biological tool. The reader is referred to the large book on this subject by G. M. Coissac (1925) and to the historical review by O. W. Richards (1933). Almost exactly one hundred years ago Faye (1849) used photographic images to fix the transit of a star across a meridian, and suggested that photographic images could also be used to analyse the movements of animals. In 1874 another astronomer, Janssen, used the "astronomical revolver" to photograph the transit of Venus across the sun's disk, and four years later he also suggested that similar methods could be used for recording the translatory movements of animals. In the meantime, Onimus and Martin (1865) had recorded the phases of the heart-beat on collodion plates, using pictures to indicate differences in size of the relaxed and contracted organ (see Coissac). Some time later, Eadward Muybridge, who worked in California but was born near London, was photographing the moving horse by means of a row of cameras set parallel to the path of the animal. As the horse ran, it tripped wires which worked the shutters of batteries of 12–40 cameras. The first pictures were taken

about 1870 and were shown for the first time in Europe at the Royal Institution in London on March 13, 1882, when Muybridge lectured on "the science of animal locomotion in its relation to design in art". Critics had been very sceptical about the possibility of photographing a moving object, but Muybridge's pictures portrayed a horse walking, cantering and even galloping.

At this time E. J. Marey (1882) was concerned with the problem of taking pictures equally spaced in time, and he improved on the zoöpraxiscope of Muybridge, in which separate pictures were arranged round a glass disk. Marey was interested in physiology and he used tambours and Ludwig's kymograph to record the movements of a bird's wing in flight. In 1891 he published photographs of insects in flight, using a rotating shutter to control exposures of about 1/25,000th of a second. He also used the camera to try to show why a falling cat always alights on its feet (1894 *a*). In the same year he published his book (1894 *b*), which was translated by Pritchard in the following year under the title *Movement*. By this time Edison had made some improvement in Marey's first projector (which appeared in 1893), perforating the film to obviate shaking movements. The first educational film was made soon afterwards (in 1898) by Doyen, who caused a stir by showing it, because it depicted a surgical operation.

Attention so far had been concentrated on the problem of slowing down movement too swift for the eye to follow: what we now call slow-motion cinematography. But in 1904 A. Pizon first demonstrated a method of speeding up motion and invented the word "biotachygraphy" (meaning "to write life rapidly") for what is now called stop-motion cine-photography. His study of the development of a colonial sea-squirt (*Botryllus*) was illustrated by a film having 775 frames, taken at intervals of twenty minutes for nearly eleven days, and this was exhibited in 1904 at the Zoological Congress in Berne. J. Ries (1909) used similar methods to study fertilisation and cleavage in the egg of the sea-urchin, and in the same year L. Chevroton and F. Vlés published the results of similar work independently carried out. They were the first to witness the "foaming" moments of living cells. Another interesting development was the use by J. Comandon (with technical help from Pathé) of the ultra-microscope in the cinematographic study of bacteria. Comandon also made films of *Amoeba*, *Vorticella*, *Trypanosoma* and spirochaetes, and of the circulation of the blood, and these were distributed as aids to teaching.

Various biologists have used cine-photomicrography in connexion

with work on tissue culture, notably Carrel and Ebeling (1926), Canti (1928), Rosenberger (1929), Lewis and Gregory (1929), Fischer (1930) and Carrel (1931). The first film of tissue culture *in vitro* was made in 1911 by H. Braus of Jena, who made exposures at the rate of ten a minute for about ten hours to illustrate the growth of nerve, pigment and mesodermal cells. Soon afterwards (1913) the first film of dividing chromosomes was made by J. Comandon and J. Joly, who used the red blood corpuscles of a newt (*Triton*). Comandon also made films of micro-organisms (1909) and of phagocytosis (1917, 1920). A. Krogh and P. B. Rehberg (1924) gave details of the methods used in the study of the circulation of blood through the capillaries. Heard (1932) made a special study of practical time-lapse cine-photomicrography.

These facts amply illustrate the importance of the cine-camera in the study of biology, though much more could be stated. As a Special Correspondent wrote in *The Times* (September 30, 1949), the cine-camera "is an unobserved and undisturbing observer; it is insensitive to atmosphere and fatigue; it can function for hours on end with a non-sleeping eye, without producing confusion and overlapping among successive images; and it can be given a privileged viewpoint not always accessible to the human eye". It can also serve as "a time-expander and as a time-compressor and it can see things in wave-lengths which are invisible to the ordinary eye". In time-lapse cine-photography pictures are taken at 10–12 seconds intervals instead of 24 per second and we are allowed to observe in about three minutes what took six hours to happen, action being speeded up two-hundred-fold. Conversely, events which are too rapid to be observed can be slowed down by a camera that will take 1–3,000 photographs a second, and with special methods up to 400,000 a second. As it can be attached to various instruments that are designed to present a picture to the eye, the camera has come to occupy a definite place in biological equipment. For the reader who is interested in modern methods, the paper of A. F. W. Hughes (1949) deals with phase-contrast cine-photomicrography and is full of practical suggestions in regard to photographic technique, the apparatus and the processing of films.

Scientific Journals

The publication of the *Transactions* of the Royal Society of London began in 1665 but modern scientific journals first appeared during the early part of the nineteenth century in various countries. Among the

earliest of them were the *Proceedings* of the Royal Academy of Sciences of Amsterdam (1812), *The American Journal of Science* (1819), *Le Journal de la physiologie experimentale* (1821) and *Müller's Archiv* (1834). Others soon followed. Another interesting development was the foundation at Leipzig in 1822 of the *Versammlungen Deutscher Naturforscher und Ärzte*. This instituted a new method of disseminating scientific knowledge by means of both meetings and publication. The German Society, which Lorenz Oken founded, held annual meetings in various German towns (Halle, Würzburg, Frankfurt, Dresden, Munich and Berlin in the early years), where the latest scientific advances were discussed freely. The membership was at first about thirty persons, but it soon rose to some hundreds. Not long afterwards the British Association for the Advancement of Science was formed and held its first meeting in 1831 at York. Sir David Brewster was virtually its founder. Other countries later set up similar associations. With the growth of scientific literature during the early part of the nineteenth century journals of abstracts appeared. *The Proceedings of the Royal Society of London* was at first (1832) made up entirely of abstracts of papers published in the *Transactions*; short original works appeared in it for the first time in 1856 (seventh volume). The *Botanischer Jahresbericht* appeared in 1874 and the *Zoologischer Jahresbericht* in 1880. Bibliographies of a periodic kind appeared about this time, the *Zoological Record* in 1864, *Index Medicus* in 1879, and *Index Kewensis* in 1893. Special bibliographies such as the *Royal Society Catalogue of Scientific Papers* also appeared during the nineteenth century, and perhaps the most interesting new development of all was the first appearance in 1869 of that international scientific periodical *Nature*, London. Scientific knowledge was becoming specialised during the nineteenth century, but during the early part of the twentieth century specialisation became much more pronounced. In 1934 Sir Charles Sherrington made a special study of the *World List of Scientific Publications*. The five most useful languages for scientific publications provided a list of more than 28,000 titles, distributed as follows: English (13,494), German (6,186), French (5,013), Russian (1,833), and Italian (1,667). Only a fraction of these deal with biology, but this subject takes its fair share. H. S. Reed (*A Short History of the Plant Sciences*, 1942) stated that, according to Wellensiek, a total of 11,000 botanical papers were published in 1938, an average of 30 per day, most of them too technical to be appreciated except by a group of specialists. B. G. Peters (*The Scope and Aims of the Commonwealth*

Bureau of Agricultural Parasitology, St Albans, 1932) wrote of 917 papers on a specialised subject (Helminthology) which were published in 346 periodicals and were enumerated in one issue (1930) of *Helminthological Abstracts* (see p. 355). Clearly, no one biologist can follow all the trends in his subject, not even with the help of abstracting and reviewing journals.

CHAPTER THREE

SOME TRENDS

The Study of Plants during the Nineteenth Century

BIOLOGISTS engaged in various fields of their subject often pick out different landmarks of progress in it. T. G. Hill (1932) recognised three periods of advancement in the study of plants after 1830. First, about fifty years (1831–82) of marked advance in plant morphology and physiology; second, the period of renaissance of botany in Britain (1875–1918); and finally, the present period from 1919 onwards. The first of these periods was characterised by a quest for a natural system of classification, the emergence of morphology from taxonomy, and the development of plant physiology. British botanists were well to the fore in regard to systematics, notable efforts being made by Robert Brown, W. J. and Sir J. D. Hooker, Lindley, Harvey, F. W. Oliver and J. Bentham, but in regard to the study of structure and function "the tale of British activity is dismal indeed", a mere handful of workers (Darwin excepted) causing " but a ripple on the botanical surface". At the beginning of this period studies mainly concerned the structure of the flowering plants, and the concepts of morphology were based largely on philosophical abstractions. Little was known about the life-histories of any plants, and hardly anything about the simpler plants such as liverworts and mosses (bryophytes) and algae, fungi and lichens (thallophytes). With so much scope for research on the development of plants a "trickle of investigation developcd into a flood", most of the credit going to Continental leaders such as M. J. Schleiden, K. Nägeli, H. von Mohl and W. Hofmeister, who made solid contributions in their fields of study. Hofmeister elucidated the development of the sexual organs and the embryo, first in flowering plants and then in the ferns and their allies and the mosses. The phenomenon of "alternation of generations" attracted him, and he was the first to give the correct explanation of heterospory, in which the asexual spore is associated with the gametophyte and the oospore with the sporophyte generation. At the turn of the nineteenth century and largely as a result of his work "the great divisions of the vegetable kingdom were so well established and so

patent, that the theory of descent (presently to be established by Darwin) had only to accept what genetic morphology had actually brought to view".

The study of plant structure was given a sound basis by Hugo von Mohl and Carl Nägeli who applied the cell theory to it. Von Mohl—a man of great technical ability and practical outlook—traced out the tissue elements and the course of the vascular system of plants, preparing the way for comparative studies. He was the first to demonstrate the action of the stomata in the leaves of plants, showing that they open and close in accordance with varying turgidity in the guard-cells which form their openings. He used polarised light skilfully in studying the nature of the cell wall and the structure of starch-grains and other constituents of plant cells. Like Nägeli, von Mohl was a pioneer of cytology, though after the turn of the century Strasburger became prominent in this field and W. Flemming, J. Schmidt and others made lasting contributions to knowledge. Plant physiologists became absorbed in osmotic phenomena, following up the earlier work of H. J. Dutrochet (1827) and utilising the results of T. Graham's investigations in colloid chemistry. The problems of carbon assimilation and respiration were also well in the foreground of botanical inquiry. Research on the metabolism and irritability of plants gained in importance, and as cytology and ecology gained adherents the economic importance of plant pathology became more evident. The study of fossil plants also came in for careful study.

The Botanical Renaissance

According to T. G. Hill (*loc. cit.*), a great change came over the study of plants from 1875 onwards. He gave credit for the botanical renaissance largely to (Sir) W. T. Thiselton-Dyer, who organised and tended the first practical botany classes in T. H. Huxley's Department at the Royal College of Science, London. Previously the teaching of botany had been associated with medicine rather than science, but it was passing into the hands of men such as F. W. Oliver, S. H. Vines, F. O. Bower and D. H. Scott, who were anatomists rather than systematists. The results of researches carried out by members of the new school were published in a new journal, the *Annals of Botany*, which first appeared in 1887. Systematics were not neglected, but became more enlightened by the use of structural and functional characters. Efforts were being made to fill up the gaps left by the anatomical work of Radlkofer and the physiological work of Haberlandt. As histological

technique was improved and knowledge of the functions, development and life-histories of plants increased, a causal morphology arose. W. Hofmeister (1868) had asserted that "the most pressing and immediate aim of the investigator" was "to discover to what extent external forces acting on the organism are of importance in determining its form" (Klebs, 1909). This new way of looking at biology was due to the influence of Darwin's greatest work.

Considering the changes that came over the study of plants during his own lifetime F. O. Bower (1938) wrote: "On first entering the university I found myself torn by a divided allegiance between the old systematic and the newer biological discipline: but very soon I allied myself firmly with the new. The fact was that in the middle of the nineteenth century two alternative disciplines were developing in the academic study of plants, and already in 1875 their difference was clearly reflected in the current literature. They were, it is true, fundamentally related, and the doctrine of descent would be applicable to each. But at the time they were as distinct in spirit and practice as they were in geographic localisation of their pursuit. The structural and functional method of approaching the study of plants and of their life-histories had been specially developed in the universities of the continent, and particularly in those of Germany. Under the systematic method the natural relations of flowering plants in the adult state occupied the attention of the leading botanists in Britain, almost to the exclusion of other phases of the science: and this exclusiveness characterised the work then being done in the British universities." Bowers believed that few botanists of the time could cope with both methods, "but Sir Joseph Hooker, like a Colossus, had a foot down in either camp".

C. Singer (1929) suggested that the modern era in biology opened about 1860. In the short space of about twenty years afterwards the whole biological outlook changed. This he attributed largely to the disclosure of fundamental similarities between animals and plants—which have in common their protoplasmic nature, various modes of reproduction, and physiological functions such as nutrition and respiration. But the change partly came about with the growth of knowledge about the chlorophyll apparatus of plants and its connexion with organic synthesis of substances which are used by both plants and animals. This gave biologists a fresh view of the balance of life. But a new conception of the economy in nature arose also out of a newly discovered principle of evolution.

Organic Evolution

For nearly one hundred years the doctrine of organic evolution has been associated with the name of Charles Darwin who, in 1859, expressed his ideas about it in *The Origin of Species*. But, as H. F. Osborne has shown in his sketch *From the Greeks to Darwin* (1894), the idea had simmered in the minds of men for centuries before Darwin, Aristotle having his own version of it. Osborne believed that the basis of nineteenth-century methods of studying organic evolution was laid down not by the Naturalists but by the Philosophers—by Bacon, Descartes, Leibniz, Hume, Kant, Lessing, Herder and Schelling—who in their own ways saw clearly an evolution or progressive development in time associated with the problem of mutability of species—or what came to be known as individual variation. Buffon, Erasmus Darwin, Lamarck, Goethe and Saint-Hilaire were also evolutionists before Darwin. Buffon expressed his ideas by means of *l'enchainement des êtres* and Charles Darwin did not consider his work historically "as his opinions fluctuated greatly at different periods, and as he does not enter on the causes or means of the transformation of species". To Darwin, Lamarck was the "first man whose conclusions on the subject excited much attention". In the *Philosophie Zoologique* (1809)—which Haeckel described as "the first connected and thoroughly logical exposition of the theory of descent"—Lamarck affirmed that all species, including man, are descended from other species, but in dealing with plants and animals he wavered in his views. It is odd that Charles Darwin did not take into historical account the *Zoonomia* (1794–86) of his grandfather, but arrived at similar conclusions independently. Erasmus Darwin believed that "all animals undergo perpetual transformations; which are in part produced by their own exertions . . . and many of these acquired forms or propensities are transmitted to their posterity". He clearly believed that modifications arise within the organism as a result of its reaction to the outer conditions of its life, and he asked his readers if it would be too bold to imagine that "all warm-blooded animals have arisen from one living filament".

Lamarck—whom Nordenskiöld regarded as a man of diverse interests, vague thoughts, brilliant ideas and foolish fancies—in 1816 enunciated four laws, which E. S. Russell (1916) has summarised. He affirmed that the living body tends to increase its volume and extend the dimensions of its parts, that a new organism is produced as new need arises and continues, that organs increase the degree of their develop-

ment proportionately to the use which is made of them, and that what the organisation of the individual acquires during its lifetime is preserved in reproduction and transmitted to its descendants. Darwin remarked that in considering the origin of modifications Lamarck "attributed something to the direct action of the physical conditions of life, something to the crossing of already existent forms, and much to use and disuse, that is to the effect of habit". To this last "he seems to attribute all the beautiful adaptations in nature; such as the long neck of the giraffe for browsing on the branches of trees".

Little need be said here about Darwin's life, for much has been written about it. A few points are worthy of mention. In 1831 Darwin sailed in the *Beagle*, a small ship of 238 tons, on a four-year voyage without pay. He worked in some discomfort at one end of the small chart-room, with poor equipment and no compound microscope, observing and recording all he could during what he later regarded as the most important period in his life. After this voyage, he published his *Journal of Researches* (1839, 1845) and spent many years working on biological problems as diverse as the behaviour of earthworms and the structure of cirripedes and of coral reefs. His scientific monographs alone would have brought him fame. In October 1838 he read, "for amusement", the essay by T. R. Malthus (1798) on population, and later wrote: "being well prepared to appreciate the struggle for existence . . . it at once struck me that under these circumstances favourable variations would tend to be preserved and unfavourable ones to be destroyed. The result of this would be the formation of new species."

For five years Darwin elaborated his notes, and then spent two years working out conclusions for a short sketch. For another fourteen years he still worked to the same purpose, the assembly of the evidence on which his doctrine was to rest, still unwilling to publish his findings. Meanwhile, Alfred Russel Wallace, who was stimulated in the same way by Malthus' essay, had arrived at similar conclusions and, by agreement, the two biologists presented their work jointly in a paper to the Linnean Society of London. This was in July 1858; the *Origin* was published in November 1859.

Natural Selection

During the late nineteenth century the theory of organic evolution was amply proven. Every branch of biology produced abundant evidence to show that animals and plants vary in space and in time, and quite

soon there began a search for the evolutionary significance of phenomena encountered in the study of structure, function, development and the past history of organisms. About the way in which organic evolution is brought about there has been and still is much controversy. Darwin took for granted the idea of variation occurring as a natural phenomenon, making no attempt to explain it. " No one supposes," he wrote, " that all individuals of the same species are cast in the same actual mould." He propounded the theory of natural selection, and suggested that it takes effect through the "struggle for existence" in perpetuating advantageous variations and eliminating disadvantageous ones. Wallace was more of a selectionist than Darwin, who regarded natural selection as "the main but not the exclusive means of modification".

C. Zirkle (1941) has stated that the ancient concept of natural selection was used originally to account for the existence of adaptation, not to explain the origin of new species. As an explanation of organic evolution, he pointed out, natural selection involves "a number of subordinate propositions, such as the existence of heritable variations, of population pressure, of a struggle for existence, and the consequent survival of the fit or better adapted". He gave a list of fifteen names of persons who, from Hale (1677) to Spencer (1852), described population pressure; and another list of names of thirteen persons who, from Al-Jahiz (ninth-century) to Spencer (1852), have described the struggle for existence. Several scientists of the eighteenth and nineteenth centuries, he affirms, "almost grasped the full significance of natural selection, but just failed to recognise all of its implications", notably Rousseau (1749), Prichard (1808, 1826), Laurence (1819), Saint-Hilaire (1833), Herbert (1837), Spencer (1852) and Naudin (1852). Darwin came to realise that W. C. Wells (1813) had applied the principle of natural selection to the evolution of man, and that Patrick Matthew (1831) gave "precisely the same view on the origin of species" as Wallace and himself, also seeing clearly "the full force of the principle of natural selection". Shrylock (1947) has suggested that the ideas of Wells were ignored by historians and little known to scientists because presented in a hesitant and half-apologetic manner to a world which was not yet ready for them, and on account of the ease with which they were lost under the elaborate title: *An account of a female of the white race of mankind, part of whose skin resembles that of a negro; with some observations on the causes of the differences in colour and form between the white and negro races of men.*

Ample proof has accumulated that natural selection is operative in

evolution and acts on variations, but the origin of variations is a question which remained open long after the rise of cytology during the nineteenth century, and even after the rise of genetics in the twentieth. Natural selection is now applied to the fundamental agents of inheritance and development, the genes, which are largely responsible for the establishment of the characters of an organism. The most fundamental problems of biology have been and are being tackled by methods inspired by Darwin's work. The publication of the *Origin of Species* brought about a complete reorientation of biology. At first there was violent controversy over the new doctrine of evolution, and this had the effect of bringing various biological matters into public view. The lay public strove to understand evolution, and hosts of writers endeavoured to explain it. This rise in public consciousness of biology which Darwin's work evoked was later maintained and even heightened by momentous discoveries in other fields.

The Study of Animals during the Nineteenth Century

The study of animal structure, like that of plant structure, arose out of systematics and progressed by the discovery of "laws" which rule the diversity of animal life. One of these—the law of economy, or unity, of type—was formulated largely by French and German comparative anatomists led by Cuvier, who taught that the greatest diversity of structure arises in a limited number of animal types in which the relative amounts of structural materials varies. Another, which was clearly recognised by H. Milne-Edwards (1827), is the principle of structural and functional "division of labour" in the constitution of organisms in relation to varying degrees of perfection. The delegation of different functions to various parts of an organism implies the elaboration of organs, structural differentiation following in the wake of functional. Milne-Edwards later (1851) adopted a teleological point of view and asserted that " Nature has gone about her work as we would do ourselves according to the light of our intelligence, if it were given us to produce a similar result" (quoted by E. S. Russell, 1916). The structural differences seen in various animals seem to follow a number of general types—the insect and molluscan, for instance—each perfected in its parts or its entirety and adapted to certain conditions of life. Bronn (1858) was also interested in the problems of animal structure, and he formulated a number of principles of progressive development which lead up to structural diversity (see Russell, *loc. cit.*). He laid stress on the variety of form produced by the

functional response to environment, or adaptation, and he tried to work out the possible connexion between taxonomic groups and adaptational forms on the basis of locomotory movements. But it was not from advances in morphology or taxonomy that the new concept of organic evolution arose, but rather from the study of the organism in its relation to the environment and the study of life in the past, or palaeontology.

In his book *Für Darwin* (1864) Fritz Müller put forward his "nauplius theory", according to which the nauplius, zooea and other crustacean larvae were taken to represent phylogenetic stages in the ancestry of the higher Crustacea. According to Rádl (1930): "Darwin appreciated the originality of Müller's work, and had it translated into English. Haeckel saw even more in Müller's method, and, following it, he evolved his fundamental law of biogenesis." The nauplius theory was soon discarded, though not before Anton Dohrn had added to it the zooea theory, which assumed that the nauplius is the ancestral form of all crustacea, and the zooea the form from which the higher crustaceans arose. By widening the application of the nauplius theory Haeckel developed his general law. In 1869 T. H. Huxley produced his monograph on medusae. The diploblastic nature of such animals was shown to be essentially the same as that of early vertebrate embryos. By the time his book appeared it was known that most marine coelenterates, worms, molluscs and echinoderms pass through a diploblastic stage of development, and on these facts Haeckel built up his Gastrea theory (1874), according to which all metazoan animals are descended from a two-layered form, the gastrula, development being along two main lines: coelenterates remained free-swimming and developed radial symmetry; worms and more highly organised forms developed a creeping mode of life and developed bilaterality.

Another feature of the nineteenth-century work was the quest for transitional forms between the invertebrates and the vertebrates. A. Kowalevsky was the first to suggest vertebrate affinities for the tunicates (sea-squirts and their allies), which von Baer mistakenly regarded as molluscan forms. Kowalevsky compared such animals with Amphioxus, which Pallas discovered in 1774 and regarded as a shell-less mollusc, but which he (in 1864) had shown to have vertebrate affinities. Many zoologists accepted Kowalevsky's suggestions, but not all: Semper regarded worm-like forms as ancestral to the vertebrates, Hubrecht specified nemertines, and Patten forms related to the king-crabs (*Limulus*). Rádl (*loc. cit.*) gave a list of nearly a score of the more

important forms which at one time or another figured as transitional in such Darwinian speculations. See also W. H. Gaskell *et al.* (1910).

The Study of Function

Physiology, the study of function, was established as a distinct science during the early nineteenth century, and one of its greatest exponents was Johannes Müller—"one of those monumental figures that the history of every science brings forth but once" (M. Verworn, 1899). Müller was incited by the idea put forth by his teacher C. A. Rudolphi that "comparative anatomy is the surest support of physiology; without it physiology is scarcely conceivable", and he applied his energies to the founding of an aspect of physiology that is only now beginning to develop, namely comparative physiology. He steadfastly asserted that "physiology can only be comparative", and he published the results of his own investigations in the *Archiv für Anatomie und Physiologie* (founded 1834)—which he edited for many years and which came to be known as Müller's *Archiv*. Existing physiological knowledge was summarised in his *Handbuch der Physiologie des Menschens* (1834–40). Singer (1931) rated him as "among the greatest biologists of all time", and among his pupils were many whose names became famous later—Schwann, Henle, Helmholtz, Du Bois-Reymond, Kölliker and Virchow—men who greatly advanced analytical biology during the next fifty years. Carl Ludwig was also a prominent early physiologist with many now famous pupils—Pflüger, Pavlov and Heidenhain, for instance. Ludwig's "endless fertility in the invention of apparatus" was "shared by many physiologists since his time, down to Keith Lucas in the recent past" (H. T. Pledge, 1939). He was the pioneer of the method of automatic recording of physiological results on smoked paper by means of rotating drums, which lends itself well to the study of voluntary muscle, heart action and nerve physiology, though now largely superseded by much more refined methods. C. Lovatt Evans (1928) has said that the new English physiology "bore the stamp of the men who created it". Histology developed in Britain through Sharpey, muscle-nerve physiology—which for about thirty years "threatened to eclipse all other branches of experimental work"—through J. Burdon-Sanderson (1881). Francis Gotch (1906) described early work on nervous response and chemical co-ordination. During the twentieth century both aspects of physiology have developed by refinement. W. D. Halliburton (1902) described trends in the development of chemical physiology. Chemistry and mathematics became

essential to the physiologist, and the perfection and successful use of physical instruments in experiments, as well as refinement in the accuracy of working out experimental data, has largely been dependent on mathematical physics.

Notable nineteenth-century landmarks in traditional animal physiology—which are too numerous to mention here—have been set down by various recent writers: for instance, A. Castiglioni (1941), D. Guthrie (1946) and K. J. Franklin (1949). In such functional studies of animals emphasis was laid on vertebrate tissues, notably the tissues of the frog and small mammals. The nearness of physiology to medicine produced a strong desire to investigate animals closely related to man, and striking achievements were made in regard to the study of the heart and vascular system, the blood, cerebrospinal liquid and lymph, respiration and metabolism, digestion and the absorption of food, renal function, internal secretion and the action of the nervous system. All such fields now constitute branches of vertebrate physiology which call for specialist treatment. Biochemistry is closely linked with physiology, and it calls for such treatment also, particularly in regard to enzymes, hormones and other substances of a protein nature. Nearly all such work has been directed toward one main end—to understand and interpret various perfected physiological mechanisms. Modern biological progress has often resulted, however, from an application of the cell doctrine to physiology as well as histology, pathology, embryology and other biological disciplines. There are some persons who believe that general physiology is just another name for cell physiology although biochemists often have to deal with groups of cells in making their analyses, because of the additive effect which is then obtained. Physiologists of wider biological outlook also keep in mind the origin of more highly organised forms from simpler organisms, and the newer study of function, comparative physiology, is more concerned with the evolution of physiological mechanism than with the perfected functional mechanisms of any single class of animals or plants. The noteworthy book, *Comparative Animal Physiology* (Editor, C. L. Prosser; 1950), deals with a score of functional topics—such as nutrition; feeding and digestion; nitrogen excretion; respiration and metabolism; photo-, chemo-, phono- and mechano-reception; cilia; amoeboid movement; muscles and electric organs; bioluminescence; chromatophores and colour change; endocrine mechanisms; and nervous systems—and it carries a list of more than 3,500 references to the original literature.

Vitamins

It is well known that disease may be caused in man and animals by a lack of balance in the diet. From the early seventeenth century lemon and orange juices were known to act as curative agents against scurvy, and during the eighteenth century cod-liver oil came into clinical use for the prevention and cure of rickets, a disease which has been prevalent in Britain for many centuries. Not until the late nineteenth century, however, was serious attention given to the so-called deficiency diseases, the impetus coming in 1881 from the discovery by the Russian scientist Lunin that mice soon die when fed on a diet of pure proteins, fats and carbohydrates and require also some natural food such as milk for the sake of the "other and unknown substances essential to life". A few years later (in 1886) the Dutch Government sent a Commission to the Dutch East Indies to investigate the crippling Oriental disease beri-beri, and two precious years were spent in a quest for some micro-organisms which might be the causal agent before a fortunate accident—the feeding of experimental chickens on scraps of food for the sake of economy—led Eijkman and his assistant Grijns to investigate diet. The Dutchmen soon discovered that hens fed on a diet of polished rice develop the disease within a few weeks, but are speedily cured by a diet including the husks removed in the polishing process. By the lack of something contained in the husks of rice-grains birds develop the symptoms of polyneuritis and are unable to fly, walk, or even stand, and in man such a deficiency produces the more dangerous wasting and paralysing disease beri-beri. In the case of rickets, which affected lion cubs in the London Zoological Gardens, Sir John Bland-Sutton discovered that the cure lay in some substance or substances contained in fresh fat.

During the early part of the twentieth century the late (Sir) Frederick Gowland Hopkins was engaged in rearing animals on synthetic diets. As early as 1906 he emphasised that as animals feed on the tissues of other animals and on plants their food must contain countless other substances besides proteins, carbohydrates and fats, and probably highly complex food factors of an essential nature. In 1912 he referred to the essential substances as "accessory factors of the diet" and founded the science of vitamin nutrition. In the same year Casimir Funk invented the name "vitamine" under the impression that all accessory food factors belonged to the same chemical class. When it became evident that the substances are not necessarily amines (nitro-

genous substances mostly derived from amino-acids) the final "e" was dropped. Since that time a number of vitamins have been discovered, purified, crystallised and assigned chemical formulae (see Dawes, 1947). Some of them have been synthesised and, as research proceeds, the number steadily increases. They are still grouped together in spite of chemical differences as a matter of convenience because they are substances that cannot be easily identified. Some of them are soluble in watery liquids, others in fats, and their importance lies first and foremost in their being substances which must be included in the dietary of animals which cannot synthesise them or store them in their bodies. Their absence from the diet produces more profound effects than could be predicted on *a priori* grounds, yet they do not contribute to the energy-content of the diet. Their most vital function seems to be participation as catalysts or coenzymes in the processes of oxidation which take place in the cells of the body, and in some respects they grade almost imperceptibly into the category of hormones. As an example of progress made in the study of vitamins the account of the vitamin B complex by F. A. Robinson (1951) can be consulted.

Endocrines and Hormones

During the eighteenth century a few enlightened biologists were aware that some glands in animals, unlike the salivary, gastric and intestinal glands, are devoid of ducts leading into other internal organs. A. von Haller, in 1745, disproved Galen's belief that the thyroid gland lubricates the pharynx by showing that the gland has no outlet for such a secretion as would achieve this result. In 1766 Haller realised that the thyroid and thymus glands secrete directly into the blood. The loss of such glands was soon found to have a deleterious effect on animals. In 1775 Bordeu saw that castrated males lose the secondary characters associated with maleness, and in 1849 Berthold castrated a cock bird and then transplanted into it the testis of another cock, noting both the loss of the comb and its subsequent restoration. The real significance of testicular secretion into the blood was then evident. Soon afterwards, Thomas Addison (1855) proved that faulty secretion of the adrenal glands produces in man the disease now known by his name. One year later C. E. Brown-Séquard demonstrated that a rabbit cannot live without adrenal glands, and Vulpian noted the different staining reactions of the outer (cortex) and inner (medulla) regions of the glands. About the same time Schiff discovered that thyroid removal invariably produces fatal results.

Anaesthetics were first used by H. Hickman at Ludlow in 1824, and by C. W. Long at Jefferson, Georgia, U.S.A., in 1842 (see D. Guthrie, 1945). After the turn of the nineteenth century their use had improved operative procedure in regard to both man and animals, and the study of "ductless glands" was intensified. Claude Bernard (1859), investigating the glucogenic function of the liver, invented the term "internal secretion" to denote the direct passage of glandular secretions into the blood stream. That such secretions may act as "chemical messengers" in the sense of producing effects in distant tissues, much as "messages" are transmitted by the nervous system, was known to Brown-Séquard and d'Arsonval (1891), who introduced this term. Following up Langerhans' discovery in 1869 of "islets" of special tissue in the pancreas of animals, J. von Mering and O. Minkovski (1889) excised the gland and produced experimentally the condition of diabetes, becoming satisfied (1893) that the "islets of Langerhans" produce a secretion of their own. The active principle of this secretion was called insulin by Sir E. Sharpey Schafer in 1913 and was isolated by F. G. Banting and C. H. Best in 1921.

The thyroid came into focus again in 1871 when Fagge associated cretinism with atrophy or loss of this gland. In 1874 Gull described the condition called Gull's disease (now known as myxoedema), which he regarded as an adult form of cretinism, and in 1886 Horsley removed the gland from monkeys and induced conditions similar to both cretinism and myxoedema. In 1895 A. Magnus-Levy demonstrated a lowered metabolism in animals having a deficient thyroid secretion, and also the restoration of the normal rate by administration of dried gland. J. F. Gudernatsch (1912, 1917) excised the thyroid gland of tadpoles, which then failed to metamorphose into frogs but could be induced to do so by feeding them with the gland. W. W. Swingle (1919) first showed that the absence and presence of inorganic iodine produced the same effects. Murray in 1891 administered a glycerine extract of sheep's thyroid orally for the relief of myxoedema, and not long afterwards (1899) A. Oswald proved that the active iodine-constituent is attached to protein, forming the substance thyroglobulin. During the twentieth century progress was continued. On Christmas Day 1914 E. C. Kendall isolated and named the active principle thyroxine, and in 1927 C. R. Harington and G. Barger synthesised it and established its chemical formula. It is now known that the normal human thyroid holds about 2 mg. thyroxine per gm. of dried tissue, making the average total store 10–15 mg. According to D. Marine (1922) a condition of

deficiency arises when the content of thyroxine falls below 1 mg. per gm. of dried tissue (see C. H. Best and N. B. Taylor, 1945).

TABLE 2.—THE HORMONES OF ANIMALS

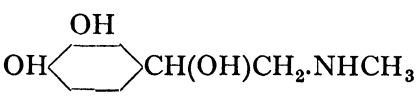
Hormone	*Source*	*Effect produced on*
Gastrin	lining of stomach	secretion of gastric juice
Secretin	lining of duodenum	secretion of pancreatic juice
Cholecystokinin	lining of duodenum	control of gall-bladder
Thyroxine	thyroid gland	general metabolism
Parathyrin	parathyroid glands	calcium metabolism
Insulin	pancreas (Islets of L.)	glucose metabolism
Kallikrein	pancreas	blood vessels (vaso-dilation)
Acetylcholine	spleen	blood vessels (vaso-dilation)
Cortin	adrenals (cortex)	metabolism
Corticosterone	adrenals (cortex)	control of sodium
Andrenosterone	adrenals (cortex)	reproduction in the male
Adrenaline	adrenals (medulla)	nervous system: sugar metabolism
Testerosterone	testes	reproduction in the male
Ande osterone	testes	reproduction in the male
Oestradiol	ovary	reproduction in the female
Oestrone	ovary	ditto (oestrus cycle)
Oestriol	ovary and placenta	ditto (oestrus cycle)
Progesterone	ovary (corpus luteum)	ditto (womb and placenta)
Phyone	pituitary (anterior lobe)	general (skeletal) growth
Prolan A (FSH)	pituitary (anterior lobe)	menstrual cycle; pregnancy
Prolan B (LH)	pituitary (anterior lobe)	growth of corpus luteum (ovary)
Prolactin	pituitary (anterior lobe)	growth of milk (mammary) glands
Thyrotropic pr.	pituitary (anterior lobe)	growth of thyroid gland
Adrenotropic pr.	pituitary (anterior lobe)	function of adrenal glands
Pancreotropic pr.	pituitary (anterior lobe)	secretion of insulin
Metabolic pr.	pituitary (anterior lobe)	metabolism
Ketogenic pr.	pituitary (anterior lobe)	carbohydrate metabolism
Glycotropic pr.	pituitary (anterior lobe)	carbohydrate metabolism
Anti-diuretin	pituitary (posterior lobe)	urine formation
Oxytocin	pituitary (posterior lobe)	control of unstriped muscles
Vaso-pressin	pituitary (posterior lobe)	blood vessels (vaso-dilation)
Chromotropic factor	pituitary (posterior lobe)	pigmentation of frogs, fishes, etc.

The concept of chemical co-ordination of function was studied by W. M. Bayliss and E. H. Starling (1904), in whose laboratory the name

"hormone" was invented by W. B. Hardy. They were interested particularly in the way in which the pancreas is stimulated to liberate its digestive secretion, and although I. Pavlov in 1897 had suggested a nervous mechanism they soon came to realise that the chemical agent concerned was the substance "secretin", which they had found previously (1902) in extracts of the lining of the intestines. It became clear that secretin passes from the intestinal mucosa to the pancreas by a roundabout route through the blood stream, what is now a classical example of purely hormonal co-ordination of function. H. H. Dale and P. P. Laidlaw (1912) prepared very active solutions of this hormone, and in 1933 the isolation of almost pure crystals was reported. Bayliss has remarked (1927) that after the action of secretin had been demonstrated, the identification of hormones became "the ambition of a new generation". One of the first pieces of research after his own was that of J. S. Edkins (1906), who studied the substance which regulates the flow of gastric juice, her results being confirmed by Baron E. Maydell (1913). R. W. Keeton and F. C. Koch (1915) proved that this effect is brought about by the action of the hormone gastrin.

The distinction between nervous and hormonal co-ordination of function and the possible evolutionary connexion between them has been best observed in the case of the adrenal glands. The first attempts to define the properties of the active principle adrenaline were made by G. Oliver and E. A. Schafer (1895), who injected extracts of the gland into animals which then showed a considerable rise of blood pressure. F. M. Balfour (1878) had observed that the internal region of the gland (the medulla), which is the part that yields adrenaline, has the same origin as the "sympathetic" nervous system, and Alfred Kohn (1902, 1903) showed that the cells of the medulla arise from cells associated with the sympathetic system along the main axis of the body. Rudiments remain in various locations—along the aorta and in the carotid gland, for instance—but each mass of a pair forms a ganglion, which is the precursor of the medulla, and the scattered remains, paraganglia. Because they stain brownish with potassium dichromate the cells of the medulla came to be called "chromaffine" tissue, which was soon demonstrated in all vertebrates. J. F. Gaskell (1914, 1919) then suggested that the chromaffine cells are the common ancestors of both the cells of the medulla and those of the sympathetic nervous system. Their presence is correlated with the existence of a contractile blood circulatory system, so that their probable function soon came to be regarded as the regulation of contractility. Some years previously,

Takamine (1901) had isolated adrenaline and determined its chemical formula,



Of two possible isomers of this methyl-amino derivative of pyrocatechol only the *l*-form exists in the adrenal glands. Adrenaline—which has been known also as epinephrine, adrenin, suprarenin, etc.—was synthesised in 1904 by F. Stolz, and in 1905 by H. D. Dakin. It is only one of many substances formed by the cortex of the adrenal glands, which yields about twenty crystalline steroids (see C. H. Best and N. B. Taylor, 1945). The most complex endocrine gland, however, is the pituitary, which twentieth-century research has shown to be a kind of "master gland", for it exercises control over the thyroid gland, the sex glands and the adrenals. We shall reserve our consideration of this relationship for a later chapter, mentioning here only the discovery of hormone-inhibitory substances which also circulate in the blood. This idea was first expressed by P. J. Möbius (1906), who found that the blood of a sheep which has suffered operative removal of the thyroid gland can neutralise the action of the thyroid hormone. The first person to use an hormonal preparation as an antigen (see p. 330) and induce the production by the animal of hormone-neutralising substance was F. Blum (1932), who called the latter "catechin" (see J. B. Collip, H. Selye and D. L. Thomson, 1940).

Plant Hormones

The twentieth-century discovery of hormones in plants was the outcome of the observations made by A. P. de Candolle (1832) that the movements of the stem and leaves in response to light produce differential growth effects on their opposite sides. T. Swarbrick (1948) has outlined subsequent developments. Darwin (1881) also noted the bending over of seedlings towards a lateral source of light and he believed that the transmission of some "influence" from one part to another could bring this about. What that influence is was not discovered for thirty years (by which time research on animal hormones was in full swing), when P. Boysen-Jensen (1911) cut off the tips of growing barley seedlings and replaced them with intervening films of various kinds set between the cut surfaces. A thin film of gelatine permitted the passage of some substance from the growing tip to the

region of curvature; an impervious film prevented its passage. Some years previously, in 1904, L. Errera showed that the apical buds of young pines form secretions of some sort which, so long as the apical bud is intact, prevent upward growth of lateral shoots. And a few years afterwards, in 1917, J. Loeb advanced his theory of root- and stem-forming hormones in *Bryophyllum.* Many biologists have, in recent years, attacked a number of related problems (see F. A. Went and K. V. Thimann, 1937). Stalk (1921) adopted the method of impregnating agar blocks with hormones, and Went (1927–28) developed this technique. In 1934 Thimann extracted such substances from plants, and in 1936 Laibach applied them in the form of pastes. At Utrecht, Kögl (1931–35) extracted minute quantities of growth-promoting substances of this kind from the urine of man and animals, calling them *auxins*, which were later identified as auxin *a* and auxin *b*. Another form discovered in yeasts was called heterauxin, and found to be identical with indolylacetic acid. During the past decade a number of chemical substances have been found to have growth-promoting properties in regard to plants, notably phenyl-acetic acid and *a*-naphthalene-acetic acid, which soon came to have various uses in horticulture. They seem to be formed in the regions of most rapid growth and to be carried away to remote regions, where they induce enlargement of cells rather than cell multiplication.

Cytochrome

A notable contribution to biology was made by C. A. MacMunn (1884–86), who studied with a microspectroscope the absorption spectra of the tissues of animals killed by bleeding. He discovered absorption bands due to substances chemically related to the non-protein part of haemoglobins, *i.e.* haematins, which he called myohaematin and histo-haematin. His work was criticised by some physiologists who believed these substances to be merely decomposition products of the pigment, but such critics were silenced by his affirmation that the spectra were distinctive and could be obtained with substances from the tissues of insects which do not have haemoglobin. Nevertheless, his work was completely neglected until 1925, when D. Keilin described similar spectra obtained with extracts of the tissues of many aerobic animals and attributed them to a substance which he called *cytochrome.* The spectra contained four absorption bands, strictly representing three distinct haemochromogens each of which has two of them, one of the bands being triple. Cytochrome was soon demonstrated in baker's

yeast, many mammalian tissues (but not nerve), insect tissues, aerobic bacteria and other organisms, and it soon came to be regarded as an essential component of all aerobic cells. In nitrogen the bands are clearly visible, but in air or oxygen they quickly disappear. In the spectra of muscles of living insects the bands appear when the insect struggles, even when in air, and when its struggles cease the bands at once disappear. Thus it became evident to Keilin that cytochrome can exist in "reduced" and "oxidised" forms, and that it is essentially an oxygen-carrier. Like other haemochromogens, however, cytochrome is not spontaneously oxidised and it will not combine with oxygen in watery solutions. Neither is it capable of forming loose compounds with oxygen as haemoglobin does. For oxidation some catalyst is required, an enzyme of a specific kind such as cytochrome oxidase (see p. 208).

The Rise of Genetics

During the twentieth century the study of heredity has been transformed into the modern science of genetics. Fifty years ago, in J. S. Huxley's words (1949), it was "just a series of speculations weighed down by superstition and leavened by a few tentatives of scientific study. Yet to-day it is rapidly becoming recognised as the most central and fundamental of all the life-sciences". The story of the rise of genetics is now traditional. In 1900 three botanists—Hugo de Vries in Holland, Carl Correns in Germany, and Erich Tschermak in Austria—independently discovered certain principles of heredity only to find that these had been discovered already by an Austro-Silesian monk named Gregor Johann Mendel. The more important of two papers which Mendel published, *Versuche über Pflanzenhybriden*, was printed in the *Transactions of the Natural History Society of Brünn*, in Bohemia (Czechoslovakia), in 1877, and reprinted in 1910. It was reprinted also in several other journals and, with modifications, in W. Bateson's book *Mendel's Principles of Heredity* (1909), but till 1900 the paper was either ignored, overlooked, or unappreciated. Several of Mendel's contemporaries knew about his work, but did not mention it or mentioned it only in a deprecating fashion in their own writings. R. A. Fisher (1936) has remarked that the paper was not difficult to understand, and the journal in which it appeared was not obscure. Few persons would perhaps have realised its significance at the time of publication but "some there certainly were; and had the new facts and methods come to the knowledge of Francis Galton, the experimental

analysis might well have been established twenty-five years earlier than it in fact was". "Each generation, perhaps, found in Mendel's paper only what it expected to find; in the first period a repetition of the hybridisation results commonly reported, in the second a discovery in inheritance supposedly difficult to reconcile with continuous evolution. Each generation, therefore, ignored what did not confirm its own expectations. Only a succession of publications, the progressive building up of a *corpus* of scientific work, and the continuous iteration of all new opinions seem sufficient to bring a new discovery into general recognition" (Fisher, *loc. cit.*).

About 1857, possibly earlier, Mendel began to cross (hybridise) edible peas (*Pisum sativum*), plants which are easy to pollinate and to protect from foreign pollen. He noted the points of resemblance and difference between certain varieties, and convinced himself of the constancy of several pairs of characters—the round or wrinkled shape of the ripe seeds, their yellow or green colour and that of the seed-pods, and the tallness or dwarfness of the plants, for instance—and then studied them through several generations of the hybrids. He did not merely note the development of the characters, or their failure to appear, in the hybrids, but determined the *frequency* of their appearance in the progeny resulting from various crosses. His counts put the phenomena of the inheritance for the first time on a numerical basis, and the new principles which he eventually revealed became known as Mendel's Laws.

Some of the details of Mendel's experiments are obscure, and Fisher (1936) attempted to reconstruct them. In 1858 Mendel made several crosses, notably for the seed characters: round × wrinkled and yellow × green. From the first of these crosses he obtained enough seeds to raise 253 plants in 1859; from the latter cross enough to raise 258 plants. All these seeds would have been round and yellow, characters which were shown to be dominant to wrinkledness and green colour. In 1859 the 253 plants raised from the seeds resulting from the round × wrinkled cross produced 7,324 seeds, of which 5,474 were round and 1,850 wrinkled. The 258 plants raised from the seeds resulting from the yellow × green cross produced 8,023 seeds, of which 6,022 were yellow and 2,001 green. In each case, it will be noted, the ratio for each pair of contrasting characters was roughly 3 : 1. In the following year self-pollination of the plants raised from the yellow seeds produced again the 3 : 1 ratio, showing that the genetical ratio obtained is 1 : 2 : 1; one-quarter of the yellow seeds contain only the factor for yellowness,

one-half of them are hybrids showing only the dominant character, and all the green seeds contain only the factor for greenness. With Mendel's later experiments we need have no concern at this point. Suffice it to say, in the words of J. S. Huxley (1949), that "Mendel's most fundamental discovery, on which indeed the whole of modern genetics rests, was that the basis of heredity consists of material units in the reproductive cells; that these units are self-perpetuating and self-reproducing and do not blend or get diluted when crossed; and that they can be recombined to give new and true-breeding combinations". These units, E. B. Wilson (1925) wrote, "are like cards in a pack, which may be shuffled and redistributed in continually new combinations, without in the least losing their individual characters. All this, evidently, suggests that the units of heredity are dependent upon separate material bodies or substances that undergo corresponding combinations, dissociations and recombinations".

T. H. Morgan (1932) remarked that Mendel's work was "not entirely heaven-born". Many biologists before Mendel were interested in hybridisation. Alexander Seton (1822), John Goss (1822), Thomas Knight (1823), Naudin (1861–65) and Thomas Laxton (1868–72) also experimented with peas, and Naudin noted the "segregation" of "two specific essences" in the second generation of hybrids, suggesting that these are handed on from the hybrid parent plants in the ovules and pollen. He did not make back-crosses in order to test his hypothesis, however, and he did not express his results numerically, two drawbacks which make his work fall far short of Mendel's. Hybridisation was of interest also to zoologists, and Darwin (1868) summarised what was known about it. Galton turned to the study of heredity in 1863. He also experimented with such characters as the weight and sizes of the seeds in peas, and also with stature, eye-colour and proneness to disease in man. He was the first to demonstrate "particulate" inheritance in animals, and he showed that some characters originate in one parent and some in the other. He also upheld the idea of "alternative" inheritance, supposing that the individual might inherit most of his characters from one parent, and he recognised in regard to skin colour the "blending" type of inheritance. His great merits were attempts to systematise conflicting observations on heredity and variation and the formulation of the so-called law of ancestral inheritance, according to which the two parents contribute jointly one-half of the inheritance, the other half being derived from the grandparents (one-quarter), great grandparents (one-eighth), great-great-grandparents (one-sixteenth)

and so on to previous progenitors, the sum of the entire series adding up to unity, the whole inheritance (Fig. 15).

Mendelism and Cytology

Zoologists made their influence felt in the field of cytological genetics by their studies of the behaviour of the chromosomes in cell division, during both the period of maturation of the germ cells and at the time of fertilisation. The full recognition of Mendel's genius came with the microscopical observations of A. Kölliker, W. Flemming, H. Fol, E. van Beneden, Oscar Hertwig and T. Boveri on animal cells, and W. Hofmeister, E. Strasburger, H. A. de Bary and others on plant cells. By about 1860 it was known that the union of sperm and ovum (syngamy) inaugurates the formation of a new individual, but not till Oscar Hertwig watched the sperm nucleus pass through the translucent cytoplasm of the sea-urchin egg and realised that it would unite with the ovum nucleus was it clear that biparental reproduction calls for the fusion of just one sperm nucleus with the ovum nucleus. In 1879 Hermann Fol was fortunate enough to be the first to witness the penetration. By 1885 E. Strasburger and others had studied the behaviour of the chromosomes during cell division and it was becoming evident that heredity rests on the basis of the cell nucleus. In that year A. Weismann produced his book in the "germ-plasm". Up till this time Lamarck's view had been upheld, namely that modifications acquired by an organism during its lifetime are transmissible to the offspring. Weismann's theory of the segregation of the germ-plasm caused biologists to revise their ideas on the inheritance of parts developed or modified through use and disuse. Ten years later Bateson showed that if small variations can be handed on to the offspring there still remains the problem of the origin of discontinuity seen in existing species of animals and plants. Soon afterwards H. de Vries put forward his mutation theory, recognising three types of change: *progressive*, meaning the introduction of something new; *retrogressive*, or the loss of something; and *degressive*, or the reviving of old characters. To his credit goes not this classification but the stressing of sharply marked germinal changes which appear suddenly, for this brought important consequences in the study of heredity.

In the early part of the twentieth century advances in genetics were rapid and the parallelism between the behaviour of the chromosomes at meiosis and Mendelian segregation was soon determined (see A. H. Sturtevant and G. W. Beadle, 1940). The full significance of this was

later established in America by T. H. Morgan and his school who, by means of experiments, localised the heritable units, or genes, in the chromosomes. The chance discovery of C. E. McClung in 1902 and N. M. Stevens in 1905, and E. B. Wilson, T. H. Morgan and others later on, of X-chromosomes was the beginning of our knowledge of sex determination. Linkage was discovered in 1906 by W. Bateson and R. C. Punnett working with sweet-peas, and in the same year R. H. Lock showed that linkage is attributable to genes situated in a single chromosome pair, crossing-over to the exchange of materials between the members of such a pair. When it was argued that some organisms possess more pairs of genes than pairs of chromosomes Spillman insisted that this did not militate against the idea of segregation unless the number of genes segregating independently was in excess of the number of segregating characters. F. A. Janssens then took up the study of chiasmata and in 1909 the study of crossing-over began.

Other discoveries too numerous to mention here further advanced the study of genetics during the early part of the twentieth century. Most notable was the discovery by Woodworth and by W. E. Castle in 1901 of a most suitable subject for work on the phenomena of inheritance, namely the fruit-fly *Drosophila melanogaster*, which has a life-cycle of short duration (about ten days) and only four chromosomes. For a number of years various biologists experimented with this animal, inbreeding it and studying the effect of selection on it, and in 1910 T. H. Morgan announced the discovery of several mutant types, one of them sex-linked. The laboratory of Columbia University soon came to have a large collection of other mutants. For an account of what has been achieved with this remarkable insect see W. P. Spencer (1947). In 1910 came Morgan's general theory of linkage, which is due to the combination in the gametes of pairs of genes, and the discovery that the strength of linkage is in inverse ratio to the possible occurrence of crossing-over, which is the interchange of corresponding sections of the chromatids of a chromosome pair. In 1913 A. H. Sturtevant constructed the first chromosome map—a diagrammatic representation of the arrangement of genes in a chromosome. In 1916 C. B. Bridges showed that crossing-over occurs in the tetrad stage of meiosis in *Drosophila.*

Other important discoveries were the production of mutations by means of X-rays, which opened up a vast field of research (see D. G. Catcheside, 1948), the discovery in 1933 by E. Heitz and H. Baur of giant chromosomes in the salivary gland cells of insects and their

demonstration in such cells in *Drosophila* by T. Painter later on. Most notable was the discovery in 1934 by E. Anderson of multiple chromosomes and the phenomenon of polyploidy in plants. This, together with the discovery in 1937 of the effect of the alkaloid colchicine by A. F. Blakeslee and A. G. Avery, has meant that by comparatively simple experimental procedure (the application of a dilute solution of colchicine and other substances since discovered to parts of plants, *e.g.* seeds, roots) the doubling of chromosomes can be achieved and entirely new species of plants brought into existence. Wheats exist as diploids with 14 chromosomes, tetrapoids with 28 and hexaploids with 42 chromosomes. Hybridisation has played a part in producing bread-wheats by crossing diploid and tetrapoid forms. By recently developed methods of multiplying the chromosomes the biologist is able to do in a very short space of time what nature takes ages to produce.

New Light on Evolution

The late nineteenth-century reaction against Darwinism was attributed by J. S. Huxley (1942) partly to neglect by zoologists, who were attracted by the prospects in comparative morphology and embryology, but largely to W. Bateson's work (1894) on discontinuous variations, which did not harmonise with Darwin's concept of small continuous variations. Darwinism became more and more theoretical at the beginning of what J. S. Huxley called "the period of the mutation theory". According to the new theory the raw materials of evolution consisted of substantial germinal changes, or mutations, which made the rôle of natural selection seem insignificant. The theory was largely the work of H. de Vries (1901, 1905) with the evening primrose (*Oenothera*), but T. H. Morgan and others contributed to it. The early form of Mendelism concerned well-marked and widely different characters, and it appeared to be supported by the concept of discontinuous variations, though not by that of apparently non-inheritable continuous variations. The rise of biometry, and its rapid development in the hands of Karl Pearson, Weldon and others, marked a new period in the advance of evolution theories. Mathematics could now be applied to the problems of evolution. But the biometricians and the Mendelians came into an early conflict. This was described by Punnett at the one-hundredth meeting of the Genetical Society of Great Britain in a concise statement of developments between 1900 and 1906 (see G. Pontecorvo, 1949). Huxley considered that both sides were to blame: the biometricians for applying themselves to hypothetical

modes of inheritance and genetic variation; the Mendelians for refusing to believe that continuous variation could have a genetical basis. The result of this conflict was a serious decline in Darwinism by 1914. The discoveries of the Mendelians seemed to clash with the facts of palaeontology, mutation theories did not agree with the idea of adaptation, and newly disclosed facts in experimental embryology ran counter to the classical conception of recapitulation. But further advances in various departments of biology quickly removed the opinion that Darwinism was becoming old-fashioned. Mendel's laws were found to apply to unicellular as well as multicellular animals and the developments in cytogenetics, experimental embryology and ecology revealed new ways of tackling evolutionary problems. Quarrels were resolved and all branches of biology acquired an evolutionary outlook. The unification of biology during the past thirty years has revived Darwinism in a new form.

Micromerism

The success of the atomic theory in physics and chemistry set many biologists in quest of atomic explanations of biological phenomena. For that brand of "atomism" which has been applied to living things Y. Delage in 1903 invented the term "micromerism". He discussed the theories which arose during the nineteenth century, and S. J. Holmes (1948) has reviewed the subject from the modern standpoint. The first ideas of this kind date back to the early Greeks, who believed that materials drawn from various organs of an animal's body may be assembled in the generative products and used to form corresponding parts of a new organism. Similar views were upheld by John Ray in 1692, Maupertius in 1744 and Erasmus Darwin in 1796. During the nineteenth century Charles Darwin (1868) put forward an independent theory of pangenesis, according to which the cells of the body give off minute particles ("gemmules") which multiply when nourished and assemble in the germ-cells, ultimately to develop in the new organism into cells like those from which they were derived. Brooks (1883) elaborated this theory, suggesting that the male animal stores up in its sperms particles that tend to perpetuate novel characters of a progressive kind, and the female animal, which has no such capacity, transmits the characters thus gained from the male.

According to Delage, Herbert Spencer (1864) was the first person to conceive of minute vital particles, which he called "physiological units", intermediate between chemical molecules and living cells.

According to Holmes, a somewhat similar idea was upheld in 1864 by Brücke, who believed that cells consist of vital units, just as a multicellular organism consists of cells. Spencer's "physiological units" were credited with a polarity which made possible the building up of organic form as snow crystals build up snowflakes, and they were used in conjunction with the then unchallenged theories of Lamarck to explain the phenomena of development, regeneration, variation, hybrid vigour and the transmission of acquired characters. W. Haacke (1893) put to similar use a theory of units having a rhombic form and a protein nature ("gemmes") and their aggregation into larger bodies ("gemmaires") of characteristic form for each species of organism. C. Nägeli (1884) had already suggested that particulate crystalline albuminoids ("micelle") join to form filaments and networks of what he called "idioplasm" and, although some of his ideas were soon discarded, the concept of micelles has persisted in modern conceptions of protoplasm.

Most theories of micromerism take into account the possible multiplication of unit particles. The plastidule hypothesis of L. Elsberg (1877) and E. Haeckel (1877) assumed, however, that the nutrient medium of the cell is transformed by such particles so as to form new units. Other theories attributed to the particles a life of their own, such as bacteria possess. Improvements in cytological technique led to the idea that the nucleus is the location in which "idioplasm" is formed. J. Loeb, H. Driesch and others supposed that the nucleus liberates enzymes into the cytoplasm of the cell, setting up various vital reactions there. H. de Vries (1889) supposed that various kinds of particles ("pangenes") pass into the cytoplasm, which in consequence becomes modified in various ways. A. Weismann (1904) assumed that the germ-plasm of animals possesses numerous parts, each of which stands in a particular relation to certain cells or groups of cells in the organism, determining the production of particular parts of it during development. Weismann's theory of "determinants" has helped to clarify some of the facts of heredity and variation. In its advanced form it assumed various *orders* of units: "biophores" were the simplest type of unit, and these were regarded as compounded into groups known as "ids" and rows of groups known as "idants" to make up the complex structure of a chromosome. A "biophore" was regarded as the determinant of a particular part of the organism, and development was considered to be a process of parcelling out of determinants. The coming of experimental embryology brought about the fall of this theory.

During the twentieth century the concept of micromerism has developed along with advances in cytogenetics. Mendel's discoveries threw an emphasis on unit characters and showed how these could be combined in reproduction and then segregated according to the laws of chance. The concept of the "gene" was soon reached. Hundreds and possibly thousands of genes are arranged serially along the length of a chromosome, and they are duplicated at each mitosis. Mutations came to be regarded as the result of modification of such invisible particles, which were known only by the positions (*loci*) they occupy in the chromosomes. The conception of genic interaction then arose, and finally the more difficult question as to the nature of the gene and its relationship to the smallest known living thing, the virus particle. Before the coming of Mendelism most biologists were antipathetic towards the idea of vital units; afterwards, it was not enough to follow the physiologist and dispense with any units of a higher order than chemical molecules. The existence of plastids of various sorts was an encouragement to the micromerist, and the gene became almost "an article of faith". Differences of opinion still persisted, however. Goldschmidt did not regard genes as "bodies", and produced evidence that gene mutation may result from chromosome breakage and the reunion of parts of a chromosome which implied unusual contacts. Such "position" effects are the results of new linear arrangements of genes in chromosomes and not the chemical alteration of genic substance. R. Goldschmidt also put forward the view that the chromosome may be regarded as a giant protein molecule—a long chain of polypeptides bearing numerous radicles—and a mutation as any change in the spatial relationship of its integral parts. In such a concept the gene appears to be a radicle or side-chain of that molecule. It has been suggested that the antagonism between the micromerists and their opponents may disappear when more is known about the composition of protoplasmic units which lie at the root of living phenomena. Advances in knowledge bring increasing difficulty in distinguishing between the living units or genes and the molecules of autocatalytic enzymes of the living cell. Micromerism may have a wider application in the future than it has had so far in physiology and pathology and the micromorphology of the cell, where it has been largely restricted to phenomena associated with reproduction. It may well turn out that some form of micromerism will be necessary to explain all the phenomena exhibited by the living cell.

CHAPTER FOUR

PROTOPLASM AND CELL

THE name protoplasm denotes the living substance of animals and plants, most of which possess non-living parts as well, generally protoplasmic derivatives which serve for protection and support of the living substance. If this name falsely suggests uniformity of chemical composition, it also indicates the existence of a common *kind* of substance, and this generally takes the form of cells. Cells vary considerably in shape, size and function, both in different organisms and in different parts of the same organism, but their analysis is the usual way of studying protoplasm. For very many years this was done by means of crude staining methods, but nowadays all the resources of biology and many of those of chemistry and physics have been brought to bear on the problems of cell structure and function. The main constituents and components of cells were revealed by the comparatively simple methods of the nineteenth century, so that Leydig (1857) and Max Schultze (1861) were able to define the cell as nucleated protoplasm. E. Strasburger (1882) distinguished between the nucleus and the surrounding protoplasm and for these used the terms nucleoplasm and cytoplasm respectively. Each region has its own bounding membrane, so that we have to note both nuclear and plasma membranes, and these are concerned with exchanges of energy effected between the various parts of the cell and the environment in which it lives. The nucleus is the regulator of cell life and, when alive, it shows little optical structure, but the "fixed" nucleus contains a deeply staining substance which W. Flemming (1879) called "chromatin". This at times is clearly arranged in the threads that Waldeyer (1888) called "chromosomes", and these display characteristically complex behaviour when the cell divides in reproduction and are the bearers of the inheritance. The cytoplasm is optically fairly homogeneous, but it has inclusions of various sorts which may be granules or droplets of foodstuffs, or may be integral parts of cell machinery.

Protoplasmic Viscosity

Living protoplasm was soon found to have some of the properties of a liquid, though not a Newtonian liquid, and chemical analyses have

revealed that it may be nine-tenths water. Early students of the cell such as M. J. Schleiden and Hugo von Mohl may have suspected as much when they considered protoplasm to be a "slime", but E. Brücke (1861) suggested that vital phenomena require a substratum having a definite organisation which would not be compatible with liquid structure. The flowing movements of an amoeba and the streaming of granules (cyclosis) in some plants also suggest liquidity, and other considerations may also be made. Robert Brown (1828) discovered the oscillatory movements of fine particles which go by the name Brownian movement, which is mathematically impossible in solids. W. Kühne (1864) observed that an electrically stimulated amoeba rounds itself off and becomes spherical like a droplet of liquid. A. Lister (1888) showed that the slime fungus *Badhamia* can be filtered of its usual complement of dark brown spores by inducing it to creep through wet cotton wool. As Sir W. M. Bayliss stated (1927, p. 6*a*): "It is difficult to understand how a substance other than a liquid could be separated up into fine threads, which immediately run together again to form a mass like the original one."

Many early biologists regarded protoplasm as a viscous fluid, but to such as are interested in the mechanics of the cell it is important to have some measure of protoplasmic viscosity, not merely in different parts of the same cell at any time, but also in the parts of various cells during different phases of cell life. Viscosity, which is the inverse of fluidity, has been defined roughly (L. V. Heilbrunn, 1943, p. 62) as "the force which tends to hold the particles of a substance together when a shearing force acting on the substance tends to pull it apart". Of a number of liquids, the more viscous will tend to flow more sluggishly than the less viscous. One unit of viscosity is the *poise*, and the viscosity of water at ordinary temperatures is about one-hundredth of this unit, *i.e.* one centipoise. Protoplasmic viscosity cannot be determined by ordinary methods, in which the rate of flow of the liquid through a tube is observed. But various other methods have been found applicable, though none is really satisfactory. Whatever the method, it is necessary to discriminate between hyaline and granular protoplasm, and some exceptionally high viscosity values determined have been due to numerous inclusions, or, in the case of Protozoa, to special fibrillar organs.

Many early biologists (see F. Reinke, 1895) used the method of gently crushing a cell and measuring under the microscope the rate at which the protoplasm flows out into the surrounding medium.

Much depends here on the nature of the ions in the external medium. By the method of microdissection C. L. Kite (1913) determined the degree of resistance to the passage of a needle through the cytoplasm. W. Seifriz (1920), who first gave clear ideas on the relative viscosities of different parts of a cell, introduced a series of ten "viscosity values" corresponding to percentage solutions of gelatine, and he compared these with the viscosity of well-known substances. Studying amoebae Seifriz found the ectoplasm (superficial cytoplasm) to be about as viscous as bread dough (8 in his scale), the endoplasm (deeper cytoplasm) to be slightly less viscous than paraffin oil (4 in the scale) and the nucleus to be very liquid (2–3 in the scale). A. L. Heilbronn (1914) used the "falling sphere" method and, studying the cells of a bean-plant, determined the rate at which starch-grains fall through the cytoplasm, noting that it was eight times slower than in water, but might sometimes be slower. According to Stokes' Law the rate varies inversely with the viscosity. Substituting a centrifugal force for gravity, and observing the rates of movements of granules in the cytoplasm, L. V. Heilbrunn (1926) determined the viscosity of the protoplasm of sea-urchin eggs. J. E. Harris (1935) used the Einstein equation for Brownian movement in determining viscosity in the egg of the worm *Sabellaria* and checked his results against those obtained by centrifuge methods, finding a value of 20 centipoises. Heilbronn (1922) inserted minute iron rods into the cytoplasm of slime fungi, and compared the rotation by means of electro-magnets with that obtained when the rodlets were twisted in various liquids.

The improvements made in microscopy and in histological and cytological technique from 1870 onwards gave a tremendous impetus to the study of protoplasm and the cell, and biologists filled in the intervals between their study of cells and tissues under the microscope with speculations about the nature of protoplasm. These early theories have been thoroughly reviewed by many writers, notably by Y. Delage (1895) and E. B. Wilson (1925), but they can be mentioned briefly. The first person to realise that apparently homogeneous protoplasm may have an invisible structure was O. Bütschli (1892). According to the granular theory of R. Altmann (1893), cytoplasm consists of innumerable minute granules set in a semi-fluid matrix. To such granules J. von Hanstein (1882) gave the name "microsomes", which is still used in cytology, but with different implications. The chief objection to Altmann's theory is that his "granules" were not specific structures about which a definite physiological inquiry could be made, but a

hotch-potch of cell inclusion of various kinds. Fibrillar theories served no better purpose. According to W. Flemming (1882) the fundamental structure of protoplasm is a tangle of minute fibrils lying in a fluid matrix (the filar theory), but he came to admit (1897) that it may have other types of structure. Fibrils indubitably exist in certain cells, but the microfibrillae of Flemming were probably mitochondria and other bodies. C. Frommann (1875), the first to advance a definite theory of protoplasmic structure, visualised a network of fibrils, the basis of the reticular theory of E. Klein, E. van Beneden, J. B. Carnoy and J. Heitzmann. According to the alveolar theory of Butschli (1894), protoplasm has a foam- or froth-like structure, such as might be produced by the crowding together of minute droplets about 0·1 μ diameter dispersed in a continuous fluid. Bütschli made artificial emulsions which showed a similar structure, and his theory fits fairly well the appearance of protoplasm in the eggs of echinoderms, but not those of vertebrates.

A great blow was struck at all such theories by W. B. Hardy and A. Fischer independently in 1899, for it was shown that when albumen is fixed in various ways (by the use of corrosive sublimate, formalin, etc.) it may show all the various kinds of structure indicated by them. Biologists have come to realise that protoplasm is not an ordinary liquid, neither is it physicochemically homogeneous, nor chemically a true solution. It most nearly answers to the description of matter in the colloidal state, which Bayliss (1927) has discussed, and the ultra-microscope reveals innumerable particles dispersed throughout a medium that forms a continuous phase. In general, colloids are of two kinds, called lyophob and lyophil systems according to the solid or liquid nature of the dispersed phase, the continuous phase being fluid in each case. Fog is a kind of colloid, and so is indian ink, but such lyophob systems are uncommon in protoplasm, whereas lyophil systems or *emulsoids* are universal. (For an account of progress in colloid science see the book in this series by A. Findlay (1948), p. 228.) The usual criterion of colloid nature is that the dispersed particles shall be outside molecular limits, yet beyond the powers of resolution of the microscope (about 0·1 μ). The commonest examples of lyophil colloids are the proteins, of which protoplasm is the source. Modern research is much concerned with the submicroscopic structure of protoplasm, but we must revert at this point to broader and more general considerations.

Chemical Elements in Protoplasm

Many biochemists have aspired to make chemical analyses of protoplasm, which shows comparative uniformity of composition. The suggestion that protoplasm is of the nature of a "giant molecule" has been made, but analyses can give no proof of this. The water-content varies considerably, but generally it ranges between 70 and 90 per cent. Next in importance to water come organic substances such as proteins (15–21 per cent.), fats (13–14 per cent.) and carbohydrates, of which there may be less than 1 per cent. in animal cells. Salts are also present. Special methods mentioned in Chapter Two have revealed an astonishing array of chemical elements in protoplasm, at least sixty of the ninety-odd known elements being in some way associated with protoplasm (see A. P. Vinogradov, 1935). The purposes of these elements are several and various. Carbon and nitrogen contribute to the framework of colloidal protoplasm and with reactive groups formed of sulphur and phosphorus they constitute what have been called the plastic and storage elements (W. R. Fearon, 1940). Hydrogen and oxygen are the elements of energy exchange, while calcium, magnesium and others are the skeletal elements. Iron, copper, manganese and others are catalytic elements; calcium, magnesium and cobalt are the activators of enzymes. Many elements which have been found in protoplasm in minute amounts may be there by accident, but it would be unwise to dismiss them so lightly, for many substances may be lethal in fair amounts but beneficial in small quantities, and even in the present state of knowledge it is not possible to state what the presence of certain elements implies in terms of cell structure or cell physiology. In some instances some obvious function is evident. Iron and copper are required for the formation of the blood pigments haemoglobin and haemocyanin, and copper also plays some part in their formation. Manganese is essential for the manufacture of chlorophyll by plant cells, and is required for normal spore-formation in some moulds which get on very well without chlorophyll, and for the growth of some animals. But for the most part the uses to which chemical elements are put in protoplasm have still to be worked out, though the method of micro-incineration has already provided some information. For a summary of these results see Heilbrunn (1943).

Animal and Plant Cells

Animal cells are generally naked masses of protoplasm. The falsely called "resting" nucleus, which is best known in its fixed and

stained condition, consists of a net-like formation of lightly stained materials bearing irregular masses of deeply stained material, the "chromatin" of the histologist and the nucleic acids of the cytochemists. This appearance is not seen in the living cell and it is now attributed to artefact. The living nucleus is made up of its membrane, a clear liquid

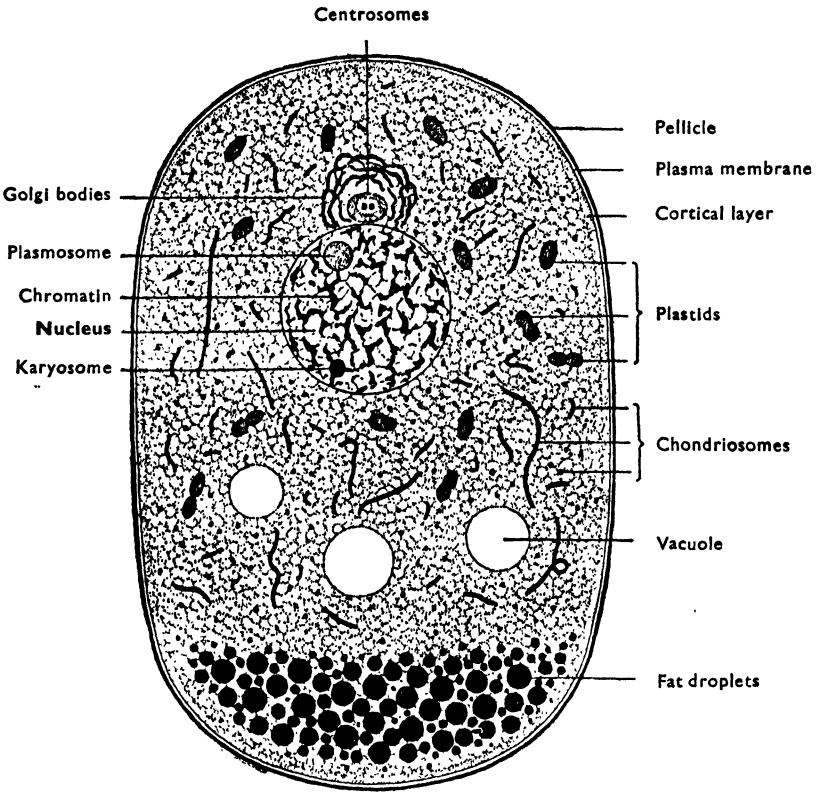


Fig. 1. General diagram of a cell. From Wilson, 1925. (The Macmillan Co.)

of fairly low viscosity (the nuclear sap), small bodies known as nucleoli (or a single nucleolus) and thread-like chromosomes, which may not in some instances be visible, though probably present at this time. The cytoplasm contains a number of inclusions set in an apparently homogenous medium, the cell sap. Some of these inclusions may be droplets of fatty substances, or granules of starchy materials, and their presence is not invariable, for they may be used up during cell life. Such inclusions vary enormously in size, chemical constitution and physical

consistency. Other inclusions of a more permanent nature are the mitochondria and the Golgi apparatus. In addition there is a small rounded body, which T. Boveri (1888) named the "centrosome" and which Flemming (1875) first saw in eggs of *Anodonta*. Situated in the centre of this is a small, deeply staining granule, the centriole, which is invariable in some cells but not in others. Van Beneden regarded it as a persistent cell organ and Boveri as the "dynamic centre" of the cell. Just prior to cell division, as these biologists discovered in 1887, the centriole divides and the two granules thus formed pass to opposite poles of the cell to take part in the formation of the spindle, an array of fibrils on which the chromosomes are set. In some animals the spindle has a nuclear origin. In the vicinity of the centrioles two sets of similar fibrils having a stellate appearance are formed; they eventually unite with the spindle to form the amphiaster, a characteristic and essential structure which is fully formed during cell division. The whole structure has a viscous nature and its elements can be moved by means of a microdissection needle, but it is likely that these are formed by a kind of protoplasmic streaming.

Plant cells have certain characteristics of their own. Naked protoplasm characterises certain reproductive cells in algae and the plasmodia of the slime fungi, but the plant cell is generally enclosed in a cell wall, which was once believed to be a living structure, but it is now believed to arise at cell division. At the outset, the cell wall is probably a liquid film in which calcium pectate is deposited, but subsequently it is extended, thickened and strengthened by the deposition in or on it of further materials, and later still a secondary layer is laid down on this primary layer, and this is modified by the formation of an opening (the *pit*) and a minute valve-like structure (the *torus*) which occupies it. The cell wall is mainly composed of cellulose, but pectins and other substances may be incorporated in it. Some cell walls are hardened by deposition of lignin but others are mucilaginous. The cell wall is quite independent of the plasma membrane, which is fundamentally the same as in animal cells. The nucleus also has essentially the same structure. Mitochondria and a Golgi apparatus have been demonstrated in some plant cells and the centrosome exists in some lowly plants, though apparently not in the typical cells of higher plants, but the most distinctive inclusions of plant cells are the plastids and the vacuolar apparatus. The plastids are absent from some lowly forms, but in higher plants they may be colourless leucoplasts, amyloplasts, which are centres for starch formation, chloroplasts containing

the green pigment, chlorophyll, or the vividly coloured chromoplasts found in the cells of flowers and fruits. All such plastids arise from minute granules known as proplastids, which multiply by division and are shared between dividing cells. Highly specialised chloroplasts exist in some microscopic plants, and various pigments to be mentioned later originate in the chloroplasts of higher plants. The conspicuous vacuolar system of plant cells is filled with complex watery solutions and it plays an important part in osmotic phenomena.

Mitochondria and the Golgi Apparatus

The granules known as mitochondria were first studied systematically by R. Altmann (1894), who regarded them as micro-organisms and devised a method for demonstrating them, though they had been seen previously by Flemming and others. C. Benda in 1898 named them and first recognised them as cell organs, and R. R. Bensley and N. L. Hoerr (1934) first isolated them for purposes of chemical analysis. They are granules, rodlets, or filaments of low refractive index, but they may tend to form networks, and they are very soluble in alcohol and acetic acid, so that they disappear in some methods of fixation. Treated with solutions of Janus green they stain bluish green. During cyclosis in some plants they may alter their shape and they are supposed to be semi-liquid. They grow by accretion at the ends, as well as in girth if starch or fat is deposited in them. They are found in bacteria, diatoms, and practically all plants from the fungi to the angiosperms, and in practically all animals from Protozoa to man. Though sometimes dispersed widely in a cell, they may be confined to particular regions, *e.g.* adjacent to the basal membrane, near blood vessels, or in groups around the nucleus. In senescent cells the mitochondria may disappear, and in red blood cells their disappearance is associated with the appearance of haemoglobin. In plant cells they may disappear as chlorophyll is developed. In early development, mitochondria may be the only cell organs present and they may later be transformed into various products of differentiation. According to the eclectosome theory of Regaud (1909) they are a kind of plastid capable of transformation into very diverse products. In some recent works (*e.g.* P. Portier, 1917–19; I. E. Wallin, 1922, 1923) they are said to have the bacterial nature which Altmann attributed to them.

In recent years, mitochondria have been collected by differential centrifugation methods described by Claude (1941, 1943) (see Butler, 1949). They consist of about one million protein molecules and

contain 25 per cent. lipoids and 8–10 per cent. ribonucleic acid. For the reason that they contain concentrations of oxidising systems of cells they are probably very much concerned with the utilisation of energy and the oxidation of fats. In the modern view (see G. H. Bourne, 1950), mitochondria are heavily charged with enzymes which are concerned with cell metabolism, and they can be regarded as centres of cell respiration. Some of the enzymes they carry are involved in the Krebs tri-carboxylic acid cycle and may be concerned with the degradation and synthesis of proteins, carbohydrates and fats, the three chief classes of foodstuffs. Mitochondria also contain vitamins A and C, in addition to various members of the vitamin B complex which are concerned with cell metabolism. Aneurin (B_1), riboflavin, and nicotinamide are respectively constituents of the enzymes co-carboxylase, cytochrome oxidase and co-enzyme I. Pyridoxin, also present in mitochondria, is a constituent of transaminase. The study of mitochondria has thus indicated the existence of a very close association between vitamins and enzymes in cell metabolism.

The Golgi apparatus was discovered in the germ cells of a snail by La Valette St George (1867) and first described by G. Platner (1885). Camillo Golgi used a modified silver impregnation method in 1898 and found this "apparato reticulo interno" in nerve cells. In the cytoplasm of many cells N. Holmgren (1899) and others found systems of canaliculi which remained clear when the rest of the cytoplasm took up stain, and in 1908 Ramon y Cajal gave the name Golgi-Holmgren canals to include both kinds of structure. The apparatus may tend to disappear by partial solution in alcohol, and some parts of it have an affinity for silver salts and blacken when treated with osmium tetroxide. The Golgi apparatus may occupy an area of cytoplasm equal to the size of the nucleus, and though it is often net-like it tends sometimes to become an aggregate of rods and spherules, which are often clearly seen in oogenesis and spermatogenesis. Whether or not the apparatus exists in fungi, algae and bacteria is doubtful. The literature dealing with the Golgi apparatus is very extensive but the attention of the reader may be directed to recent studies carried out at Oxford by J. R. Baker (1944, 1946, 1947, 1949), A. J. Cain (1947, 1948) and O. L. Thomas (1947, 1948), and also to the book by G. C. Hirsch (1939). That some of these descriptions of the Golgi apparatus have been rejected by J. B. Gatenby and T. A. A. Moussa (1950) goes to show that great difficulties of interpretation assail highly experienced cytologists. However, there can be no objection to the modern conception of the Golgi

apparatus as a system of lipoid-protein spheres in which various substances are segregated—primarily substances which are harmful to the living cell but also secretory products which are synthesised by the action of mitochondria (G. H. Bourne, 1950).

The Cell Membrane

Several hypotheses have been put forward to try to explain the nature of the surface membrane of the cell, which I. Langmuir first regarded as sieve-like. At the surface of a liquid molecules show a regular arrangement, and the question as to what substances shall pass through the membrane once seemed to be decided by the size of the interstices between these molecules. The difficulty of explaining why some substances known to have small molecules were unable to pass whilst others with larger molecules were able to do so suggested that the size of the interstices could be altered, both by the action of substances outside the membrane and also by the combination of substances in the cell with the molecules of the membrane. In the last decade of the nineteenth century, E. Overton studied the absorption of various substances by cells, notably aniline dyes, which are well known to be taken up avidly by fatty substances and lipoids such as lecithin and cholesterol. Overton became convinced that the rapid penetration of fat-soluble substances into the cell was due to the lipoidal nature of the surface membrane. When dyes that are not soluble in fats were found to enter cells readily this lipoidal theory received a setback. The difficulty of penetration by water and the ease with which some ions penetrate also militate against it. Such theories seem to be applicable to artificial membranes, for the molecules of substances having fewer than forty-five atoms can pass through collodion membranes. G. H. A. Clowes (1916) suggested that watery and lipoidal phases might exist together in a cell membrane by the action of balanced ions, postulating phase-reversal such as one can obtain in oil-water emulsions by modifying the critical balance of sodium and calcium ions, or other monovalent and divalent cations. A watery continuous phase would facilitate the entry of watery substances into the cell; a lipoidal continuous phase the entry of lipoid-soluble substances.

The cell membrane is indispensable to the life of the cell. Prick it with a microscopic needle and the protoplasm may protrude and form a new membrane at its surface, but tear it instead and the protoplasm pours out and mingles with the watery liquid outside. First and fore-

most, the membrane is a protective film with a measurable surface tension, and it exerts an inwardly directed pressure. But it is also a selective barrier allowing some substances to enter or leave the cell, but restraining others. At the same time, the cell membrane protects protoplasm against mechanical and chemical agents of destruction and it is the seat of an electromotive force. Recent study of cell membranes has opened up several fields of physiological research. The membrane does not dissolve in water, but it has a watery consistency. The membranes of unequal cells in contact with one another bulge towards the larger just as if they were soap-bubbles or other artificial watery films. Errara's Law states that the pressure inside a bubble is inversely proportional to the radius, and the same is approximately true of cells.

Blood corpuscles and some other cells can be stretched to twice or thrice the normal length or diameter and will return to their former shape when the tension is released. This suggests that the cell membrane is not entirely watery—for the elasticity it shows is not a property of liquids. To get over this difficulty the first necessity was to assume that the cell membrane is a solid monomolecular film, its thinness and rigidity facilitating surface-tension phenomena. Later on, it was necessary to modify this simple conception, and to regard the cell membrane as a composite thing constructed out of a bimolecular layer of lipoidal materials interposed between two molecular layers of protein or, at its most complex, out of several layers of heterogenous materials. This helps to explain the ease with which such different water- and fat-soluble substances can pass through the membrane. The properties of some artificial membranes can be explained in terms of a sieve-like arrangement of molecules, but the selective permeability of the cell membrane does not lend itself to such an easy explanation. A lipoidal film could be expected to facilitate the rapid entry into the cell of fat-soluble substances, but not the easy passage of water through the cell membrane. The membrane has a dual or multiple nature.

Clowes suggested that watery and lipoidal phases might coexist in the cell membrane by the action of balanced ions. By shaking oil and water together we get a crude emulsion that soon breaks down into layers of oil and water, but by adding a trace of sodium or potassium salt to the water we get instead a stable emulsion in which water forms the continuous and oil the discontinuous phase. If we add instead a trace of calcium or barium salt the emulsion is stable, but has phases of an opposite nature. Everybody who has tried to wash greasy plates

in hard water has some experience of phase-reversal of this kind. Hard water is rich in calcium and in consequence the continuous phase of grease (or oil) sticks to the china; but the addition of soda or sodium soap to the water gives an alternative emulsion in which the oil is discontinuous and is easily removed by the watery continuous phase. The ratio of sodium to calcium in living cells is not dissimilar to that which causes the breakdown of an ordinary emulsion of oil, but there is some evidence of modification of the cell membrane by alteration of the balance. The dominance of monovalent ions (sodium and potassium) promotes an emulsion with a watery continuous phase and this would favour the entry of watery substances into the cell; but the dominance of divalent ions (calcium and barium) produces a lipoidal continuous phase that favours the entry of fat-soluble substances into the cell. The cell membrane is probably capable of periodic alterations of this kind, and as it is protoplasmic it is also able to use energy to do work, so that it is more complex and variable than any artificial membrane with which we can compare it.

Cell Division

It is nearly one hundred years since R. Virchow (1858) penned his famous aphorism *Omnis cellula e cellula*, all the more remarkable because the studies of the cell and of development were in their infancy. Not for many years was the full significance of the phrase understood, because the mode of cell division was unknown, but in the end it came to be realised that no other mode of origin of cells was conceivable than by the division of pre-existing cells. Cell division was first seen by Prévost and Dumas (1824) in the developing egg of the frog, and then, during the next ten years, by several botanists (Brongniart, Meyen, Mirbel and von Mohl) in plants. After the formulation of the cell theory various zoologists (Kölliker, 1884; Remak, 1841, 1858; and Virchow) and botanists (von Mohl, Nägeli) were attracted to the subject. After studying blood cells in the embryo chick Remak imagined division to be a simple process starting from the middle of the cell and gradually proceeding outwards, the nucleolus, then the nucleus and finally the cytoplasm becoming involved. His view was accepted till, soon after 1870, examples turned up in both plants and animals of what seemed to be the disappearance of the nucleus. As its membrane disintegrated, stellate cytoplasmic formations which Flemming (1892) called "asters" appeared in the cell, the first to study them—though Remak saw and drew them—being H. Fol (1873–76) working

with the eggs of medusae and molluscs, and L. Auerbach (1874) studying nematodes. Auerbach believed in the complete disintegration of the nucleus (karyolysis) and its re-formation after division. But as more and more fixed and stained materials were examined it became clear that the nucleus did not disappear, though it did undergo profound changes. Remak's scheme was then amplified by Flemming (1879), who recognised an *indirect* as well as a *direct* mode of division. In the former, nuclear materials seemed to be spun into long threads that eventually split lengthwise, every part dividing equally, so far as could be made out. Changes were seen to take place in the threads—shortening and thickening, for instance—and it was to the condensed bodies that W. Waldeyer (1888) gave the name *chromosomes.*

To this process of cell division W. Schleicher (1878) gave the name karyokinesis, but Flemming (1882) proposed the alternative term mitosis, and the name amitosis for the direct mode of division, and these terms have been the more popular. Such terms have often been used in connexion with the division of cells, but it is obvious that they often denote only nuclear changes. C. O. Whitman (1887) used the term cytokinesis to denote the cytoplasmic changes occurring during indirect division, and E. B. Wilson (1925) put forward a scheme which brings in all these terms. We may put this down as follows:—

I. Amitosis: direct division.
II. Mitosis: indirect division.
    1. Karyokinesis (nuclear transformation).
    2. Cytokinesis (cytoplasmic changes).
        (*a*) Division of the cytoplasm purely and simply.
        (*b*) Meristic changes or distribution.
            (Chondriokinesis . . . relating to mitochondria.)
            (Dictyokinesis . . . relating to the Golgi apparatus, etc.)

Amitosis is not a general method of cell division, occurring only in a few instances, notably in Protozoa and also in leucocytes and in the cells of some connective tissues. First the nucleus elongates and becomes constricted near its middle region. Then the two approximately equal halves draw gradually apart, after which the cytoplasm is halved in a similar manner, each half eventually rounding off with one of the nuclear fragments within itself. Sometimes the nucleus is divided by the development of a transverse partition. The nucleolus may initiate direct division, as Remak asserted, but it often remains in

an undivided condition in one of the daughter cells. Amitosis occurs in cells of a transitory nature, for instance in the cells of embryonic membranes, and when it occurs without cleavage of the cytoplasm we get a binucleate or a multinucleate condition. Amitosis is regarded by some writers as a modified form of mitosis.

Mitosis

This type of cell division is split up, purely for convenience in describing what are really continuous changes, into various stages, or phases, which are known as prophase, metaphase, anaphase and telophase. In some books the anaphase is subdivided into early and late phases, and sometimes a prometaphase is recognised between prophase and metaphase.

The prophase is characterised by the appearance of the coiled threads, or chromosomes, which are separate from their first appearance and not in the form of a continuous spireme as the early cytologists believed. The chromosomes are believed to exist in the resting nucleus, but they are not demonstrable in it, probably because they are highly hydrated and obscured by abundant nuclear sap. At the beginning of prophase, at any rate, they become evident in fixed materials, probably because dehydration is taking place within them. This process continues beyond prophase and into metaphase, when, in such preparations, the chromosomes are seen at their best. From their first appearance, the chromosomes are seen to be double, the two threads or *chromatids* lying together along their whole lengths. Enlargement of the chromosomes during this phase may be due to the production of new materials, but shortening and thickening occurs subsequently, and during this process the spirals of the threads are tending to unwind themselves. Minute constrictions are seen in some chromosomes; these are the spindle attachment.

The chromosomes invariably exist in pairs, which can generally be recognised by size or shape somewhere in the nuclear region of the cell. The members of any pair are said to be *homologous*, and the number of pairs is said to be the *haploid* number, that of the individuals the *diploid* number. The chromosomes may at this stage consist of dissimilar and often very unequal granules, the *chromomeres*, discovered by W. Pfitzner (1882). The centrosome then undergoes change, the centrioles separating and moving to opposite poles of the nucleus.

The end of prophase is generally marked by the disintegration and disappearance of the nuclear membrane, but in a few Metazoa and in

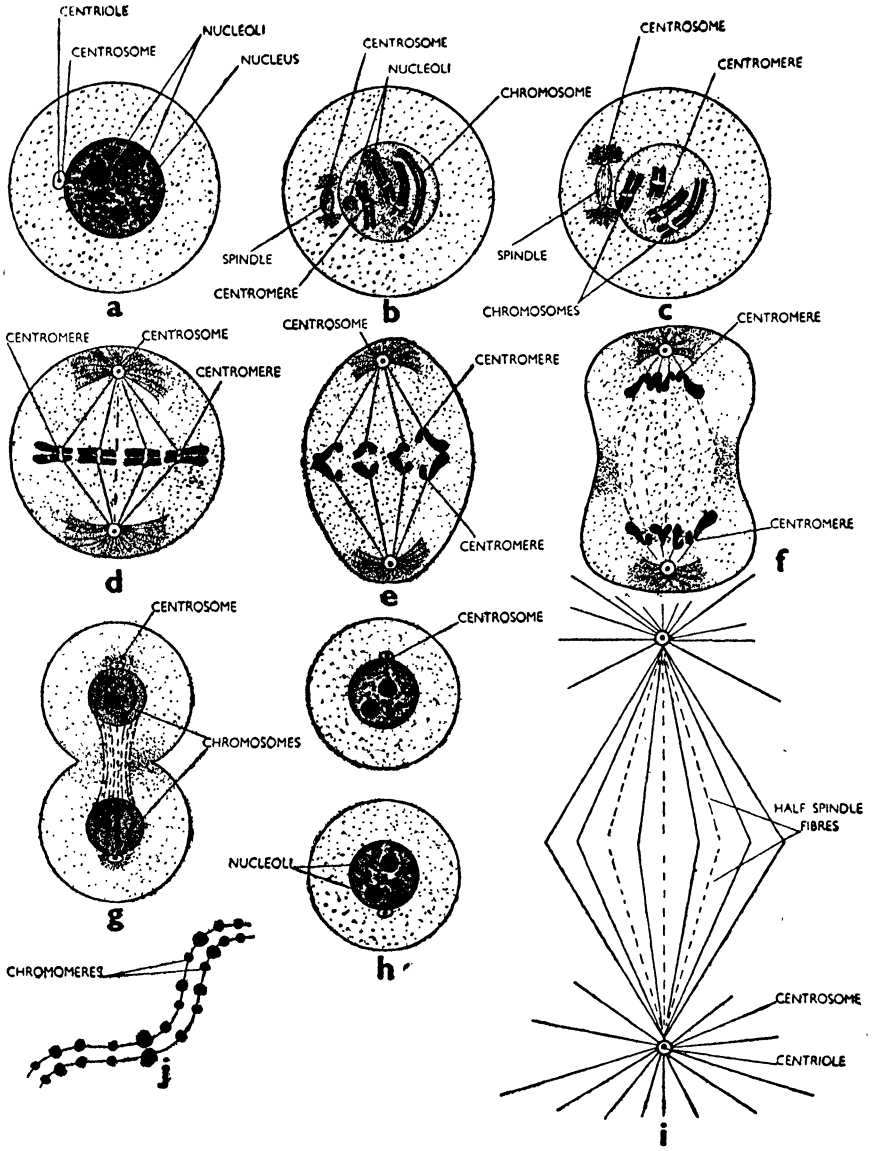


Fig. 2. Diagram to illustrate the stages of mitosis. a, non-dividing nucleus; b, c, early prophase; d, metaphase; e, f, early and late anaphase; g, telophase; h, daughter cells; i, achromatic figure; j, prophase chromosomes to show arrangement of chromomeres. From Gresson, 1948. (Edinburgh University Press.)

some Protozoa the whole process of mitosis may take place beneath a complete nuclear membrane. With the loss of the membrane in other forms the chromosomes lie free in the cell, bathed in nuclear sap, from which no doubt various kinds of spindle elements seen in different organisms are formed. Sometimes both asters and spindle elements are wanting and therefore, unless appearances are deceptive, not essential to the stages which follow. In most Metazoa the asters are formed from cytoplasmic materials and they unite with the spindle elements formed out of nuclear sap, so that the completed spindle apparatus is a compound structure originating in both parts of the cell. The chromosomes were formerly believed to attach themselves to the spindle elements, but it is now known that they are attached by special spindle-attachments from their origin. The whole arrangement depends on the sizes and numbers of the chromosomes and also on the nature of the spindle. The long chromosomes of salamander leucocytes are arranged so that their attachments form a circlet around a central spindle. Small chromosomes imbedded in the spindle show the same sort of attachment. Spindle-attachments, which vary from one chromosome to another but are constant for particular members of the chromosome group, themselves show details of structure, and some cytologists regard the minute granule in the middle of the spindle-attachment as the real organ uniting the chromosome with the spindle. No trace of structure is seen, however, in the chromatids, which are apparently cylindrical and rod-like, though special methods have demonstrated a spiral structure, and this is concerned with the contraction seen during prophase. Towards the end of metaphase the spindle-attachments of chromatid pairs seem to repel one another, for the chromatids begin to move apart from this point and to pass along the sides of the spindle towards the poles.

During the early part of anaphase the chromatids move further apart, their spindle-attachments becoming widely separated, so that if small they are discrete, though if long they may still be associated with one another at their ends. As soon as these chromosome movements are complete the middle region of the spindle elongates considerably, so that the two sets of chromatids are drawn still further apart. The causes of the elongation are unknown; what is known is that the elongated region still has the consistency of a gel.

At the inception of telophase the two sets of chromatids, one unit from each chromosome, become grouped at each end of the spindle. They are of the same number at each pole and, it might also be noted,

the same number as of chromosomes in the original cell. The polar caps of the spindle now disappear by a process of solution, though the middle region of the spindle may persist for some time longer. The chromatids now become modified to form the chromosomes of the newly formed cell which results after partition of the cytoplasm. During the resting stage which follows division each chromatid splits lengthwise, so that once again we have a cell with the full complement of chromosomes, each consisting of a pair of chromatids lengthwise arranged.

The duration of mitosis varies considerably from about thirty minutes to several hours. Chromosome numbers are constant for any species of animal or plant (see Wilson, 1925).

Meiosis

The fertilisation process in animals and plants involves the union of two special cells (gametes) to form a single resultant cell (zygote) which, in the case of multicellular forms, gives rise to a new individual by further cell divisions. The process involves a possible increase in the amount of nuclear material, and if this is to remain constant for each species of organism there must be somewhere in the cycle of changes a compensating reduction. This was realised by Weismann in 1887, and the modifying division is known as "*meiosis*", or reduction, which was first demonstrated by J. B. Farmer and J. E. S. Moore (1905). This does not happen at the same time or in the same place in all organisms. In animals generally it takes place in the gonads, in higher plants it takes place in the sporophyte generation, which is different from that in which the gametes are produced. It results in the sorting out of the haploid groups of chromosomes in one or other of two peculiar mitoses during which reduction occurs. The two maturation divisions have features in common with ordinary mitosis, but differences occur which we might now consider.

During prophase of the first meiotic division, which shows various phases—leptotene, zygotene, pachytene, diplotene and diakinesis—the homologous pairs of chromosomes approach one another. They then make contact at various points, and become intimately associated in the condition of *synapsis*, so that the cell now shows the haploid number of double (*bivalent*) chromosomes. About the same time it becomes apparent that each member of any synaptic pair is really double, longitudinal splitting taking place just as in mitosis. The chromosomes now appear not double but quadruple, the four members of each *tetrad*

being a chromatid. At the end of the first meiotic prophase the cell displays the reduced number of tetrads. During the two meiotic

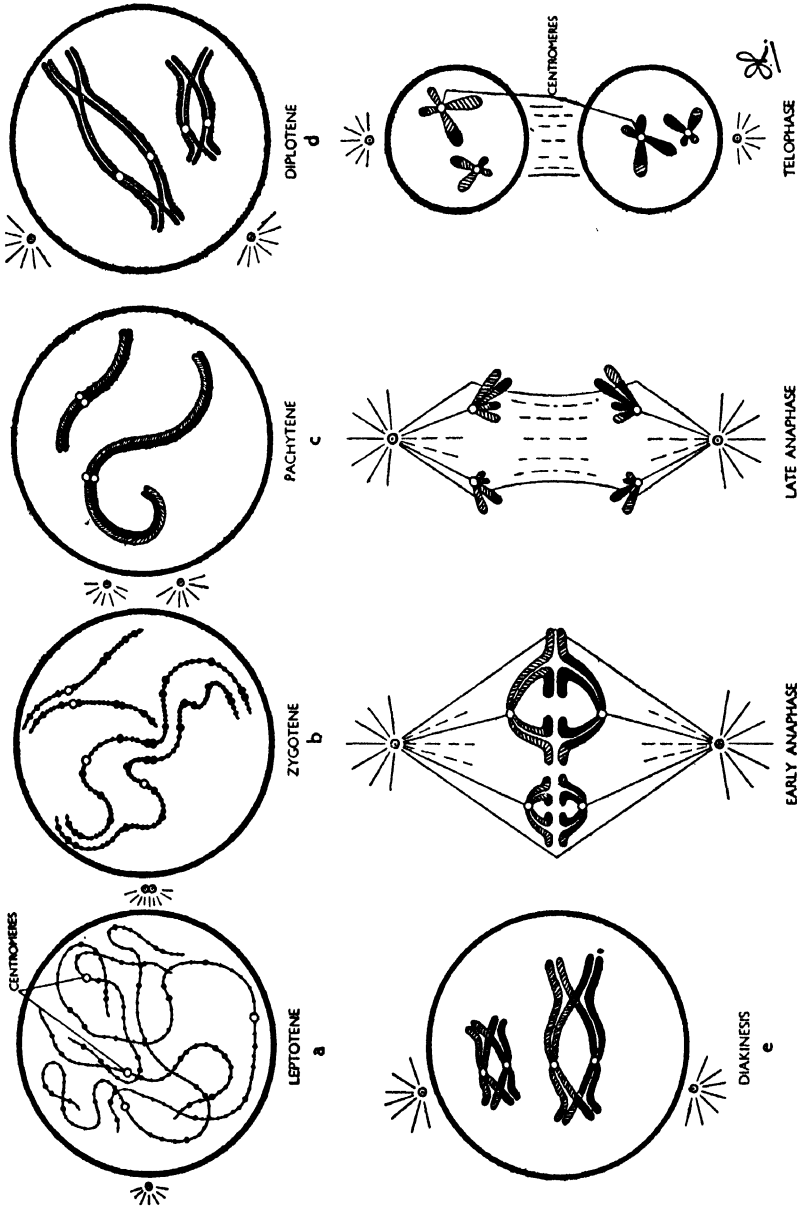


Fig. 3. Diagram to illustrate the stages of meiosis. From Gresson, 1948. (Edinburgh University Press.

divisions the four chromatids of each tetrad are distributed to the four resultant nuclei, so that each nucleus has one of them. The homo-

logous chromosomes are separated at *disjunction*, or reduction proper, the two associated chromatids going towards one pole of the spindle as a *dyad*, the members of which are separated at the next division. At the close of meiosis each of the four resultant nuclei thus has a set of monoploid chromosomes, comprising one chromatid from each tetrad, which was at the outset a longitudinal half of one member of each of the pairs of homologous chromosomes in the diploid complement. If we represent a chromosome complement of three pairs of homologous chromosomes (diploid number 6) as Aa, Bb and Cc we should find that at the end of meiosis two of the four nuclei have A and the other two a, similarly two have B and the other two b, and two C and the other two c. We can see readily that a range of eight possible combinations is possible —namely, ABC, ABc, AbC, Abc, aBC, aBc, abC and abc. Not all of these combinations could be realised by the formation of four nuclei, of course, but all of them would undoubtedly turn up in the meiotic divisions of just a small group of cells. In organisms with much larger chromosome numbers correspondingly much larger groups of cells would be necessary to produce all the possible combinations of chromosomes, but in the gonads, where gametes are produced in prodigious numbers, many possible chromosome arrangements come into being. And when the full complement of chromosomes (diploid number) is attained after the union of such cells in pairs (syngamy) even greater variety of chromosomal composition is attained.

Nucleic Acids

The first chemical investigation of cell nuclei was made by F. Miescher (1897), who extracted from the nuclei of pus cells (1868) and the heads of the salmon's spermatozoa (1872) a hitherto unknown chemical substance which he called nucleic acid. When this substance was identified in the somatic cells of other animals and in plant cells its fundamental importance was realised and the "chromatin" of the histologist became an anachronism. Nuclei are largely composed of nucleic acid combined with protein to form nucleoprotein. The nucleic-acid molecule consists of four mononucleotides—each a compound of phosphoric acid, a pentose sugar and a nitrogen group, generally a purine or pyramidine base—in short, it is a tetranucleotide.

The two main varieties of nucleic acid were found respectively in the thymus gland and in yeast, and they are sometimes called thymus nucleic acid and yeast nucleic acid. In the former the sugar is *d*-2-desoxyribose ($C_5H_{10}O_4$), in the latter *d*-ribose ($C_5H_{10}O_5$), facts indicated

by the alternative names desoxyribose nucleic acid and ribose nucleic acid. Both types exist together, however, in both plant and animal cells and they can be identified by the staining test known as the Feulgen reaction, treatment with nucleases, ultra-violet spectroscopy and other methods. Desoxyribose nucleic acid seems to be located mainly in the nucleus, ribose nucleic acid in the cytoplasm. According to Davidson (1947), the nucleolus of a rat-liver cell contains a central mass of ribose nucleic acid and a peripheral aggregate of desoxyribose nucleic acid. In the fasting animal such cells show a loss of glycogen and stored protein, but the amount of desoxyribose nucleic acid remains almost constant, while the amount of ribose nucleic acid falls. In the development of a sea-urchin's egg the cytoplasmic ribose form decreases in amount, but the desoxyribose form increases in amount, so that the total nucleic acid content remains constant. Nuclear supplies of the desoxyribose form are synthesised at the expense of the cytoplasmic ribose form. The old quarrel between the "cytoplasmists" and "chromatinists" (see E. A. Minchin, 1915, and the poem in *Punch*, **143**, 245) was thus eventually resolved.

Ribose nucleic acid is abundant in cells which manufacture protein—for instance, in the cells of the gastric glands and pancreas, the cells of a growing tissue and ripening germ-cells. On the other hand, cells which display marked physiological activity but do not specially synthesise protein contain very little ribose nucleic acid. This nucleic acid exists (as nucleoprotein) in minute cytoplasmic inclusions, or microsomes, which also contain hydrolytic enzymes such as amylase and dipeptidase and various respiratory enzymes such as peroxidases, dehydrogenases and cytochrome oxidase. Microsomes thus have the equipment and materials for biosynthesis and the means of obtaining free energy from nutrients to carry it out. The microsomes of red blood cells contain haemoglobin, those in the islet cells of Langerhans insulin, and those in the hypophysis the melanophore-expanding principle, *i.e.* characteristic synthetic products. They are essentially granules of ribose nucleic acid and the agents of protein synthesis in cells.

According to J. Brachet (1947) the segmenting egg of a sea-urchin, which hardly increases in size, is gradually depleted of its ribose nucleic acid. Conversely, the segmenting egg of a chick synthesises much protein and the production of ribose nucleic acid is no less important than its utilisation. When the growth of an embryo slows down, however, and new protein is not being produced, the amount of ribose nucleic acid falls considerably. According to T. Caspersson (1947)

several years of teamwork on various examples of protein synthesis have shown that part of the "chromatin" apparatus of the nucleus (the nucleolus-associated chromatin) secretes proteinaceous substances. These accumulate, making up the bulk of the nucleolus, and then diffuse out towards the nuclear membrane. Outside the nuclear membrane ribose nucleotides are produced intensively, and at the same time cytoplasmic proteins increase in amount, their synthesis being associated with the nucleic acid changes. This is true whether the proteins are those required during growth or those used in the secretions of a gland cell.

C. D. Darlington (1945) put two and two together very succinctly when he pointed out that while C. Darwin was at work, G. J. Mendel was engaged in his studies of particulate inheritance, O. Hertwig witnessed the fusion of nuclei at fertilisation, and F. Miescher discovered nucleo-proteins. It has been the task of twentieth-century biology to put these discoveries together. We now realise that the particles Mendel inferred exist in the nucleus of the cell, which Hertwig observed closely, and that they consist of nucleoproteins such as Miescher isolated. It is nucleic acids which give nucleoproteins their unique power of self-reproduction; and this in turn is the essence of growth, reproduction and heredity. Thus, reasoned Darlington, three hitherto separate aspects of biology at last became components of the same biological problems.

Darlington (1947) has also remarked: "In the chromosomes we have discovered how to make chemical processes structurally visible." The processes he referred to are physiological activities with a bearing on heredity and development, mechanical activities concerned with events taking place during cell division, and joint physiological and mechanical activities which bear on the distinctions between mitosis and meiosis, processes which also "reach out towards the relations of viruses, plasmagenes, microsomes and the determinants of cancer". He added: "We are now witnessing, after the slow fermentation of fifty years, a concentration of technical power aimed at the essential determinants of heredity, development and disease. This concentration is made possible by the common function of nucleic acid as the molecular midwife of all reproductive particles. Indeed it is the nucleic acids which, in spite of their chemical obscurity, are giving to biology a unity which has so far been lacking, a chemical unity." For much recent information on the nucleic acids, and more than four hundred selected references, see J. N. Davidson (1950).

CHAPTER FIVE

REPRODUCTION

REPRODUCTION in animals and plants is achieved in very many ways, but the methods adopted fall into two main categories: "asexual reproduction", which requires only a single parent and is independent of sex, and "sexual reproduction", which calls for the co-operation of two parents and depends on sex. Asexual reproduction in animals has much in common with vegetative propagation in plants; it occurs in many invertebrates, but not in roundworms, wheel-animalcules, starfishes and their allies, molluscs and arthropods. Many Protozoa reproduce asexually by means of "fission". The nucleus gradually elongates, becomes constricted and divides into equal halves, and the cytoplasm then constricts and divides similarly, so that two nucleated individuals arise in place of the original parent. If the parent happens to be an amoeba the new forms are recognisably amoebae, but in *Paramecium* one of the individuals has neither mouth nor gullet at first, though these parts soon develop. The outstanding feature of this type of reproduction is that the parent disappears as an individual and is replaced by two new forms, a fact which has given rise to the notion that Protozoa are immortal. Such forms may perish as a result of accident, however, having no more than potential immortality. In some Protozoa—trypanosomes, for instance—the nucleus divides into several pieces and the cytoplasm is partitioned in such a way that each piece of nucleus gets its proper share. This method of "multiple fission" at once produces numerous small individuals, and it is commonly associated with spore-formation.

Many multicellular animals also reproduce asexually. A common method in coelenterates, ascidians and some ringed worms is "budding". The hydra often bears a small bud, sometimes several buds, which involve the entire body-wall and include an outgrowth of the digestive cavity, or enteron. After the bud has developed a mouth and a circlet of tentacles it becomes constricted at the base and is liberated as a new individual. Budding may produce a colony of individuals, as in *Obelia*, where the hydroids communicate with one another through a common tissue, the coenosarc, and a common enteric cavity. Some zooids are nutritive, but others are set apart as reproductive individuals, or

blastostyles. On these, secondary buds develop and eventually give rise to free-swimming male and female individuals, or medusae. Such methods produce complex colonies in siphonophores such as *Physalia* and *Velella* by budding from a medusoid form. The common jelly-fish, *Aurelia*, arises as a hydra-like individual, or planula, which fixes itself to weeds or rocks and soon becomes partitioned into a number of saucer-like disks set one above another. The modified planula, or scyphystoma, casts off small disk-like larval jelly-fishes, each of which is gradually transformed into an adult male or female jelly-fish.

A special type of budding occurs in Syllid worms as a prelude to sexual reproduction (see F. A. Potts, 1911). Some forms detach the hindmost part of the body, but only after this has developed the rudiments of a head, so that at one stage the worm has the odd appearance of a sexually mature worm attached by its head region to the tail end of an asexual form. Otherwise, budding in Syllids may produce a unilateral series of individuals of which the oldest and most mature are the hindmost, and the whole chain moves about for a time as a single unit, though the individuals of the chain eventually break apart and live independently. The most remarkable form, *Syllis ramosa*, produces a branched chain of individuals.

Some fresh-water sponges produce special buds, or gemmules, by internal budding. Gemmules are small clusters of cells covered by protective materials. They are produced in summer, but they survive after the death and decay of the parent, sink to the bottom of a pond, remain quiescent during the winter, and develop to form a fresh crop of individuals during the following spring. Moss-animals, or Bryozoa, also produce internal buds, or statoblasts, which float near the surface in lakes, often in such large numbers as to make the water turbid. They are dispersed by water currents in the lake and may remain dormant in winter, but form a fresh community of moss-animals during the next spring. Complex types of budding occur in ascidians, which form colonies of various kinds (see N. J. Berrill, 1950). Salps such as *Doliolum* produce buds on a ventral process, or stolon, but they migrate over the body and attach themselves to a dorsal finger-like lobe, the cadophore, developing into three main types of individuals; gastero-zooids are feeding individuals, "gonozooids" are future sexual form, and "phorozooids" are forms which "nurse" the gonozooids in early development.

Sexual reproduction is effected by means of two kinds of germ-cells, the spermatozoa and ova, the union of which is known as "syngamy".

In Metazoa the two kinds of gametes are markedly dissimilar, but in Protozoa they may be all alike (isogametes) or dissimilar in the same way that sperms and ova are. Such microgametes and macrogametes

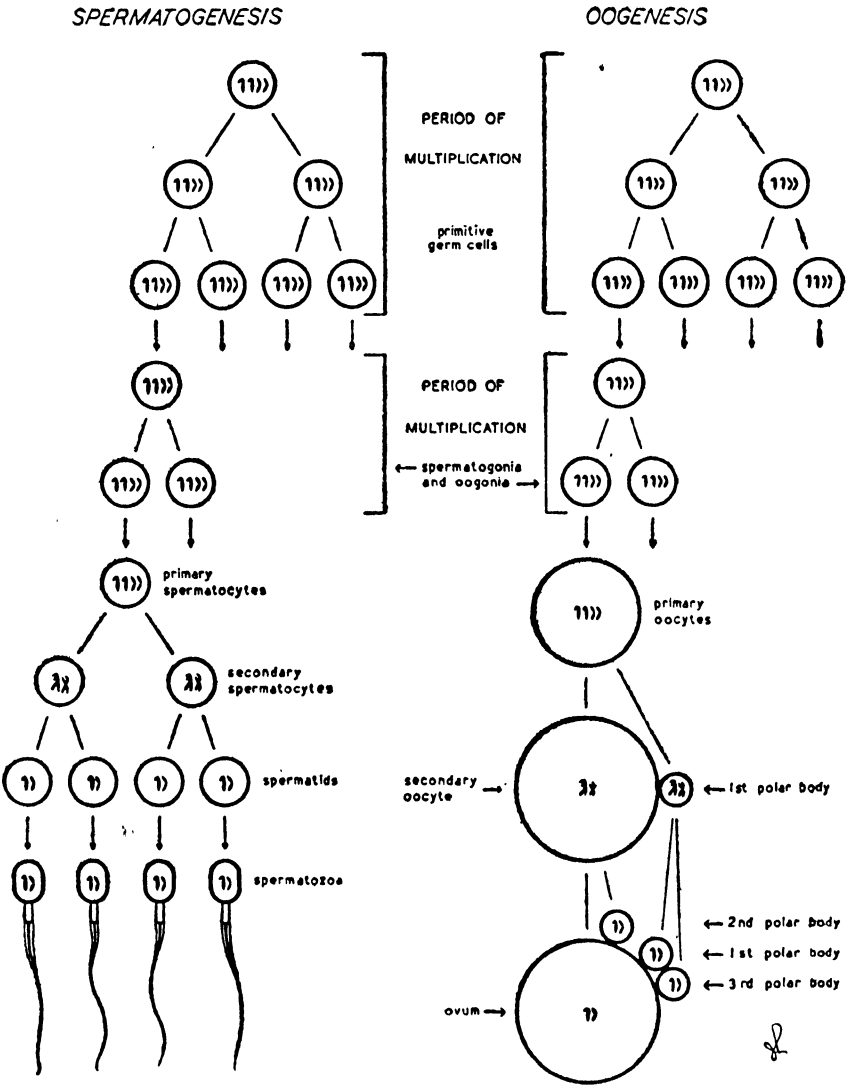


Fig. 4. Diagram to illustrate the stages of gametogenesis. Note the process of "reduction". From Gresson, 1948. (Edinburgh University Press.)

provide a strong contrast with the gametes of Metazoa, however, in those instances in which the entire protozoon body forms the gamete, which is an instance of "hologamy". Gametes which arise in Protozoa

out of small fragments of the body illustrate "merogamy". Protozoa having isogametes do not display any of the differences generally associated with sex. The beginnings of sex dimorphism—the structural and functional differences shown by male and female organisms—may be said to originate in anisogamous Protozoa, though in general the differences apply only to the gametes and not to the body as a whole. We must not press this point, therefore, because a real distinction between the sexes can exist only in metazoan animals, which not only set aside particular organs in which the gametes develop, but also modify other parts of the body for the maintenance of the gametes and their transference from one place to another. Parts of their bodies are modified in such ways that males and females become mutually attracted to one another and this furthers the ends of sexual reproduction by methods impossible to Protozoa.

The first prerequisite for fertilisation is the assembly of the sperms and ova in some suitable location, and animals achieve this end by various means. Generally speaking, all that is required to ensure fertilisation is to convey the sperms to some point near the ovum, for this cell has some sort of chemical attraction for sperms so that they make the final stages of the journey by their own efforts. Sexual union, or copulation, is a common method of achieving this purpose, though there are many animals in which it does not occur. Many marine animals shed enormous numbers of eggs and sperms into the sea, where fertilisation occurs by chance unions. This method may seem wasteful, but reckoned by practical standards it achieves what is required, namely the propagation of the race. A female plaice may shed half a million eggs during one breeding season, yet unfertilised eggs are rarely found. Other fishes show even greater fecundity, the flounder bearing about one million eggs, the cod nearly two millions, the turbot nearly seven millions, and the ling about thirty millions. Wastage in these instances is due to the very high rate of mortality of the larval fishes rather than to defects in the method of fertilisation. The chances of fertilisation may be increased by the swarming of sexually mature animals. The shoals of herring and cod sought by fishermen are spawning swarms, and many invertebrates display complex rhythms of spawning activity which are correlated with particular phases of the moon, the tides and other natural phenomena. Such rhythms are often so ingrained in the animal that they persist even after it has been transferred to a dark and tideless aquarium.

Spermatozoa may be enfeebled by the dilution of dense swarms in

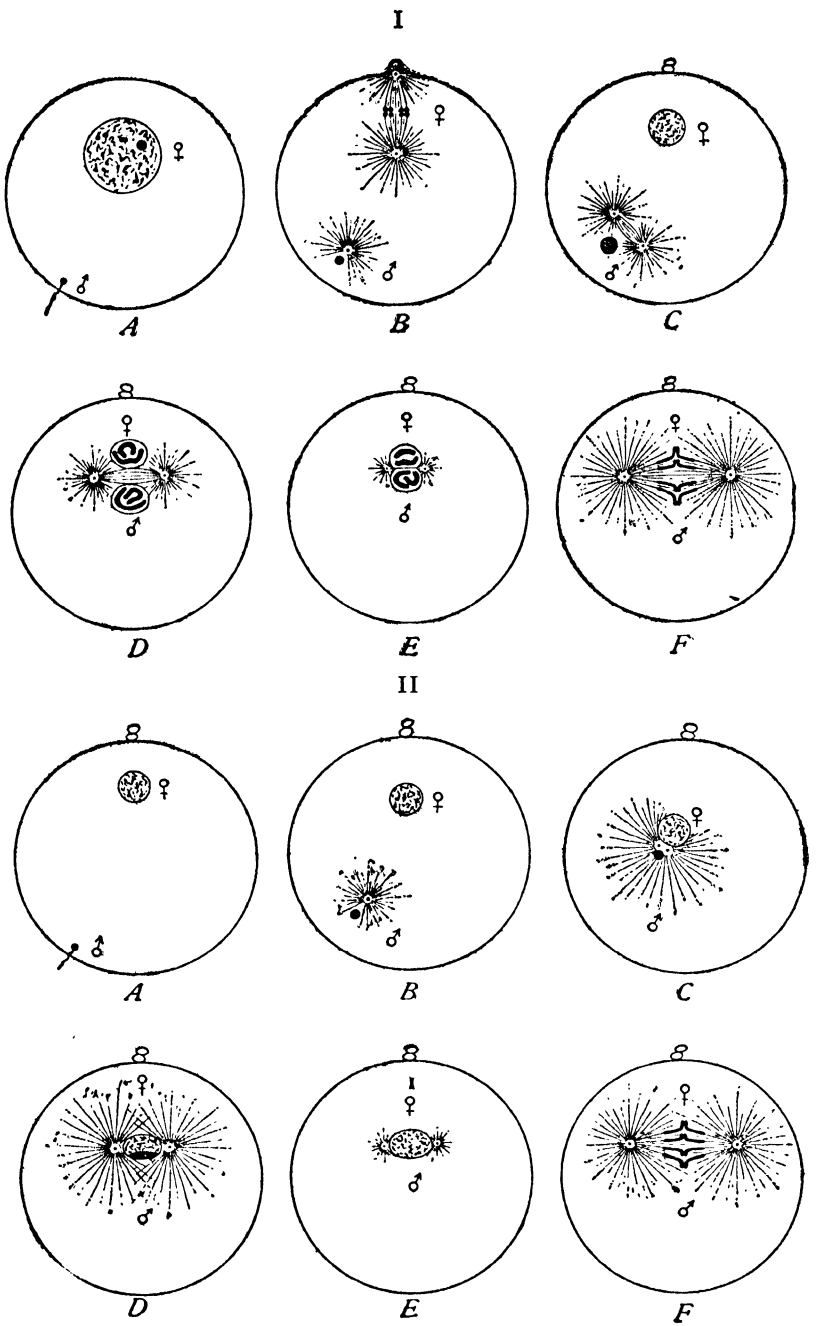


Fig. 5. Diagrams of the sea-urchin (I) and the *Ascaris* (II) types of fertilisation. *A*, entrance of sperm. In I, *B*, *C*, approach of pronuclei, division of sperm centre; *D*, sperm aster divided, fusion of pronuclei; *E*, fusion nucleus; *F*, first cleavage figure. In II, *B*, sperm aster and first polar spindle; *C*, sperm amphiaster; *D*, union of pronuclei; *E*, ensuing pause; *F*, first cleavage. From Wilson, 1925. (The Macmillan Co.)

which they are emitted, and it is unlikely that they would remain viable if they were disseminated in fresh water as they are in the sea. The male salmon sheds his milt over the eggs as they lie in holes in some river-bed where the female deposited them. Land animals face the greatest problems of reproduction, however, and very strange methods are sometimes adopted in order to bring the sperms and ova together—for instance the male spider's method of spinning a small web and shedding the sperms on it, for the female to transfer to her genital opening by means of a syringe-like palpal organ on the feelers, or pedipalpi. Sperms are essentially modified for an aquatic existence, however, as the tail-like swimming organ indicates, and in land animals they are nourished and nurtured by the liquid, or semen, which accompanies them into the female's body during copulation. Birds and reptiles have only to bring the cloacal apertures of the body into apposition in order to achieve insemination, but in sharks and mammals success is assured by the development of a special intromittent organ, the penis, by means of which sperms are placed high up in the female ducts and have to use their swimming powers only during the last stages of the journey to meet the ova. In many higher vertebrates the success of sexual reproduction depends largely on highly efficient forms of sexual behaviour and the mating instincts.

Alternation of Generations

The theory of an alternation of asexual and sexual generations was first applied by Steenstrup (1842, 1845) to coelenterates, trematodes and tunicates, animals which produce offspring that do not resemble their parents but which in turn produce other forms that do come to show the parental characters. Following the discovery by Munier-Chalmas of dimorphism in Foraminifera, J. J. Lister (1895) established the principle in regard to Protozoa. Many animals with which even the elementary student has to deal illustrate this alternation of a sexual and an asexual form in the life-history. The hydroid *Obelia* is sexually mature as a medusa, which sheds eggs or sperms into the sea. Here fertilisation occurs, and a minute creeping form, the planula, arises which soon fixed itself to the substratum and proceeds by a process of budding to found a branched colony bearing nutritive individuals (hydroids) and reproductive individuals (blastostyles), the latter giving rise to a fresh crop of medusae. Trematodes such as *Fasciola* develop a sequence of larvae which develop in snails. A miracidium hatches out from the egg and penetrates the mollusc. From germinal cells in

its body rediae are formed which also contain germinal cells, and these give rise to the third type of larva, the cercariae, which eventually become mature forms in the body of a new host, some vertebrate such as the sheep or cow. Regular alternation of generations also occurs in some ringed worms, for instance *Syllis* and some species of *Nereis*, but in this instance both sexual and asexual forms are adults modified according to the needs of the two methods of reproduction.

The alternation of generations which is seen in plants was established as a fact by W. Hofmeister (1851), who disclosed the succession of a sexual (gametophyte) and a spore-producing (sporophyte) generation in mosses, ferns, conifers and other plants. The leafy fern-plant is a sporophyte, and the spores which develop in capsules (sporangia) under the fronds severally give rise to small bisexual individuals, or prothalli, which produce both eggs and sperms, the fertilised egg in turn producing the fronded fern-plant. In mosses, seed-plants and others the two generations are not independent as they are in the fern; the gametophyte generation remains permanently attached to the sporophyte, like an ectoparasite on its host. The chromosome number differs in the two forms, being haploid in the gametophyte and diploid in the sporophyte. Various text-books of botany indicate the chief characteristics of the life-cycle in various plants, generally indicating by diagrams where chromosome reduction takes place.

In 1856 N. Pringsheim applied the idea of an alternation of generations to algae such as *Oedogonium* and *Coleochaete*. Ten years later Haeckel distinguished between the development of reproductive and vegetative shoots in plants and a true alternation of generations, which he called "metagenesis", and in 1868 L. J. Celakowsky used the term "homologous" to indicate the type of alternation seen in algae which produce similar but alternating sexual and asexual forms, and the term "antithetic" to denote the type seen in mosses and ferns, in which the two generations differ notably in size and appearance. For the method of development of asexual forms from the sexual without recourse to the use of sperms and ova, W. G. Farlow (1874) used the term "apogamy", and for that where spores are formed by other than the usual method of spore-formation Pringsheim used the converse term "apospory".

Parthenogenesis

It was known to Aristotle that the eggs of some animals develop into normal individuals without having been fertilised, a phenomenon

known as virgin-birth, or parthenogenesis. In his quest for the eggs of aphids Leeuwenhoek dissected many adults, and when he discovered one which contained about sixty miniature individuals the phenomenon was rediscovered. Failing to find males, he concluded that the young forms arose by virgin-birth. Not until the late nineteenth century, when the cytological mechanism of sex came in for close study, was parthenogenesis properly understood, though strange life-histories were noted long before they could be explained. We now know that two clearly marked types of parthenogenesis are distinguished by the haploid and diploid chromosome numbers of the individual animals. The diploid is the more common type, occurring in aphids, phylloxerans, daphnids, ostracods and a few other animals. The haploid type is found in many Hymenoptera, such as ants, bees and wasps, and also in some bugs (Hemiptera) and arachnids. Both types occur in rotifers and gall-flies, and transitional types are also characteristic of some Lepidoptera and Hymenoptera in which haploidy occurs at first but is transformed to diploidy. Various writers have dealt with characteristic life-histories, and D. W. Cutler (1918) outlined many of them.

The eggs of some water-fleas (Cladocera) remain dormant in winter but during the following spring they develop into females which give rise to the first of a series of parthenogenetic generations during the summer. During the autumn, males appear, and these fertilise sexual eggs, which acquire a thick, resistant coat and form a crop of winter eggs. In the related Ostracods males are unknown, and cases are recorded of their maintenance in aquaria for more than thirty years in a maleless condition, parthenogenesis thus being obligatory. The fertilised eggs of aphids also inaugurate a parthenogenetic series, but during the summer wingless "stem-mothers" appear. At certain seasons winged forms migrate to fresh plants, and towards the end of the year these females lay parthenogenetic eggs from which wingless males and sexual females develop, and fertilisation produces the resting egg of the winter. A somewhat similar cycle occurs in rotifers such as *Hydatina senta.* The winter egg develops into a female which produces eggs parthenogenetically, and these yield other females of the same type, but at certain times a generation can arise and produce eggs which do or do not require fertilisation. All fertilised eggs develop into parthenogenetic females, and after several generations sexual forms appear. If the smaller eggs from these are fertilised they give rise to parthenogenetic females, but if unfertilised they develop parthenogenetically into males. The gall-fly *Neuroterus lenticularis* arises from a fertilised

winter egg as a parthenogenetic female, which lays eggs in oak buds. From the eggs males and females arise during the summer, and the fertilised female lays her eggs in the soft tissue of young oak leaves, the stock from which the asexual generation arises in the following spring. In bees and wasps the fertilised eggs give rise to queens and workers—respectively females and imperfectly developed females; while the unfertilised eggs give rise parthenogenetically to drones, or males. Summarising what was known in his time, Cutler recognised three types of parthenogenesis: *accidental*, in the sense of taking place only occasionally, as in *Bombyx mori*; *facultative*, in the sense of producing eggs which may be fertilised or not, as in ants, bees and wasps; and *obligative*, where eggs cannot be fertilised because males do not occur. Cutler was careful to note that in all known instances fertilisation produces a female, but parthenogenetic eggs either males or females.

In recent years our knowledge of parthenogenesis has been extended by cytological investigations, and F. A. E. Crew (1946) has provided a summary of what is known. He has shown that diploid parthenogenesis such as occurs in aphids, daphnids and gall-flies gives rise to individuals which may be either male or female, but that in haploid parthenogenesis such as occurs in rotifers and bees the individuals are exclusively males. In natural diploid parthenogenesis there is always an associated absence of meiosis; the failure of meiosis during oögenesis enables parthenogenetic females to produce only individuals of the same kind. C. D. Darlington (1932) has classified the various ways in which meiosis is suppressed; chromosomes may pair incompletely at the first metaphase, or there may be failure in the pairing of chromosomes in pachytene and metaphase, but perhaps the most remarkable fact is the formation of two daughter nuclei and their fusion in the earliest stages of development. Early workers in this field realised that parthenogenesis was due to some failure of cell division during maturation of the egg; C. S. Minot (1877) and F. M. Balfour (1880) believed that the egg was unable to produce polar bodies, but A. Weismann (1886) discovered a polar body in the parthenogenetic egg of *Polyphemus*, and this was confirmed for *Aphis* by F. Blochmann (1887) and for *Daphnia* by Kühn (1908). Blochmann also proved that the fertilised eggs of *Aphis* produce two polar bodies (which was later found by Weismann to be true for ostracods and rotifers), and that in insects the polar bodies are not completely extruded but remain near the periphery of the ovum. T. Boveri (1877) suggested that parthenogenesis might be due to the fusion of the second polar body with the ovum nucleus, much as a sperm

might fuse with it, and A. Brauer (1893) showed that in one type of parthenogenesis in *Artemia* this is actually the case.

The chief cytological facts regarding the modified maturation divisions of parthenogenetic eggs were considered and classified by L. Doncaster (1920) and are too technical to be discussed here. Advances in our knowledge of natural parthenogenesis since 1920 may be found in the book by A. Vandel (1931) and the reviews by W. E. Ankel (1927, 1929), and M. J. D. White (1945) has given much cytological information about the phenomenon and has discussed its evolution. Various biologists have stressed the external causal factors of parthenogenesis: Kurz (1874) suggested that increased salt concentrations in evaporating watery media bring it about in *Daphnia*; Maupas (1890, 1891) suggested that differences of temperature bring it about in rotifers; A. Issakowitsch (1905) believed that both starvation and low temperatures are effective in the case of *Daphnia*; and M. Nussbaum (1897) also believed that variations in nutrition are effective in producing the sexual forms of rotifers. G. H. Shull (1910) came to conclude that these factors are ineffective, but that the chemical composition of the watery medium is decisive for the production of males, and D. D. Whitney (1914) was led by experimental results to believe that change of diet is concerned with the production of the sexes in rotifers. Weismann (1875) believed that reproduction is sexual in the appropriate season irrespective of external conditions, and suggested that the change from one mode of reproduction to the other is an inherited character. Yet many experiments have indicated that parthenogenesis can be produced artificially, the first of these (by A. Tichomiroff, 1886) being the establishment of parthenogenesis by treating the eggs of silkworms with sulphuric acid, or by subjecting them to mechanical friction (see Morgan, 1927). J. Loeb drew attention to this fact by his experiments with sea-urchin eggs, which can be induced to develop by various kinds of treatment—with mineral salts, acids and alkalies, for instance. In echinoderms and vertebrates alike many physical and chemical agencies will dispense with the need for fertilisation by inducing the unfertilised eggs to develop—hypertonic solutions of salts or sugars, fatty acids, fat solvents, etc. E. Bataillon (1911) induced the egg of the frog to segment by puncturing it with a needle, and when this was dipped in a droplet of the animal's blood or lymph development proceeded further (Voss, 1923); eggs activated in this way have developed past metamorphosis, showing that the sperm is not always necessary for the initiation of development.

Spermatozoa

Much of our knowledge of spermatozoa has arisen from studies of the physical and chemical agencies which affect them and from the

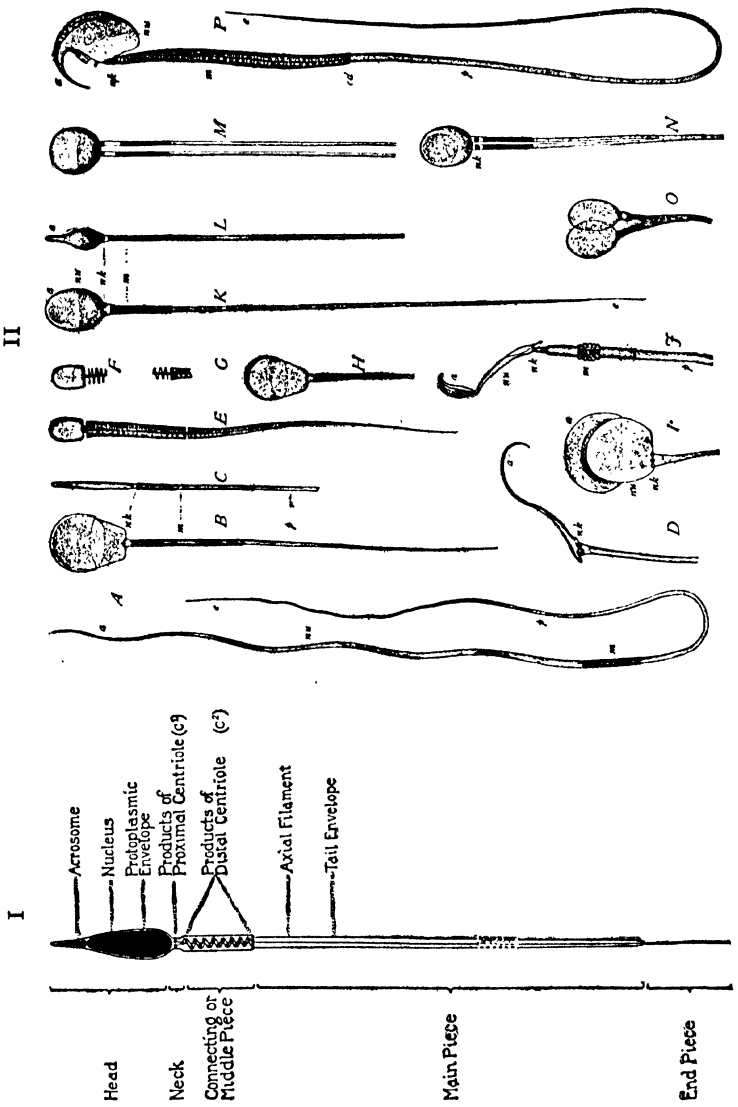


Fig. 6. I, Diagram of animal sperm, based on structure as seen in mammals. Broken lines indicate a long section of tail omitted. II, The spermatozoa of some mammals: *A, Echidna*; *B, C*, deer (*C* in side view); *D*, squirrel (side view); *E*, bat; *F* and *G*, details of the same; *H*, wolf; *I*, ♂, guinea-pig (♂ in side view); *K, L*, man (*L* in side view); *M, N, O*, abnormal sperms, partly double; *P*, field mouse; *a*, acrosome; *cp*, distal centriole or its products; *e*, end-piece of flagellum; *m*, middle-piece; *nu*, nucleus; *nk*, neck; *p*, main piece of flagellum. From Wilson, 1925 (II after Retzius). (The Macmillan Co.)

study of fertilisation. Spallanzani (1785) interested himself in the effect of temperature on the activity of sperms, and Kölliker (1856) marked the effects produced by various external agents on the sperms of mammals. J. J. Gemmil (1900) and E. J. Cohn (1918) noted the effects

of diluting suspensions of sperms in relation to fertilisation of the egg, J. Gray (1913), J. Loeb (1914–15) and R. S. Lillie (1916) investigated the physicochemical conditions affecting the sperms of echinoderms, C. Hartman (1927) studied the sperms of hibernating bats, and Mall and others have been interested in the life-span of human sperms. The work of W. Waldeyer (1906), G. Retzius (1902–14), E. Ballowitz (1913) and others revealed the extremely varied types of sperms taken from various animals and plants. A typical sperm such as exists in sponges, echinoderms and vertebrates is a uniflagellate form with a short head, middle segment and long tail. The sperms of flatworms are unusual, resembling trypanosomes, and those of roundworms are ovoid bodies which become amoeboid after entering the female's body, while crustacean sperms are rounded bodies with hook-like processes. In some animals male- and female-producing sperms show dimorphism. The antherozoids, or spermatozoids, of plants are rarely uniflagellate, generally having two long flagella and a spiral body, and in some ferns there is a conspicuous tuft of cilia. The work on structure as revealed by the ordinary microscope is covered in great detail by E. B. Wilson (1925), that on the activity of sperms in relation to external agencies by T. H. Morgan (1927). A recent electron microscope study of ram spermatozoa carried out by J. T. Randall and M. H. G. Friedlaender (1950) has revealed a wealth of exquisite detail which is not evident in ordinary microscopy. Previous studies of the same kind were made by L. H. Bretschneider (1947, 1949), C. J. and B. P. Reed (1948), E. B. Harvey and T. F. Anderson (1943) and F. O. Schmidt (1934), and ultra-violet microscopy has revealed that one of the chief constituents of the head is nucleic acid (T. Caspersson, 1949). Recent studies made by T. Mann (1949) have evaluated the concentration of sperms in the ram—2–5 millions per microlitre of semen—and the volume of ejaculate —0·7–2 per ml.

Fertility

By comparison with other animals the more highly organised vertebrates are not very fertile, but as their eggs are prepared for embryonic development and a more sheltered early life the ends of reproduction are equally well served. The fertility of birds and mammals is affected by many factors (see J. Hammond, 1941). From the earliest historical times men have known that the nesting season of birds, the rutting season of game animals and the menstrual periods of women are phenomena associated with reproduction. The traditional

time for reproduction is the spring, when most insectivorous and carnivorous mammals and rodents breed. Ruminants such as the sheep and the deer breed only during the autumn and winter, however; and polar bears are born only during midwinter. Birthdays are often events which concern a whole family at one time, not merely individuals.

The amount of daylight may play a part in seasonal breeding activities (see W. Rowan, 1938). The wild jungle fowl breeds only during a limited part of the year, but the slight seasonal variation in the fertility of domestic poultry due to diminished periods of daylight during some months of the year can be abolished by the use of artificial light (D. C. Kennard and V. D. Chamberlain, 1931). Starlings also may have their ovaries aroused to activity during midwinter by the aid of light (T. H. Bissonnette, 1931), and mammals such as the ferret and the racoon may be induced by this means to mate in midwinter, though normally their breeding activities are restricted to the summer months. Sheep which are transported across the Equator will adjust their breeding season to fit in with the new daylight conditions (see F. H. A. Marshall, 1936, 1937). To some mammals, however, the seasons of the year make no difference. Some lemurs have a restricted breeding season, but most monkeys and apes breed throughout the year, like human beings.

Human fertility stands at a low level as compared with that of other vertebrates (see S. Zuckermann, 1936). A normal woman produces an egg thirteen times a year for a total of about thirty years, and she can hardly bear more than about thirty children unless multiple births occur. Modern social developments have tended to reduce even this low level of fertility. The functional activity of the ovary of a mammal is controlled by the anterior lobe of the pituitary gland, the malfunction or removal of which causes atrophy of the gonads and the accessory sex glands. So long as the degeneration has not proceeded too far, however, the activity of the reproductive organs can be restored by the implantation of the gland concerned, and the implant may originate from the same or some other suitable species of mammal. The gland produces the gonadotropic hormones, which are first liberated into the blood of girls just before puberty is reached, and are no longer produced in women after the menopause. The limits of sexual life may be lengthened in women and domestic animals by the use of hormones and by the control of other factors. Some control of diminished fertility may also be gained by means of the retarding action of anti-gonadotropic hormones.

The male animal was formerly regarded as unimportant in regard to fertility, but recent work suggests that this is a fallacy. Sterility or loss of fertility in man and many animals may be due to defective sperm production. The issue is not just a question of sterility or full fertility, however, for all sorts of quantitative conditions have a profound effect on fertility. The normal ejaculate of human semen (3–6 c.c.) may contain 200 million spermatozoa and while, theoretically, only one sperm is needed to fertilise the ovum, in specially observed instances human pregnancy has failed to occur when less than 60 million sperms were emitted during copulation (see S. R. Meaker, 1934). High concentration of sperms is needed for full fertility, and diluted suspensions of viable sperms may lead to sterility. Reduced litters in rabbits have also been attributed to this cause by A. Walton (1927). Even when sperms are not deficient in numbers they may be abnormal in structure or lacking in virility, further causes of sterility. An excess of protein or a deficiency of vitamin E in the diet may impair spermatozoa. The life-span of sperms may also have some bearing on this question of fertility. The sperms of some fishes can live inside the body of the female for almost one year, and those of bats can survive the winter in this situation and serve to fertilise the eggs during the following spring. The sperms of birds do not remain viable for such long periods as these, but they may be stored for some time after one act of copulation and used for the fertilisation of twenty to thirty eggs produced at intervals during a period of about one month. Mammalian spermatozoa have a still shorter life inside the body of the female, the period ranging from about 38 days for the rabbit (J. Hammond and S. A. Asdell, 1926) to about 5 days for the horse (Hammond, 1938).

The fertility of domestic animals has been increased by means of artificial insemination, which greatly reduces wastage of sperms. This art was practised by Arabs with horses in the distant past and the first scientific experiments on the method were conducted about 1780. A single ejaculate from the male animal can be conserved and used to fertilise a number of females belonging to the same species—for instance, 2 sows, 8–12 mares, 10–40 cows and as many as 30–40 ewes (see F. H. A. Marshall and J. Hammond, 1949). By means of artificial insemination nearly three thousand ewes have been fertilised by one ram in one breeding season. Sperms can also be stored in tubes and they keep well for short journeys at comparatively low temperatures and can be sent abroad. Lambs have been produced from ova fertilised by sperms stored for a week in the laboratory, and also by sperms sent from this

country to Poland and other places abroad. Calves have been born in Holland as a result of fertilisation of ova by sperms collected in Britain and sent across the Channel by post (for other information see Hammond, 1941). The method of artificial insemination has also been applied to human reproduction, both in America and in Britain, and here also some claim advantages for it, though opinion is not unanimous in its favour. At any rate, the method indicates that the virility of spermatozoa is a factor in fertility which can be controlled.

The Sexual Cycle of Mammals

Reproduction in mammals takes place according to a cyclical process termed the "oestrus cycle". This affects such organs as the ovary, uterus, vagina and mammary glands, and it culminates in the condition of "oestrus", or "heat". Females of some species of mammals will consent to copulate with the male only during the period of "heat", but this may correspond to the entire breeding season, though generally it is a much shorter period. The fox is "monoestrus", *i.e.* has one oestrus period only during its breeding season, but other mammals may have several oestrus periods and are said to be "polyoestrus". This oestrus cycle comprises four phases, which are known as dioestrus, pro-oestrus, oestrus and metoestrus. The first phase is one of quiescent sexual life comparable with the longer periods of "anoestrus" which are interposed between successive breeding seasons. A similar phase prevails also during pregnancy, when the oestrus cycle is held in abeyance till parturition has occurred. Pro-oestrus is the phase of approach to "heat" during which the generative organs awaken to activity. Oestrus is the period of "heat" or desire, when males become tolerable to the female, whose vagina has become tumescent and particularly sensitive. By this time the uterus has been prepared for the reception of the egg, should this perchance be fertilised, containing the "uterine milk"—exudates, extravasated blood corpuscles and epithelial debris—on which the embryo will feed phagocytically during the earliest stages of its development. The mammary glands have become slightly swollen, as if in readiness for producing milk when this is required. As a rule, an ovum or several ova are released from the ovary at this time, though ovulation occurs in the rabbit, cat and ferret only when copulation has taken place. The behaviour of the female is also modified during oestrus, for she tends to prepare for the arrival of the young. If pregnancy does not occur, certain changes take place which are reminiscent of pregnancy and constitute a phase called

"pseudo-pregnancy". This leads on to the metoestrus phase, during which the vagina loses its tumescence, the uterus is cleared of its contents and the mammary glands are reduced to their former size. Sexual activity thus gradually dies down, and the dioestrus phase is reached once again. In women, the oestrus cycle has been greatly modified, for menstruation represents only its final disruptive stage.

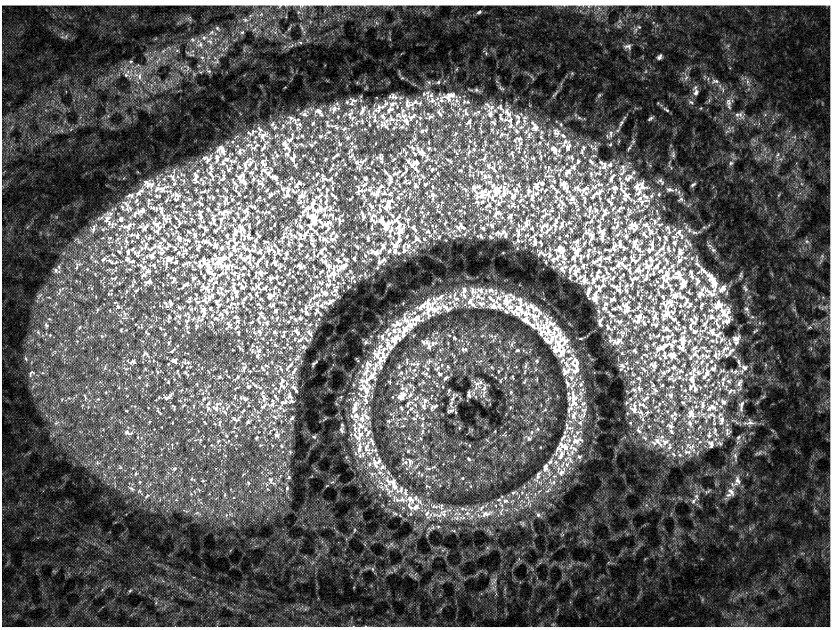


Fig. 7. Ovum of the cat, sectioned *in situ* in the ovary, lying in the Graafian follicle within the *discus proligerus*, the latter forming an investment (the *corona radiata*) of the egg. Within the corona is the clear *zona pellucida*. Magnification 215 diameters. From Wilson, 1925. (The Macmillan Co.)

Sex is determined by the inheritance, but the sex hormones of vertebrates play a part in its maintenance (see Burrows, 1945). They are chemical substances belonging to the class of sterols—androgens in the male and gynaecogens in the female—and their production is controlled by prolans formed in the anterior lobe of the pituitary gland and secreted into the blood. The sexual cycle of the female depends primarily on the pituitary factors "prolan A" and "prolan B", which are otherwise known respectively as the follicle-stimulating hormone (F.S.H.) and the luteinising hormone (L.H.). The former controls the development of the Graafian follicles and the production of the sex

hormones (oestrogens), and the latter is concerned with the formation of the corpus luteum and the production of the luteal hormone (progesterone). Oestrogens exist in both male and female mammals, but they are more abundant in the female. The most active of them—oestradiol ($C_{18}H_{24}O_2$)—is produced in the ovary, as is oestrone ($C_{18}H_{22}O_2$), but oestriol ($C_{18}H_{24}O_3$) is formed in the placenta during pregnancy. The injection of oestrogens into the body of the normal female greatly accelerates the onset of oestrus, causing rapid growth of

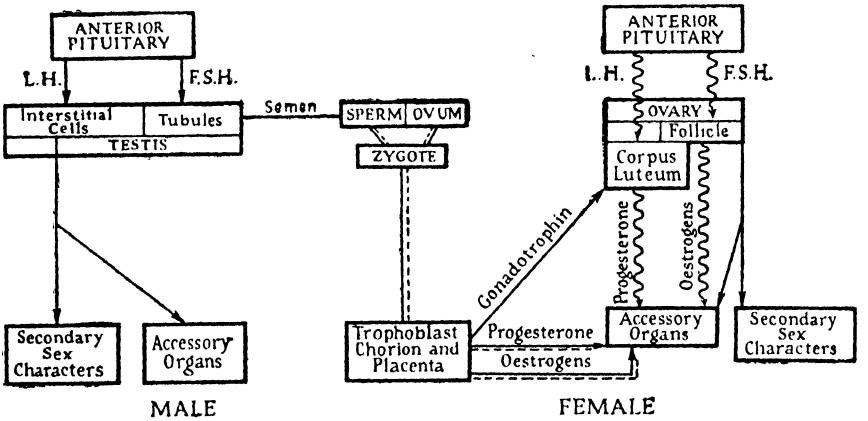


Fig. 8. Diagrammatic summary of the interrelationship of hormones concerned in reproduction. L.H., luteinising hormone; F.S.H., follicle stimulating hormone. From Winton and Bayliss, 1948. (J. & A. Churchill.)

the vaginal and uterine epithelium. The effect of stimulating the mammary glands to secrete milk is sometimes ascribed to the oestrogens, but this is brought about by the action of "prolactin", a hormone secreted by the anterior lobe of the pituitary gland. Progesterone ($C_{21}H_{30}O_2$) is formed in the yellow (luteal) cells which multiply in the Graafian follicle when the ovum has been shed. If pregnancy ensues, the hormone is secreted in large amount and this has the effect of inhibiting further oestrus (or further menstruation in women) during the period of gestation. It also plays an important part in the maintenance of pregnancy, facilitating the firm union of the early embryo imbedded in the wall of the uterus, and in the formation of the placenta, or after-birth. Apart from pregnancy, progesterone has an effect on the changes that occur in the wall of the uterus during the premenstrual phase.

The gonadotropic hormones of the pituitary gland thus exert their influence during different parts of the oestrus or menstrual cycle, prolan

A during the early part, prolan B during the later. The continued secretion of prolan B during pregnancy stimulates the corpus luteum far beyond its normal degree and leads to the production of increased amounts of progesterone. Oestrogens are excreted and appear in the urine about the middle of the menstruation period, but they disappear before the menstrual flow begins, whereas during pregnancy when the cycle is held in abeyance they appear in much greater amount, presumably because they are no longer required to maintain the cyclical changes. Progesterone is also produced in unusually large amount at this time, but is not excreted, presumably because it is needed for the regulation of uterine growth. The agents that bring about the secretion of gonadotropic hormones by the pituitary gland are little known, but some action must take place through the eyes, since light has the profound effect of awakening the sex organs during anoestrus. Nutrition is of considerable importance also, because the special winter feeding of cattle may be used as an alternative to increased and extended illumination in prolonging the reproductive period.

In the male animal there is no such complex cycle of oestrus, though cyclical changes can be recognised in some instances and the genital ducts are maintained in a proper condition by androgens. Testerosterone ($C_{19}H_{28}O_2$) originates in the interstitial cells of the testes from androstane ($C_{17}H_{26}(CH_3)_2$) and is excreted in the reduced form of androsterone ($C_{19}H_{26}O_2$) and as other sterones. These derivatives of cholesterol and other sterols have to do with the maintenance of maleness, as is proved by injecting them into animals that have become eunuchs as a result of experimental castration, but which then recover the characteristics of the normal male animal. The normal supply of the hormone is dependent on the activity of the anterior lobe of the pituitary gland, so that in both sexes there is co-operation between the gonads and the pituitary gland for the maintenance of sexual function.

CHAPTER SIX

DEVELOPMENT

UNLESS life is cut short by accident, multicellular animals undergo change from the moment of fertilisation to maturity, and even to the last stages of senility and death. Adult animals do not change much, and we can ascertain what they do and how they do it from a representative slice of their existence taken at any time. What an embryo is and does to-day, however, may tell us nothing of what it will be and do to-morrow, and changes wrought by the lapse of time become very important. Complexity is continually increasing by the bending, folding and twisting of parts that increase also in bulk and chemical complexity. The ovum is apparently just a cell, but it has the potentiality to develop into a starfish, a worm, a mouse, or a man no matter what moderate influences are brought to bear on it. Interference with development may distort an embryo, giving it a cyclopian eye or two heads, but it will not give us a mouse from the egg of a rat. The potentiality of the ovum is a physico-chemical organisation which reflects the degree of complexity attained by the parents. If these were triploblastic animals, mesoderm will make its appearance during development; if they were vertebrates, a backbone will arise; and if they were birds, feathers will appear. Early during its development distinctive characters will arise and will give us some indication of the zoological status of the parents. As J. G. Huxley and G. R. de Beer (1934) proclaimed: "Animal development is truly epigenetic, in that it involves a real creation of complex organisation. It is also pre-determined, but only in the sense that an egg cannot give rise to an organism of a species different from its parents. The development of each individual is unique. It is the result of interaction of a specific hereditary constitution with its environment. Alteration in either of these will produce alteration in the end result."

Recapitulation

Like other sciences, embryology has passed through three stages: descriptive, comparative and analytical. In the first of these, factual

observations were collected and interpreted according to traditional opinion. In the comparative stage, groups of facts were classified and correlated, with fruitful results, during the early nineteenth century, when K. E. von Baer established fundamental principles such as the conception of the germ-layers and of the gradual increase of complexity which is established during development. During the second half of the nineteenth century evolution theory gave a new meaning to the formalistic statements of embryology. Adult animals and plants were then regarded as the terminal shoots of a branching phylogenetic tree, and individual development was likened to the hidden portions of the tree lying between the branches and the root. Because the developing organism gradually acquires the grade of organisation possessed by its parents, it was easy to imagine that development might provide clues regarding the course of racial history, or phylogeny. The embryo might, as it were, retrace the steps taken by its ancestors. K. E. von Baer, who was not an evolutionist, was content to note close resemblance between the embryos of various animals. His "Biogenetic Law" taught that during development general characters arise before special, which arise from the less general as these arise from the more general, and that divergence between different species of animals increases during development. Ernst Haeckel regarded resemblances as indications of common ancestry and believed ontogeny to be a true recapitulation of phylogeny. Relationship was taken as kinship, and stages in development were regarded as retraced stages of evolution, larvae such as the blastula and gastrula replicas of a common ancestral form, and gill-clefts in the mammal embryo characters that once formed part of adult structure. As P. Weiss (1939) has stated: recapitulation "was acknowledged as an explanatory principle, and methods current in the study of *history* were applied to the field of embryology".

There was not long to wait, however, for proof that an embryo which proceeds from a simple to a more complex type of organisation does not necessarily follow in the footsteps of its ancestors. First came a realisation of the fact that ontogeny, being of very limited duration, could not possibly provide more than the broadest indication of racial history. Stages sometimes have to be omitted and, more importantly, stages have to be intercalated in order to provide for the needs of the embryo. Larval and embryonic life call for special organs that would be incongruous in an adult. Larvae must float or swim in order to be widely distributed through a watery medium, even though they are destined when adult to lead sedentary lives. Embryo birds and

mammals are protected by the amnion, or caul, and breathe and excrete by means of the allantois, and neither of these structures could ever have found a place in adult anatomy. Adaptive larval and embryonic organs often arise during development, robbing this process of its directness. The ovum has to develop into a particular kind of organism, and it must also provide for the maintenance of that organism during development.

W. Garstang (1929) remarked that to some zoologists "larval stages represent foregone ancestors, and all they have to do is to account for discrepancies. As the chain of adult ancestors is drawn out, at each new evolutionary advance the former adult is succeeded by a new one, and slips back into the ontogeny as a developmental stage." He gave three reasons for not accepting this theory: first, the assumption in spite of contrary evidence that new steps in evolution are first manifested in adult life; second, its inconsistence with the actual course of development, when various organs often appear independent of any probable phyletic time-scale; and third, the ignoring of genetic principles, which allow us to assume that an ontogenetic stage resembles an extinct ancestor, but not that it is an inheritance of it.

G. R. de Beer (1930, 1940) wrote a detailed criticism of the "outworn" theory of recapitulation, and he showed that the principle of heterochrony explains the appearance of characters later, at the same time, or sooner in successive ontogenies. In regard to youthful and adult characters he recognised eight possibilities. The youthful characters of an ancestor may in a descendant's ontogeny appear (1) only in the young stages as larval adaptations (*caenogenetic* characters) which have no effect on a phylogenetic series of adults, (2) in the adult condition, taking the place of old adult characters so that the ontogenies of ancestor and descendant show progressive *deviation*, and (3) in the adult as bodily characters which are retarded relative to the reproductive organs, yielding sexually mature larvae by *paedogenesis*, or *neoteny*. The characters of young and adult ancestors may appear (4) in the ontogeny of the descendant only in the young stages, so that in the adult the characters are rendered vestigial by *reduction*. Characters of the adult stage in the ancestor may in the ontogeny of the descendant appear (5) in the adult stage, giving individual, varietal and racial characters by *adult variation*, or (6) in post-adult stages (never realised), the characters being reduced to vestiges by *retardation*, or (7) in the same stage, but no longer the adult stage, addition having been made at the end of previous ontogenetic history by *hypermorphosis*, or (8) in the young stages precociously by *acceleration* of development, and

be persistent or not. The second and third possibilities are anti-recapitulatory (neogenetic), the seventh and eighth recapitulatory (palingenetic). The reader is referred to G. R. de Beer's interesting book (1940) for a full discussion of these and other striking features of the relation between ontogeny and phylogeny.

Experimental Embryology

The experimental and analytical phases of embryology arose during the latter part of the nineteenth century. According to P. Weiss (1939) " it was largely men with medical interests, pathologists and anatomists and histologists, who indulged with increasing emphasis in a study of the organism not as a product of the past but as a product of the present ", for " only knowledge of the *actual causes, factors* and *mechanisms*, normal as well as aberrant, operative in transforming the individual from the egg to the adult could satisfy their inquisitiveness and bring them nearer to their goal; to understand the reasons for deviations from the normal course ". At a time when morphology was flourishing in Germany under the leadership of Carl Gegenbaur, and when Darwinism had fought its biggest battles in Britain, Wilhelm His (1874) explained chick development in terms of the movements of elastic plates and tubes, and illustrated his views by means of mechanical models. He was the first person to suggest the existence of organ-forming regions in the developing chick, and to try to map them out. His work inspired Wilhelm Roux to experiment with the living eggs of the frog. In 1883 Roux published his work on the time of determination of the main axes of the frog's embryo, and during the next twenty years he formulated many profitable lines of experimentation in embryology. In 1888 he tried to mark out early cells of the embryo so as to trace out their fate; but his minute pricks tended to heal without leaving a trace, and larger marks tended to produce deformities, so it was left to others to work out a completely new method of experimentation. Hans Driesch (1891) isolated the two blastomeres of the egg by shaking, and obtained two larvae from the separated cells. C. Herbst (1900) used calcium-free sea-water for separating the blastomeres of sea-urchin eggs, and Hans Spemann (1901–3) confirmed the results of Oscar Hertwig (1893), H. Endres (1895) and A. Herlizka (1897), who constricted the two blastomeres of the newt's egg by means of fine ligatures and obtained twin embryos artificially, as well as partial duplications—such as a larva with one body but two heads—by incomplete constriction of the early cells. W. Vogt (1925) hit on the method of marking certain cells of the early

embryo with harmless dyes such as Nile blue and neutral red, which H. D. Goodale (1911) had first used in America. When the fate of the marked cells had been traced out during gastrulation it became possible to prepare topographical charts of later organs on diagrams of earlier stages of development. Such "fate-maps" were later prepared for other groups of animals, for R. Wetzel (1925) applied vital staining to bird embryos, L. von Ubisch (1925) and S. Hörstadius (1928) to echinoderm larvae. The task conceived by Wilhelm His was thus accomplished.

Another fruitful method of experimentation was heteroplastic transplantation, which was instituted by G. Born (1894, 1897), who joined together parts of embryos belonging to different species such as frog and toad, and obtained individuals which continued to develop. Ross G. Harrison (1898) used similar methods, but chose species having differences of pigmentation in order to trace the fate of the separate parts. He defined heteroplastic grafting (1935) as "the union of parts of organisms of different species into a single individual, or the combination of individuals of different species in double or multiple organisms living parabiotically". The Chimaera of Greek mythology was thus realised. In 1907 H. Winkler was the first to produce plant chimaeras by grafting tomato and nightshade, and the so-called "hybrids" which were produced were recognised as chimaeras by E. Baur (1909, 1910), who made microscopical studies of experimentally produced geraniums and plants of the nightshade family. Spemann (1921) used delicate operative techniques to remove certain presumptive areas of embryos of the same or other species, so that the fate of such regions could be traced *in situ* both in normal regions and in incongruous situations. He introduced the term "animal chimaeras" into the literature of embryology, and E. Taube (1922) gave a good account of such forms.

Much early work in experimental embryology was published in Roux' *Archiv für Entwicklungsmechanik der Organismen*, which was founded in 1895, and in the *Journal of Experimental Zoology*, which first appeared nine years later. The term chosen by Roux is untranslatable, and the anglicised term "developmental mechanics" has not been popular outside Germany. Driesch preferred the term "developmental physiology" and English writers "experimental embryology", or "causal embryology". But what is implied in all these terms is explicit; namely, the causal analysis of all developmental processes. Huxley and de Beer (1934) have referred to the work of Driesch, Boveri,

Wilson, Herbst, Morgan, Brachet and Jenkinson in the phase which followed the initiation of experimental embryology, when much knowledge was amassed and epigenesis was proved experimentally, and also to the part played by Spemann and Ross Harrison and the theories of C. M. Child which came later. Child not only linked the facts of regeneration with those of embryonic differentiation but provided a scientific basis for a field hypothesis for early development. Experimental embryology also advanced as a result of fruitful contacts with physiology, notably in regard to hormone action, with genetics, and with studies on growth. Early developments were reviewed by T. H. Morgan (1897). His small book was the first of its kind to be written in English; it contained 192 pages plus 13 pages of references. In 1927 the same biologist published his *Experimental Embryology*, a large book of 766 pages, with a list of literature more than one hundred pages long. These facts fairly indicate the early growth in importance of experimental embryology, on which subject many books have since been written. Huxley and de Beer showed that the present stage consists of a filling-in as a result of intensive research of the framework of general principles, and the deepening of the science by a search for the physicochemical basis of the empirical biological principles which have been discovered during the early stages.

The Early Development of a Frog's Egg

The egg of a frog or a newt is a spherical cell already having that form of differentiation which is called polarity. The upper pigmented animal pole contains cytoplasm and nucleus, the lower non-pigmented vegetative pole yolky protoplasm, since yolk has a higher specific gravity than protoplasm. The main axis of the egg is vertical and it passes through both poles. The entry of the sperm exerts a threefold effect: it stimulates the egg to develop; it conveys to the egg genes of paternal origin; and it determines the sagittal plane, and therefore bilateral symmetry. The point of entry was shown by Roux (1903) and J. W. Jenkinson (1907, 1909) to mark the future mid-ventral line, though the only visible change in the egg is the appearance of a pigmented trail, the grey crescent, which marks out the future dorsal surface. The three axes of the future embryo are thus fixed before segmentation of the egg begins. Cleavage results in the production of more than one thousand small cells, or blastomeres, which are small in the animal hemisphere but larger and yolky near the vegetative pole. These are arranged in the form of a hollow ball, the blastula, which has

a central cavity, or blastocoele. Development proceeds with gastrulation, during which animal blastomeres spread over vegetative ones

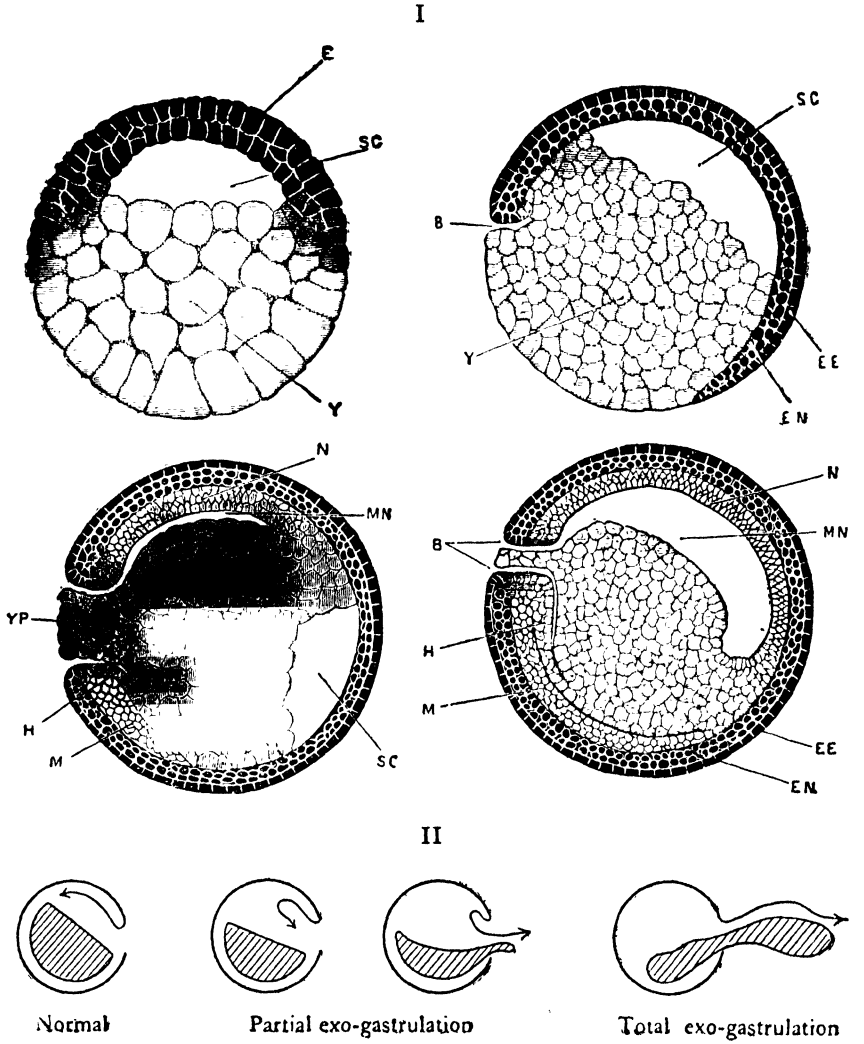


Fig. 9. I, Diagrams illustrating gastrulation in amphibia by means of vertical longitudinal sections through the embryo. B, blastopore; E, roof of blastocoele; EE, EN, ectoderm; H, ventral lip of blastopore; M, mesoderm; MN, archenteron; N, its roof; SC, blastocoele; Y, yolk cells; YP, yolk plug. II, Diagrams (obverse of I) illustrating normal gastrulation and exogastrulation. From Needham, 1942. (Cambridge University Press.)

(epiboly) and invaginate, first dorsally, then laterally, and finally ventrally. Invaginated cells form the lips of an opening, the blastopore,

and ingrowth leads to the formation of a new central cavity, the archenteron, or future gut, which gradually displaces the blastocoele as it enlarges. The fully formed gastrula then elongates to form a neurula and while this is taking place germ-layer formation ensues, so that the neurula has various organs—for instance, a rudimentary brain, notochord, gut and mesodermal somites. Later development is concerned with the elaboration of these organs and the formation of others such as the eyes, ears, nose, skeleton and heart.

Mosaic and Regulative Eggs

The egg of a starfish is almost yolkless and it forms a blastula having many similar blastomeres. If up to the four-cell stage at least the blastomeres are shaken apart, each of them will develop into a perfect embryo of reduced size, as Driesch (1900) first showed. If instead the blastomeres are partially separated, the developing larva may become a monster with some parts of the body duplicated. When two such eggs are combined before segmentation a single embryo results. Such eggs, the parts of which have no fixed fate, are known as "regulative eggs". In recent years it has been found that a developing egg may be regulative to the late blastula stage, in which case a part that is removed and transplanted into some other situation in another blastula will develop into the particular parts characteristic of the new situation. Alternatively, the early blastomeres of other ova will not develop into complete larvae when shaken apart, and later blastomeres when grafted into a second embryo develop into the particular part which they would have formed in the original embryo. Such eggs, which have their fate more or less fixed from the start, have been called "mosaic eggs". In some developing embryos, therefore, there must be a sorting out of materials into qualitatively different sorts; in other embryos equivalent partition. The distinction between regulative and mosaic qualities is not always so definite, however; the blastula which develops from the frog's egg is regulative, but the gastrula is mosaic. The fate of the early blastomeres is not irrevocably fixed till gastrulation has occurred. Gastrulation has brought about an important alteration in the organisation of the embryo.

The Primary Organisation Field

Many studies, largely inspired by Spemann, have proved that the dorsal lip of the blastopore in an amphibian embryo (early blastula) is

not just a static part of the rim of an opening but a dynamic region through which the ingrowing blastomeres pass during gastrulation. Materials which will bring about the formation of the head pass through first, those relating to trunk and tail afterwards. These materials form directly the notochord and the rudiments of mesoderm, which form the longitudinal morphological axis of the embryo, along which growth potential is graded, forming an axial gradient. If the dorsal lip of the blastopore is removed from the early embryo of a newt and pushed underneath the superficial (ectoderm) cells of another embryo of the same age, the first embryo fails to develop a nerve tube and the second embryo develops its own and a supernumary nerve tube. Evidently the cells of the dorsal lip are concerned in some way with the formation of the central nervous system of the future animal. The dorsal lip contains some substance which "organises" the development of the nerve tube. Spemann (1921) first described the "organiser" effect for a specific "centre", but as Weiss (1939) has shown, he had in mind a regional effect and was the first to use the term "organisation field" which superseded the term "organisation centre" for a broader effect than was at first implied. A. Gurwitsch (1922) put forward a similar idea, and Weiss (1923) established the "field" character of this phenomenon of organisation. As the blastomeres of the organisation field cannot be distinguished visually from others lying outside it, organisation must at first be of a chemical nature, *i.e.* a form of chemo-differentiation.

The distinction between self-differentiating and induced organs was shown neatly by J. Holtfreter (1933), who treated the gastrulae of the axolotl with chemical solutions which did not interfere with cell proliferation but which prevented the normal invagination of blastomeres. In the abnormal process of "exogastrulation" the notochordal and mesodermal rudiments are developed, but they lie outside the ectodermal part of the embryo. The "organiser" is thus kept distant from the superficial ectoderm and the nerve tube does not develop. That the notochord of the exogastrula contains the "organiser" is evident when it is removed and pushed underneath the ectoderm of another embryo, for this then develops a supernumary nerve tube. Moreover, the ectoderm of the exogastrula is just as competent to respond to the "organiser" as is that of the normal blastula, as is shown by the way it develops into nerve tube when notochordal tissue is pushed underneath it. The exogastrula fails to develop a nerve tube because the "organiser" and the appropriate competent cells are not brought

together. The notochord and the mesodermal somites cannot be induced to develop by the action of other parts of the embryo; they are self-differentiating parts, and they constitute the primary field of organisation in the main axis of the embryo. The nerve tube, and therefore the central nervous system of the future animal, is determined by the influence of other parts of the embryo; it is an induced organ, and it forms the primary induction field of the embryo. The "competent" parts of the embryo develop as a result of the action of the "organiser" or, as it came to be called, the "evocator".

Chemical Embryology

Spemann's experiments were carried out with embryo newts but his conclusions were soon found to apply also to embryos of sea-urchins, insects, fishes, birds, mammals and other animals. According to J. Needham (1939) the first biochemical approach to problems of development was made in 1931 when it was shown that crushed blastomeres from the organisation field of an embryo retain their powers of evocation. The same was soon found to be true of boiled, frozen and dried blastomeres, and experiments were then set up to test various substances for this quality of primary inductor capacity. The best results at Cambridge were obtained with unsaponifiable fractions of ether extractions made on neurulae; in the rival school at Freiburg, higher fatty acids, nucleoproteins and glycogen were found to display such activity. In 1933 J. Needham, C. H. Waddington and D. M. Needham (1934) evoked the formation of nerve tube from competent cells otherwise destined to produce skin by the use of ether-soluble substances, and in the same year J. Holfreter showed that the "evocator" exists in some tissues removed from various adult animals. F. G. Fischer, E. Wehmeier and L. Jühling (1933, 1934) proved that muscle adenylic acid and thymonucleic acids act in the same way, and finally C. H. Waddington, J. Needham, W. W. Nowinski and R. Lemberg (1935) proved that the "evocator" is probably a sterol, while C. H. Waddington and D. M. Needham (1935) showed that some oestrogenic agents and one carcinogenic agent, by nature synthetic hydrocarbons, bring about evocation. These data hold unusual interest in view of the fact that the sterols are often concerned with normal and abnormal growth. The non-specific action of evocators implies that the tissues of the embryo have some complementary importance, developing only into the kind of organ which is found in that type of embryo. The evocator of a chick induces the formation of nerve tube in a newt, but this is of

amphibian, not avian, type. Chemical substances handed on in the inheritance are in some way responsible for this fixity of pattern.

J. Needham (1937) pointed to the paradox that although the evocator is a non-living chemical substance, organisation involves the regional differentiation observed by Spemann, who tested the inductive capacities of various fragments of evocator at different levels of the embryo. The "head-organiser" at head-level determines a secondary head, complete with eyes and ears, but at trunk-level a complete secondary embryo; the "trunk-organiser" at head-level organises a complete secondary embryo, but at trunk-level only trunk and tail. What is involved in evocation is not known, but in grafting experiments which lead to the formation of supernumary organs it is clearly work on the part of the host tissues. When G. V. Lopaschov (1935) cultivated isolated fragments of dorsal blastoporal lip *in vitro* he obtained only fragments of notochord and striped muscle; but when several fragments were allowed to fuse they produced pigment cells, epidermal cells and sometimes nervous tissue and brain.

Self-differentiation

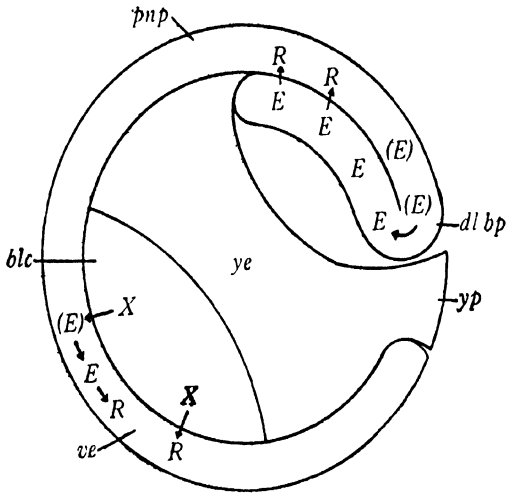
When a newt gastrula is divided into future head and trunk regions, and the halves are allowed to develop separately, each will form that part of the body which it would have formed in the intact animal (J. Holtfreter, 1931). The anterior half forms a well-developed but trunkless head which bears eyes, ears, nose, mouth, skull, brain and other cephalic parts, and the posterior half develops the rudiments of a backbone, spinal cord, kidneys, limbs and other parts, but not a head. Each half of the embryo has developed independently of the other, or has undergone self-differentiation. The same is true of smaller fragments removed from the body of the embryo. T. S. P. Strangeways and H. B. Fell (1926) cultivated a fragment from the side of the head *in vitro* and found that it developed an eye, and H. B. Fell and R. G. Canti (1934) took part of a thickening from the wall of the trunk and found that it produced a limb with typical jointed skeletal parts. P. Stöhr (1924) cultivated a fragment of mesoderm from the ventral wall of the trunk, and watched it develop into a four-chambered embryonic heart, which soon began to pulsate rhythmically. At the time of explantation this mesodermal fragment appeared to be identical with other samples of mesoderm, but it was endowed with the capacity to develop into a part having a characteristic histological structure and a unique function; it had powers of self-differentiation, even when

grown outside the body of the embryo. Such facts imply that, at the neurula stage, an embryonic amphibian is a sort of mosaic of regions each of which can differentiate into some part of the future animal. Some such regions arise from blastomeres carrying the primary evocator, others from blastomeres which have the competence to develop along certain lines when they come under the influence of the evocator and to establish subsidiary fields of organisation.

Secondary Organisation Fields

The broad outlines of the future animal are determined by the primary organisation field of the embryo, but many details of structure which are added later arise by the action of subsidiary fields. Chemo-differentiation takes place within the primary field, and polarised regions of the embryo are established which determine the positions and formations of the limbs, eyes, nose, ears, heart, gut and other organs and parts. The embryo soon loses its general characteristics as these secondary fields are set up. Each such field has a certain amount of local control over development, or emancipation, so long as its development is in harmony with that of other regions and parts and with that of the embryo as a whole, but the developing parts have some plasticity and can be moulded by the dynamic energy which permeates the entire embryo. The classical work on correlations in eye development was carried out by Spemann (1901). The first rudiments of eye structure to be formed are the optic cups, which grow out of the fore-brain. In some amphibians these contain the evocator for producing lens, which develops by the invagination of superficial ectoderm cells. If an optic cup is removed from one such embryo and transplanted underneath the skin of another embryo, a lens rudiment develops where skin only would have been formed (Harrison, 1904). This happens even when the rudiment is placed in an incongruous situation such as the flank of the embryo. In other amphibia, however (*e.g.* the edible frog), the lens is a self-differentiating part. The limbs arise from disk-like regions on the flanks of the embryo during gastrulation (S. R. Detwiler, 1929). Their potency lies in the mesoderm, the ectoderm having no power of evocation. If the limb-bud is transplanted into a part of the embryo in which a limb would not normally develop it still forms a limb, because it is self-differentiating. If cells which would not normally have formed parts of a limb are introduced into the graft, they co-operate with their associates to form a limb in the new situation. Once the rudiment of an organ or part has been organised it goes on with its

I



II

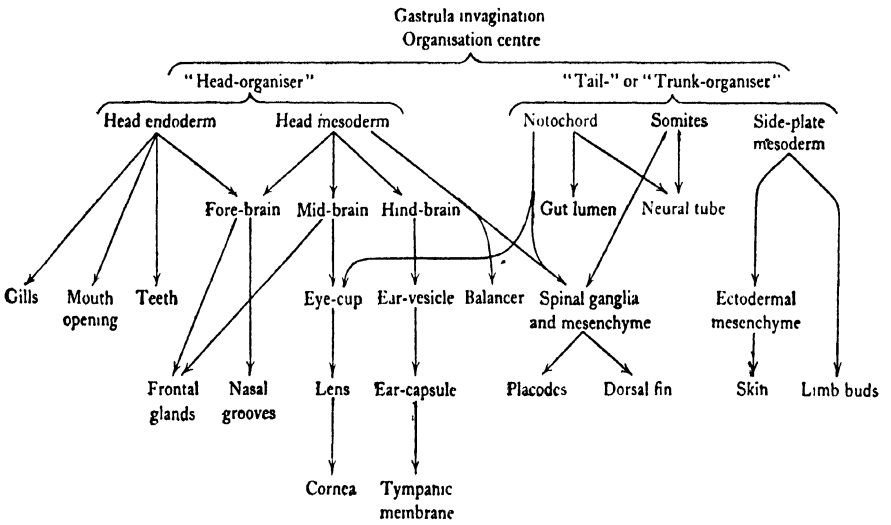


Fig. 10. I, Diagrammatic longitudinal section of amphibian gastrula illustrating direct and indirect induction. *blc*, blastocoele; *dl bp*, dorsal lip of blastopore; *pnp*, neural plate; *ve*, ventral ectoderm; *ye*, yolk; *yp*, yolk plug. *X*, chemical substance; *E*, free evocator; (*E*), masked evocator; *R*, response (neural tube formation). II, Diagram showing the succession of inductors of various grades in the development of vertebrates. From Needham, 1942. (Cambridge University Press.)

development, even in an odd situation, and it will induce adjacent cells to develop in harmony with it. The mesoderm of the early limb-bud rudiment contains the particular organisation field which achieves this effect, the overlying ectoderm merely conforming to the particular kind of growth that is made. Even when the limb-bud is grown *in vitro* it makes an attempt to develop into the particular kind of limb to which it would normally have given rise, parts such as the upper arm or leg and the digits developing the characteristic bones of a pentadactyl limb.

Most of the embryonic organs are self-differentiating and some of them will not outlive their normal span of life when cultivated *in vitro*, which is as good as saying that the span of usefulness of an organ to the animal is a function of the organisation field which produces that organ. In some instances, a normal organ is formed only when two or more organisation fields merge with one another. The heart of a vertebrate animal is formed out of two embryonic blood vessels that approach one another, come into contact, and ultimately merge to form one enlarged vessel which begins to pulsate as soon as muscular tissue is added to the outside. If some neutral tissue is interposed between the two heart rudiments, to prevent them from establishing contact, two hearts develop instead of one, and if the lateral heart rudiments are suitably subdivided it is possible to obtain an embryo with several hearts instead of one (G. Ekman, 1924). Similarly, by partial division of an arm-rudiment or a leg-rudiment a double arm or leg can be induced to develop. This may seem like carrying experiment too far, but accidents of development often produce malformations and there is a science of monsters, or teratology.

Weiss (1939) has emphasised that "malformations are merely modifications of the standard developmental patterns, rather than developmental innovations". When the first two blastomeres of the segmenting egg separate and continue their development, identical twins result; but if separation is incomplete a double-headed monster may arise. By the use of simple chemical solutions C. R. Stockard (1907–10) produced cyclopean embryos of a fish (*Fundulus*), some of which hatched normally and lived for more than a month, apparently able to see. Human cyclopean monsters usually die before birth, or survive for only a few hours afterwards, but L. Paolucci (1874)—who was the first person to produce monsters experimentally—reared several thousand monster chicks. He realised that "the anomaly and the monstrosity appear at certain epochs of development as a result of

a modification in the evolution of an isolated organ or of a more or less considerable number of organs" and that "they are the result of a change in the direction of the force which determines the successive appearance of different parts of the embryo" (quoted by H. B. Adelmann, 1936). The division of a field of organisation into component fields may be expected to produce an embryo or a part showing partial if not complete duplication. Embryonic tissues have great powers of regeneration, and when some accident of development tends to interfere with the normal course of events there is an attempt on the part of the embryo to get as near normality as is practicable, but when an organisation field loses its identity by division into component fields each of the resultant components undergoes self-differentiation in an attempt to fulfil its destiny.

The Modern Outlook in Embryology

Writing in 1940, J. Needham discussed the changed outlook in embryology. In 1930 little could be said about biochemistry and morphogenesis; ten years later it was possible to record "remarkable advances in knowledge centering round the biochemical nature of the 'morphogenetic hormones' which act in normal embryonic development, forming a hierarchy of inductors." He referred to gastrulation as "the turning-point in vertebrate development". To understand the metabolic changes which are taking place in the gastrula is a necessary prelude to the relating of biochemical and morphogenetic processes, for "at the heart of morphogenetic processes there is a metabolic factor, not only because the proteins of the cell structure on which in the last resort morphological architecture must be based are built up by enzymic reactions, but also because the stimulating substances, the morphogenetic hormones, are themselves chemical molecules with a metabolic origin and a metabolic fate". In order to facilitate measurements of the metabolism of parts of the gastrula extremely fine manometric methods were devised, particularly the adaptation of the Cartesian-diver technique introduced as an "ultra-manometer" by K. Linderstrom-Lang and D. Glick. This instrument is about two thousand times as sensitive as the Warburg manometer which is often used for the determination of respiratory exchanges. By this means certain measures of metabolism showed that the dorsal lip of the blastopore is about three times as active as the ventral ectoderm. But Needham was forced to conclude that "although the progress made in the last ten years in these fields has been very great, we can nevertheless

see now that owing to the special difficulties of the subject, especially perhaps the presence of evocator in ventral ectoderm, it may be more like fifty years before we can expect to have certain knowledge concerning the chemical nature of the naturally-occurring substances involved in embryonic induction". "Like so many other biological problems, this has turned out to be more complex then the first explorers thought."

In the Conclusion of his further work, *Biochemistry and Morphogenesis* (1942, 1950), Needham stressed that "the polarity and symmetry properties of embryos will never be understood except in the light of a knowledge of the dynamic structure of the egg-cell ". The problem of these properties led to the fundamental problem of modern biology, the "nature of cytological and morphological organisation". Needham showed that "the fields of chemistry and morphology are not so sundered as is often supposed. Organising relations are found at the molecular level and at the colloidal and paracrystalline level, the level of protein macromolecules and highly polymerised substances, just as clearly as at the anatomical level itself". Even in this, "the earliest stage of any real theory of living organisation, we can yet see that biological order, like crystal order, but on a much more complicated plane, is a natural consequence of the properties of matter, and one characteristic mode of their manifestation". This did not mean the end of the embryologist's task, which was taken to be "the revealing of the causal sequence whereby the organisation of the fully formed organism arises from the lesser organisation of its zygote", but only the beginning.

Embryology and the Concept of Organism

The concept of the organism and of its relations with constituent cells has been called "the central problem of biology" (V. B. Wigglesworth, 1948). Weiss (1940) suggested that "every step in development reveals the cell in a double light; partly as an active worker and partly as a passive subordinate to powers which lie entirely outside its own competence and control", and Hans Przibram (1926) believed that "the cells play a greater role in subdividing living matter in a way necessary for restoration of the nucleo-plasmatic equilibrium than in morphogenesis". As the cells of an animal's body are held to be genetically identical, cytoplasmic elements must be concerned with the ways in which they diverge during differentiation. S. Wright (1945) and D. F. Poulson (1945) put forward the idea of self-duplicating

"plasmagenes" in the egg, controlled or synthesised by genes in the nucleus and transmitted through the cytoplasm. Plasmagenes have the capacity to become modified chemically and to multiply in the altered form. The chemical modifier may result from gene-controlled chains of reactions inside the cell, or hormonic induction from outside it.

Some writers, *e.g.* A. Fischer (1946), have regarded the organism as a chemical continuum, or giant molecule, and C. H. Waddington (1940) also upheld the idea of continuity above the level of the cell, while G. A. Baitsell (1940) compared the cell to a protoplasmic crystal composed of an enormous number of linked protein molecules. Such molecules extending in a continuum from the level of the gene to submicroscopic and microscopic structure probably yield specific protein bodies in which molecule, crystal and cell shade one into another. S. Edlbacher (1946) attributed developmental potencies in living systems to molecular arrangements in a species-specific protein matrix. V. B. Wigglesworth (1945, 1948) suggested that even supracellular fabric is a chemical continuum—a "molecule" in the sense that it is held together by chemical bonds—continuity from cell to cell providing for the unity of organism. He rejected Richard Goldschmidt's conception (1938, 1940) of orderly differentiation by successive emissions of "hormones" or evocators, each of which reacts in its turn with appropriately developed parts of the organism. Determination—or what Wigglesworth calls "crypto-differentiation"—is a phase of differentiation during which the organism becomes a mosaic of areas destined to different ends, and it is supposedly under the control of "field forces". These are identified by Wigglesworth with the qualities possessed by active centres for taking up materials that are necessary for particular determinations, surrounding zones being inhibited from developing such centres. Individuation is regarded as an autonomous process of release of potencies and inhibitions.

Wigglesworth showed that in insects the epidermis is the "prime mover" in morphogenesis. Its individual cells form executive units, but the non-cellular chemical continuum, which is the essential organism, determines what functions shall be attributed to a given cell. Chemical activities in the continuum have their effects on activities taking place some distance away, perhaps by absorption of particular substrates from the medium. At one point of this self-determining system a lead is taken and chemical change (determination) takes place which inaugurates the formation of a given part. At other points there is chemical inhibition of similar change, which may be permanent or only

temporary. In these parts new chemical changes supervene and these lead to the determination of subsidiary parts, and "so the process goes on, alternating suppression and release of potencies proceeding from a leading point and so creating an illusion of a 'determination stream' along an 'axial gradient'. Interwoven with this autonomous system is genic action, either localised within cells or diffused throughout the body, and the action of hormones." "The profoundly different characters of larval and adult insects", stated Wigglesworth, "exist potentially, already determined, side by side within the cells. Circulating hormones control the realisation of these latent characters."

CHAPTER SEVEN

GROWTH

GROWTH generally implies increase in size or weight. Inanimate objects such as crystals grow by accretion, but even simple living things grow by the arrangement and rearrangement of countless submicroscopic particles, old and new, and in more complex organisms cellular additions must be made and apportioned between already complex organs, for growth concerns cells as well as the individual as a whole. Growth may mean additions of living protoplasm, or of fats, starches and imbibed water as well, and non-living materials such as cellulose, chitin, keratin and mineral salts may

TABLE 3.—THE DURATION OF PRE-NATAL AND POST-NATAL LIFE IN SOME MAMMALS. (*After* HEILBRUNN, 1943.)

Animal	*Gestation Period* (weeks and days)	*Normal Length of Life* (years)
Mouse and rat	3 — 0	3–3½ and 2½
Rabbit	4 — 2	5–7
Beaver	6 — 0	20–25
Cat	8 — 0	9–10
Dog	8 — 4	10–12
Guinea-pig	9 — 0	4–5
Lion	15 — 0	20–25
Pig	17 — 1	16
Sheep and goat	21 — 3	10–15
Monkey	22 — 6	12–14
Hippopotamus	30 — 0 to 35 — 5	40
Polar bear and reindeer	34 — 2	40–50 and 16
Chimpanzee	37 — 1	15–20
Man	40 — 0	70–80
Cow	40 — 5	20–25
Horse	47 — 1 to 50 — 0	40–50
Rhinoceros	72 — 6 to 78 — 4	40–45
Elephant	89 — 5	70

be incorporated in skeletons and shells during growth. In some instances the growth of planarians may imply becoming smaller, and Child (1941) was disposed to regard it as "not merely increment but

both increment and decrement of substance, as transfer of substance either to or from an organismic system as a consequence of protoplasmic constitution and activity".

Other factors add to the complexity of growth. The *tempo* of growth may vary enormously; a mouse grows for only a few weeks, a man for more than twenty years. Growth may cease at maturity or not, and it may be either retarded or accelerated before birth or the hatching of the egg; fishes grow throughout life, and while some birds are helpless at hatching, the chick can walk and peck almost from the moment it leaves the shell. Growth may be accompanied by the development of new organs and parts, and it may call for complex structural and physiological adjustments such as the outgrowth of nerves towards the muscles they will excite to movement. The proportions generally change during growth, and even behaviour may be much modified, and life must continue as if nothing unusual were happening. Growth is indeed not one but a multitude of problems.

Differentiation

Early growth is multiplicative in the sense of increase in the number of nuclei or embryonic cells. In later development these cells will increase in size and weight, a phase of intussusceptive growth supervening. Some cells will eventually become specialised for various tasks, or differentiated. The process of differentiation modifies the degree of complexity and organisation seen in an animal, partly by increasing the number of kinds of cells as blood, cartilage, bone, muscle and skin develop, and partly by increasing the number of organs and parts. As morphological heterogeneity is increased a definite pattern of structure is gradually established. The parts of the animal grow at various rates in accordance with a specific growth pattern, but this may be modified later by functional interaction between perfected parts. Growth and differentiation are only parts of whole function, however, and metabolism permeates the animal as a functional whole.

Under certain conditions, as J. Needham has shown, differentiation and growth can be disengaged or put out of gear. When living cells are cultivated *in vitro* they multiply, and then, according to the conditions of culture, they may wander out into the medium and grow without undergoing further change, or they may differentiate into several distinctive types of cells and, if tissue and medium are well chosen, into characteristic parts of a limb or organ. The eye of a chick grows well when transplanted on the chorio-allantoic membrane of

another chick, and although it does not attain the normal size it has the same degree of histological structure; growth is diminished but differentiation is unaffected. Growth in the sense of cell proliferation is distinct from histological differentiation, and this from morphological alteration, or organogeny. The three kinds of process are mutually dependent in the growing organism, for normally there is no disengagement but instead a precise and harmonious adjustment between them.

The Control of Growth

We may well ask why it is that a well-nourished animal or tissue ceases to grow, for tissue-culture experiments lead us to suppose that there is no *a priori* reason why growth should stop. The cells in a culture multiply indefinitely, far outstripping the life-span of the animal from which they came. Their growth is unrestrained, and this seems true also of undifferentiated cells in the body of an animal. Cells lose their embryonic character when they become specialised, differentiation being a kind of ageing. In the animal's body functionally exhausted cells are replaced by differentiating embryonic cells, cells hitherto restrained but now freed from restraint. The life-span of different kinds of cells in the animal's body varies. Nerve- and muscle-cells form "permanent" tissues, for they cease to divide in early development and their numbers thus tend to become constant. The so-called "stable" tissues have a more extended multiplicative phase which may continue in the adult, and the "labile" tissues permanently retain the power to multiply. Blood cells live for only two or three weeks and are then replaced from perennial sources in the marrow of the long bones and the lymph glands. Previously these cells were kept under restraint, and in other instances the restraint on growth may be exercised permanently unless accident or functional disorder induces cells to differentiate in order to heal wounds or otherwise repair damage. The condition of wholeness in animals seems to uphold certain forms of growth restraint, though the presence on it or in it of tarry substances or parasitic worms, or chronic local irritation due to heat, may lift the restraint on growth and lead to malignant forms of growth.

Growth restraint is evident at all stages of development. We develop two not many pairs of limbs like a crab, and our noses grow out of the front of the head, not the back. Noses, incidentally, are less restrained during later than earlier adult life, for otherwise there would

be less variety of shape and size in older persons. Restraint limits the first cleavage of the ovum to a particular plane of space. In plants the tip of a shoot has a terminal bud; nip this off and axillary buds which would have been inhibited develop into branches. The establishment of the main axis of an animal's body inhibits the growth of other parts, and when subsidiary axes eventually develop these also inaugurate minor forms of growth restraint. The growth of an embryo involves competition between many parts, not all of which can grow at one and the same time.

Pulses of Growth

Human growth is patchy and uneven. During the second month of foetal life the head is of maximum relative size, towards the end of the gestation period the lower abdomen is proportionally at its largest.

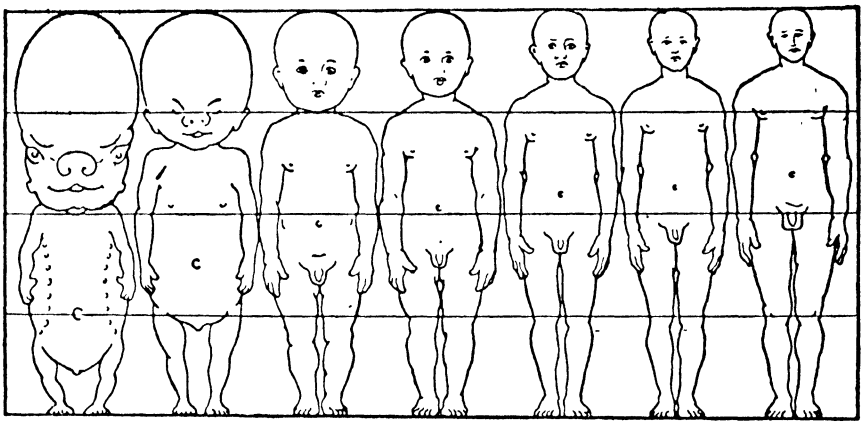


Fig. 11. Diagram illustrating the changes in the proportions of the human body during growth. From Hammond, 1944. (Edward Arnold & Co.)

Legs are longest during the early part of adult life, so that there are great differences between the times at which maximum relative size is attained by the bodily parts. The body as a whole displays two phases of very rapid growth, one circumnatal and the other adolescent. During the month before birth the foetus increases its weight by one per cent. per day, a rate of growth which, if continued, would produce a fifteen-stone baby in one year! H. A. Harris (1933) recognised three alternating phases of rapid and slow growth after birth, calling them "springing-up" and "filling-out" periods. The first springing-up

period occupies the first year of life after birth, the second occurs between the fifth and seventh years, and the third is associated with puberty. The filling-out periods occur between the first and fifth years, between the seventh and eleventh, and during maturity with the final consolidation of growth. Intensive growth taxes the resources of the body, which is prone to certain ailments of infancy and childhood —rickets, scurvy and digestive troubles during the first springing-up period, measles, diphtheria and whooping-cough during the second. The filling-out periods are recuperative in the sense that the body then consolidates its gains and musters its resources for further growth, but the teeth grow rapidly during such periods.

TABLE 4.—SHOWING THE PERCENTAGE OF THE HUMAN BODY WEIGHT TAKEN UP BY VARIOUS ORGANS.

(*After* HARRIS, H. A., but I have added the third column to emphasise the relative smallness or largeness of certain organs at birth.)

Organ or Part	*Percentage of Body Weight* (human)		
	New-born	*Adult*	*Ratio* n-b/a
Muscles	25·05	43·3	0·58
Skeleton	13·7	17·5	0·78
Brain	12·3	2·2	5·6
Liver	4·6	2·75	0·6
Stomach and intestines	2·1	2·1	1·0
Heart and kidneys	0·76 (0·75)	0·46	1·63
Thymus	0·26	0·04	6·5
Eyes	0·24	0·02	12·0
Spinal cord	0·18	0·06	3·0
Thyroid	0·16	0·05	3·3
Pancreas	0·11	0·15	0·73

More fundamental rhythms which underlie these pulses of growth affect various organs differently. The skeleton conforms to the growth of the muscular system, lungs and thorax. Various writers have distinguished between the rapid early growth of the brain, spinal cord and eyes, and the more even growth of other organs. R. E. Scammon (1923) noted rapid growth of the brain and eyes till the human infant is eighteen months old. The eyes of the two-year-old are three-fifths of adult size, and those of a child of seven years have almost completed their growth. Lymphoidal tissue, the tonsils, the thymus and lymph glands grow rapidly during childhood, but then more slowly till puberty. The thymus retrogresses and even disappears. The genital organs

grow slowly during infancy, remain quiescent between the second and tenth years, and grow rapidly for about two years before puberty and during adolescence. Pulses of growth are perhaps more important to the clinician than to the biologist, but both are interested in the animal as a mosaic of parts that grow at various rates. The growth of the body as a whole is the sum of growth in its parts, but in man and other animals stature is largely determined by the growth of the backbone and some other parts of the skeleton.

In a study of human growth based on records concerning more than two million individuals and collected during the past one hundred years, Morant (1950) has observed interesting secular changes in the tallness of males in Britain. The maximum mean height is constant at about 67½ inches for the general population, but the age at which it is attained is not, being earlier in the poorer than in the richer social classes. Individuals of any class which are deemed fitter because selected for service in the Armed Forces also reach full stature earlier. In 1880 the maximum mean height was reached at an age of about 26 years, and in 1945 at an age of about 21½ years, the speeding-up of growth being more marked in recent years and in the poorer social classes. After maturity is reached and up to an age of 30 years height diminishes, and in Morant's opinion the decline is not due to selective death rate or secular increase in height in the population, but may be due to shrinkage of the intervertebral disks of the spine, or to changes in muscles and joints having to do with the maintenance of the erect posture. Of one thing he is certain, however, British adolescents are taller now than formerly. The rate of growth in man has been speeded-up, and changes in the condition of life have probably brought this about.

Ways of regarding Growth

When contrasting the work of two famous students of growth P. B. Medewar (1945) wrote: "To Minot we owe a simple theoretical background for the study of size, as it varies with age; to D'Arcy Thompson an instrument which has brought the shape of the living organism into the domain of mathematical inquiry. Each had a grand scheme in mind. Minot planned to reveal a significant connexion between the processes which, in the course of development, find expression variously as growth, differentiation, decay, and death. His methods of analysis have been developed in a fashion which has become progressively more laboured and more intimately numerical; that is to say, more and more

'mathematical' in a sense which he took special steps to repudiate. The Method of Transformations, in D'Arcy Thompson's hands, brought to light a formal unity and coherence in the relationship between animals whose outward diversity distinguished them in a multitude of particular and subordinate ways."

These two biologists had entirely different ways of looking at the problems of growth. Charles S. Minot (1911) deplored the widespread opinion that "no science is accurate until its results can be expressed mathematically", and regarded it as an error born of the belief that mathematics can express complex relations. He asserted that "mathematics have a very limited scope, and are based upon a few extremely rudimentary experiences, which we make as very little children and of which no adult has any recollection", and that "we cannot anticipate that there will ever be a mathematical expression for any organ or even a single cell, although formulae will continue to be useful for dealing now and then with isolated details". Adopting a different point of view, the late Sir D'Arcy W. Thompson (1917, 1942) showed that mathematics can explain much that would otherwise remain obscure in growth. He studied the rates of growth in man and animals, the form of cells and groups of cells, spicules and spicular skeletons, the logarithmic spiral in its relation to the growth of shells, the shapes of teeth, tusks and horns, the arrangement of leaves (phyllotaxis) in plants, and many other aspects of growth and form. He discussed the effect of temperature, climate and osmotic factors in growth, growth as a kind of catalysis, and growth by regeneration and repair. His considerations of the structure and arrangements of bones called forth a study of the comparative anatomy of bridges and other mechanical structures, and he explained the honeycomb of the bee in terms of hexagonal symmetry. These and other topics received the light of his extensive knowledge and persuasive personality in the masterly and delightful book *Growth and Form* (1917, 1942). The new analytical approaches which he made to the study of growth have been discussed by a host of writers. He regarded all changes of shape as indicative of growth, believing that "the form of an organism is a phenomenon to be referred in part to the direct action of molecular forces, in part to a more complex and slower process indirectly resulting from chemical, osmotic and other forces, by which material is introduced into the organism and transferred from one part of it to another". "It is this latter complex phenomenon," he said, "which we usually speak of as growth."

In formulating his well-known theory of transformations, D'Arcy

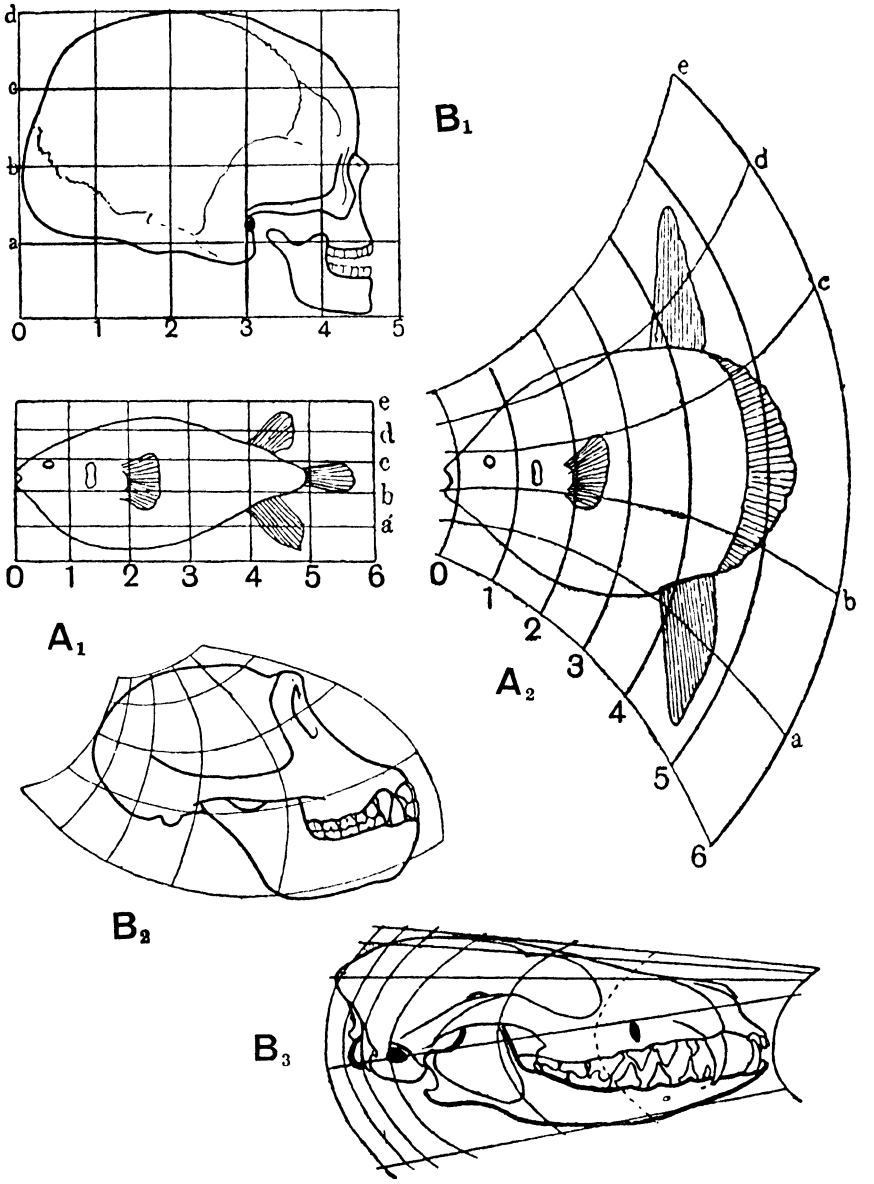


Fig. 12. Diagrams illustrating the transformation of the outline of a porcupine fish (A_1) into that of a sunfish (A_2) by the regular deformation of rectangular co-ordinates. B_2 and B_3, outlines of the skulls of chimpanzee and dog respectively, derived in the same way from the outline of the human skull (B_1). From D'Arcy Thompson ,1942. (Cambridge University Press.)

Thompson admitted that "there are a vast multitude of organic forms which we are unable to account for, or to define, in mathematical terms; . . . to define the complicated outline of a fish, for instance, or a vertebrate skull, we never even seek a mathematical formula". He stressed, however, that the morphologist aims to compare related forms rather than to define them precisely, and "the deformation of a complicated figure may be a phenomenon easy of comprehension, though the figure itself may have to be left unanalysed and undefined". Such a deformation he made by inscribing on a lattice of Cartesian co-ordinates "the outline of an organism, however complicated, or a part thereof; such as a fish, crab, or a mammalian skull", and treating "this figure, in general terms, as a function of x, y". Simple deformation of the system provides "a new system of co-ordinates whose deformation from the original type the inscribed figure will precisely follow". The new figure corresponds to the old figure "under strain". In this way, and by extending methods practised by Dürer and other artists of earlier centuries for the study of human proportions, D'Arcy Thompson dealt with complicated shapes of animals and their parts, showing how structures can be transformed as between one form and another in ways which illustrate the fact that the actual differences are due to differential growth. The problem of extending such methods as he used to include the three planes of space, so that the shape of a solid object could be understood instead of just an outline of it, was left to "other times and to other hands", and it has been tackled in recent years by Medewar (1945) and others.

Growth Curves

If we regard growth as increase in size we have still to distinguish between growth in length and growth in volume or mass with passage of time. The use of the yardstick, the balance and the clock or calendar show that increase in length and in mass are not equally obvious. While a young plaice doubles its length, weight may increase eightfold. Length is doubled in two years, weight in two months. According to the "Cube Law" of Herbert Spencer (1871) weight increases in proportion to the cube of the length. This holds good only for a truly spherical organism, and as few animals maintain this, or indeed any constant shape, growth generally takes place at various rates in different directions. Attempts have been made to express growth data by many different mathematical expressions; O. W. Richards and A. J. Kavanagh (1945) put the number of equations at well over 150, Sholl (1950) at

296. Many methods have been used also for expressing the data graphically, but Medewar (1945) has stated that from six main types of integral and derived curves of growth "the majority of our useful inferences about the nature of growth in size can be drawn". He also formulated a number of simple general rules and put forward the view that "only one fundamental generalisation can be made about the relationship between the size of an organism and its age", that which is expressed by the equation

$$\frac{d \log W}{dt} = K.f(t).$$

In special cases where $f(t)$ is a constant function of t, growth is of constant compound interest type.

Relative Growth

The analysis of growth is simplified by leaving out of consideration the time factor (t), and by considering the sizes of organs and parts in relation to one another and to the body as a whole. Some organs and parts alter in relative size with increase in absolute size of the body. A. Pezard (1918) called this "heterogonic" growth, C. Champy (1924) "dysharmonic" growth. The first attempt to formulate a general law of differential growth was made by J. S. Huxley (1924), who employed the formula $y = bx^k$ to describe the relationship between the rate of growth of a part (y) and the whole organism, or some other part (x). According to E. C. R. Reeve and J. S. Huxley (1945) the same formula was used by O. Snell (1892) and E. Dubois (1898, 1914) to express the relationship between the weights of the mammalian brain and body, and by L. Lapicque (1898) and B. Klatt (1919) in dealing with the growth of organs in birds. The same writers have discussed the question of terminology, which was standardised by J. S. Huxley and G. Teissier (1936), and also some formal difficulties and other matters regarding relative growth. The formula at present used is a slightly modified form $y = bx^\alpha$, and in this the term b is a proportion constant (the "initial growth index") and α is the differential growth coefficient ("equilibrium constant"). Some organs grow faster than the body and enlarge in relative size during growth; others grow more slowly than the body and diminish in relative size. The two examples represent positive and negative allometry. The special case in which a part grows at the same rate as the body is called "isometry", and the special case of negative growth in which a part becomes absolutely

smaller is called "enantiometry". The evolution of the allometry concept has been discussed by O. W. Richards and A. J. Kavanagh (*loc. cit.*), and E. C. R. Reeve and J. S. Huxley (*loc. cit.*) have discussed some examples of deviation from simple allometry. The main virtue of the allometry concept is that it lays emphasis on the fact that growth is multiplicative and follows the compound interest not the simple interest law.

When two sets of values are plotted on a logarithmic scale the multiplicative nature of growth is easily revealed, for equal spaces on such a scale represent equal amounts of multiplication, not addition. In regard to allometry an increase in size from 10 to 50 has the same significance as an increase from 1 to 5, or from 7 to 35, though the amounts of additive growth are very different in the three instances. The value of the growth coefficient is determined from the slope of this logarithmic curve. Such curves reveal the positive allometry of various limbs of crustaceans and other arthropods in relation to the body, and a similar relation between one part and another—for instance, the trunk relative to the head in flatworms, the face in relation to the cranium in the dog and baboon, and the casque of the hornbill or the antlers of the deer relative to the length of the body. Other organs can similarly be shown negatively allometric—for instance, the brain of various mammals after birth, the heart of many vertebrates, the limbs of the sheep and some of the limbs of the hermit crab at various times during development. Such periods of positive or negative allometry may be longer or shorter periods during the life of the animal, sometimes for the entire post-larval or post-natal stage, but this is not to say that the growth coefficient is unalterable, and indeed in crabs parasitised by the copepod *Sacculina* changes occur in the allometry of the pincers in the male and the abdomen in the female. The differential growth coefficient is constant only so long as certain conditions prevail.

An animal of constant shape would need to maintain an isometry in respect of all its parts during growth, and it is very unlikely that any animal can do this. Animals with a fixed growth period attain a more or less definitive shape at maturity, though change in shape may occur by retrogression due to senility. On the other hand, fishes and crustaceans grow throughout life and may never attain a fixed form. A final adult size and fixed proportions arose out of specialised features of growth during the later stages of evolution of life on earth. It is characteristic of mammals and birds, insects and spiders, and only a few other animals.

Organs and parts that are shed periodically and regrown subsequently provide a special case of relative growth. The antlers of the deer are shed each year and the new antlers are generally larger than their predecessors, though illness, old age and other factors may reduce both the weight and the number of "points". The relative weights of antlers and whole body follow the law of allometry, however, but more growth is made than is indicated by such growth curves carried over a number of years, because growth must start afresh from zero every season. This and similar considerations in regard to regenerative growth have given the growth coefficient an added significance, for it indicates not the amount of growth made but the total amount of growth that can be made; it is an index of "growth limitation", or "growth partition", as R. C. Robb (1929), V. C. Twitty and J. L. Schwind (1931), and J. S. Huxley (1932) have all maintained. This is illustrated in the regeneration of lost limbs in crustaceans when the actual growth rate falls to normal levels as the limbs approach normal size.

J. Needham (1932) believed the concept of allometry to be just as important to the biochemist as to the morphologist and anatomist, and he considered the question of chemical allometry in embryonic animals. In regard to the developing chick, plotting non-protein nitrogen against dry or wet weight on a double logarithmic grid almost invariably gave a straight-line curve. Of particular importance is the fact that "the slope of the line for a given substance or group of substances is almost if not quite identical for widely different organisms". Thus, when total ash is plotted against dry weight of embryo there are close resemblances in animals as different as cephalopods, fowls and some cartilaginous fishes. The similarity of chemical development is revealed in other instances also—in regard to water content, nuclein content, the dry substances of brains, and calcium in many different animals. As such plotting enables us to abstract from morphological form, nutritional factors, absolute values of magnitudes, and the time taken for development, we are left with a system of relations or ratios which may turn out to be the same in all animals. Such a fundamental chemical plan of animal growth should be regarded as deformable in space-time, just as morphological shapes were dealt with by D'Arcy Thompson. In Needham's opinion, the essential processes of growth in all animals, whatever their form and size, proceed according to a definite plan which marks out the chemical constitution of the organism at any stage of its life-history.

Growth Gradients

Some crustaceans have two large claws of different size and proportions on right and left sides of the body. One claw of the fiddler crab (*Uca pugnax*) displays positive allometry, the opposite one isometry. The large claws of other crustaceans may show different degrees of positive allometry on the two sides of the body, so that with growth the two become relatively larger but at different rates, one always gaining on the other. The various regions of a crustacean limb also display different degrees of allometry, so that the relative sizes alter. Most rapid growth generally occurs near the tip of the limb, growth intensity falling off towards the base and, as a rule, the higher the degree of allometry in the entire limb and the steeper is the gradient extending through its component parts. Similar growth gradients exist in the parts of other animals, persisting for various periods during development. A high growth ratio and a steep gradient in the limb of the foetal lamb combine to give the animal relatively long legs by the time it is born, but subsequently the limb becomes negatively allometric and the gradient within it is reversed. The limbs become relatively longer during pre-natal growth, but relatively shorter during post-natal growth, when differences of relative size in the parts of the limbs also diminish.

The idea of gradients is embodied in the law of antero-posterior development, according to which the formation of the embryo begins in front and gradually spreads to the rear, so that the head may be well advanced in its development before the trunk and tail have appeared. The antero-posterior gradient is supplemented in bilaterally symmetrical animals by a dorso-ventral gradient with a high point dorsally in vertebrates but ventrally in invertebrates. Gradients of various sorts exist from the egg stage onwards, and C. M. Child (1915, 1941) expounded a general physiological theory which indicates how certain regions of a developing embryo dominate others and mould them into subsidiary forms. That these gradients are physiological he showed in various ways, notably by demonstrating that regions with different rates of growth differ in their susceptibility to poisons and narcotics that interfere with respiration and other functions of living cells.

J. S. Huxley (1932) suggested that growth gradients within a limb are special cases of an orderly mechanism for the distribution of growth potential throughout the body. One illustration used by D'Arcy Thompson in his theory of transformations related the globe-fish

(*Diodon*) and the totally different sun-fish (*Orthagoriscus*). This could be regarded as a biological instead of a geometrical exercise. If the young globe-fish could be treated in such a way that the hind region of the body acquired a region of very high growth intensity, growth falling off anteriorly, its proportions would subsequently approach more and more closely to the form of the sun-fish during growth, for the differences between the two fishes can be regarded as mainly due to differences in the distribution of growth potential along the main axis of the body. In other transformations similar differences manifest themselves in alterations of shape and form; for instance, transformations relating to limbs and their skeletal parts, limb girdles, etc. Differences of form are arrived at by varying intensities of growth along the primary and subsidiary gradients in the body and its parts.

Accretionary Growth

The growth of shells, horns, antlers and other hard parts of animals that grow by accretion is additive, not multiplicative, though Medewar (1945) has pointed out that the tissues which produce such structures may themselves multiply and enlarge according to the compound interest law. As the animal ages, the rate of accretionary growth may also fall off, so that diminishing amounts of material are produced in unit time. Growth remains of the simple interest type, however, only the rate of interest, as it were, varying. This is true of the shells of some Protozoa and molluscs, the median horns of the rhinoceros, the paired horns of oxen, sheep and antelopes, and the tusks of many animals. A horn grows by the secretion of keratin over a limited area of epidermis on the head. On this horn area keratin is produced perpendicularly to the surface, but the area itself increases in size as the animal grows, so that larger sheets of keratin are laid down as time proceeds. If the horn area did not grow, the horn would be cylindrical; if keratin were added uniformly to the horn this would become conical. In the latter case the precise shape of the horn would depend on the rate of keratin production and the rate of enlargement of the horn area; rapid formation of keratin and slow enlargement of the horn area would produce a long, tapering horn; slow keratin formation and rapid enlargement of the horn area would give a short horn with an obtuse point. The foremost horn of the rhinoceros curves backwards, however, more keratin being produced in front than behind, In fact, a more or less regular gradient of growth occurs along the horn area, with a high point in front and a low point behind. There is also a slight gradient from

the median to each of the lateral edges of the horn area, though lateral enlargement of the horn area itself largely accounts for the tapering of the horn in the transverse plane.

The successive increments of new growth in the horn of the rhinoceros, like those of molluscan shells, are "gnomons"—that is to say, areas that can be added to a figure without altering its shape—and these produce the characteristic curve of the horn, which is a logarithmic spiral. Growth of this kind occurs whenever the new increments are produced as non-living materials and when there is a constant ratio between the increments at the two ends of the growing part and a regular gradient of growth between these points. Under these conditions, gradients of growth produce an organ of constant instead of constantly changing shape. Some species of rhinoceros have two horns in the median plane, and the hinder is invariably the smaller of the two, being also of lesser curvature, which indicates a flattening of the growth gradients as it is continued across the two horn areas. Smaller amounts of horn arise on the hinder horn area, between the two ends of which there is also less difference in the amounts of horn produced; the hinder horn area is the lower part of the entire gradient of horn production. In the region between the two horns the skin has no capacity to produce horn, but this blank region does not obscure the fact that the two horns are produced by one continuous gradient.

Horns that grow out from the sides of the head show considerable differences in the amounts of material produced by the more median and the more lateral regions. The horns of sheep, oxen and antelopes thus grow in a backwardly directed spiral, but there is also a superimposed spiral at right angles to this, with the result that the horn is corkscrew-like. The amount of "shear" in such horns depends on the amounts of growth made in different parts of the horn area; a marked difference as between median and lateral regions yields a lot of shear, as in the horns of sheep; a slight difference, the slight shear seen in the horns of goats and antelopes.

Growth and Nutrition

Growth cannot be normal if nutrition is faulty. Animals must be supplied with the raw materials of protoplasm, and also with substances required for maintenance during growth. Amino-acids are notable requisites; not more than about thirty are known, yet ten or eleven of them are essential because they cannot be manufactured in

the body rapidly enough to allow of normal growth; these are phenylalanine, tyrosine, tryptophane, histidine, methionine, threonine, valine, lysine, leucine, isoleucine and, possibly, arginine. These and other amino-acids are the building bricks of growth; from them the animal synthesises its own characteristic proteins during growth. Other notable requisites are vitamins and hormones. The perversion of growth known as "rickets" is due to a lack of certain vitamins in the diet of the growing animal. The limb bones may be grossly misshapen because of faulty bone formation, which normally takes place in three stages. The bone is modelled in pro-cartilaginous cells and transformed into cartilage by the deposition of matrix around them, and this is later calcified, invaded by blood vessels and converted into bone. Two kinds of cells bring about the simultaneous destruction of cartilage and osteogenesis: "osteoclasts" devour the cartilage, and "osteoblasts" wander into the eroded regions and lay down phosphatic materials in regular patterns, generally around blood vessels. The form of the bone is retained throughout the process, bone being laid down almost as quickly as cartilage is removed.

Long bones grow in three parts—two "heads" and a "shaft"—which remain discrete till puberty and fuse only when skeletal growth is complete. Regular columns of cartilage cells develop at the ends of the shaft, forming the epiphyses. When the columns reach a certain critical length, nutrition, which is effected by means of water-borne substances, becomes precarious and it is at this stage that calcification ensues. According to H. A. Harris (1933) the proliferation of epiphyseal cells depends on a regular supply of water-borne substances, particularly vitamin B_1. The calcification of senescent cells is accelerated by ultra-violet light, ergosterol and vitamin D_2, and it sets up a condition resembling aseptic inflammation due to some foreign body. The eruption of blood vessels which follows is a direct consequence of this, and it leads on to the osteogenesis. The differentiation of mesenchyme cells into osteoclasts and osteoblasts depends on an adequate supply of vitamin A. In the rickety animal all three phases of bone formation are faulty; the cartilage cells proliferate excessively, calcification is deficient, and bone formation is imperfect. Avoidance of rickets therefore calls for adequate amounts of the three vitamins concerned. A shortage of B_1 may lead to the formation of epiphyses five times the normal length, and a shortage of D_2 permits islands of uncalcified tissue to remain. If vitamin D is administered to the rickety animal, lime is deposited where it would be found in the normal

animal and a line of "healed rickets" restores the usual relationship between calcified and uncalcified cartilage. In the presence of vitamin A, ossification ensues and rickets is cured, provided it was not too serious in the first place. To avoid rickets calcium and phosphorus must be available to the animal, of course, but these elements are not generally deficient and they may even be passed out of the body unused by the rickety animal.

John Hammond (1947, 1950) has considered the effect of nutrition on the growth of farm animals. The method of considering increase in weight in relation to time proved to be the most suitable in regard to both total live weight and the weights of organs and tissues. The breeder is particularly interested in the fact that the constituent organs and parts grow at different rates, because increase represents varying amounts of bone, muscle and fat. The head and the bony parts of a sheep or pig have much less value than the loin and the fat depots. The head and skeleton attain their fastest rate of growth in early life, parts such as the loin and the fatty tissues in later life. Various breeders have proved that an organ or part is most susceptible to nutritional effects when growing most rapidly. C. P. McMeekan (1940–41) reared inbred pigs on two nutritional levels, one high (H) and the other low (L), for sixteen weeks, at the end of which time the proportions of the two sets of animals were markedly different; for instance, brain weight was 91 gm. and 82 gm. in the H and L animals respectively, whereas the muscle of the loin weighed 1798 gm. and 500 gm. High plane nutrition most affects parts which develop relatively late, which happen to be parts of greatest value in food production. McMeekan then divided his sixteen-week-old pigs into four lots: the H and L groups were each divided, one lot of each being given a high level of nutrition, and one lot of each a low level. The four groups high-high (HH), high-low (HL), low-high (LH) and low-low (LL) were reared to a final weight of 200 pounds and then slaughtered, the periods taken being 180, 240, 240 and 300 days respectively. The curves of growth for the four sets of animals represent pigs of quite different proportions and, more importantly, different chemical composition. The proportions were in fact characteristic of various genetic types of pigs; the HH pigs resembled the English breeds of pork pigs, the HL resembled pigs of the Danish bacon type, the LH resembled the lard hogs of some parts of U.S.A. and certain pigs of Hungary and Roumania, and the LL pigs resembled unimproved breeds of Germany and elsewhere. Pigs fed on a high plane of nutrition when young have a massive skeleton and do not fatten if the plane of

nutrition falls in later life. Young pigs fed on a low plane of nutrition have stunted skeletons, and the shortened body fattens grossly if the plane of nutrition is raised in later life.

Analysing the effects of different levels of nutrition on the growth of various parts of the pig's body, Hammond suggested that parts which develop early are not affected very much by the nutritional level

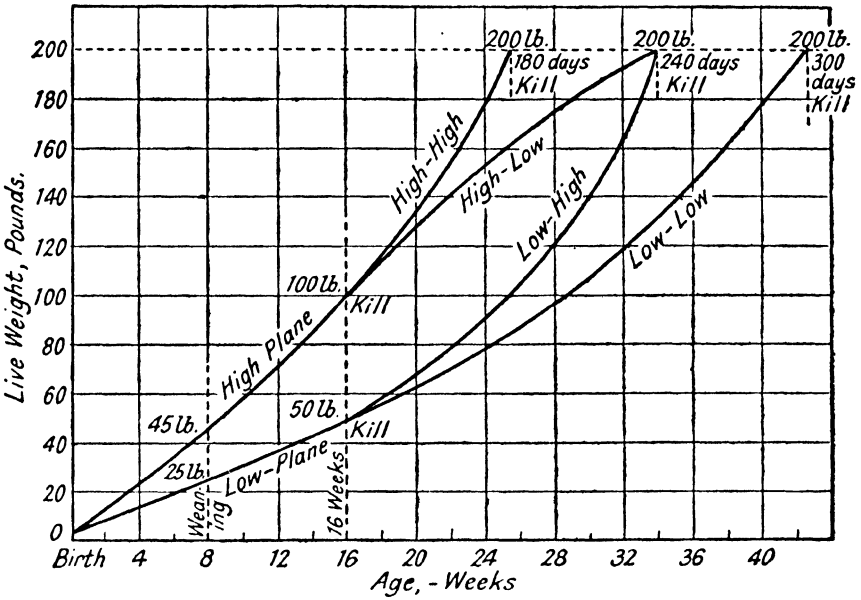


Fig. 13. Plan of McMeekan's experiment to determine whether or not the composition and conformation of the pig can be changed by altering the shape of its growth curve. From Hammond, 1944. (Edward Arnold & Co.)

in later life, but parts which develop late are greatly affected. During growth, the developing parts do not all lay equal claims to available nourishment, but gain priority in the order brain, bone, muscle and fat. He indicated the degrees of priority diagrammatically by numbers of units. If the level of nutrition is reduced, the rate of growth of all parts is lowered, and if the fall in nutrition be assessed at one unit, the growth of fat fails altogether. Further reduction by one unit will stop the growth of muscle, and will cause the animal to use its own fat as a source of nourishment. The more vital parts have the first priority over food. In this class during the early stages of pregnancy are the placenta and the foetus, the claims of which are reduced somewhat during late pregnancy. The importance of these facts lies in the

protection of the early embryo against low levels of nutrition such as it might encounter during later life. The same general environmental effects will hold good for man, though the human growth curve differs from that of a farm animal in its long juvenile period. This evidently implies that whereas animals such as a cow or a rat pass through precarious early stages of growth *in utero*, and therefore in a comparatively uniform environment, the corresponding early stages of human growth take place after birth, and are subject to the vagaries of a less controlled environment. The level of nutrition affects the mental as well as the physical development of human children, so that there is a greater risk of nutritional disturbances of development reaching a critical pitch.

Hormones and Growth

The proper functioning of endocrine glands in the growing animal is just as important as correct nutrition. One of the most essential hormones is thyroxine, the iodine-containing derivative of tyrosine which is secreted by the thyroid gland. Unlike some hormones, thyroxine can be administered by way of the mouth, being unaffected by digestive secretions, though its normal course is through the blood stream. A deficiency of thyroxine leads to the condition of cretinism in infants and myxoedema in adults. The cretin suffers from arrested growth, deformity and idiocy, which begin to appear about six months after birth. The myxoedematous adult becomes obese and bald, slothful and stupid in habit as well. Thyroxine regulates both growth and metabolism, for in myxoedema metabolism may be reduced by three-fourths of its normal value. Over-secretion of the thyroid leads to a high metabolic rate, loss of weight, and a highly nervous mental state, symptoms which are evident in exophthalmic goitre. The thyroid also controls metamorphosis of tadpoles of the frog and other amphibians, its removal leading to an extension of larval life in which general growth continues. When normal tadpoles are fed on thyroid gland, or food containing thyroxine, they become frogs much sooner and at a much smaller size than usual. After treatment with thyroxine the tadpoles of the American bullfrog change in a few weeks instead of three years, and the Mexican axolotl, which would otherwise remain a permanent neotenic larva, becomes a normal adult salamander just as quickly.

Other glands which play some part in growth are the parathyroids and the pituitary. The parathyroids are situated near the thyroid and

they secrete parathyrin (parathormone) into the blood, with the result that calcium is mobilised and the amount of phosphate circulating in the blood is reduced. Too much parathyrin in the blood brings about the retention of calcium in it and leads to the rarefaction of bony tissue; too little parathyrin in the blood leads to other abnormalities of ossification and of metabolism. The pituitary is also regulatory. The anterior lobe produces the lipoidal hormone "phyone", which seems to work independently of hormones derived from the thyroid and the ovaries that stimulate the growth of epithelial, connective and bony tissues. A deficiency of phyone leads to infantilism, excess to gigantism and acromegaly, in which the lower jaw, the hands and the feet become greatly enlarged. Several other pituitary hormones have some effect on growth. The thyrotropic principle stimulates the development of the thyroid gland in the young animal and regulates its secretion. The adrenotropic principle also has an effect on the thyroid as well as on the adrenal cortex, and the metabolic principle is important because it stimulates metabolism. Hormones also play some part in sexual physiology, and the pancreotropic principle regulates the production of insulin and thus affects sugar metabolism, so that it is not without effect on growth.

The effects of hormone deficiencies are clearly seen in certain types of dwarfs and giants. Achondroplastic dwarfs are short and stocky, with a large head and short, twisted limbs. The bones of the skeleton are short, thick and knotted at their extremities, the skull broad and short. Poor growth reduces the size of the bridge of the nose, and the upper jaw does not grow out far enough, so that the lower jaw protrudes and the teeth do not meet. Such flat-faced dwarfs clearly indicate endocrine disorder, and they often die at birth. In domesticated animals their type is represented by certain fancy breeds of dog—for instance, the French bull and the dachshund. The ateliotic dwarf is quite another being, generally bright and intelligent and of normal shape. Growth in his case seems to continue for about six years after birth and then to stop abruptly, the cartilages of the wrist and ankle persisting and the shaft and heads of the long bones remaining discrete. Sometimes the sex organs suffer arrested development, but dwarfs of this type may marry and produce normal children. In addition to these two main types there is often in human beings an odd mixture of characters suggesting both achondroplasia and aletiosis—for instance, a flat face and short arms with fingers that do not reach the thigh instead of extending half-way along it. Similar characters are seen in some

breeds of dogs, for the Pekingese has an achondroplastic head and limbs, and gigantism is associated with acromegaly in the Saint Bernard and the mastiff (C. R. Stockard, 1931).

Growth also produces other human types, which fall into two main categories, the "linear" and the "lateral". The former is thin and quick-growing, the latter stocky and slower-growing. The linear person has a narrow head, closely-set eyes, a nose having a high and narrow bridge, and a small, tight mouth and crowded teeth. The neck is slender, the shoulders angular and the extremities long. Physiological characters also conform to type; the eye tends to be near-sighted, puberty is reached relatively early, and the voice breaks suddenly. The lateral person has a broad head, widely-set eyes, a broad nose and mouth and well-spaced teeth. The trunk is bulky, the neck short and thick, the shoulders rounded and the extremities stocky. Puberty is reached relatively late, and when the voice breaks it becomes a tenor, not a bass. Men display these types better than women, and the differences are determined by the inheritance but can be modified by external factors. They exist in all "races" of mankind, and each type is prone to certain diseases and disorders. In all men also are characters which are reminiscent of the embryos of other animals because incompletely expressed; such include the flatness of the face, the hairlessness of the body and the pale colour of the skin. The relative protraction of development leads to the persistence of embryonic characters in the adult and produces the phenomenon of foetalisation (L. Bolk, 1926).

The Growth of Plants

It is hardly possible here to touch upon the rudiments of the subject of growth in animals without considering growth in plants, which likewise has an extensive literature. W. Crocket, managing director of the Boyce Thompson Institute for Plant Research, Yonkers, New York, has recently (1948) given an account of twenty years' research at the Institute in his book *Growth of Plants*, which contains extensive lists of literature. In recent years several discussions on the subject of growth which have been published as symposia have contained information on the growth of plants. Thus, for instance, the summer conference of the Society for Experimental Biology in 1947 published its proceedings under the title *Growth in relation to Differentiation and Morphogenesis* (Cambridge, 1948), which contains articles dealing with various aspects of growth in plants—control of flowering, development of reproductive

structures, the differentiation of primary shoots, determination of leaves, geometry of phyllotaxis, experimental morphology, and morphogenic factors. The one-day discussion on March 16, 1950, at the rooms of the Royal Society, London (see *Nature*, **165** (No. 4207), June 17, 1950), also included consideration of plant growth. F. G. Gregory noted that in one sense plant growth is permanently embryonic, for changes of form occur throughout a plant's life. The form of higher plants is governed by the relative development of leaf and stem, by the tendency to produce secondary axes or branches, by the absolute sizes and shapes of leaves and their arrangement on the stem, and by the duration of growth of primary and secondary stems. He suggested that the form of the leaf does not lend itself to the type of analysis practised by Sir D'Arcy W. Thompson, for its shape is independent of cell size or shape and is a function of local variations in the rates of cell division, which is related to the synthesis and distribution of the plant hormones, or auxins. Progress has been made, however, in the study of modes of increase of height and weight, leaf surface, number of branches, flower buds and fruits, all of which reveal the influence of climatic and nutritional factors as governing agents. Analyses of growth have not yet been extended to growth in controlled environments, due to a lack of facilities in Britain. Even so, Gregory states, the study of mature organs will not suffice, for the problem of growth and form in plants centres on meristems and growing points.

CHAPTER EIGHT

HEREDITY

SOME of Mendel's experiments involved more than one pair of contrasting characters (allelomorphs) and the results led to the formulation of his second law, according to which these will behave independently of one another in the inheritance. This law of independent assortment accounts for the results obtained, for instance, when plants derived from yellow and round peas are crossed with others derived from green and wrinkled peas. All the hybrids produced (F_1) have yellow and round seeds, but when these are grown and crossed they yield progeny (F_2) in every random sample of which nine are yellow and round, three are green and round, three are yellow and wrinkled, and one is green and wrinkled. When the colour and shape of the peas are taken separately the ratio yellow/green is 3 : 1 and the ratio round/wrinkled is also 3 : 1, but some of the yellow peas are wrinkled and some of the greens are round. The 9 : 3 : 3 : 1 ratio is compounded out of the two 3 : 1 ratios.

Chromosomes and Heredity

The importance of Mendel's discoveries became evident when his laws were seen to apply not only to peas and other plants but also to animals such as snails, insects, fishes, amphibians, birds and mammals, including man. It lies in the demonstration of a universal mechanism whereby orderly results are brought about by the segregation of allelomorphic genes during the maturation of the germ-cells, and their recombination during reproduction. The "factors" that lead to the development of definite characters are the genes, which are situated at certain points (their *loci*) on the chromosomes of gametes and somatic cells. In the cross yellow-round × green-wrinkled peas one pair of homologous chromosomes in the F_1 hybrid carry the genes *Y* and *y*, which determine yellow and green colour, and another pair the genes *R* and *r* for round and wrinkled seeds. The law of independent assortment is fully intelligible in the modern sense if we assume that these four genes are distributed one of each pair to the gametes of the hybrid and recombined in pairs in the zygotes of the F_2 generation. A

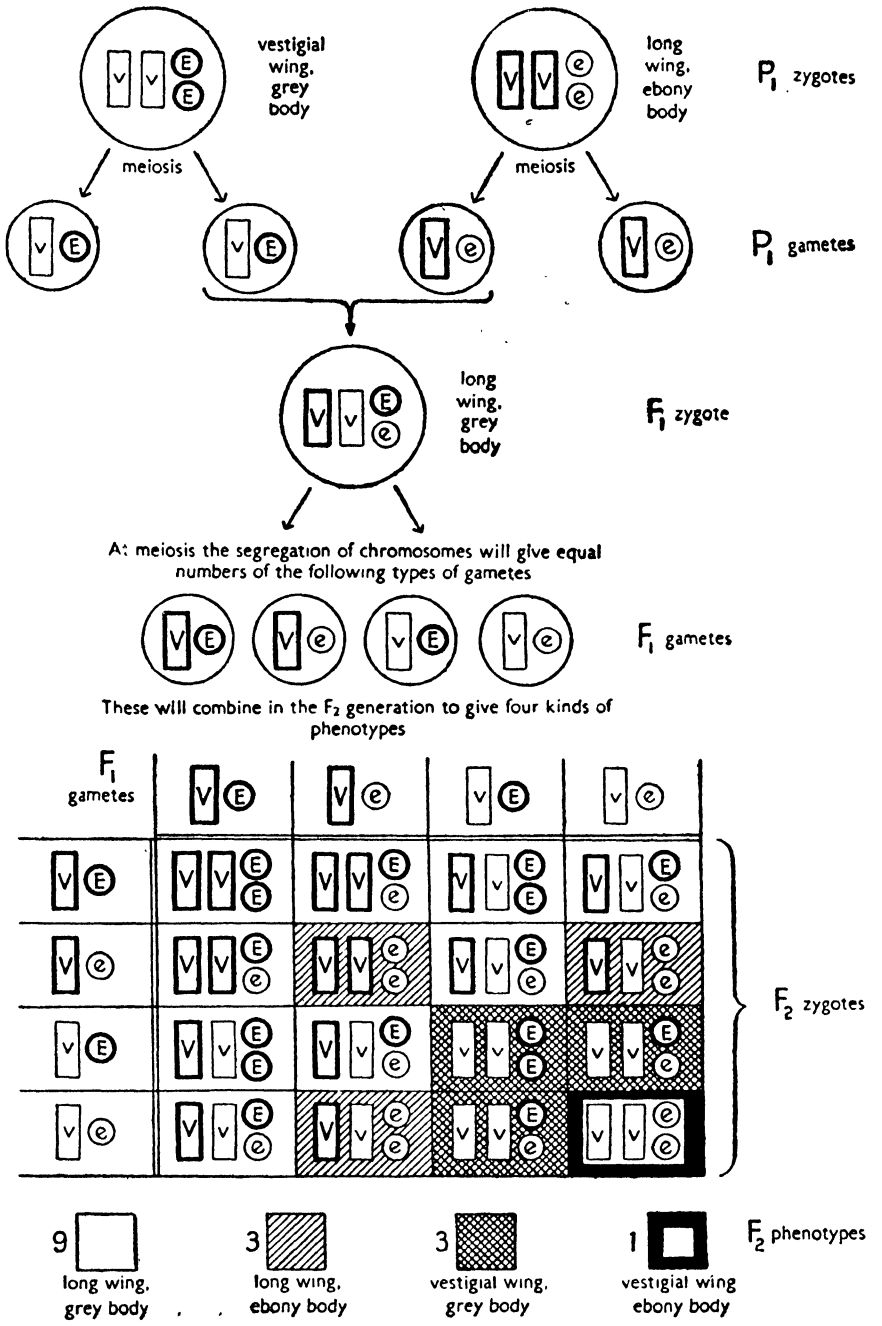


Fig. 14. Diagram to illustrate independent assortment in the fruit-fly, *Drosophila*. From Gresson, 1948. (Edinburgh University Press.)

zoological example is afforded by crossing fruit-flies (*Drosophila*). When an ebony fly with long wings is crossed with a grey fly having short wings, the F_1 hybrids are all long-winged, grey flies. If we let *W* represent the gene for long wings, *w* that for short wings, *G* the gene for grey, and *g* that for ebony, the results of the cross indicate that grey is dominant to ebony and long wings are dominant to short wings. The long-winged ebony fly has the genetic constitution (*genotype*) *GGww*, the short-winged grey fly *ggWW*, and the gametes are of two kinds in the two sexes, namely *Gw* and *gW*, so that the genotype of the long-winged grey hybrid is *GgWw*. The eggs and sperms of this F_1 hybrid are of four kinds, which carry the genes *WG*, *Wg*, *wG* and *wg*. The sixteen kinds of offspring that develop from the zygotes formed by the chance unions of the four kinds of sperms and eggs form four main groups: *nine* grey, long-winged, *three* ebony, long-winged, *three* grey, short-winged and *one* ebony, short-winged. The main groups thus give the 9 : 3 : 3 : 1 ratio already considered in regard to peas.

Mammals are more familiar to many of us than fruit-flies and many of them display contrasting characters that behave in the inheritance in much the same way as the characters considered for fruit-flies. Some concern the colour and texture of the hair or fur, *e.g.* black and red coats in cattle, black and white fleeces in sheep, banded and solid colour in pigs, black and chestnut (or grey and any other colour) in horses, short and long hair in cats, grey and white colour in mice, and normal and rex fur in rabbits. In these examples the dominant character is mentioned before the recessive.

Incomplete Dominance

Hardly had Mendel's work been properly understood when it was realised that dominance is never as complete as he supposed. H. D. Darbishire (1908) showed that in the cross round × wrinkled seeds in peas, the starch-grains in the round seeds of the hybrid are intermediate in shape between the quite distinct forms of the parents. Incomplete dominance is also seen in the garden plant called the four-o'-clock (*Mirabilis jalapa*), which may have red or white flowers that breed true for colour. When the red-flowered and white-flowered plants are crossed, however, the hybrid has pink flowers and if these are selfed the next generation includes red-, pink- and white-flowered plants in the ratio 1 : 2 : 1. If we assume that the red colour is determined by a gene *R*, and the white colour by the allelomorph *r*, the combination *Rr* expresses itself by a blended effect of pink colour.

The gametes of the hybrid carry either the gene for red flowers or that for white flowers, and at fertilisation three kinds of zygotes will be produced representing the combinations *RR*, *Rr* and *rr*, but those of the *Rr* type (pink-determining) will be twice as numerous as either of the others.

A blending effect is seen also in the Andalusian breed of fowls, which is slaty-blue in colour, shading into blue-black on the neck and back. When inbred, such birds produce splashed white, blue and black offspring in the ratio 1 : 2 : 1. The blue Andalusian is a hybrid which compares with the pink four-o'-clock, and the black and splashed white birds resemble the red- and white-flowering plants in that they breed true for colour when inbred. In the blending type of inheritance shown by Shorthorn cattle the cross red coat × white coat produces roan offspring, the colour of which is due to mingled red and white hairs in the coat.

Genotype and Phenotype

We have seen that the obvious characters of an organism, or its *phenotype*,[1] may give us an unreliable impression concerning its hereditary constitution, or *genotype*,[1] which may contain recessive genes. Tall pea-plants may bear a gene which in the homozygous condition determines shortness; long-winged or short-winged fruit-flies may carry the gene for the antithetic characters; and fowls with the walnut-type comb may carry the genes for both the rose- and pea-type combs. The genotype of an organism can be determined in the first instance only by breeding experiments, for it is the behaviour of the chromosomes during the maturation of the germ-cells and the new combinations which arise at syngamy that determine the genotype.

Another point must be stressed here. Tallness does not make a pea-plant, nor wings an insect, any more than the colour and the comb make the fowl. Organisms are made up of many characters and some of these are invariably neglected for the sake of simplicity in the descriptions of breeding experiments. The phenotype of an animal or plant is the final expression of such genes as are dominant or can, if recessives, react with dominant genes to produce a blended result. Many factors are present in the genotype which exert their effect only when new combinations arise because of reproduction and produce homozygous

[1] These terms were invented in 1909 by W. Johannsen.

recessives. Only a part of the whole inheritance of each parent is handed on to the offspring, and this helps to explain why the offspring never completely resembles either of its parents in all characteristics. New combinations of genes will have their effect on development and growth, which are affected also by factors in the environment, and this implies that some of the characters of an organism cannot be defined adequately in terms of either the genotype or the phenotype. If we choose to regard the chromosomal constitution of the zygote as the genotype of an organism, we have to admit that the way in which this is expressed in the phenotype will largely depend on the factors which control and modify development and growth.

Multiple Allelomorphs

We have so far considered characters which are produced by genes that associate to form an allelomorphic pair, but in some instances a character may be affected by more than two alternative factors, or by what T. H. Morgan (1914) called multiple allelomorphs. One well-known example, the albino series in rabbits, includes the common pink-eyed albino and the Himalayan albino—which has pink eyes and white fur but pigmented feet, tail, ears and snout. Both types of albino are recessive to the normal wild type with a pigmented coat, and dominance is complete as regards the pigmentation. Crossing produces an F_1 generation which, when inbred, produce fully coloured and albino offspring in the ratio 3 : 1. This would lead us to suppose that pigmentation is due to a gene *P*, albinism to its allelomorph p^a in the common albino and p^h in the Himalayan. If these recessive genes p^a and p^h are distinct, each should have a corresponding allelomorph and when the common albino is bred with the Himalayan full pigmentation should arise in the F_1 generation. This is not the case, however, for the F_1 generation arising out of this cross is made up entirely of Himalayan albinos, while the inbreeding of these individuals gives rise in the F_2 generation to Himalayan and common albinos in the ratio 3 : 1. It is well known now that the genes corresponding to p^a and p^h exist in different gametes, so that a pigmented rabbit may carry one or the other of them, but not both. The genes p^a and p^h themselves constitute a pair of allelomorphs, though either of them can act as a member of a different pair with *P*, the gene for full pigmentation. This is only a part of the story, for the albino series in the rabbit includes at least six multiple allelomorphs, and in the fruit-fly multiple alleles for eye-colour involve many more genes than this.

The Action of Genes

It is easy to give the erroneous impression that certain genes are concerned with the production of particular characters. The specific effects of certain genes are well known. They may be *quantitative*, as when a gene affects the length of the bristles of a fruit-fly, or *qualitative*, as in the inheritance of the blood groups in man. A. R. Moore (1910, 1912) first suggested that genes may affect the rates at which processes proceed. *Rate-genes* are such as produce a time effect as in the development of the eye-pigment of many animals—for instance, the fresh-water shrimp *Gammarus* (E. B. Ford and J. S. Huxley, 1927)—and *plus-minus genes* may modify the amount of differentiation that occurs during development—for instance, the degree of venation that occurs in an insect's wing. Other genes are important because they affect various patterns of development, altering the nature of the pigment that is deposited in a particular pattern in an insect's integument, or the kind of growth that is evident in the feather germs of a bird's skin. In recent years genes have become recognised which cannot be identified by individual effects in regard to total variation—as, for instance, in human stature. The effects of these *polygenes* may, however, be additive, in which case they may contribute to various degrees of continuous variation. Such effects must be carefully discriminated from similar effects produced by environmental conditions. On the other hand, we have the phenomenon of *pleiotropy*, discovered by L. Plate (1910); this is an effect produced by a single gene which sets in motion two or several chains of reactions and may produce in the end uncorrelated physiological events. C. D. Darlington and K. Mather (1949) mention a gene which gives rise to anomaly of cartilage, leading to narrowing of the trachea, dilated lung cavities and other deleterious physiological conditions, and finally to death of the animal. These writers also deal with many other effects of genic action which cannot be mentioned here.

Gene and Character

C. Stern (1949) has discussed the relation between gene and character. The problems of genic action belong partly to "molecular biology" but often transcend the molecular level. Like other biological processes of structural and functional kinds, genic action is based on the same levels as biochemistry and biophysics, but it extends to new and higher planes of organisation. Stern defined a character as "any observable

product of genic action" and he recognises as a "product" not only the result of immediate molecular interaction between gene and protoplasmic environment but other results which may be removed from this by several or even numerous steps. Some such characters may be molecular in an elementary sense, but others may be new molecular species or modifications of old ones which mark the beginnings of the phenomena concerned with determination, differentiation, organ formation and function, and regulation which link up with behavioural phenomena and ecological interrelations. He thinks that we do possibly know of characters that constitute intermediate products of genic action—for instance, antigens and enzymatic differences in yeasts and in the fungus *Neurospora.* He stressed that for most characters of metazoan animals the relation between genes and characters is not "one-to-one"; there is a "long multidimensional network of interrelations between many genes and their interweaving reaction sequences" in consequence of which changes in many genes may affect the "same" character. He cited the case of the maize-plant in which at least fifty genic loci are concerned with chlorophyll production, change in any locus affecting the formation of the pigment, and *Drosophila,* in which more than forty loci have some action in determining the colour of the eyes. Change in one locus may indeed affect more than one character: for instance, the proportions of an internal organ as well as eye or body colour in this fly.

Mutations

A change in any unit of heredity constitutes a mutation, which does not solely concern a gene or a chromosome, because the cytoplasm may determine the development of some characters of an organism. Mutations of various kinds are known, but they have in common rare occurrence and sudden appearance. As they are germinal by nature they can be perpetuated in the inheritance. The appearance of a white-eyed mutation in the normal red-eyed stocks of *Drosophila* formed the basis of a new stock, and more than one hundred thousand other mutations have been induced by experiments with this insect. Individual biologists have discovered hundreds of natural visible mutants and more than one thousand natural and experimentally produced lethal mutants (W. P. Spencer, 1947). Mutations have been perpetuated also by selective breeding of domestic animals, to form the stocks from which the short-legged Ancon sheep, the hornless Hereford cattle and the greyhound and other breeds of dogs have arisen. Many

mutations are of a deleterious nature and therefore cause some concern to live-stock breeders; such are decreased fertility, defective muscle and indifferent milk-yield in cattle and poor wool quality in sheep. Occasionally, however, mutations have been of great value, as in the case of the Doppellender calf, which has duplicated muscles in the hindquarters and loin and is much more productive of red meat than most calves.

Most mutations can be traced to chromosomal aberrations during the maturation of the germ-cells. A chromosome may break, one piece of it becoming attached to the homologous chromosome, so that one part of the chromosome is represented twice (*duplication*), or to some other chromosome (*translocation* or *crossing-over*). Crossing-over may be reciprocal, both chromosomes involved losing a part, each to the other. Individuals in which this has happened are called heteroploids, a term which also includes those cases in which there has been loss of part of a chromosome (*deletion*). Duplication or translocation may involve a small or a considerable portion of a chromosome. Small duplications have slight effects, larger ones effects that are roughly proportional to the lengths of chromosomal materials which are duplicated—in the fruit-fly effects such as alteration of wing-shape, modification of bristle arrangement and abnormalities of the eyes. In the heterozygous condition the effects may be more serious; the loss of one-half of the X-chromosome, for instance, results in early death.

Other mutations may involve not one but an entire set of chromosomes, giving the individual two or more sets of haploid chromosomes (*polyploidy*). Polyploidy is common in plants, much less common in animals, and it may be the result of hybridisation between two or more species of organism (*allo-polyploidy*) or derived by the action of the germ-cells of one parent species (*auto-polyploidy*). If during maturation of the germ-cells reduction does not occur, the gametes may possess the diploid number of chromosomes instead of the haploid number. The fertilisation of a normal ovum by a diploid sperm gives rise to an individual with three sets of chromosomes, a *triploid*, or, when both kinds of gametes are diploid, an individual with four sets of chromosomes (*a tetraploid*) arises. In plants higher groups of *polyploids* are known, for instance, *hexaploids*, in which the individual has six sets of chromosomes in place of two—the normal diploid set. Polyploidy is important because it is one of the devices whereby new species arise. For an account of the types of polyploids, and their classification and significance, see the review by C. L. Stebbins, Jn. (1947). Polyploidy

has also been considered by E. R. Sears (1948) in regard to wheats and their relatives, by S. G. Stephens (1947) in regard to cottons, and by P. C. Mangelsdorf (1947) in regard to maize.

Sex Determination

Sperms and ova are apparently uniform things of their kind, but their union gives rise to males and females in about equal numbers, giving the impression that sex is determined by some simple mechanism. Nevertheless, sex determination proved to be a problem involving cytological difficulties and it required the combined efforts of many biologists over twenty years to work it out. Mendel (1870) believed that the sexes arise as a result of some kind of segregation, and during the early years of the present century this opinion received the support of E. Strasburger, W. Bateson, W. E. Castle, L. Doncaster, C. Correns and others. The first to associate the chromosomes with sex determination were cytologists working on spermatogenesis in insects. H. Henking (1891) and F. C. Paulmier (1898) saw that some of the spermatocytes of insects have an odd piece of chromatin and that others lack it. In 1901 C. E. McClung made the bold suggestion that there are two kinds of sperms and that the accessory chromosome is the agent that determines maleness. His work was followed up by W. S. Sutton (1902), E. B. Wilson (1905), N. M. Stevens (1905) and others and, in spite of early errors of observation (see F. A. E. Crew, 1946), the fact was eventually established that the genetical constitution of an animal varies according to sex, and that in different groups of animals it is sometimes the male (most animals) and sometimes the female (moths, butterflies, birds) which transmits the gene that determines maleness. One sex is homogametic and the other heterogametic, and the genes which determine sexuality are located in one pair of chromosomes, the sex chromosomes, which leave a residue of chromosomes that are not involved, the *autosomes*. The genetic constitution of the homogametic female includes the genes XX, which are segregated in the ova during maturation. The corresponding male is heterogametic, maturation resulting in the separation of genes designated X and Y in the sperms. Two kinds of zygotes may thus arise at fertilisation; for the ovum may be fertilised by X- or Y-carrying sperms. The zygotic composition XX then determines femaleness, and XY maleness. In instances where the Y chromosome has not been found, the determinant genes of the male are represented as XO.

Linkage

Linkage is the antithesis of independent assortment of genetic characters. Mendel was not aware of it, but it was known to early breeders, who observed that some characters can be separated easily in the inheritance, while others are generally transmitted together. The elucidation of linkage was facilitated by Morgan's theory of the gene, according to which a chromosome is composed of a linear series of these smaller units which generally go together in the hybrid and emerge together in its gametes. W. Bateson and R. C. Punnett (1906) first observed the effects of linkage in sweet-peas, and similar effects were soon noted in other plants and in animals, including man, which brought about modification of Mendel's second law. The fruit-fly, *Drosophila melanogaster*, which was first used in genetical experiments by Woodworth and W. E. Castle (1901), proved to be a fruitful subject for analysis, which was carried out notably by T. H. Morgan, C. B. Bridges, A. H. Sturtevant, H. J. Muller and others of the American school. In the short space of about ten years numerous heritable mutations were produced in this insect, and as they were discovered every one of several hundreds of mutations were found to fall into one or another of four groups of characters, linkage groups. The fact that the haploid number of chromosomes in the fly is also four gave good grounds for assuming that each linkage group corresponds to one chromosome, and further tests proved the truth of this assumption. "If the free assortment of Mendelian units be compared to the random shuffling of cards in a pack," wrote E. B. Wilson (1925), "we must add the qualifying assumption that certain of the cards tend to stick together in certain groups which may reappear as such in successive deals."

Sex-linked Characters

Linkage is best known in its relation to genes that exist in the sex chromosomes, for no matter how little these may have to do with sex the characters they determine will be associated with it in the inheritance; they will be sex-linked. As the Y chromosomes do not exist in some animals, sex-linked characters must be determined by the genes in the X chromosome, which will be apportioned between the sexes. The first instance of sex-linked inheritance to be recorded was in regard to eye-colour in *Drosophila*. The normal wild fly has red eyes, but in one variety the eyes are white. Morgan discovered that the result of the cross red-eye × white-eye was dependent on sex. A cross

involving a white-eyed male and a red-eyed female produces hybrids that are red-eyed in male and female alike. When these are inbred, all the female offspring are red-eyed, but one-half of the males are white-eyed. In the reciprocal cross (red-eyed male × white-eyed female) the hybrid generation is made up entirely of red-eyed females and white-eyed males, and when these are crossed their offspring consist of equal numbers of red-eyed and white-eyed flies in both sexes. The latter type of inheritance is sometimes called the "criss-cross" type, for the male transmits his sex-linked characters to his grandsons by way of his daughters. It is met with in regard to the barred plumage of some birds and many other characters, including some human disorders.

Because it is sex-linked, colour-blindness is much commoner in men than in women—about eight per cent. of all men being colour-blind, or anomalous colour-matchers (J. B. S. Haldane, 1948)—but a woman with normal vision may act as a "carrier" and transmit colour-blindness to her sons. The genes for normal vision (C) and for colour-blindness (c) form allelomorphs carried by the X chromosomes, and there is complete dominance. The mother's two X chromosomes may carry both dominants (CC), in which case she is normal; when they carry one dominant gene and one recessive (Cc) she is a carrier, and when they carry two recessives (cc) she is colour-blind. The single X chromosome of the male can carry either C or c, giving an option only between normal vision and colour-blindness. The various possibilities that arise in consequence of certain matings can be worked out according to a simple scheme (Table 5), and it can easily be shown that all the offspring of two colour-blind parents will be colour-blind. If the father is colour-blind and the mother normal, however, all the sons will be normal and all the daughters will be carriers. If the father is colour-blind and the mother is a carrier, the daughters will be colour-blind or carriers and the sons colour-blind or normal, the chances for each sex being even. If the father is normal and the mother is a carrier, half the daughters will be carriers and half normal, and half the sons will be colour-blind and half normal.

The dangerous human disorder haemophilia—in which the blood does not clot normally when exposed to air, so that slight wounds may produce fatal results—is propagated in the same way as colour-blindness, by sex-linked recessive genes. According to J. B. S. Haldane (1948) there are seventeen human pedigrees known in which *both* disorders are found. The gene for haemophilia (*h*) and the

allelomorph for normal blood-clotting (*H*) exist in the two X chromosomes of an apparently normal carrier mother. Half her sons by a normal man will be haemophilic and half her daughters will be carriers, her other offspring being normal, sons and daughters alike. Other

TABLE 5.—SCHEME ILLUSTRATING THE TRANSMISSION OF HUMAN COLOUR BLINDNESS. COLOUR-BLIND PERSONS DENOTED BY SQUARE BRACKETS; CARRIERS BY ROUND BRACKETS; NORMAL PERSONS BY NO BRACKETS.

	FATHER Colour blind somatic cells [cXY] sperms cX Y		FATHER Normal somatic cells CXY sperms CX Y	
MOTHER Colour blind somatic cells [cXcX] ova cX cX	CHILDREN		CHILDREN	
	daughters	*sons*	*daughters*	*sons*
	[cXcX]	[cXY]	(cXCX)	[cXY]
	[cXcX]	[cXY]	(cXCX)	[cXY]
MOTHER A "carrier" somatic cells (cXCX) ova cX CX	CHILDREN		CHILDREN	
	daughters	*sons*	*daughters*	*sons*
	[cXcX]	[cXY]	(cXCX)	[cXY]
	(CXcX)	CXY	CXCX	CXY
MOTHER Normal somatic cells CXCX ova CX CX	CHILDREN		CHILDREN	
	daughters	*sons*	*daughters*	*sons*
	(CXcX)	CXY	CXCX	CXY
	(CXcX)	CXY	CXCX	CXY

possibilities involved in sexual unions can be worked out as for colour-blindness by letting the genes *h* and *H* take the place of *c* and *C* in the scheme. Haemophilic sons generally die in childhood, but may attain maturity and produce children. All the daughters of a normal mother by a haemophilic father would be carriers and all the sons normal. A normal man of a haemophilic family may marry in the full knowledge that he cannot transmit the recessive gene *h* to his children, but his sisters might well be carriers because of sex-linked inheritance. Women haemophilics are unknown and must be very rare, but notable male haemophilics include the last Czar of Russia and the late King of Spain.

The Blood Groups

Until fairly recently human blood transfusion—which was first practised in 1818 (see G. Keynes, 1947)—was a dangerous undertaking, because the blood from some donors causes the corpuscles of the recipient's blood to cluster together, or agglutinate, and tend to block the blood vessels. During the early part of the twentieth century—largely due to the work of Landsteiner, Jannsky, Moss and a few other persons—it was discovered that human blood falls into one or another of four main types, and the identification of these blood groups of the ABO series has gradually made transfusion much safer. Both recipient and donor now have their blood groups determined before transfusion takes place, so that incompatibility between the two samples of blood rarely arises.

Originally known by the Roman numerals I, II, III, IV, the four blood groups are now known as AB, A, B and O. Some of them contain specific antigens (agglutinogens) and agglutinins of several kinds which exist respectively in the red corpuscles and the plasma. Agglutination of the blood occurs when certain agglutinogens and agglutinins come into contact with one another. The corpuscles of blood belonging to the group AB contain agglutinogens A and B, those of group A only A, those of B only B, and those of O contain no agglutinogens. The plasma of AB individuals contains no agglutinin, but blood of the A group contains α (Anti-A), that of the B group contains β (Anti-B), and that of the O group both α and β. Agglutination of the blood occurs when A agglutinogen reacts with α agglutinin, or B with β, so that precautions can be taken to prevent the mixing of samples of blood which are incompatible because containing the reactant agents. In transfusion, blood is not used if its corpuscles will be agglutinated by the recipient's plasma. The converse—injecting blood that will agglutinate the recipient's corpuscles—is less dangerous because the donor's blood plasma becomes diluted by the recipient's plasma and loses some of its potency. From the data in Table 6 it is clear that individuals belonging to group O can give their blood to individuals of any group; they are universal donors. Individuals of the A, B and AB groups can donate blood to their own blood group, and A and B individuals can act as donors to an individual of the AB group. In regard to accepting blood, O individuals must have blood of their own type, but A and B individuals can have either blood of their own types or blood of the O group. AB individuals are universal recipients.

he need for care in transfusion is evident when we realise that in ritain little more than three per cent. of individuals are universal cipients, though more than forty-five per cent. are universal donors.

The facts are not as simple as stated, because there are two kinds of glutinogen A, which exist in four subgroups of blood known as A_1, $_1B$, A_2 and A_2B. The corpuscles in samples of blood belonging to the

ABLE 6.—RELATIONSHIP BETWEEN THE BLOOD GROUPS OF DIFFERENT INDIVIDUALS, THE AGGLUTININS AND AGGLUTINOGENS, AND THE REACTIONS WHEN SAMPLES OF BLOOD ARE MIXED (+ AGGLUTINATION; – NO AGGLUTINATION, TRANSFUSION PRACTICABLE).

DONOR	Blood Group of the Individual → ↓	RECIPIENT			
		AB	A	B	O
Agglutinogens in the Corpuscles		Agglutinins in the Serum			
		None	β	α	$\alpha\beta$
A, B	AB	–	+	+	+
A	A	–	–	+	+
B	B	–	+	–	+
None	O	–	–	–	–

$_2$ and A_2B groups react less vigorously than those of the A_1 and A_1B oups, so that greater care is required when making tests than would herwise be necessary. There is also an additional agglutinin, anti-O $_2$), which occurs rarely in A_1, B and A_1B sera and reacts with all corpuscles. About one-fifth of the individuals of the A and AB oups in this country have agglutinogens of the types A_2 and A_2B.

Genetically, the blood groups form a series of multiple allelomorphs ee Ford, 1942). Group O is controlled by the pairing of two recessive enes (*g*) and has a single genotype (*gg*), groups A and B by genes G^a nd G^b, both of which are dominant to *g*, so that the genotypes may be $^aG^a$ or G^ag and G^bG^b or G^bg. Group AB arises by the interaction of ne dominants G^a and G^b, so that the single genotype can be represented

as G^aG^b. In the gametes of four kinds of individuals (O, A, B and AB) the three genes (G^a, G^b and g) exist singly, and in ten possible types of union it is easy to determine within limits the kinds of blood groups that could or could not arise in the offspring. When both parents belong to the O group, A, B and AB groups could not appear, and similarly the union of two A individuals could not give rise to B and AB groups, and the union of A or B and AB or two AB individuals could not produce children of the O-blood group.

The subgroups A_1 and A_2 are produced by two genes G^{a1} and G^{a2}, which form a pair of allelomorphs with one another and with G^b and g. Diminishing dominance is indicated by the series G^{a1}, G^{a2}, G^b and g, and the first two genes are able to interact separately with the third to produce the A_1B and A_2B groups, which have the genotypes $G^{a1}G^b$ and $G^{a2}G^b$ respectively. The genotypes of the groups A_1 and A_2 are not equally obvious, unless dominance is taken into consideration; the former can be either $G^{a1}G^{a2}$ or $G^{a1}g$, the latter only $G^{a2}g$. These considerations indicate that further limitations are imposed on the blood groups of the children of the unions between individuals belonging to certain blood groups, and although these may be important in medical jurisprudence they need not concern us here.

Mention must be made, however, of the existence in human red blood cells of agglutinogens other than those mentioned so far. The corresponding agglutinins occur only rarely in human serum, but exist in the sera of other mammals. One series includes the agglutinogens M and N, either one or both of which invariably exist in human blood, so that in this series there is no analogue of O in the A, B, AB, O series. The other series includes the Rh factor, so called because a related form exists in the rhesus monkey. The Rh factor is said to exist in Britain in the blood of seven out of every eight human beings. The remaining section of the population react to the introduction of the Rh antigen into their blood by forming an antibody (agglutinin) against it, with harmful consequences. The only condition under which the antibody is produced is when an Rh-negative woman is carrying a foetus bearing the Rh agglutinogen, for the blood of the mother then reacts by producing the antibody, which may pass through the placenta and cause a haemolytic disease in her offspring. It is for this reason and because the Rh antibodies are difficult to determine that transfusion of blood to a woman after parturition (or miscarriage) can only be safely made with Rh-negative blood. More detailed information concerning the Rh factor and many other matters concerning the determination of the

blood groups can be found in the War Memorandum No. 9 of the Medical Research Council (H.M. Stationery Office, London, 1943, 1944).

Cytoplasmic Inheritance

While it is clear that genes located in the chromosomes are transmitted from one generation to the next, and are responsible for the inheritance of many characters, it is not certain whether certain cytoplasmic units of cells are also transmitted in the same way. E. Caspari (1948) has carefully considered the question of cytoplasmic inheritance, concluding that such transmission does take place. In some instances it is brought about by certain plastids, in others by plasmagenes and viruses. General qualities of the cytoplasm, such as a certain degree of osmotic power or viscosity, are also transmitted by the cytoplasm of the egg. Since the sperm contains little cytoplasm—hardly more than a thin membrane covering its surface—the question of cytoplasmic inheritance largely concerns what is handed on by the mother. In some instances, induced cytoplasmic changes, or "dauermodifications", have been transmitted through the mothers of several successive generations. In plants, the transmission of plastids from parent to offspring is a well-established fact. The speed of propagation of plastids and the ability to form chlorophyll or not are gene-controlled, but in some instances these qualities seem to depend on the nature of the plastid itself. Examples of characters which are transmitted by cytoplasmic inheritance include pollen sterility in maize and pathenogenicity in rusts, and also sensitivity to carbon dioxide in *Drosophila.* The cytoplasmic constituents concerned with this type of inheritance have been termed the "plasmon", which C. D. Darlington (1939, 1944) regards as corpusculate. The type of transmission which has been attributed to viruses is possibly analogous to the transmission of yeast and bacterial symbionts by insects and the transmission of a spirochaete by ticks and plant viruses in seeds and pollen grains. The existence of plasmagenes, which are self-reproducing gene-products found in cytoplasm, was first suggested by Lehmann in 1939. They were named by Wright in 1941 and they are assumed to be free cytoplasmic replicas of genes. The existence of such genetical units does not militate against the usual genetic theory, for the plasmon depends on the presence of certain genes in the chromosomes, and it is likely that the study of cytoplasmic inheritance will throw further light on the physiological action of genes.

SOME APPLICATIONS OF GENETICS

Forage Crops

The importance of forage crops is recognised in various types of agriculture, particularly in regard to the grassland type of farming (see D. H. Robinson, 1947). Accordingly, in recent years more emphasis has been placed on the breeding of improved types of forage plants and on associated problems in cytogenetics. In this country several phases of this type of work were summarised in the *Report of the Fourth International Grassland Congress at Aberystwyth* (1937) and the literature on such subjects was summarised in the *Yearbook of Agriculture of the Department of Agriculture, U.S.A.* (1937). The more recent work has been covered in a recent review by S. S. Atwood (1947), who has dealt with breeding methods used in regard to various forage crops—blue-grasses, timothy, orchard grass, rye-grasses and fescues, prairie and other grasses, alfalfa, red, white and sweet clover, and also various leguminous plants. He covered a very extensive literature (350 papers, reviews and books) and stressed that recent research has advanced particularly in regard to polyploidy, apomixis and sterility. Inbreeding is easy of achievement with forage plants, but inbred lines—which when outcrossed frequently display hybrid vigour—have not been put to commercial use, partly because severe loss of fertility may accrue. Mass selection is an alternative which has given rise to most of the improved varieties, however, and is being used. Another method which includes some of the features of both inbreeding and mass selection is strain-building, which was described by T. J. Jenkin (1937). It implies selecting certain individuals having desirable qualities which conform to definite standards and then combining them in a composite strain, a method which has been practised for many years at Aberystwyth, where much work on breeding of forage plants has been carried out. At this Plant Breeding Station in Wales strain-building has had its most extensive application (see T. J. Jenkin, 1943). Here also much work has been carried out on red and white clovers by R. D. Williams (1937, 1939, 1941). The origin and performance of British types of red clover was described by W. Williams (1945), who has also described the types of white clover which are best adapted to conditions in Britain. White clover is a highly polymorphic species and it has given rise to many strains by natural selection and by experimental mass selection.

Animal Breeding

Like the raising of commercially useful plants, animal breeding depends on the application of genetical principles to control certain pairs of genes—to group these so that desirable characters will appear in the phenotype, or to eliminate them if they are concerned with the production of undesirable characters. The prime character desired is viability, but cattle are bred for milk-yield and beef-producing qualities, sheep for wool and mutton qualities, pigs for fecundity and

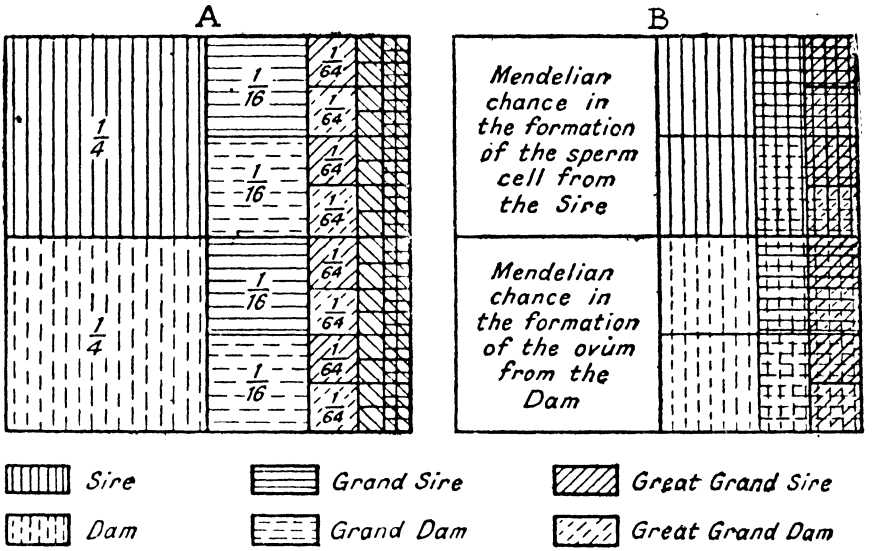


Fig. 15. Diagram of the relative part played by the different ancestors in the genetical make-up of an animal. A, as formulated by Galton, each ancestor being considered singly; B, as calculated from the Mendelian theory when random mating is practised. From Hammond, 1944. (Edward Arnold & Co.)

pork qualities. Inbreeding—which is the mating of brothers and sisters, parents and their offspring, and other closely related offspring—serves to concentrate the hereditary qualities of a few individuals in a single prolific line of descent, like self-fertilisation in plants. The stud, herd, or flock book enables breeders to segregate animals with desirable qualities for inbreeding, and it minimises the possibility of introducing undesirable qualities into the inheritance of blood stocks and aims at progressive improvement. Inbreeding has some disadvantages—for instance, reduction of size, fecundity and vigour in the stock—and it may produce structural abnormalities and defects. From the breeder's point of view the advantages outweigh the disadvantages, however,

because defective individuals can be weeded out of a stock by rigorous selection. In human families such selection cannot be exercised, and consanguinity is condemned, though it was permitted in the royal families of ancient societies in Egypt and Peru.

Inbreeding owes its success and failures to the isolation of homozygous types. No animal is homozygous for all its characters, but as inbreeding proceeds the degree of homozygosity increases until a limit of uniformity and stability is reached. In some instances deleterious homozygous recessives appear. These may be viable forms greatly lacking in vigour—such as the furless rabbit and the porcupine pigeon—or they may be forms which have a very short life. The homozygous yellow mouse dies in the uterus of the mother within a few days. The allelomorphic genes which determine lethal as well as desirable qualities appear together more frequently during inbreeding than in random matings of the original stock.

Animal breeders have long known that animals produced by a first cross may be larger, stronger and more resistant to deleterious conditions than either of the parents, and they may mature at an earlier age. This quality of hybrid vigour is now as well known in silkworms, fishes, mice and guinea-pigs as it was formerly in the mule and the hinny. It is well known also in many plants (see E. M. East and D. F. Jones, 1919; W. G. Whaley, 1944; and E. Ashby, 1948). It is most marked when both parents are pure-bred, and it depends on heterozygosity in the genotype. Cross-breeding is often a commercial undertaking—trying to get the best out of two breeds of animals by combining their qualities. In recent times, a pooling of the hereditary resources of distinct breeds has produced hardy stocks able to live under poor conditions of life, and cross-breeding is regularly practised in Britain for producing mutton and fat lamb. Cross-breeding of cattle was introduced into England by the Romans, who brought their long-horned cattle here, and the result of crossing these animals with the native Celtic black cattle is still evident in the Welsh and other breeds which combine long horns with a black colour. Norsemen helped to develop such breeds as the Galloway and Aberdeen-Angus cattle in the north of England and the Polled White and Red Polled in the south, for they introduced the polled character. Perhaps the first attempt to apply Mendel's laws to inheritance in farm animals was in regard to the dominant gene for polledness in cattle (R. R. Shrode and J. L. Lush, 1947). A more recent example of cross-breeding which has rapidly improved rather poor stock is "grading-up", which means crossing the

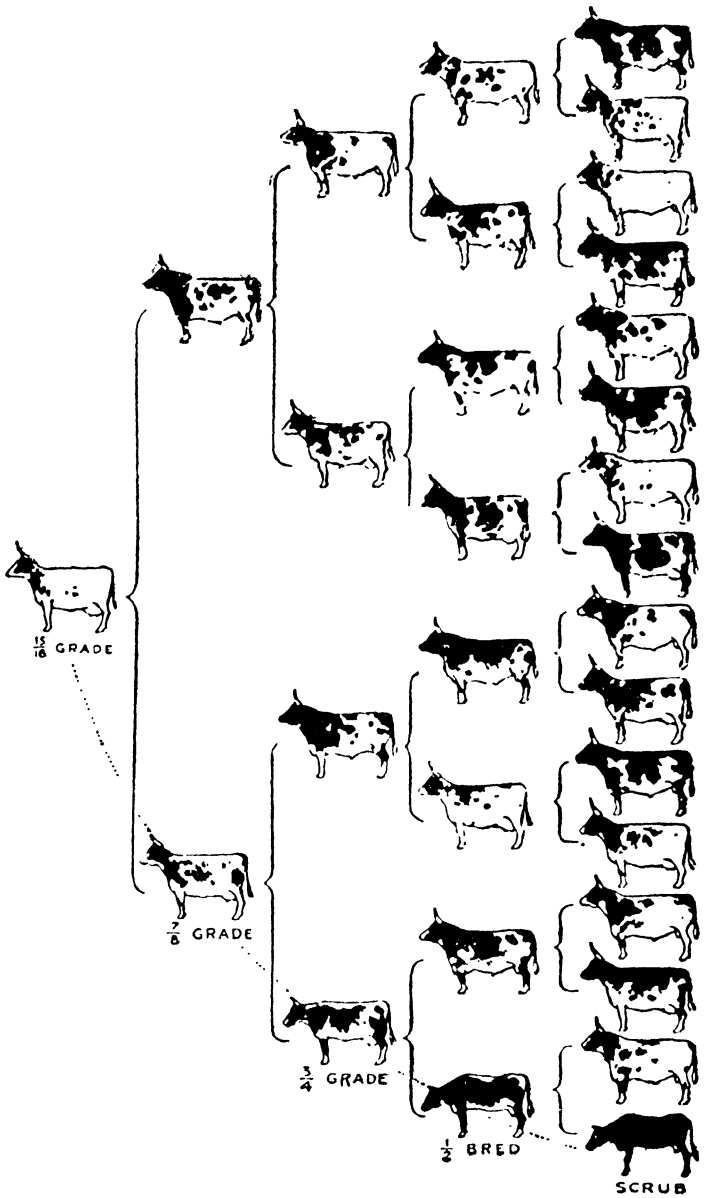


Fig. 16. Diagram illustrating the system of "grading-up" a scrub cow (lower right) with pure-bred Ayrshire bulls. Compare with the relative part played by different ancestors in Fig. 15. From Hammond, 1944. (Edward Arnold & Co.)

poor breed with pure-bred males having desirable qualities. In the course of about five generations the pure-bred characters introduced by grading-up may help to produce a strain that is difficult to distinguish from the pure stock, both in appearance and in physiological performance.

Carefully controlled animal breeding has improved stocks of domesticated animals by methods not applicable in nature. When artificial fodder is available at all times of the year, the breeder can rear cattle which digest and assimilate synthetic food to best advantage, *i.e.* convert them into human food. Breeding for meat qualities often implies trying to reduce the size of skeletal parts and the quantity of fat on the carcass. Improved breeds of pork, lard and bacon pigs have lost the heavy head and shoulders of the wild boar and have acquired the large loin of breeds such as the Berkshire. The speed with which the proportions alter during development also concerns the breeder, who wants a large animal as soon as possible. Improved breeds become marketable at an earlier age, the Suffolk lamb of three months attaining the same size as the adult wild mouflon.

Genetic factors are involved in both the yield of milk given by cows and the colour of the butter fat in it. A system of multiple allelomorphs probably controls the grading of fat colour from an undesirable white to a desirable yellow, though green pigment must be included in the diet if the fat is to be yellow. In poultry genetic factors control the colour of the egg-yolk and the egg-shell as well as the yield of eggs. In mammals, too, fertility is controlled by genes, though death and atrophy of unborn young may be due to physiological qualities in the mother which cannot so far be ascribed to individual genes, as well as to homozygous recessive genes, for the females of some breeds of rabbits lose just as many foetuses when mated with males of other strains as when mated with those of their own breed.

J. Hammond (1947) has stressed the fact that most of the inherited characters of farm animals which are important in meat-production are fully expressed only when the environmental conditions—and particularly nutritional factors—are carefully controlled. Good beef-qualities in cattle call for sound nutrition throughout development. The notable breeds of good beef-cattle (Hereford, Shorthorn, Aberdeen Angus, for instance) thrive in areas where nutrition is likely to be good, and in poor country the herds deteriorate and must be reinforced with breeding stock from regions where nutritional conditions are good. Crew has also shown the difficulty of disentangling the effects of

heredity and environment, and has said that the most important environmental factor is the live-stock breeder himself! The breeder is concerned not so much with a particular breed of animal as with breeds that will thrive under certain external conditions. His task involves the stocking of poor pastures as well as good, the breeding of resistance to particular kinds of disease as well as good viability and quick growth, and the improvement of the reproductive activities of farm animals. The breeder must be a knowledgeable person in the fields of nutrition, bionomics and sexual physiology as well as in the field of genetics. He is now faced with an enormous literature; the recent review by Shrode and Lush (1947) on the genetics of cattle cites 237 original papers and reviews.

Genetics and Human Affairs

As we have seen, the methods of genetics can be applied to man. Every human generation is a new group of individuals resulting from the segregation and recombination of genes during reproduction. New gene combinations must be continually arising, but some evidence serves to show that special talents in music, science and the arts tend to "run" in certain families, and that feeblemindedness, criminal tendencies, deaf-mutism and other undesirable qualities are inherited in various strata of human society. The ability to perform various tasks on which a high value is set is not inherited in purely genetical fashion, however, for the effects of nature and nurture are entangled in human inheritance as in the breeding of animals. Parents act as models for their children and also give them opportunities which tend to favour the emergence of special talents which, as a result of familiarity or economic policy, are often a reflection of those of the parents. We have to admit, however, that there is some genetical basis for some undesirable human qualities which cannot always be corrected by medical or moral science, or by favourable conditions of nurture.

In 1883 Francis Galton founded the science of eugenics, which deals in the application of genetic principles to human reproduction with a view to improving the standards of human life. It is not certain whether this can best be attained by what Crew called "the public eugenic conscience" or by restrictive laws applied to procreation. Some improvement would certainly accrue from improved conditions for human development. The genetic equipment for useful and successful life is supplied to most individuals before birth, and it can be utilised by good conditions of nurture. The future of the human

race depends less on the production of a few outstanding individuals of exceptional talent than on the setting up of a good average standard of performance by many healthy individuals (F. A. E. Crew). Man has gained outstanding control over the general background of life and has already acquired much knowledge which could be put to good use if applied to the betterment of human life.

More than forty years ago William Bateson (1906) lectured on the inheritance of brachydactyly, congenital cataract, albinism, haemophilia, colour-blindness and other defects in man. J. B. S. Haldane (1948; lecture, 1946) has stated that during the ensuing years the investigation of numerous human pedigrees has revealed more than one hundred different human abnormalities which arise by single gene substitutions, several hundred more probably arising in this way. E. A. Cockayne (1933) compiled lists of 80 instances of abnormal skin, hair, nails and teeth due to the action of dominant autosomal genes, 18 to autosomal recessives and 13 to sex-linked genes. Problems of human inheritance may be complex or comparatively simple. Eye-colour and other pigmentary characters seem to be controlled in steps by the action of many genes, and to some extent also by environmental conditions, but the genetical basis of immunity is simpler, antigens being produced by direct genic action. For a detailed statement on "Immunogenetics" see M. R. Irwin (*Advances in Genetics*, i, 1947).

Haldane selected three of many lines of progress in genetics for their special importance. First, the demonstration that genes are material things located at particular points in the chromosomes and composed at some stage of their existence of desoxyribose nucleic acid, as O. T. Avery, C. M. MacLeod and M. McCarty (1944) suggested. Second, the elucidation by R. Goldschmidt and others of the causal connexion between a gene and its manifestation. This has led on to such work as the genetical studies of arginine and other essential metabolites in *Neurospora* by G. W. Beadle, E. L. Tatum and others, and the genic control of development by H. Grüneberg, C. H. Waddington and others. Third, the study of the genetics of populations and their application to the problems of evolution. In this last field many well-known geneticists have played important parts: T. Dobzhansky, N. P. Dubinin, R. A. Fisher, J. B. S. Haldane, G. Teissier, P. L. l'Heritier, Tsetverikov, Sewall Wright and others.

The methods used in these three main lines of investigation are all applicable to human heredity. Human chromosomes have been carefully studied by T. Painter (1923), P. C. Koller (1937) and others.

Haldane believes that the final aim of formal genetics should be to enumerate and locate all the genes (thousands, and possibly tens of thousands of them) which exist in man and to deduce their respective, highly specific biochemical functions. Such a study, he claims, would create "an anatomy and physiology of the human nucleus, which would be incomparably more detailed than the anatomy and physiology of the whole body as known at present". It might give also "the possibility of a scientific eugenics, which may bear the same relation to the practices now or recently in vogue in certain countries as chemotherapy bears to the bleedings and purgations of early medicine". Other results of such a study may be even more important, for "a knowledge of the human nucleus may give us the same powers for good or evil over ourselves as the knowledge of the atomic nucleus has given us over parts of the external world".

G. Dahlberg (1948) has reviewed existing knowledge of the genetics of human populations. In his opinion, human genetics deals with two main questions: what the children of any given marriage will be like; and what the future make-up of a population will be, its present constitution and possible crosses taking place in it being known. He has stressed the important difference between experimental genetics, in which the environment can be strictly regulated so that the investigator can concentrate on hereditary factors which determine certain characters, and human genetics, where this simplification of analysis cannot be practised, and he has shown that much must be done before populations can be assessed from the genetical point of view, an outstandingly important task for the future.

CHAPTER NINE

TAXONOMY

TAXONOMY simply means orderly arrangement, and in biology this implies the grouping of animals and plants according to resemblances and differences, which is also known as systematics. To set out a satisfactory scheme of classification the taxonomist must select from the many structural and physiological characters of organisms those having a real value for his purpose, and the student who uses such a scheme is provided with the simplest grouping of characters that willenable him to distinguish one kind of organism from another. Early biologists regarded classification as just a convenient way of cataloguing organisms and many mistakes were made by attaching too much importance to superficial characters and to habits. For instance, whales were classified with fishes, and birds with bats, although both whales and bats suckle their young and are therefore mammals. The concept of evolution gave a tremendous impetus to the study of taxonomy, calling for arrangements based on kinship, and because blood relationships are difficult to determine it is inevitable that taxonomic schemes which satisfy everybody are practically impossible to devise. We often have to guess at the real relationships between many organisms, more information being required about them than is generally available. As the boundaries of biology widened, however, artificial systems gave way to more natural schemes, and when the ideal system is devised it will turn out to be a genealogy of organisms. Some of the earlier trends in taxonomy have already been mentioned. One of the greatest difficulties is definition of the units of classification. Attempts to define genera and species have given rise to much controversy in the past. A species can be regarded as a group of individuals closely resembling one another because of common descent from the same or very closely allied ancestors, and rather sharply marked off from all other species by the disappearance of intermediate forms. A genus is often regarded as an assemblage of species that have more in common with one another than with any other species. Such elementary definitions as these would hardly satisfy the professional taxonomist, but they serve the most general purposes. Genera are then arranged

together to form families, and these are collected into still higher taxonomic groups, orders, which are grouped into classes and finally phyla. A phylum is one of the major divisions of the animal or plant kingdom, and it thus contains all the other groups—classes, orders, families, genera and species—in a descending series. All such groups may be subdivided for convenience into smaller intermediate groups—

TABLE 7.—EICHLER'S (1883) SCHEME OF CLASSIFICATION OF PLANTS

A. CRYPTOGAMAE
- Division I. THALLOPHYTA
  - Class. ALGAE * (5 groups)
  - Class. FUNGI † (3 groups, including Lichens)
- Division II. BRYOPHYTA
  - Group I. HEPATICAE (Liverworts)
  - Group II. MUSCI (Mosses)
- Division III. PTERIDOPHYTA
  - Class 1. EQUISETINEAE (Horsetails)
  - Class 2. LYCOPODINEAE (Lycopods)
  - Class 3. FILICINEAE (Ferns)

B. PHANEROGAMAE (≡ Spermatophyta: seed plants and flowering plants)
- Division I. GYMNOSPERMAE (Cycads, Conifers, etc.)
- Division II. ANGIOSPERMAE
  - Class. MONOCOTYLEAE (7 orders)
  - Class. DICOTYLEAE
    - Subclass. CHORIPETALAE (21 orders)
    - Subclass. SYMPETALAE (9 orders)

* In some modern schemes the series of the Algae form four classes: Cyanophyceae (Blue-green algae), Chlorophyceae (Green algae), Phaeophyceae (Brown algae), and Rhodophyceae (Red algae).

† In some schemes the series of the fungi contains four classes: Schizomycetes (Bacteria), Phycomycetes (Moulds), Ascomycetes (Yeasts, etc.), and Basidiomycetes (Rusts, Smuts, etc.).

subclasses, suborders, subfamilies, subgenera and subspecies. The last-named are often called varieties, and they are species-in-the-making. A modern scheme of classification of animals to classes is shown in Table 8.

To illustrate simply how such a scheme works let us say that "cats" belong to several species, and the domestic cat (*Felis catus*), the tiger (*F. tigris*), the lion (*F. leo*) and the puma (*F. concolor*) all agree in having the teeth of a typical carnivore and retractile claws, for which reason they are grouped in the family Felidae. Dogs also have this kind of dentition, but not retractile claws, so that they are placed in a different genus (*Canis*) and family (Canidae). The wolf is *Canis lupus*,

TABLE 8.—SCHEME OF CLASSIFICATION OF ANIMALS

Sub-kingdom. PROTOZOA
*Phylum. PROTOZOA (Unicellular animals)
Class. RHIZOPODA (SARCODINA) (Pseudopodial forms; e.g. *Amoeba*)
Class. MASTIGOPHORA (FLAGELLATA) (Flagellate forms; e.g. *Euglena*)
Class. CILIOPHORA (CILIATA) (Ciliate forms; e.g. *Paramecium*)
Class. SPOROZOA (without pseudopodia, cilia or flagella; e.g. *Monocystis*)

Sub-kingdom. PARAZOA
*Phylum. PORIFERA (Sponges; e.g. *Sycon*)

Sub-kingdom. METAZOA (Multicellular animals)

DIPLOBLASTICA
*Phylum. COELENTERATA (Jelly-fish and allies)
Class. HYDROZOA (Hydroids, etc.; e.g. *Hydra*)
Class. SCYPHOZOA (Jelly-fish; e.g. *Aurelia*)
Class. ANTHOZOA (Sea-anemones, corals, etc.; e.g. *Actinia*)
Class. CTENOPHORA (Sea-gooseberries; e.g. *Pleurobrachia*)

TRIPLOBLASTICA
*Phylum. PLATYHELMINTHES (Flatworms)
Class. TURBELLARIA (Planarians; e.g. *Leptoplana*)
Class. TREMATODA (Flukes; e.g. *Fasciola*)
Class. CESTODA (Tapeworms; e.g. *Taenia*)
*Phylum. NEMATODA (Roundworms; e.g. *Ascaris*)
Phylum. NEMERTEA (Proboscis-worms; e.g. *Lineus*)
Phylum. ROTIFERA (Wheel-animalcules; e.g. *Rotifer*)
Phylum. CHAETOGNATHA (Arrow-worms; e.g. *Sagitta*)
Phylum. POLYZOA (Moss-animals; e.g. *Bugula*)
Phylum. BRACHIOPODA (Lamp-shells; e.g. *Lingula*)
Phylum. PHORONIDEA (Tube-worms; e.g. *Phoronis*)
*Phylum. ANNELIDA (Ringed-worms)
Class. POLYCHAETA (Bristle-worms; e.g. *Nereis*)
Class. OLIGOCHAETA (Earthworms; e.g. *Lumbricus*)
Class. HIRUDINEA (Leeches; e.g. *Hirudo*)
Class. ARCHIANNELIDA (*Polygordius*) and GEPHYREA (*Sipunculus*)
*Phylum. ARTHROPODA (Jointed-limbed inverts)
Class. ONYCHOPHORA (e.g. *Peripatus*)
Class. CRUSTACEA (Crabs and Crayfish; e.g. *Cancer, Astacus*)
Class. MYRIAPODA (Centipedes and Millipedes; e.g. *Scolopendra, Lithobius*)
Class. ARACHNIDA (Scorpions and Spiders; e.g. *Scorpio, Aranus*)
Class. INSECTA (Insects)
*Phylum. MOLLUSCA (Shellfish and allies)
Class. AMPHINEURA (Chitons; e.g. *Chiton*)
Class. GASTEROPODA (Snails and Slugs; e.g. *Helix* and *Arion*)
Class. LAMELLIBRANCHIATA (Bivalves; e.g. *Mytilus, Ostrea, Anodonta*)
Class. CEPHALOPODA (Cuttlefish; e.g. *Sepia*)
Class. SCAPHOPODA (Elephant-tooth shells; e.g. *Dentalium*)
*Phylum. ECHINODERMATA (Starfish and allies)
Class. CRINOIDEA (Sea-lilies; e.g. *Pentacrinus*)
Class. ASTEROIDEA (Starfish; e.g. *Asterias*)
Class. OPHIUROIDEA (Brittle-stars; e.g. *Ophiura*)
Class. ECHINOIDEA (Sea-urchins; e.g. *Echinus*)
Class. HOLOTHUROIDEA (Sea-cucumbers; e.g. *Holothuria*)

TABLE 8 (*continued*).

*Phylum. CHORDATA (Vertebrates and allies)
  Subphylum. ACRANIA (Head without a cranium)
    Class. HEMICHORDATA (*Balanoglossus*)
    Class. UROCHORDATA (Sea-squirts; e.g. *Ciona*)
    Class. CEPHALOCHORDATA (Lancelets; e.g. *Branchiomma*)
  Subphylum. CRANIATA (Head with a cranium)
    Class. CYCLOSTOMATA (Lampreys and Lags; e.g. *Petromyzon* and *Myxine*)
    Class. CHONDRICHTHYES (SELACHII) (Sharks, Skates, Dogfish)
    Class. ACTINOPTERYGIA (Bony fishes)
    Class. CHOANICHTHYES (Lung-fishes)
    Class. AMPHIBIA (Frogs, Newts, Salamanders, etc.)
    Class. REPTILIA (Lizards, Snakes, Turtles, etc.)
    Class. BIRDS (Ostrich, Emu, etc.; Flying Birds)
    Class. MAMMALIA (Duck-billed Platypus, Echidna, Marsupials and Eutherians)

(The more important phyla are marked thus: *)

the fox *C. vulpes* and the jackal *C. aureus*. Bears do not have cutting (carnassial) teeth like the typical carnivore, and they walk on the soles of the feet, not the tips of the digits; they belong to the genus *Ursus* and the family Ursidae. All three families mentioned have the common characters of the order Carnivora, which distinguish them from cows and horses (Ungulata) and other hairy animals that suckle their young, all of which belong to the class Mammalia. Other classes of backboned animals (Vertebrates, or Chordata) typically produce eggs, and of these Fishes possess fins, Amphibia five-toed legs and a glandular skin, Reptilia a scaly skin and Birds a feathery skin; such classes are fairly well defined and make up the phylum Chordata. Backboneless animals, or Invertebrata, form a number of phyla which are subdivided similarly into lower groups, and the whole animal kingdom can thus be represented as having a number of tree-like arborisations, which idea has been summarised as a "tree of animal life". This last belies the facts of zoology, however, for often "twigs" cannot be joined with a "branch", and "branches" with the main "stem". Whatever twigs and branches existed in the past have largely been obliterated, though a few traces of them may appear as the fossil remains left in rocks.

Certain features of animals enable us to determine relationship. Homologous structures show similarities of origin, and different as the limbs of many vertebrates may appear in different species—being variously used as flippers, legs and wings—when we compare their structural parts we are impressed by fundamental similarities of structure. Muscle for muscle and bone for bone they often conform down to the last particular, and when we also take into account early

development the correspondence is nearly complete. Such parts arise from similar embryonic rudiments throughout the entire vertebrate series. Similarity of origin cannot be the result of accident, but is due to the inheritance of certain characteristics from a common ancestral form. Conversely, organs and parts which have a similar use or function are said to be analogous, and they may show superficial points of resemblance no matter how different were their origins. The whale's flippers resemble the fins of fishes, and the wings of birds and bats not only serve to keep the animal in the air but have a similar origin, so that they are both analogous and homologous. The wings of an insect are thin membraneous outgrowths of the body supported by veins and they bear no inner resemblance to the limbs of any vertebrate. Many of the mistakes made by early taxonomists were largely due to a failure to distinguish between analogous and homologous parts, the former often erroneously being taken to indicate relationship.

Sometimes relationships are obscured because organs and parts remain undeveloped (rudimentary) or become atrophied (vestigial). The embryo whale may have a coat of hair like any other mammal, as well as the rudiments of hind-limbs, but the adult retains only a few stiff bristles and shows no external trace of such limbs. Some snakes retain only the merest vestiges of hind-limbs in the form of minute claws near the anus, but dissection reveals the vestigial skeletal supports for such a limb. Vestiges may be numerous in the body of an animal—two hundred of them are found by the expert in the human body, notably the vermiform appendix, certain muscles of the external ear, muscles which in other animals twitch the skin, the pineal organ, or third eye, and the *plica semilunaris*, or third eyelid. When certain functions are lost, the organs responsible for those functions tend to become useless, and they may retrogress to the extent of leaving no trace, thus tending to confound the taxonomist in his quest for common characters.

Species of Animals and Plants

No biologist can give a really reliable estimate of the number of species of existing animals and plants. S. H. Vines (1900) estimated the number of plant species as "little short of 200,000", claiming that future studies, especially of the lower microscopic forms, would no doubt bring the total up to 300,000. Sir A. Shipley (1909) suggested that the number of animal species then named must also exceed 300,000. J. W. Judd (1910) tried to estimate the species of both plants and animals

and to take into account new species which are described by naturalists every year—which he put at 1,500 for plants and 1,200 for animals—as well as the rather inaccessible and unvisited regions of the earth, the very imperfectly known depths of ocean, and "the almost infinite varieties of minute and microscopic forms". He believed that any competent judge would consider one million to be, if anything, an underestimate of the number of species in existence. W. T. Calman (1930) pointed out that in 1758 Linnaeus named and described about 4,370 species of animals but that from the time of Linnaeus monographs, synopses and revisions of all sorts and sizes have appeared, to try to make possible the identification of species without "demanding a life-time of study for each special group". Such works aim at being intelligible to the properly trained student, even if he knows nothing about particular groups. Year by year the "torrent of publications" catalogued in the *Zoological Record* increases, and the Zoological Department of the British Museum "may fairly claim to have done more towards this re-editing of the *Systema Naturae* than any other institution in the world". In 1896 the German Zoological Society began to publish *Das Tierreich*, with the ambitious aim of revising all species of living animals. After very many years, only a small part of the ground had been covered, and many parts already published had become obsolete because of the progress of research. According to J. Stephenson the *Revision of Oligochaeta* (earthworms and their allies) prepared by Michaelsen (and published in *Das Tierreich*, 1900) dealt with exactly one-half of the species enumerated by the same authority in 1928! Calman also pointed out how difficult a matter it is to induce an expert to enumerate the species in groups with which he is specially concerned. Mammals are referred to anything from three to twenty thousand species, "according to the view taken as to what constitutes a spécies" Nevertheless, Calman ventured an estimate of the number of described species of animals as about 750,000, perhaps one-quarter of which could be suppressed as invalid. He pictured systematic zoology as "being smothered under the products of its own activity". There are "difficult residues" in most orders of animals, even in families and genera, and the delimitation of species is sometimes little more than a matter of personal taste.

It is of some importance to try to evaluate the numbers of species, however difficult this may be, and T. Dobzhansky (1941) quotes estimates of plant species made by Carl Epling as totalling 266,700, this number being made up as follows: Angiosperms, 150,000; Fungi,

70,000; Mosses, 15,000; Algae, 14,000; Pteridophytes, 10,000; Liverworts, 6,000; Bacteria, 1,200; Gymnosperms, 500. He put the total number of animal species at 822,765, this number comprising Arthropods, 640,000; Mollusca, 70,000; Echinoderms, 4,800; Annelida, 6,500; Platyhelminthes, 6,000; Coelenterata, 9,500; Protozoa, 15,000; Chordata, 60,000; and all other groups 10,965. J. S. Huxley (1942) accepted the estimate of R. Hesse (1929) for animal species recognised up till 1928 as a total of between three-quarters of one million and slightly more than one million, between one-half and three-quarters of them insect species. The detailed figures are as follows: Insects, 500,000–750,000; Sponges, 4,500; Coelenterata, 9,000; Echinodermata, 4,200; Annelida, 7,600; other worms, 9,000; Molluscoidea, 3,300; Mollusca, 80–104,000; Crustacea, 15,500; Myriapoda, 8,100; Arachnida, 28,000. The actual number of species is probably much larger than indicated here, even allowing for improper assignments; the numbers increase annually and may be expected to go on increasing for many years, especially in regard to groups such as the Insecta.

Names of Animals

Various biologists have attempted the almost hopeless task of preparing lists of the names of genera and species of animals and plants. In regard to animals the first of these was prepared by L. Agassiz more than one hundred years ago, and it was followed by Scudder's *Nomenclator Zoologicus* and the Prussian Academy of Science publication *Nomenclator Animalium Generum et Subgenerum.* None of these is satisfactory, because neither complete nor up to date. The great work of C. D. Sherborn, *Index Animalium,* has dealt with determinations made and published up till 1850. Henceforth the lists published annually in the *Zoological Record* were the only supplement, until S. A. Neave and R. W. Lloyd privately edited and published their *Nomenclator Zoologicus* (4 vols., 1939–40), which contained a list of more than 225,000 names of species and genera of animals known from the time of publication of the tenth edition of *Systema Naturae* (1758) to the end of 1935. By 1946 the edition was almost sold out and in that year and by agreement with the Zoological Society of London a Neave-Lloyd Fund was set up so that similar publications could be issued once every ten years. The first of these, volume five of the series, was published in 1950 and dealt with the generic names—more than 18,000 of them—which were set up during the period 1935–45, and included

names inadvertently omitted from previous volumes. This invaluable publication lists genera or subgenera, gives the name of the author and the date of the publication in which he created the name, and refers the units to their appropriate classes or orders. These are of course scientific names, the value of which is to enable zoologists of any nationality to refer to particular types of animals. In regard to specific names the scientific terminology is indispensable, for obviously the use of vernacular names which vary from one country to another, and even from one locality to another in the same country, is confusing. The mallard, to take one example, is known by more than thirty different common names in Britain alone, and there are many other examples in regard to both animals and plants.

The New Taxonomy

W. T. Calman (1930) referred to the fact that since the time of John Ray systematists have believed in the existence of a Natural System of Classification, and since the time of Darwin it has seemed plain that such a system must be based on phylogeny. Towards the end of the nineteenth century the chief end of zoological research was deemed to be the reconstruction of the evolutionary history of animals, but now, except in certain aspects of palaeontology, "one might almost say that the phylogenetic period in the history of zoology has come to an end". The relation between a Natural System of classification and phylogeny is not as simple and straightforward as it once seemed to be, and bad mistakes have been made, such as attempts to derive vertebrates from arachnids and echinoderms from cirripedes. Calman pointed out that categories established by specialists in other fields of biology—physiologists, ecologists and geneticists—often cut across the boundaries of such natural groupings as can be devised by the taxonomist, and he observed that both divergences and coincidences deserve closer consideration than they get. The functions and habits of animals have an evolutionary history behind them, but this cannot be separated from the history of the organisms that display such phenomena. During the latter part of the nineteenth century comparative morphologists tried to determine the relative importance of structural characters by noting the extent of their persistence through the various divisions of the animal kingdom, but with increased emphasis on experimental methods this point of view is not always kept in mind. In such work little account seems to be taken of the enormous variety of animal life, though some advances in, say, physiology may

be attributed to the fact that the physiological laboratory has a more varied fauna than it used to have.

Discussing the museum zoologist's view of taxonomy, W. T. Calman (1940) suggested that a systematist who works in such a place as the British Museum (Natural History), "where the staff are, year after year, constantly unpacking and studying great collections from the uttermost parts of the earth and from the depths of the seven seas, one gets an impression, more vivid perhaps than can be gained anywhere else, of the unending diversity of animal form". In spite of the vast numbers of known animal species, such an expert receives new species "almost every day". "What is very remarkable and significant, however, in this constant influx of novelties, is the rarity of the unexpected. The diversity is indeed unending, but it runs in well-defined channels. Seldom, very seldom indeed, do we come across a species for which there is not a place waiting in the accepted classification." This fact gives the systematist much confidence in the Natural System of classification. "The *Systema Naturae* becomes for us an objective reality, not merely a convenient filing device." In the words of T. H. Huxley (1877), "the things classified are arranged according to the totality of their morphological resemblances, and the features which are taken as the marks of groups are those which have been ascertained by observation to be the indications of many likenesses and unlikenesses". The systematic categories are mostly based on "an enumeration and evaluation of morphological resemblances without explicit reference to phylogeny", which is commonly misconceived in the form of "family trees", whereas, in organisms which reproduce sexually, the ancestry of an individual can be represented only by means of a network of connexions. Botanists seem to be less sure than zoologists about the phylogenetic explanations in their schemes of classifications, partly because "the morphology of plants is vastly simpler than that of all but the simplest animals", partly because hybridisation in plants has complicated the pattern of the phylogenetic tree.

When opening a discussion on morphology and the fine structure of organisms at the rooms of the Linnaean Society of London (February 23, 1950), C. F. A. Pantin referred to structural resemblances of organisms that are not brought about by community of descent, but arise because particular chemical substances are employed as constructional units (see J. R. Baker, 1950). Pantin traced out the growth of ideas regarding the causes of structural resemblance, and pointed out that the system of classification was originally regarded either as the

expression of an underlying plan or else as the working out of a divine idea. When evolutionary doctrines arose, classification and homology were explained in terms of common descent. Physiologists, however, regard the "lower" animals as stages in the evolution of man, and it is odd that the relation between learning and nervous structure in a cuttlefish can help to explain a corresponding relation in man, for this cannot be regarded as an example of homology as understood by early evolutionists. Similarly, biochemical parallels exist between the metabolic processes of unrelated forms. According to Pantin, the early evolutionists regarded organisms as forms of putty-like plasticity which could be moulded this way or that by selection operating on small random variations; they would be better compared with forms built out of the standard parts of a child's constructional set, each having limitations imposed on it by its own structure. The number of kinds of more complex forms that can arise from simpler forms is limited, and when similar complex forms appear in unrelated organisms parallelisms arise that do not fall into the conventional categories of homology. The taxonomist may unwittingly use two kinds of structural characters when formulating his schemes; some of them inherited from a common ancestor, but others arising out of the latent possibilities in the chemical and physical properties of the materials which must be used. Thus the taxonomist must be just as interested as the physiologist in submicroscopic morphology—or what L. E. R. Picken at the same meeting called "fine structure", which was defined as the "realm of organisation that lies between molecules on the one hand and what is visible with the light-microscope on the other".

J. S. Huxley (1940) has pointed out the profound influence which developments in modern biology have exerted on the outlook of taxonomists. Taxonomy has been transformed during a quarter of a century from "a specialised, rather narrow branch of biology, on the whole empirical and lacking in unifying principles . . . into one of the focal points of biology". He added: "the problem of systematics, regarded as a branch of general biology, is that of detecting evolution at work. Specifically, its chief question is how discontinuity of groups is introduced into the biological continuum . . . and how continuous change is effected in a group even when new discontinuity is not arising." He also made a number of practical suggestions; first, augmentation of scientific staffs in the world's great museums, so that routine work is reduced to a minimum for any taxonomist, who may then gain opportunities to correlate systematics with other branches of biological

research; second, better liaison between systematic and other branches of biology, so that the taxonomist gains the co-operation of geneticists, ecologists and other biological workers, particularly such as might be established in suitable laboratories, field stations and such-like institutions. This might lead to a refinement of taxonomic practice, particularly in such groups as have been well investigated. Attempts might be made to make linear measurements, perhaps leading to the formulation of growth coefficients that would enable the taxonomist to determine the proportions of an organism during various phases of its life-cycle. Statistical correlation might also permit conclusions to be made which could not otherwise emerge, and other statistical devices such as standard deviation would lead to a measure of variability, which is important from several points of view. O. W. Richards (1938) believed that such taxonomic and biometric methods might in some instances prove to be as valuable as have been the methods of modern genetics. The New Systematics will "give a much more detailed picture of the actual facts of the diversity of organic nature and its distribution in groups and in character gradients over the globe; it will reveal many facts and principles of great importance to general biology and through it taxonomy will become the field of major interest for all those concerned with the study of evolution at work" (J. S. Huxley, 1940).

Speciation

One important aspect of the problem of evolution is the origin of all the distinct biological groups such as genera, species, subspecies and varieties. Species have apparently arisen sometimes because of geographical agencies. The dispersal of animals has permitted biological divergence to such an extent that the widespread descendants of a single species have become transformed in the course of time into a number of regional species. Related geographic species are generally adapted to specific climatic conditions, which may act as a kind of barrier to restrict or prohibit interbreeding. Even in the same geographical region, however, there may be various ecological differentiations as a result of functional specialisation, for different types of habitats have their own kinds of species which have no chance to interbreed. Other barriers arise by modifications of the organs of sexual reproduction to prevent copulation. Species are thus of several kinds, and consequently they are not easy to define simply. In the field they must be readily distinguishable by characters that are easily seen

and may have no bearing on ecology, cytology, genetics and other branches of biology. The systematist utilises any convenient characters, not necessarily critical in the sense of indicating how the species came into existence. Ultimately—as J. S. Huxley (1942) has proclaimed—several criteria will have to be combined in the definition of a species. Infertility with related groups is one proof of specific distinction, and to this can be added three qualifications taken together—distribution through a geographical area consonant with a single origin, a certain degree of constant morphological and genetical distinction from related groups, and the absence of intergradation with related groups.

In discussing different modes of speciation, Huxley recognised several possible fates that may befall a single species of organism. It may be gradually transformed sufficiently to warrant having a new specific name; it may separate gradually into two or more divergent lines that become mutually infertile and in other respects merit new names; it may hybridise with another species, and the hybrid may by a doubling of the chromosomes at one move form a new species (two species uniting to form one); or, it may show a chromosomal aberration that yields a new species (two species from one). Hybridisation in plants often involves more than two species and it may have complications and possibilities that do not exist in animals. Species-formation may be continuous and either successional or divergent; or abrupt and either convergent or divergent; or reticulate and convergent and divergent at one and the same time. Types of species may be arranged according to (*a*) their mode of origin, (*b*) the kind of isolation that is operative, (*c*) the nature of the barriers to fertility, and (*d*) environmental factors to which they are related. The four main kinds of factors are "time, space, function and intrinsic mechanism"; the four "resultant modes of speciation are transformation in geological time, geographical divergence, ecological or adaptive divergence, and separation through genetic accident". Thus, according to Huxley, the four main kinds of species are "successional", "geographical", "ecological" and "genetic".

The gradual transformation of one species into another has characterised the evolution of horses, camels, elephants and tapirs, as well as molluscs and echinoderms. Time is a very important factor in the origin of successional species, but it cannot operate alone, and geographical considerations have to be made. The full series of successional forms is rarely shown in a strict stratigraphical sequence, and to achieve this result the evolving forms would need to remain in a

particular locality for long periods of time. Instead, they are generally migrant forms that move under the stress of a changing climate, or else to satisfy the urge to invade new territories, with the result that the full series must be sought in different geographical areas, where various new adaptations arise in different members of the series and do not necessarily conform with one another.

Many related species of animals have geographical ranges that do not overlap, but overlap may be clearly evident for the genera to which they belong. In general, progressively greater degrees of overlap between the geographical ranges characterise the taxonomic groups in an ascending scale—for instance, varieties, subspecies, species, genera, families and orders. This is readily explicable from the modes of origin of geographical differentiation outlined above. The origin of a number of new species (or subspecies and varieties) from a common ancestral form is clearly illustrated in birds and mammals, as well as in many fishes and some invertebrates, notably butterflies. As examples, the British and Continental species of robins and also British, Continental and Hebridean song-thrushes and hedge-sparrows have been cited. Distinct species of voles exist in Islay, Eigg, Orkney, Rousay, Westray and other islands of Scotland; distinct species of field-mice in St Kilda, Fair Isle, Foula, Shetland, Mull, Rum, Cumbrae and Arran.

According to Huxley (1938, 1939 *a*, *b*) one of the general features of variation is the tendency for characters to change gradually and continuously over large areas, thus giving rise to character gradients, or "clines", a term invented by J. Ramsbottom. Environmental factors tend to produce graded adaptive characters, which are superimposed on broader variations due to differences of temperature, humidity, intensity and duration of light, and other factors that can be associated with latitude, altitude and other geographical characteristics. More restricted gradients are associated with ecological factors between one habitat and another, but the whole range of gradients of variation are interlocked with one another and correlated with the ranges of environmental conditions that are seen in passing from the poles to the Equator, from mountains to plains and other low-lying districts, from the sea or lakes to land, and from one habitat to another.

Recent Developments

E. Mayr (1948) has also reviewed some developments which have transformed orthodox systematics into the new, grouping them in

three lots. The first represent modification of Linnaean species which are well defined but "without dimensions", having no extensions in space or time. The new concept of species takes into account geographically variable or polytypic species. Second, while the older naturalists regarded the individual as the basic unit, the type-specimen of a species was deemed "typical" and such individuals as disagreed with it were considered to be varieties of it. However, no individual can be regarded as "typical", a term which indicates the "statistical constants" of the population to which the individual belongs, so that the population becomes the basic taxonomic unit. Third, the definition of a species was formerly morphological, and it depended on the degree of structural difference between two forms, whereas the biological definition of a species which has largely superseded it emphasises the "distinctness" of the gap between two forms, measuring this by the possibility or impossibility of exchange of genes by interbreeding. Most of the evidence for these developments has been reviewed by J. S. Huxley (1940, 1942) and E. Mayr (1942), who provided up-to-date summaries of the taxonomic literature. Since 1942, as Mayr (1948) has shown, new sets of problems have arisen, tending to show that agreement has been reached on a number of points by animal systematists: that species of animals are "real things", which are generally well defined; that reproductive isolation forms a reliable biological criterion by which a species can be defined; that species may be composed of populations distinct enough to be recognised as subspecies or geographical races, polytypic species including several subspecies; that specific differences are invariably subject to geographical variation; that in geographical or spatial isolation geographical races tend to drift apart in a genetical sense; that prolonged and sufficiently complete isolation permits isolating mechanisms to arise which stand in the way of interbreeding between two daughter species; and that generally there is a "bridge-less" gap which is maintained by such isolation mechanisms between species inhabiting the same locality. According to Mayr, the most active fields of systematics at present are perhaps concerned with the nature and definition of species and their geographical structure, or intraspecific variation, and with the various types of discontinuity between species, their origin, maintenance by isolating mechanisms, and breakdown in hybridisation. After detailed discussions of many observations on the nature of species he concluded that they must be regarded as "natural units characterised by their reproductive isolation from other such

units". He regards the species which the taxonomist makes on the basis of morphological criteria as "merely inferences from the species in nature" and suggests that when the specific rank of a natural population is in question, morphological data must be supplemented by ecological differences and the completeness of reproductive isolation. The most important isolating mechanisms are sometimes extrinsic factors such as geographical barriers and conditioned behaviour, but sometimes intrinsic factors having a genetical basis. They have given rise to a large literature, the details of which are given by Mayr.

In a lecture delivered in February 1949, J. Smart (1950) noted that up till fairly recently the systematist was expected to define the "species", a task which became progressively more difficult until he could say little more than that "a species was such a segregate of organisms as he decided to designate as a species", a matter on which the competent systematist had "very shrewd opinions" however, as was shown by developments in the classification of birds from the time of C. L. Brehm's work in 1831 to the time of Hartert's in the period 1903–21. Greater precision of taxonomic assignments has arisen out of biometrical studies and statistical analyses of data, though such elaborate methods could hardly be extended in a limited future to the whole field of systematics. Organisms of economic importance usually get priority where such treatment is involved, and there are practical limits to what can be achieved in this and other specialised applications such as the genetical, serological and biochemical. Smart believes that perhaps "we ought to designate as such the 'pheno-species' which the morpho-systematist believes to be the equivalent of the tested and analysed 'geno-species'. Sometimes a relatively simple analysis (*e.g.* of zoo-geographical data in the case of a 'pheno-species' with a small restricted world population) would make it practically certain that a particular 'pheno-species' was in fact a 'geno-species'. In other cases the long and elaborate analysis is quite impracticable unless the organisms be of major economic importance". Smart points out that the zoologist now tends to regard a "geno-species" as "the world population of an organism where, apart from barriers imposed by the physical environment, there is, or is believed to be, a potentiality for exchange of chromosomal material throughout the entire population". This definition also is unsatisfactory in that it applies only to forms which reproduce sexually, or which employ sexual reproduction fairly frequently in the succession of generations.

Classification of Plants

The development of various systems of classification of plants has been outlined by D. B. Swingle (1946) and for the post-Darwinian period by H. A. Airy Shaw (1950). During the past hundred years the most important of these were due to G. Bentham and J. D. Hooker, von Sachs, Eichler, and Engler and Prantl. Bentham and Hooker extended the systems of de Jussieu and de Candolle, and their system for thirty years "dominated the botanical world". At the Kew Herbarium the authors had unrivalled facilities at a time of great prosperity, and they gave a more elaborate arrangement for spermatophytes. The *Genera Plantarum* of these botanists (1862–83) formed a complete series in which dicotyledonous plants, gymnosperms and monocotyledonous plants were given equal rank, equivalent to classes. Classification of cryptogams awaited the development of the microscope. J. von Sachs (1882) classified the Thallophyta nearly as well as Bentham and Hooker classified the Spermatophyta, making four classes which distinguished between plants having chlorophyll or not, and between the algae and fungi. Eichler's modified system (1883) classified plants into two great groups: Cryptogamae formed three divisions—Thallophyta, Bryophyta and Pteridophyta; and Phanerogamae two divisions—Gymnospermae and Angiospermae, the latter containing monocotyledonous and dicotyledonous plants. The number and relative positions of floral parts was illustrated by "floral diagrams". The arrangement of the lower plants was improved. The great treatise of Engler and Prantl, *Die natürlichen Pflanzenfamilien* (1887–1909), was an extension of Eichler's system (Table 7) which covered the entire plant kingdom, and it was supplemented by Engler and Gilg's *Syllabus der Pflanzenfamilien* (10th edition, 1924). Both followed the Englerian system, which is widely used for its broad treatment of the entire plant kingdom. Between these various taxonomic schemes there is a lack of accord, which Swingle attributes to various causes—the difficulty of determining phylogenetic relationships and the greater convenience of artificial systems, confusion in regard to names and arbitrariness of groupings. In regard to present tendencies Swingle states "we have reached a stage where the most progressive systematists are content with nothing short of phylogenetic arrangements for all groups of plants, although some feel that so complete an accomplishment can never be realised. Any other plan is looked upon as artificial and temporary, or merely unscientific convenience—an expedient for some special purpose".

In a lecture given in 1948 H. K. Airy Shaw (1950) also referred to the tendency during the twentieth century to bring "phylogeny" more and more into taxonomic discussions, but he also mentioned signs of reaction to this outlook. J. S. L. Gilmour (1937, 1940) suggested that the existence of numerous points of resemblance between organisms does not necessarily imply close relationship; in human families, cousins are often more alike than are brothers and sisters born of the same parents. Advances in systematics are coming about not solely through morphology but because new knowledge is arising out of many biological disciplines. Anatomical characters are often of great value to taxonomy, and C. R. Metcalfe (1946) showed how they are helping the botanist to modify and correct schemes of classification. K. N. Kaul (1935, 1942) has determined distinctive patterns of ground tissue in various genera of palms, which can now be classified according to stem structure alone. F. Rochleder (1847) indicated certain correlations between chemical characters and taxonomic status, and these are now becoming better known. The Magnoliaceae, Lauraceae and Myrtaceae produce characteristic aromatic oils, and in some instances where apparent chemical relationship exists even in "unrelated" forms —for instance, nicotine in *Anabasis* and *Nicotiana*, and oil of wintergreen in other not very closely related plants—refined methods have indicated the existence of distinct substances, or else different proportions of the same substance. L. S. Moyer (1934) correlated certain of the latex properties *Euphorbia* with both taxonomic units and geographical locations. Modern cytology is demonstrating that non-living cell inclusions such as starch-grains, oxalate crystals and various alkaloids may provide differential taxonomic characters. Starch-grains differ in size, shape, number and chemical reaction in different plants. The study of cell nuclei provides distinctive characters such as variety in number, shape, size and types of behaviour in chromosomes, and some families of plants (*e.g.* Ranunculaceae and Berberidaceae) have been revised on this basis (see W. C. Gregory, 1941). C. D. Darlington (1940) suggested that a basic number of seven chromosomes lies at the origin of all families of woody Angiosperms and Gymnosperms.

W. B. Turrill (1949) has enumerated a number of ways in which plant geneticists have been of service to taxonomy. He expressed the opinion that "protein chemistry may one day enable all plant determinations to be made and phylogeny unravelled from fragments in test-tubes". Turrill also stressed (1950) that plant characters must

be taken at all stages of the plant's life-history and that all such characters are ideally necessary in making systematic allocations. Physiological characters must be regarded as equally important with structural, differences due to the play of external factors on the genetical constitution of the organism must be determined and given recognition, and genetical variability must be assessed. The genetical limits of species and the relative value of sterility and other barriers can also be determined. F. C. Stern (1949) discussed the relationship between chromosome numbers and taxonomy, and in regard to species of cotton plants (*Gossypium*) Harland believes that the taxonomist can establish logical schemes of real validity, but that the "final polish" will often be given by cytological and genetical data. In palaeobotany and plant geography also important contributions have been made to taxonomy, and ecological studies have shown the probable existence of "species-pairs" and "species-groups" which are distinct only because ecological barriers exist between them (Turrill, 1942).

H. K. Airy Shaw (*loc. cit.*) drew attention to two outstanding contributions to modern taxonomy. Hans Hallier's "extensive, heterogeneous, undigested" output was spread over thirty years (1890–1920), but Bunzo Hayata made a "concentrated, clearly presented" contribution "published in one main instalment (1921)". After deft character sketches of these two men—one German and the other Japanese—Shaw noted that Hallier was not satisfied to allow taxonomy to rest on a basis of morphological characters concerning the reproductive organs; only the broadest possible basis was good enough —including all aspects of plant study such as "comparative morphology of the vegetative organs; comparative anatomy, ontogeny and embryology; phytochemistry, physiology and ecology; structure of pollen and seed coat; relation to climate, seasons and the surrounding organic world, plant geography, palaeophytology, etc." According to Shaw, the importance of Hallier's contribution to taxonomy lay "in the breadth of his grasp of the whole immense problem of plant relationships".

Hayata made "a clean break with traditional systematic methods" in setting up his "Dynamic System" on a broadened genetical basis. In his belief all plants "share" or "participate" in the work of enormous numbers of units, or "genes". He used the term "share" in the sense of work to be effected in the future, and the term "participate" in the sense of work accomplished. "All individuals alike," he stated, "possess innumerable genes or factors. The former (the individuals)

present various phenomena according as, on the one hand, the latter (the genes) are apparent or latent; and on the other according to the different combinations or segregations of apparent genes. Consequently, the relation of one individual to the others, in phenomenal (phenotypic) appearance, is the relation of mutual participation or sharing of latent and apparent genes in individuals" (quoted by Shaw). G. E. du Rietz (1930) supported these views in an important discussion of them, expressing the opinion that "Hayata certainly is right both in pointing out that every natural system must form a *network* and not a phylogenetical tree, and in rejecting the idea of *one* single static system", adding that this system "will prove a most excellent working case for the great reform of higher botanical taxonomy that is so greatly needed" (quoted by Shaw, *loc. cit.*).

In Hayata's system a taxonomic unit will vary in position according to characters considered; the use of a few characters will give an easy classification of the unit, but the use of many will make the placing of a unit in a comprehensive scheme more difficult. But Hayata was inclined to believe that phylogeny is often an illusion. And Shaw thinks that if *all* possible (known) characters are taken into account, "any 'convenient' scheme of classification may well disintegrate and dissolve before our eyes into a kind of three-, if not four-dimensional network whose meshes link innumerable ill-defined 'centres of condensation', rather like an incipient galactic system—a state of things which could hardly serve any practical purpose from the classificatory point of view". Hayata's system is an attempt to display "the whole truth", while practical schemes must be content to represent "a few aspects of the truth at any one time", much as the geographer tries to represent certain physical features of the globe on a plane surface.

CHAPTER TEN

SOME FUNCTIONAL PROBLEMS

Photosynthesis

THE two most fundamental processes of living cells may fairly be said to be photosynthesis and respiration. The former is better known in Europe as carbon-assimilation and it takes place in plant cells which contain the green pigment chlorophyll. That green plants have this capacity to take up carbon dioxide from the atmosphere has been known for much more than one hundred years (see p. 20). In 1860 J. B. Boussingault confirmed all the essential features of the early work and demonstrated that the process starts as soon as the plant is illuminated and stops as soon as it is put in the dark, and in 1864 G. G. Stokes showed that the green substance by which the synthesis of sugars and starches from the elements of carbon dioxide and water is achieved is a mixture of two green substances, and that two yellow substances can also be extracted from leaves. The green pigments were shown by R. Willstätter and his colleagues (1913) to be chlorophyll *a* ($C_{55}H_{72}O_5N_4Mg$) and chlorophyll *b* ($C_{55}H_{70}O_6N_4Mg$), the other two pigments the colourless xanthophyll ($C_{40}H_{56}O_2$) and the orange-red carotin ($C_{40}H_{56}$). It has never been proved satisfactorily that the chlorophylls really are the agents which bring about the synthesis of sugars and starches, though the probability that this is so is almost a certainty. In living cells they are combined with proteins. There is no evidence that xanthophyll and carotin play any part in carbon-assimilation, though Montfort (1940) contended that they may assist by absorbing light. They occur with chlorophylls, and this is suggestive of associated function. Carotin is the precursor of vitamin A. Other carotenoids, lycopene from tomatoes and zeaxanthin from maize, are isomers of carotin and xanthophyll respectively. According to H. H. Strain—in J. Franck and W. E. Loomis (1949)—more than fifty chloroplast pigments are now known; chlorophylls number about ten, carotenes six to eight, and xanthophylls more than twenty.

The essential features of carbon-assimilation are easily demonstrated. Put an aquatic plant such as *Elodea canadensis* in water and illuminate it, and bubbles of gas are emitted. These can easily be

collected and the gas, by simple tests, shown to be oxygen. Cover a leaf with a stencil of tinfoil and put it in the sun for a few hours, and the existence of starch where it did not exist before can be shown by other simple tests, now used by elementary students. Other experiments will indicate, as T. W. Englemann first showed in 1882, that different parts of the solar spectrum are not equally effective in promoting carbon-assimilation. The most effective rays lie in the red portion of the spectrum, though certain parts of the blue are also necessary if plants are to grow and develop to maturity, for the blue rays stimulate growth, which is stunted if the plant is kept in red light.

Nearly ninety years ago Julius von Sachs proved that chlorophyll is located in the green *plastids* inside plant cells. Such bodies were called *chloroplasts* by A. F. W. Schimper (1883). According to Sachs (1865), chloroplasts do not develop if the plant is kept in darkness. It was left for Willstätter to show that chlorophyll is the catalyst concerned with carbon-assimilation. The pigment, which is probably dissolved in a resinous or waxy medium, may not be the sole participant in the process, for carbon is not bound in proportion to the amount of the pigment which is present. Like the molecules of the red blood pigment haemoglobin (see p. 209) and those of the respiratory enzyme cytochrome (see p. 208) the chlorophyll molecule is built up of four pyrrol rings (C_4H_4NH) arranged in a ring-like molecule as a porphyrin, each molecule of which contains 20 carbon atoms, 14 hydrogen atoms and 4 nitrogen atoms. This fundamental ring structure (porphin) together with magnesium gives porphin-phyllin, the simple chlorophyll-like substance protochlorophyll synthesised by P. Rothemond (1935). It is further interesting that for the production of chlorophyll by the green plant iron is necessary, a deficiency of this element producing the yellow leaf-colour of chlorotic plants. This may be significant in view of the fact that in haemoglobin and in cytochrome the iron atom is the oxygen-carrying agent. It is almost certainly significant that three such vitally important compounds of living organisms should be built on the same plan of chemical structure.

For carbon-assimilation four requisites are called for, chlorophyll and the radiant energy of sunlight, water and carbon dioxide. The manner in which carbon is bound in the synthesis of food substances is not known, however, and various hypotheses have been put forward concerning the nature of the process, and it has been variously suggested that the first-formed products are sugar, starch, formaldehyde and even

amino-acids, proteins and oils. Some botanists believe that carbon dioxide is split up into its elements, the oxygen being liberated and the carbon immediately united with hydrogen and oxygen to form a hexose sugar. The fact that this would involve a highly improbable sixth order reaction (six molecules colliding simultaneously) makes it the least likely event. Also it has been suggested that cane sugar is the first carbohydrate to be formed and that this is hydrolysed to form hexose sugars, a rather unusual synthetic procedure. The discovery that sugar-like substances formed when dioxymethylene is heated in an alkaline solution induced A. von Baeyer in 1870 to propound his formaldehyde hypothesis, according to which this substance is the first product and sugars are formed from it by the process of polymerisation. Set against this hypothesis is the fact that formaldehyde cannot be detected in leaves and is decidedly toxic to living protoplasm, an objection which has been countered by the opinion that the harmful substance may be promptly removed by instantaneous polymerisation as soon as it is formed. On the other hand, there are facts which support this hypothesis, and it is not difficult to conceive of the binding of formaldehyde by protein or other constituents of chlorophyll. Evidence in support of the theory comes from the experiments of Moore, Baly and others in which formaldehyde has been synthesised by the action of various catalysts on water and carbon dioxide under the influence of light, and from other experiments in which plants fed on formaldehyde and kept in darkness have produced sugars. If the hypothesis is correct, then six molecules of formaldehyde are converted into a single molecule of hexose sugar.

Regarding the formaldehyde theory, H. A. Spoehr (1933) has stressed the very intense efforts made for more than two decades to test this theory without any satisfactory proof or disproof arising out of the work, and has suggested that few ideas of such significance have persisted for so long without finally becoming established or, on the other hand, discarded. For a number of years the theory has not been so assiduously worked on, but the development of the radioactive tracer technique has somewhat revived it. Ruben, Hassid and Kamen (1939) used carbon dioxide containing radioactive carbon in experiments on carbon-assimilation with barley. In the leaves of the plants radioactive carbohydrates appeared, and if the radioactive carbon dioxide was administered not more than three hours after plants were placed in darkness the result was the same. In other experiments with the alga *Chlorella* these biologists sought the intermediate compounds, and

discovered most of the radioactive carbon in carboxyl groups, a smaller fraction being taken up in the light, however, than in darkness. There was no evidence of radioactive formaldehyde in such experiments. In experiments with heavy oxygen Ruben and colleagues (1941) found that the oxygen released during photosynthesis is derived from water, as was suggested earlier by C. B. Van Neil (1941), who attributed it to photo-decomposition.

Readers who seek recent specialised information on photosynthesis should consult the monograph of the American Society of Plant Physiologists edited by J. Franck and W. E. Loomis (Iowa, 1949); it contains twenty-two articles written by thirty-two specialists and more than eight hundred references to the original literature. Another important work is the Symposium of the Society for Experimental Biology, volume 5 (Eds. J. F. Danielli and R. Brown, 1951); this contains twenty-one papers written by thirty-six specialists and previously read at a meeting at Sheffield in July 1950.

Metabolism

The living cell is a complex of submicroscopic particles, mainly composed of proteins, which provide numerous interfaces at which essentially simple reactions can take place in more or less interwoven chains. The total result of such reactions may seem exceedingly simple—for instance, the oxidation of a simple sugar to carbon dioxide and water—but the stages by which this end is achieved are obscure and difficult to disentangle. The reactions do not necessarily involve only cells, for they may be linked with other reactions taking place in tissue liquids which bathe the cells of the organism. Complex enzyme systems give the cell the capacity to liberate the potential energy stored up in organic substances as free energy, which becomes available for the performance of various kinds of work. [For an interesting brief account of the biology of enzymes see the article by D. W. Ewer (1950).] That work may be participation in changes which lead to the contraction of a muscle fibre or the passing of a nervous impulse, or it may be the synthesis of organic substances from inorganic materials at ordinary temperatures and a nearly neutral chemical reaction, although the chemist could achieve the same result only by the use of much more drastic methods, unless he made use of enzymes extracted from cells. The efficiency of the organism is relatively imperfect by comparison with a man-made machine, however, and some wastage of

energy occurs. About one-fifth or one-quarter of the free energy gained by the cell is put to useful work; the remainder may serve to maintain the temperature of the organism, but most of it is ultimately lost as heat to the outside world. The complex system of interrelated reactions making up the dynamic activity of the organism is called metabolism. If one set of reactions produces free energy, we say it is katabolic; if instead it leads to synthesis and the production of kinetic energy, we say it is anabolic. The cell is at one time both anabolic and katabolic, for in it disruptive and synthetic activities may proceed simultaneously. One part of the chemical system of the cell may be running-down, while another is building itself up and storing energy. Whatever the special synthetic activity of a particular cell may be, some free energy must become available for the cell's own use, and the enzymes of the cell are concerned perpetually with the oxidation and reduction of various organic substances (metabolites) which yield free energy. Oxidations are brought about by any one of three methods, the addition of oxygen, the removal of hydrogen, or the withdrawal of electrons. In all three cases the outcome is the same: the oxidised substance loses one or more electrons. Reduction is the complement of oxidation, and therefore a gain of electrons, though this may be achieved either by the addition of hydrogen or the removal of oxygen. Sometimes, both inside and outside cells, a substance is simultaneously oxidised and reduced, in the way in which two molecules of an aldehyde (CH_2O) form one molecule of acid (CH_2O_2) by oxidation and a molecule of alcohol (CH_4O) by reduction.

Cell Respiration

As the French physiologist Bertrand first showed, more than fifty years ago, there is a notable contrast between the stability of organic substances outside the body of the organism and the ease with which these can be oxidised in the living tissues and cells. In the same year in which Ostwald defined a catalyst as an agent which accelerates the rate of a chemical reaction, Bertrand was the first to suggest that organic metabolites in cells and tissues are oxidised by means of catalysts. Cell respiration is now defined (see M. Dixon, 1937) as the utilisation of molecular oxygen by the cell for the oxidation of organic metabolites, substances which rarely react spontaneously with oxygen but which will react when suitable catalysts are brought to bear on them. Studies of cell respiration are largely concerned with the special catalysts known as respiratory enzymes, particularly their mode of action and the steps

by which they achieve their effects. Perhaps the most important chemical change in the economy of living things is the oxidation of a simple sugar such as glucose to carbon dioxide and water. But this process takes place in living organisms by steps that are obscure and difficult to disentangle from the processes of living. Oxidation is important because it is the means whereby energy is released, and it is not confined to cells, but can take place in liquids circulating through the tissues of the multicellular animals and plants. To achieve oxidation not one but a whole series of enzymes is required. The original idea of respiration was simply the union of oxygen with the substances yielding energy; in other words a simple process of combustion. But in ordinary combustion much more heat energy is required to start the process than is ever found in the body of the organism. Eventually, it became evident that some substances oxidise spontaneously in the presence of oxygen, perhaps in the cell as well as in the test-tube. This process of *autoxidation*, i.e. oxidation by contact with atmospheric oxygen at low temperatures and without the intervention of catalysts, may occur with some biological materials such as unsaturated fatty acids and lipoids and the amino-acid cystein (which contains an SH group). But it soon became apparent that it is not as simple as it seemed at first sight, for the source of oxygen may be a peroxide which can be induced to liberate active oxygen. Dakin and others achieved the autoxidation of various substances which go into the making of an animal body—butyric acid, amino-acids, lactates and glucose—all of which can be oxidised by hydrogen peroxide, and oxidise more speedily in the presence of a trace of some iron salt. Various respiratory enzymes have a fairly simple action. Oxidases reduce only molecular oxygen; they are found in the potato and in the skin of pigmented animals, and their action may be seen in the production of the dark pigment melanin. Peroxidases activate hydrogen peroxide but they have only slight biological importance, because this substance is not an important constituent of cells. Catalases liberate oxygen from hydrogen peroxide in the absence of an oxidisable substrate, but the function of such enzymes in the cell is also obscure.

M. Dixon (1937) outlined four main stages in the development of ideas concerning respiration. The first stage involves the action of an oxygen-activating catalyst. The oxygen molecule, conceived as two oxygen atoms united by a double bond, is a stable and not a reactive thing. Before oxygen will react at the low temperature of the animal's body it must be concentrated and activated. Otto Warburg concerned

himself with the problem of oxygen activation. His scheme is often called the Charcoal Model, for he showed that when an amino-acid is shaken in air, in a solution also containing animal charcoal, oxygen is taken up and the amino-acid is oxidised to end products which exist in the bodies of animals. The substance to be oxidised is adsorbed on the surface of the charcoal, as in the living cell it is adsorbed on the structural elements of protoplasm. But adsorptive power alone will not explain oxidation. Pure charcoal oxidises organic substances only very slowly, but when certain compounds of iron are present in the system and a certain technique is followed oxidation takes place more readily. Warburg, who first became interested in cell respiration in 1908, came to believe that atmospheric oxygen is taken up by the iron atoms and then handed on to the oxidisable amino-acid or carbohydrate. In other words, he discovered that iron, like hydrogen peroxide, serves as an oxygen-carrier. The enzyme which brought about this essential reaction in respiration, Warburg called the "Atmungsferment", or "respiratory enzyme".

It was soon found that the action of the respiratory enzyme alone could not account for the entire process of respiration, and hypothesis was adduced to account for indirect oxidation by dehydrogenation.

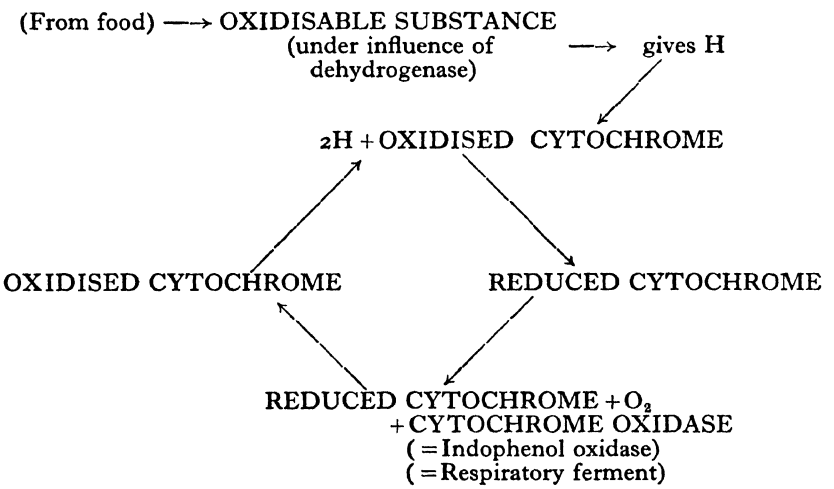
TABLE 9.—SOME DEHYDROGENASES WHICH ACTIVATE SIMPLE SUBSTRATE MOLECULES BY REMOVAL OF HYDROGEN (which is handed on to some H-acceptor). (*After* FEARON.)

Dehydrogenase	*Animal Tissues*	*Reaction*
Succinic + fumarase	Most animal tissues	Succinic acid ⟶ fumaric acid + H Fumaric acid ⟶ malic acid H
Malic + carboxylase	Most animal tissues	Malic acid ⟶ oxaloacetic acid Oxaloacetic acid ⟶ pyruvic acid
Lactic + co-enzyme	Heart, kidney, liver and other tissues	Lactic acid ⟶ pyruvic acid
Citric . .	Muscle, liver	Citric acid ⟶ acetoacetic acid
Alcohol . .	Liver, kidney	Primary and secondary alcohols ⟶ corresponding aldehydes and ketones
Glycerophosphate .	Brain, muscle, liver, kidney	*a*-Glycerophosphate ⟶ phosphoglyceric aldehyde
Glucose . .	Liver	*d*-Glucose ⟶ *d*-gluconic acid
Hexose monophosphate	Red blood cells	Sugar ester ⟶ Phospho-hexonic acid
Triose phosphate .	Muscle	Triose phosphate ⟶ phosphoglycerate
Hexose diphosphate	Muscle, liver	Activates fructose diphosphate

DEHYDROGENASES WHICH ACTIVATE COENZYMES TO BRING ABOUT INDIRECT OXIDATION OF PRIMARY SUBSTRATE BY CYTOCHROME OR FLAVOPROTEIN

Diaphorases . . Animal tissues; milk

This was largely the work of Wieland and Thunberg and it led to the discovery of a series of intracellular dehydrogenases which can activate the hydrogen atoms of organic molecules so that they can be removed by an oxidising agent. This calls for the co-operation of some reducible substance which serves as "hydrogen-acceptor". The amino-acid glutathione can exist in either the reduced or the oxidised condition in cells and serves in this way. The key to the problem of respiration in the living cell was the discovery of cytochrome by D. Keilin (1925) (see p. 69). Like the respiratory enzyme, cytochrome is chemically related to haemoglobin, and likewise the essential part of its molecule is an iron atom which can exist in either the ferrous or the ferric condition and is oxidised from the divalent to the trivalent form. Cytochrome and the respiratory enzyme together form what has been called the Warburg-Keilin system. This can bring about reversible oxidation and reduction, and with the help of dehydrogenases can achieve the oxidation of the organic substances used in metabolism. The scheme in its simplest terms (see A. von Szent-Györgyi, 1937) is this:



A food such as glucose is attacked by dehydrogenase and gives off active hydrogen atoms, which are taken up by oxidised cytochrome. Under the influence of the respiratory enzyme (which happens to be cytochrome oxidase) the now reduced cytochrome is once more oxidised and able to accept other hydrogen atoms derived from molecules of food. The oxidation of the glucose molecule is regarded not as the addition of oxygen to it but as the abstraction of hydrogen from it. It is the activated hydrogen of the molecule which is oxidised, and

by activated oxygen. A. von Szent-Györgyi (1937) claimed that the cell recognises only one fuel, and this is hydrogen, not carbon. The molecule of glucose is regarded as a number of oxidisable hydrogen atoms attached to a carbon skeleton. Oxygen plays a very limited part, being dispensed with after the first step, the oxidation of cytochrome. All that remains is an electron change and a change of valency from the ferrous to the ferric state in the iron atom of the cytochrome molecule. Oxidation is probably much more elaborate than this scheme suggests, notably by the use of many dehydrogenases (Table 9) and series of carriers.

Enzymes are also concerned with the production of carbon dioxide during cell respiration. A carboxylase discovered in yeast by Neuberg is known to exist in the higher plants. This enzyme facilitates the decarboxylation of alpha-keto acids, the production of the corresponding aldehydes and carbon dioxide. Pyruvic acid yields acetaldehyde and carbon dioxide. Such a plant-type carboxylase is not included in the enzyme equipment of animals, though the liver and the heart in some animals contain similar enzymes. Another cycle of changes which yields carbon dioxide is the so-called Krebs Tricarboxylic acid cycle. Pyruvic acid is first of all built into a larger molecule and this is then gradually transformed by series of hydrations; dehydrogenations and decarboxylations then lead to the formation of carbon dioxide.

Oxygen Transport

The oxygen-carrying capacity of red blood depends on the pigment haemoglobin, which exists in the red blood corpuscles of all vertebrates, in cells found in the blood of some worms (*Glycera*, *Capitella* and *Phoronis*) and the mollusc *Solen legumen*, and in the blood plasma of earthworms, some leeches (but not the horseleech), in a starfish (*Ophiastis virescens*) and some arthropods (*Daphnia*, *Chirocephalus* and the larva of *Chironimus*). The pigment may exist in tissues other than blood—for instance, in the pharynx and the nerve ganglia of the seamouse (*Aphrodite*), and the muscles and other tissues of the roundworm *Ascaris*. It is defined as a compound of ferrous iron porphyrin (*protohaem*) with a protein (*globin*), and it forms with oxygen a reversible compound with a scarlet colour and a specific type of absorption spectrum having two obvious bands, one in the green and the other in the yellow (see Robin Hill, 1938). The properties of specific haemoglobins in different animals (see J. Barcroft, 1928) seems to be correlated

with special physiological needs. They all have the same protohaem, but the protein is different. In mammal haemoglobin four haem molecules are joined with one protein molecule; in other haemoglobins the ratio may range up to 100/1.

Human blood forms about one-twentieth of total body weight. In a man 150 pounds weight there would be about $7\frac{1}{2}$ pounds, taking up a volume of about 3·2 litres. The total amount of haemoglobin is about 448 gm., and 1 gm. will hold 1·36 cc. oxygen (at N.T.P.), so that the *whole capacity* of the blood (for oxygen) is about 609 cc. If blood were replaced by a watery tissue liquid, the amount of oxygen held in solution would be somewhat less than 18 cc., so that by virtue of its haemoglobin the blood can carry much more than thirty times as much oxygen as could be carried by an ordinary tissue liquid. The amount of oxygen actually held by the blood at any time will depend on the partial pressure of oxygen in the gas in contact with it. If the blood is shaken in air it is almost saturated. The partial pressure of oxygen in air is 159·6 mm. Hg at normal atmospheric pressure (21 per cent. of 760 mm. Hg). With greater partial pressures than this no more oxygen could be induced to combine with haemoglobin. At lower partial pressures the haemoglobin would combine with smaller volumes of oxygen, the figures obtained from an actual experiment by Barcroft (1928) being—

pp. O_2	0	10	20	20	100 mm. Hg
percentage Hb as HbO . .	0	55	72	84	92

The construction of a graph from these figures reveals that the curve is not a straight line, as might be expected, but a rectangular hyperbola which is asymptotic, so that theoretically the blood is fully saturated only at an infinite partial pressure of oxygen. In practice, the oxygen tension necessary to give 95 per cent. saturation is called the loading tension (T_L) of the blood. If we suppose that blood leaving the lungs is 95 per cent. saturated, we can see that by the time it reaches the tissues, where the oxygen tension may be as low as 10 mm. Hg, the blood will be only 55 per cent. saturated. Under the conditions of reduced partial pressure the blood will have given up 40 per cent. of the oxygen, and as the partial pressure of oxygen in the tissues may be much less than 10 mm. Hg it may well have given up more. Raising the temperature or increasing the tensions of carbon dioxide have the effect of progressively flattening the dissociation curve, which means that relatively more oxygen will be given up by the blood under con-

ditions of higher rates of oxidation and in situations where carbon dioxide accumulates, which will be situations where oxygen is most needed. In some invertebrate animals the loading tension of the blood is only 5–10 mm. Hg. The fresh-water snail *Planorbis* or the lugworm *Arenicola* can normally gain all the oxygen they need from solution in the blood, but the stores bound up with haemoglobin are called upon

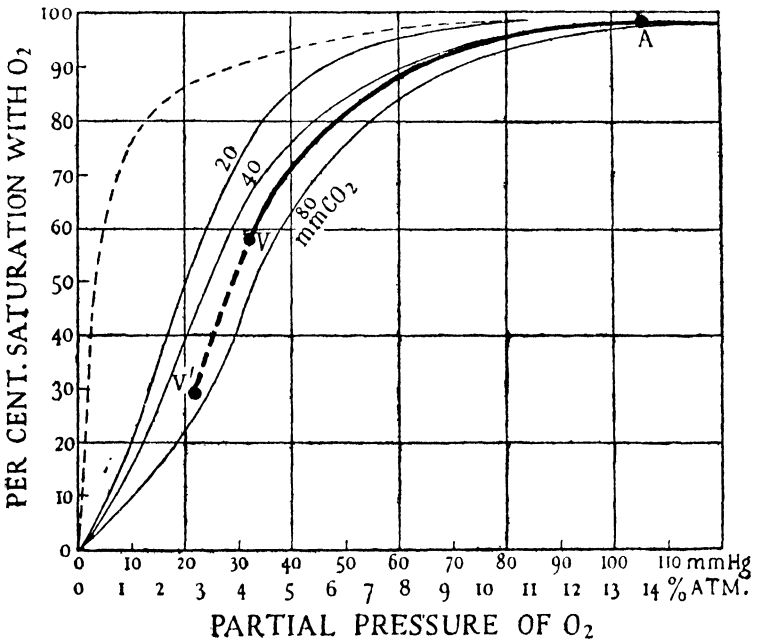


Fig. 17. Oxygen dissociation curves at various partial pressures of carbon dioxide. Dotted line is the curve for myoglobulin; note that little oxygen is given off until the partial pressure of oxygen reaches a very low value. AVV′ is the "physiological oxygen dissociation curve", A being the arterial point, V and V′ the venous points at rest and during exercise respectively. Oxygen is liberated readily by haemoglobin in the conditions of venous blood. From Winton and Bayliss, 1948. (J. & A. Churchill.)

in emergencies, when the snail is subjected to asphyxiating conditions, when the worm awaits the return of the tide in its sealed burrow. The pigment haemoglobin may thus serve for the regular transport of oxygen, its principal function, or it may serve as a device for storing up oxygen against a period of oxygen deficiency in its habitat.

Pigments other than haemoglobin are also used for oxygen transport. Some polychaete worms possess chlorocruorin, an analogue of haemoglobin which contains the prosthetic group chlorocruorohaem, a

chemical relative of protohaem but with an extra oxygen atom, to which the pigment owes its vivid green colour and its low affinity for oxygen. The protein resembles other globins, but contains different proportions of the amino-acids. Most molluscs and crustaceans have blood containing haemocyanin, which in an oxygenated condition is fairly blue. This pigment differs from others in having no porphyrin as prosthetic group and in the fact that copper occurs in place of iron. A rarer pigment is haemerythrin, which also lacks porphyrin but contains iron; it is found in the rose-madder blood of a few worms such as *Sipunculus*. Helicorubin is another iron-containing pigment and others are widespread in the animal and plant kingdoms. The pigment known as pinnaglobulin contains manganese, and the blood of ascidians a vanadium-containing pigment.

Buffering Power of Blood

Living aerobic cells are always tending to alter the composition of the external medium by depleting it of oxygen and by putting into it carbonic acid, thereby increasing its acidity. In vascular animals carbonic acid is put into the blood, the acidity of which may tend to rise also because certain cells (*e.g.* cells of the pancreas) may be abstracting alkali. In spite of these tendencies, the degree of acidity of the blood remains almost constant. According to D. D. van Slyke (1921), the pH of blood varies between 7·0 and 7·8, which corresponds to 1–5 gm. hydrogen in 100,000,000 litres. Sir J. Barcroft (1934) emphasised the smallness of this amount of variation, for this volume of liquid equals the total blood plasma of all the inhabitants of the United Kingdom. He also stressed the fact that the small amount of hydrogen ions involved marks the extreme limits between which human life is possible, for fatal coma occurs beyond one extreme and fatal convulsions beyond the other. It was pointed out that the regulation of hydrogen-ion concentration is bound up with the function of the kidney, the respiratory centre of the brain and the blood itself. Evolution has proceeded in such a way that the more highly developed an animal the more its blood resists alteration of pH because of the addition of acid. Change of pH is prevented from taking place suddenly and unduly by three processes: the excretion of acid or retention of alkali by the kidneys, the excretion of carbonic acid by the lungs, and the "buffering" of blood and the tissue in contact with it. The body liquids of a sea-urchin are only slightly buffered, and by the same mechanism (carbonate-bicarbonate system) as sea-water, but the blood of a spider-crab (*Maia*

squinado) is much more strongly buffered by means of proteins. In the red blood of man and other mammals the final stage is reached in the perfection of a highly buffered internal medium by establishing a respiratory pigment inside the corpuscles. The envelope of the corpuscle allows acid to pass through but not bases, so that when acid is added to blood plasma it or its equivalent must pass into the corpuscle, to be dealt with there by a haemoglobin-bicarbonate buffer system, leaving the reaction of the plasma unchanged.

Carbon Dioxide Transport

Carbon dioxide dissolves in water about 22–23 times more readily than does oxygen (the solubility coefficient is 0·55 as against 0·024 for oxygen). In blood the gas is rather less soluble than in water. A solubility coefficient of 0·51 indicates that 51 c.c. of carbon dioxide are carried in 100 c.c. of blood at atmospheric pressure of the gas. At 40 mm. Hg tension of carbon dioxide, which is about that in the blood, only about 2·7 c.c. carbon dioxide can be carried in ordinary solution. Experiments show, however, that 100 c.c. of blood will carry 50–60 c.c. carbon dioxide, or about twenty times as much as could be carried in ordinary solution. This gas can be expelled if the blood be exposed to a vacuum or treated with strong acid, one method being as good as the other. This suggests that carbon dioxide, like oxygen, is held in a light chemical combination. The simplest explanation is that carbon dioxide combines in the blood with sodium and other bases to form bicarbonates. This is the basis of the Bicarbonate Theory which was supported by some physiologists in Britain, but not all. When blood is compared with a bicarbonate solution, however, one big difficulty arises: a bicarbonate solution subjected to a vacuum gives off no more carbon dioxide than is involved in the conversion of bicarbonate into carbonate, and only half the quantity which is evolved by the use of strong acid. From such considerations it soon became evident that if carbon dioxide is "fixed" in blood there must be some substance also present which acts like an acid; some substance which does not interfere with the uptake of carbon dioxide when blood is exposed to increasing partial pressures of the gas, but which facilitates the complete liberation of the gas even to zero concentration when the partial pressure of the gas falls.

The bicarbonate theory implies that carbon dioxide is transported mainly as bicarbonate, and that when the blood reaches the lungs the proteins of blood, acting as weak acids, convert the bicarbonate into

carbonic acid, which becomes dehydrated to give carbon dioxide, and this passes into the air-sacs and is removed from the body by diffusion during expiration. The alternative Direct Combination Theory upheld the idea that some of this carbon dioxide is carried in direct reversible combination with blood proteins. Between 1917 and 1921 the problem was tackled by British physiologists and the bicarbonate theory gradually drew ahead of its rival. Then, as N. U. Meldrum and F. J. W. Roughton (1934) showed, data accumulated by D. D. van Slyke and others in America (and bearing on the dissociation of haemoglobin and oxyhaemoglobin as well as carbon dioxide) seemed to indicate that under physiological conditions only a negligible amount of carbon dioxide exists in blood in forms other than carbon dioxide, carbonic acid, and bicarbonate. Certain anomalies arose, however, and these could be eliminated by assuming that other forms did exist—for instance, if carbon dioxide combines with the proteins of the blood—so that the subject became controversial. In 1925, and after measuring the velocity of the reaction of oxygen with haemoglobin, H. Hartridge and F. J. W. Roughton pointed out the desirability of studying the kinetics of carbon dioxide processes in blood. During the following year O. M. Henriques took up this aspect of the problem and discovered that carbon dioxide is evolved more quickly from haemoglobin solutions than from serum. He concluded that there was no associated catalytic mechanism, but realised that there must be a very rapid and reversible direct reaction between carbon dioxide and haemoglobin—a reaction analogous to that between oxygen and haemoglobin. Accordingly, he suggested that a compound of carbon dioxide and haemoglobin must exist, and to this hypothetical compound he gave the name carbhaemoglobin. In similar experiments Hawkins and van Slyke (1930) found distinct evidence of a catalyst, and R. Brinkman and R. Margeria (1931) made the exciting discovery that blood or a haemoglobin solution markedly accelerate the evolution of carbon dioxide from mixtures of bicarbonate, even when diluted 20,000 times. One year later Meldrum and Roughton (1932) had isolated from ox blood a white substance which, even in a 1/10,000,000 dilution, was capable of accelerating this reaction. The solid extract was free from haemoglobin, and from haematin compounds; it was indubitably an enzyme, and it received the name *carbonic anhydrase*. These authors later (1934) described the mode of preparation and the properties of the enzyme in detail, and R. Brinkman (1934) gave an account of its occurrence in the lower animals, finding it in some coelenterates, worms and molluscs. The enzyme thus occurs

in animals which do not possess haemoglobin. W. H. Newton (1936) has discussed the properties and mode of action of carbonic anhydrase, and we can examine the function of the enzyme briefly, according to his conceptions. It may be as well, however, to consider first certain changes that take place in blood when it passes into regions of the body where carbon dioxide is produced. First, the gas dissolves in the plasma to form carbonic acid and then follows a sequence of ionic transferences (for simplicity they are indicated by chemical expressions: Fig. 18), which minimise the increase in acidity and facilitate the transport of carbon dioxide. Because the blood is alkaline, the colloid particles of both the plasma proteins and haemoglobin bear no charge. Consequently, haemoglobin will be attached to cations, mainly potassium, and the plasma proteins will be associated mainly with sodium ions. The membrane of the corpuscle is impermeable to both these cations, but permeable to hydrogen ions and to anions. Bicarbonates and phosphates are present in both the corpuscles and the plasma, monohydrogen phosphates of sodium (plasma) and potassium (corpuscles). Three changes may be represented. First, some of the excess carbonic acid engages the plasma proteins, the base being displaced by hydrogen ions and the HCO_3 ion associating with the sodium ion. Consequently, the bicarbonate concentration of the plasma is *increased.* Second, carbonic acid passes into the corpuscle, where it displaces the bases associated with haemoglobin and with phosphates; consequently the bicarbonate concentration within the corpuscle is also *increased.* Third, carbonic acid exchanges ions with the sodium chloride of the plasma, and hydrogen and chlorine ions pass into the corpuscle, there to engage anions and basic ions; as a result, the chloride content of the plasma is *diminished*, that of the corpuscle *increased* (what is known as Hamburgher's "Chloride Shift"). As a result of such events, additional carbon dioxide is held in the blood with only slight increase in acidity, and the corpuscle swells slightly because of an endosmotic stream.

In the reverse changes whereby carbon dioxide is eliminated in the blood passing through the lungs, most of the changes are purely ionic and thus almost instantaneous. But the dehydration of carbonic acid is relatively slow, and it is hastened by the action of the enzyme carbonic anhydrase. The enzyme is locked up in the corpuscles, however, and it cannot act across the envelope. In the lungs the low partial pressure of carbon dioxide in the air-sacs and capillaries induces the diffusion of the gas from the plasma into the air. The concentration of plasma

carbon dioxide is restored from the combined carbon dioxide in the plasma and also from the dissolved carbon dioxide in the corpuscles. Blood stays in the lung capillaries only for a very brief period (little

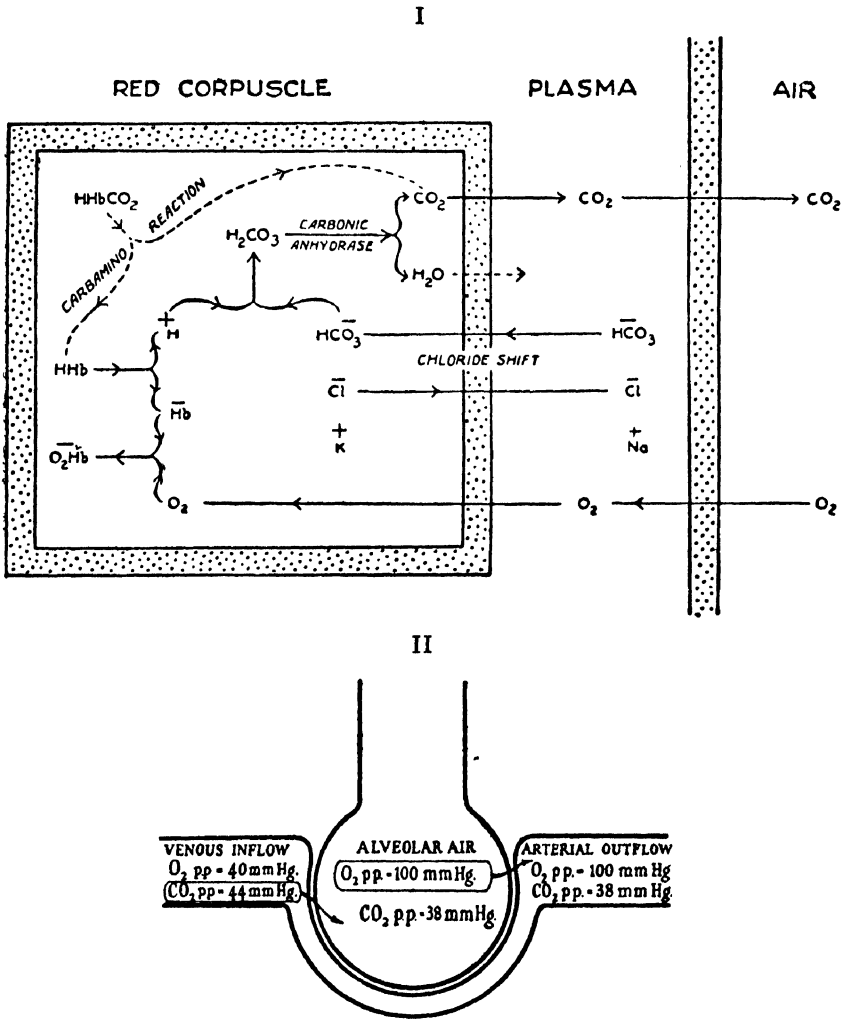


Fig. 18. I, Scheme showing the most important changes involved in the liberation of carbon dioxide from blood into air. II, Diagram illustrating gaseous exchanges in the blood flowing through the capillaries of the lung. From Winton and Bayliss, 1948. (J. & A. Churchill.)

more than one second) and as there is no carbonic anhydrase in the plasma the source of carbon dioxide is from the corpuscle. The dissolved carbon dioxide in the corpuscles is replenished from the

bound carbon dioxide (bicarbonate) very swiftly because of the action of the enzyme, and replenishment goes on so long as the supply of bicarbonate lasts. The bicarbonate ions of the corpuscles are derived from those already existing in the corpuscle and those from the plasma. Before the blood reaches the lungs bicarbonate and chlorine ions are being exchanged in equal numbers across the corpuscular membranes, but when carbon dioxide is lost from the corpuscle this equilibrium is upset, bicarbonate ions are detained by the corpuscle and fewer pass out than pass in. The balance of electrical charges must be maintained, however, and this is by the exit from the corpuscles of more chlorine ions than are passing in, a reversal of Hamburgher's "chloride shift". This interchange is almost completed (90 per cent.) in about 1·3 second, according to M. N. J. Dirken and H. W. Mook (1931), and this is approximately the amount of time available as the blood passes through the capillaries of the lungs.

It is very unlikely that the changes mentioned above are the only changes (or even the significant changes) which take place in blood under the specified conditions. Various physiologists have suggested that carbon dioxide is transported in blood in three forms: stable acid carbonates, unstable carbonic acid (which is readily dehydrated by carbonic anhydrase) and an unstable salt (probably a carbamino compound produced by the union of carbon dioxide with an amino group) which is not affected by the enzyme. But this last may not account for more than 2 per cent. of the total carbon dioxide in the blood.

Feeding Mechanisms

Many attempts have been made to classify the means whereby animals obtain and swallow their food. C. M. Yonge (1928), who reviewed our knowledge of feeding mechanisms in invertebrates, cited the work of Jordan (1913), Blegvad (1914), Hirsch (1915), Hunt (1925), Jordan and Hirsch (1927), and formulated a scheme of his own. Some animals adopted "microphagy", the eating of minute particles by various means—pseudopodial, ciliary, tentacular, setous and muscular. A few use mechanisms for taking in liquids or soft tissues—for instance, suctorial Protozoa, insects with piercing and sucking mouth-parts, and tapeworms and other parasites which imbibe food through their body surface. Most animals practise macrophagy, however, either by swallowing inactive food, by scraping and boring into other animals and plants or inanimate objects, by seizing their prey and externally digesting it, or otherwise swallowing it whole or in a triturated con-

dition. Many animals belonging to different phyla but living on similar food have perfected almost identical mechanisms for capturing and digesting their food. The type of feeding is correlated not with zoological status, but rather with the nature of the conditions under which the animal lives and the type of food organisms which are available to it. Yonge marked out several well-defined correlations——the habitat and available food of an animal, the type of feeding mechanism employed, the structure of the alimentary canal, and the nature of the digestive processes—and showed that so marked is the correlation, that knowing any two of these characters and conditions it is possible to predict the other two.

The Digestive System of Metazoa

C. M. Yonge (1937) has suggested that the original power of holozoic nutrition (feeding like an animal) determined the first appearance of animals. Essential to this type of nutrition was the possession of a cell membrane which permitted phagocytic ingestion of food. In more primitive animals this type of digestion—intracellular—must have existed already, and it has remained the typical mode in Protozoa, sponges and some multicellular animals. The last-named may be forms of primitive structure (coelenterates, turbellarians and king-crabs), or more highly complex forms (arachnids and most molluscs) which retained intracellular digestion in relation to their mode of feeding. In bivalve molluscs and echinoderms this type of digestion was supplemented by or replaced by a type of digestion depending on phagocytes of the blood. The alternative form of digestion—extracellular—was developed in connexion with the utilisation of organisms of larger size as food, organisms which were too large to be ingested by cells, and it has become the mode in the vast majority of multicellular animals (worms, myriapods, crustaceans, insects, cephalopod molluscs and Chordata). According to Yonge, the most successful groups of animals are those which can feed on and digest many kinds of food—vertebrates, gastropod molluscs, insects, crustaceans and worms for instance; or else those which collect and digest one type of food with great efficiency—carnivores such as cephalopods, turbellaria and coelenterates; ciliary feeders such as ascidians, bivalve molluscs and brachiopods; and parasites such as trematodes and cestodes. Animals able to feed on many kinds of food were most successful, probably because they were able to exploit new sources of food during their conquest of new habitats.

Digestive Enzymes

H. V. Vonk (1937) discussed the identity of digestive enzymes found in vertebrates and invertebrates. The protein molecule is attacked in both groups of animals by proteases of four kinds: proteinase, carboxy-polypeptidase, aminopolypeptidase and dipeptidase; all of which can be separated by adsorption. The proteinase of a crab has the same specificity and properties as vertebrate trypsin. In vertebrates the action of these enzymes is preceded by that of pepsin, which occurs in the gastric juice and works in a strongly acid medium. This enzyme is never found in invertebrates. The starch-splitting enzymes of vertebrates are *alpha*-amylases, which are activated by salts, chiefly sodium chloride. The amylases of invertebrates are of the same character. Inulase is not found in vertebrates, though it occurs in some invertebrates, and cellulase and hemicellulase are present in some invertebrates but not in vertebrates. The disaccharides of vertebrates are saccharase, maltase and lactase, and of these maltase is most common in invertebrates, occurring with amylase. Some invertebrates (notably the edible snail) can hydrolyse many more sugars than can vertebrates, including tri- and tetra-saccharides in their food. The fat- and ester-splitting enzymes of invertebrates have the character of esterases rather than lipases, and the converse is true of vertebrates. The notable feature of the process of digestion in vertebrates is that digestive enzymes occur in chains and attack food successively, whereas in invertebrates all the enzymes meet in some one place where digestion is performed and attack the food simultaneously. It has been on account of this localisation of digestive enzymes that the action of pepsin has become possible; the advantage to the organism is that it is not inundated with the cleavage products of its food.

Secretion of Urine

Working in London, W. Bowman (1842) first described the main features of the microscopic structure of the kidney and inferred from his work that the pressure of blood passing through the capillaries around the glomerulus would bring about the filtration of watery liquid into the kidney tubule, the cells of which would probably add to the liquid some of the well-known constituents of the urine. Working in Germany, Carl Ludwig (1844) put forward his filtration-reabsorption theory, according to which the glomerular filtrate would contain all the constituents of the urine, the liquid being concentrated whilst

passing down the kidney tubules by the abstraction of water and some other substances and the reabsorption of the latter into the blood.

During the past one hundred years very much information has been forthcoming in regard to the capacity of the kidney to reabsorb various substances which can be arranged to circulate in the blood, and the controversy regarding renal function, which arose largely because of a lack of information concerning the composition of urine during the stages of its preparation in the kidney, has largely been resolved. In more recent years A. B. Macallum (1917) has shown that kidney function is more than just excretion, namely the regulation of the osmotic pressure of the blood. The work of A. N. Richards and his associates have produced experimental proof of Carl Ludwig's theory, and H. W. Smith and his associates have devised methods for measuring the rate at which glomerular filtration proceeds under various conditions. The discovery that amphibian and reptilian kidneys can be examined microscopically whilst alive, the application by J. T. Wearn and A. N. Richards of micro-injection methods to the sampling of urine from Bowman's capsule and the different levels of the uriniferous tubules, and methods of micro-estimation have shown that the liquid which passes into Bowman's capsule is simply a protein-free plasma filtrate, which is produced by glomerular filtration, the blood pressure in the capillaries of individual glomeruli being significantly higher than the colloid osmotic pressure of the blood plasma.

Glomeruli are absent from the kidneys of a few fishes, notably the toadfish (*Opsanus tau*), and therefore the urine must be produced by the tubules. Such a kidney will excrete various dyes and other substances introduced into the blood, but does not remove glucose and a few other substances, which are probably reabsorbed. Reabsorption occurs in another fish, a sculpin, with a primitive glomerular kidney, for glucose and chlorides are absent from the urine. The loss of glomeruli in marine bony fishes is associated with water regulation. The animal is continually tending to lose water to the surrounding medium and to replace this it drinks sea-water, removes the salts from this by means of special chloride-secreting cells on the gills and utilises the remainder. The animal has to work for the fresh water it is able to get in this way, and the loss of glomeruli from the kidney reduces the amount of filtration from the blood to a minimum. On the other hand, the fresh-water bony fish is continually taking up fresh water from the external medium and, in spite of defences against over-imbibition—the scaly or slimy nature of the skin, for instance—and rapid excretion

of copious hypotonic urine, it has to face a constant threat of water-logging. J. Nash (1931) studied glomerular development in eight species of fresh-water and three times as many marine teleosts, finding up to five times the number of glomeruli in the former. Increased glomerular action implies more filtration from the blood, and a greater loss of the surplus of water which enters the body of the fish. In birds and reptiles, which, like the marine teleost, need to conserve water, glomeruli are not obliterated or severed from the tubules so as to become useless in kidney function, but the central region of the glomerulus is filled with a core of syncytial tissue or else is invaded by connective itssue, compensation thus being achieved.

CHAPTER ELEVEN

RECEPTORS AND EFFECTORS

Receptors

ANIMALS respond to changing conditions in the environment—the play of light and shade, warmth and cold, or the presence of baneful or beneficial substances, enemies or prey—but before they can do so some form of energy must act as a stimulus by impinging on the whole body, if it be protozoan, or else on some specialised part of the body. E. D. Adrian (1928) defined a stimulus as "any change in the environment of an excitable tissue which, if sufficiently intense, will excite the tissue, *i.e.* will cause it to display its characteristic activity". Cells which receive stimuli are called *receptors*, which may be isolated and scattered or grouped together as in organs such as the eye. The reception of stimuli in man is accompanied by subjective phenomena—sensations. We generally credit ourselves with five senses—vision, hearing, taste, smell and touch—but we possess less obvious senses of pressure, temperature, balance, pain and pleasure as well. Experiments show that cats and some other mammals experience sensations similar to our own, but the lower animals can tell us nothing about their sensations, or even about the action of their receptors. Many animals with no sense organs or only ill-defined ones show by their behaviour that they are sensitive to stimuli. There is something in protoplasm itself that is able to react to various forms of stimulation, as the study of Protozoa shows. The study of receptors and reception can sometimes be carried out only by close study of behaviour, and a vast literature on sensory physiology has been built up during the past one hundred years. Some notable works are shown in my list.

It is not difficult to ascertain that human beings can distinguish between sweet, sour, salt, bitter, metallic and alkaline substances by means of receptors situated in various locations on the tongue. It is not easy to determine that some fishes can make use of similar receptors scattered on the external surface of the head or, in the case of the catfish, all over the body, nor to determine that some flies and butterflies have similar receptors on the legs which enable them to discriminate between sweet, sour, salt and bitter substances as they walk over them. One

form of experiment on reception, first carried out by A. Kreidl (1893), concerns the organs of balance known as statocysts, which occur in one form or another in at least six phyla of invertebrates. At its simplest, a statocyst is a hollow sphere lined with sensory cells and containing a particle of lime, or statolith, which is free to move under the influence of the gravitational field of the earth. If the animal's body is tilted, a different set of receptors is affected by the touch of the statolith, and the animal corrects its orientation in space. When crabs moult, the statocysts open and the statoliths are lost, generally to be replaced by sand-grains. Give the animal access only to iron filings and the function of the statocyst can then be tested by the use of a magnetic force that overrides the force of gravity. Under such conditions a crustacean can be induced to swim in various incongruous positions at the will of the experimenter. If the magnet be held over its back, the animal behaves as if it were upside down.

The Main Types of Receptors

Receptors react best to a particular kind of stimulus and they are classified according to the nature of the stimuli that most concern them. We have to remember, however, that stimulation may be brought about by abnormal means. A blow on the eye evokes visual impressions, and "seeing stars" is an impression of light where none exists. Light radiations are the proper stimuli for the eye, which is therefore a *photoreceptor* (see K. Tansley, 1950). Other receptors concerned with chemical substances in a molecular or ionic state are *chemoreceptors*, and they may be associated with the senses of smell or taste, or with a more general chemical sense (see R. W. Moncrieff, 1944). *Touch* and *pressure receptors* are sensitive to varying degrees of contact with solid bodies, *temperature receptors* to radiations which we associate with warmth and cold. *Pain receptors* are generally free nerve endings which may terminate in the cytoplasm of cells all over the body. We have seen that statocysts employ the force of gravity to enable an animal to maintain equilibrium in space, and parts of the semicircular canals of the vertebrate ear serve the same function (see O. Löwenstein, 1950). For an account of the sense of hearing see the article by R. J. Pumphrey (1950).

It is unnecessary to enumerate all the various kinds of receptors possessed by animals. J. F. Fulton (1949) has dealt with the historical aspect and modern opinions regarding human receptors. Most of those mentioned occupy a superficial position in the body and belong to the

class of somatic receptors, which Sir Charles Sherrington (1906) called *exteroceptors*. These are distinguished from visceral receptors, or *interoceptors*, which are concerned with the "organic" side of life, and are located in the alimentary canal and other viscera. The sensations of hunger, thirst, nausea, visceral pain, sexual pleasure and special sensations of the circulatory and respiratory systems are due to the action of interoceptors. One class of visceral receptors, the *proprioceptors*, are concerned with the kinaesthetic sense; they are associated with muscle spindles, tendons, skeletal and connective tissues, and they help to maintain the body in a state of preparedness so that it acts more efficaceously in an emergency. For instance, they maintain the muscles of the body in the imperfectly relaxed state of muscular tone which facilitates prompt and precise movements. It is by their action that, with proper training, we can walk without conscious effort or play the piano in the dark, though they are just as concerned with the involuntary movements of the viscera as with the voluntary movements of the entire body. H. W. Lissmann (1950) had discussed their action in detail.

Adaptation to Stimulation

Before electrical, chemical, or mechanical external change can produce a response it must attain a particular minimal intensity, or threshold value. The stimulus must overcome the inertia of the receptor before this will react, and even a constant stream of energy fails to stimulate the receptor unless its intensity is changing. It is change of energy rather than energy itself which affects the receptor. Animals need to be aware of changing conditions in their environment, and they get their impressions of change through the agency of their receptors. Exteroceptors are concerned with the external environment, interceptors with the internal. When a stimulus has been operative for some time, however, and even if its energy content is changing, the response of the receptor dies down and eventually disappears. The cell has become *adapted*, or unable to respond under the existing conditions of stimulation. This happens more quickly in some receptors than in others, and the speed of adaptation may be the only criterion distinguishing one sense from another. A complex receptor such as the vertebrate eye seems to show no sign of adaptation, but this is probably due to the enormous number of receptor cells involved and the fact that none of them is subjected to prolonged stimulation.

The Action of Receptors

Touch organs are of several sorts; a Pacinian corpuscle is a minute oval body with its own nerve fibril, and another sort consists of a tiny circlet or plexus of nerve fibrils surrounding the base of a delicate hair, the bending of which magnifies the stimulus as if by some sort of leverage. The histological differences between some touch and pressure receptors is insignificant, but each kind of receptor has its own physiological qualities. Adrian (1928) experimented with isolated touch and pressure receptors of the cat, using a capillary electrometer or a Matthews oscillograph and magnifying the action currents of a single nerve fibre by means of valve amplification. When a small glass disk is caused to press on one of the toe-pads the speed with which volleys of impulses pass along the small cutaneous nerve from the pads can be recorded. A pressure of more than 10 gm. on the disk affected the pressure organs; volleys of impulses passed along the nerve for several seconds, the frequency then gradually diminishing by adaptation. A pressure of less than 10 gm. on the disk brought the touch organs into play and resulted in the passage of a rapid volley of impulses at the moment of contact, followed by very rapid adaptation taking only one-fifth of a second. It was clear that touch organs become much more rapidly adapted than do pressure organs. Most of the cutaneous receptors of animals display the same qualities as touch and pressure organs; they are easily stimulated, but their sensitivity soon passes off as a result of adaptation.

The function of receptors, in the words of Adrian (1947), is to construct in the brain "a map of certain physical events occurring at the surface of the body so as to show what is taking place in the world outside us". We can be reasonably certain that "the signals which go to the brain from these different sense organs are all alike, that they are all the trains of brief nerve impulses, varying in frequency in each fibre with the intensity of the stimulus, but varying in no other way". "The function of these sense organs is to send information to the spinal cord in the light of which the force of the muscular effort can be adjusted to the load." Muscle spindles—attenuated muscle fibres surrounded by the windings of the endings of sensory nerve fibres—produce no definite sensation but they facilitate "an elaborate interplay of different muscles, so that, for instance, the body will not lose its balance when the arm is raised, and in these movements a smooth control of movement would be impossible without the messages from the muscle spindles

to show where the loads are taken". Other forms of "stretch receptor play an equally important part in regulating the inflation of the lungs and the force of the heart-beat. In fact they are an essential part of the mechanism by which the outgoing nervous messages are adjusted to the needs of the moment."

Amoeboid Movement

This type of movement occurs in the rhizopod Protozoa (amoebae, Heliozoa, Foraminifera and Radiolaria) and also myxomycetes (slime fungi), certain endoderm cells of coelenterates, the eggs of some invertebrates and the unusual spermatozoa of roundworms (nematodes) once they have entered the body of the female. The leucocytes of the blood in vertebrates also move like amoebae. The phenomenon varies greatly in different Protozoa, according to the kinds of cytoplasmic processes (pseudopodia) which are formed, and the literature dealing with it is large. The older work was reviewed by A. A. Schaeffer (1920). According to S. O. Mast (1926) an amoeba is covered by a thin membrane (the "plasmalemma") about 0·25 μ thick. Underneath this a thin viscous film of ectoplasm is thickened at the tip of a pseudopodium to form the "hyaline cap". The deeper granular endoplasm forms an outer and more viscous plasmagel and an inner more liquid plasmasol. The plasmasol flows in the direction of motion of the amoeba, but the plasmagel remains almost stationary. As the pseudopodium advances, the granules in the plasmasol stream into it. The marine form *Amoeba limax* forms only one pseudopodium of large size. C. F. A. Pantin (1923) found that, as the pseudopodium advances, the forwardly streaming granules of the endoplasm are checked as if by a barrier near the tip, where the ectoplasm is fairly rigid, and probably consists of gelating endoplasm—part of an extending ectoplasmic tube. This is contracting continuously, forcing endoplasm forward and thus providing more materials for further gelation. A particle trapped in the ectoplasmic sheath is motionless relative to the substratum, but as endoplasm continues to flow forward it comes to lie progressively nearer the hind end of the amoeba, and here enters a zone of solation where endoplasm is being formed from ectoplasm and added to the endoplasmic stream. The causes of these cyclical phenomena are difficult to determine. One theory is that acid is being formed in the active pseudopodium, bringing about imbibition of water by and localised swelling of the outgrowth and protrusion of its tip. In the

hind part of the amoeba this acid is somehow neutralised, the imbibed water is lost and contraction occurs.

Different species of amoebae move at various rates according to external conditions. Limax amoebae generally move quicker than amoebae having several pseudopodia, and *Amoeba proteus* may double its speed when it forms only one pseudopodium. The maximum rate of movement, of little more than 3 μ per second, occurs at a temperature of 20° C., a little above this for *A. proteus*. The movement will continue for several hours in the absence of oxygen, though at a slower rate. Calcium seems to maintain the rigidity of the ectoplasmic gel, but fresh-water amoebae need this element less than do marine amoebae. Acidity reduces the rate of amoeboid movement, alkalinity accelerates it.

Cilia and Flagella

Cilia exist in animals of all phyla except Nematoda and Arthropoda, and they serve many purposes. They are locomotor organs in some Protozoa, ctenophores, planarians and rotifers, and in larval invertebrates of many kinds. Inside the bodies of metazoan animals cilia may create and maintain feeding and excretory currents, transport eggs across the coelom and along the genital ducts, or serve as cleaning agents for breathing tubes. They may even serve for the conduction of impulses. The membranellae and cirri of some Protozoa are groups of fused cilia, and they are used for driving food into the mouth, and walking about, respectively. Cilia are not derived from any particular germ layer and they are uniform in structure. The ciliary beat propels an animal that is free to move—along a spiral course if the cilia are obliquely arranged—and flushes large and immovable ciliated surfaces with water. Animals that move by means of cilia can control the ciliary beat, either to alter the direction of translatory motion or else to come to rest. Like amoeboid movement, ciliary movement takes place only in watery liquids, where less work had to be done against gravity than in air, but where more energy is expended against the resistance of the external medium.

Flagella are like cilia but much larger. A single cell or unicellular organism rarely has more than four of them. They may coexist with cilia, and in some Protozoa cilia and flagella co-operate in locomotion. Flagella also line certain chambers in sponges and some parts of the enteron of coelenterates. The tail of a spermatozoon is a sort of flagellum.

Ciliary Movement

The movements of cilia were studied much more than one hundred years ago—by Sharpey (1835–36) in tadpoles, for instance. G. Valentin (1842) recognised four main types of ciliary motion which (with their modern names shown in brackets) are: *motus vacillans* (pendular), *motus uncinatus* (hook-like), *motus infundibuliformis* (funnel-like, or rotary), and *motus undulans* (undulatory). It was soon realised that the various forms of motion could occur singly, or else in various combinations. F. Martius (1884) was the first to use the stroboscope to study ciliary movement. This is a device (see J. Gray, 1930) whereby the cilium is illuminated by intermittent light for very brief intervals; when the frequency of illumination approximates to the rate of the ciliary beat, the cilia appear to be stationary. This is the principle of stroboscopic synchronisation. Jennison and Bunker (1934) combined the use of the stroboscope with high-speed cine-microphotography, using a camera devised by Edgerton and Germeshausen (1934) which could take about 6,000 frames per second, but was used for taking photographs at intervals of 0·005 sec. Much similar work has been done in Britain, and Professor James Gray's book *Ciliary Movement* (Cambridge, 1928) covers it expertly.

Cilia are rarely more than 15 μ long and 0·1 μ thick, but they make up in numbers what power they lack on account of small size. A single *Paramecium* has more than two thousand of them, a single *Balantidium* as many as ten thousand. Under the microscope cilia reveal no optical structure, even in polarised light, consisting of homogeneous cytoplasm. The base of each cilium is connected, however, with a basal granule, and from this fibrillae extend into the cytoplasm and are sometimes caught up in a bundle passing on one side of the nucleus. A flagellum is similarly connected with a basal particle, or blepharoplast, which may be derived from the centrosome of the cell. The basal granules play some part in controlling motion, and Gray regards them as the kinetic centres of the contractile system. In some Protozoa, however, cilia will continue to beat when separated from their granules, so long as they are in contact with fragments of cytoplasm.

Ciliated Protozoa move much more rapidly than amoebae. *Paramecium* travels at an average rate of 1 mm. per second, or about six times its own length. One surprising fact about cilia is the slow rate of movement of their tips. Reckoning the length to be 0·1 mm. and the rate of movement through an arc of 180° to be twelve times a second,

J. Gray first showed that the rate of movement of the tip does not exceed twenty feet an hour. The angular velocity, however, is comparable with that of a flywheel revolving 360 times a minute. In the simplest kind of ciliary motion (pendular), the forward stroke is the effective one, the backward stroke preparatory. There is no significant difference between the strokes, however, for the cilium behaves like a somewhat rigid body with an elastic core. The commoner hook-like type of motion starts from a straight cilium, flexure beginning at the tip, straightening at the base. Flagellar motion takes place as a series of waves which extend from the tip to the base, or in the reverse direction. From the three types all other kinds of motion can be derived. On the gills of bivalve molluscs there is a combination of hook-like and pendular movements. The effective stroke is pendular, the preparatory stroke hook-like. Flagellar beats can be modified more considerably than ciliary. The flagellate Protozoa can move forward, backward, or sideways, and their motion can be slow or swift, all these effects being produced by modification of the motion of the same flagellum. Animals which are free to move may drag or push themselves along with the aid of their flagella. Flagella are thus more versatile than cilia, though probably derived from them.

There are various theories of ciliary motion. E. A. Schafer (1891, 1904) elaborated the hypothesis of R. Grant (1835). The cilium was regarded as a hollow outgrowth of the cell filled with liquid (hyaloplasm) and covered with a fine elastic membrane. The motion of a cilium was supposed to be due to the rhythmic flow of liquid in and out of it. Cilia are not known to be hollow, however, and even the largest of them could hardly have this kind of structure. M. Heidenhain (1911) suggested that a cilium consists of an elastic core enveloped in a contractile sheath, and that movement is brought about by contraction of the sheath on one side during the effective stroke, and preparation for the effective stroke by recoil of the elastic core. This theory seems to be applicable to some cilia but not to all, and Gray (*loc. cit.*) preferred to attribute ciliary motion to the redistribution of water molecules inside the cilium. Water can easily be extracted from cilia, and a dehydrated cilium bends as if at the beginning of the preparatory stroke. The condition of rest is attained presumably when water molecules are uniformly distributed throughout the cilium, which becomes convex during the effective stroke. A rough model is provided by a strip of paper which remains flat so long as it is dry but bends when moistened on one side so that the damp side is convex (Gray). If this is the

correct explanation, the redistribution of water molecules may be due to changes in protoplasmic affinity for water on different sides of the cilium, and this in turn may be accounted for by different degrees of ionisation of protein or other molecules. Despite all the work and the thought expended on such problems, however, we are still a long way from a full understanding of the mechanism of this and other kinds of motion.

Muscles

Muscles are bundles of fibres which shorten, thicken and develop a tension when appropriately stimulated. They arise in different parts of the embryonic animal and vary in position, structure, histological appearance, chemical composition and nerve supply, and also in their modes of stimulation and types of response (see A. D. Ritchie, 1928). Unstriated muscles are spindle-like cells with fibrillar cytoplasm which contribute to the structure of the walls of the alimentary canal, the urinary and genital ducts, the bladder and the blood vessels. Their contraction is slow but sustained, and not under the control of the will of the animal. Striated muscle fibres are syncytial bundles of fibrils, and these in turn are linear arrays of muscle units or sarcomeres made up of alternating bands of dark (anisotropic) and light (isotropic) materials which display precise apposition in all the fibrils of a fibre. The electron microscope reveals still finer fibrillar details. This type of muscle is characteristic of the voluntary muscles which move parts of the skeleton, thereby bringing about locomotion. Cardiac muscle is found only in the heart. It is composed of branched cellular fibres arranged end to end and showing transverse striations, and it is remarkable because endowed with powers of spontaneous contraction. Under suitable conditions, the excised heart of a vertebrate will continue to beat for many hours and even days, and the embryonic heart commences to beat before any nerve supply has been established. A. J. Clark (1927) has reviewed the work on the comparative physiology of the heart—*i.e.* the action in both vertebrates and invertebrates.

Most of our knowledge of muscles has come from the study of mammalian skeletal muscle, which varies in appearance in different animals and in different parts of the same animal. Some kinds are noticeably redder than others. The wing muscles of birds are very red, the leg muscles of a rabbit very pale, almost white, and the muscles of trained sprinters are redder than those of untrained persons. But the

differences between red and white muscles is mainly functional; red muscles contract relatively more slowly than white. Flexors are red muscles which contract fairly rapidly; extensors generally have superficial rapid components and deep slow components, fibres having approximately equal speeds of contraction being segregated at different levels, or "heads", to give a kind of functional lamination from the surface inwards.

Movable bones and their muscles are to one another what levers are to the forces that operate them, and the arrangements seen in a mammal parallel every system of levers known to mechanics. In the body of an animal the kind of leverage employed suits the work which has to be done by particular systems of parts, and this promotes mechanical efficiency. The human body contains more than three hundred muscles, together weighing more than half a hundredweight; about one-third of them are needed to bend and straighten the spine, about twenty to hold and move the head, and more than fifty to move one of the lower limbs. Walking involves the harmonious and gentle action of many of these muscles, and is proportionately valuable as exercise. Many muscles are arranged in antagonistic sets, so that when a flexor system contracts, extensor systems must relax, and *vice versa*. The flexors of the human body are mainly situated in front, the extensors behind, but the opposite is true of the limbs. By and large, the walking vertebrate can be likened to an articulated system of girders; the skeleton makes up the compression members, and the tendons, ligaments and muscles the tension members. The same is true of many invertebrates, though in arthropods there is the notable difference that the muscles are situated internally to the parts they move, not externally as in the vertebrate.

Regarded as an excitable tissue, muscle shows the same general characteristics as nerve. It can be brought into a state of activity by the direct application of a stimulus, which sets up an electrical disturbance that travels along the fibres as a wave of excitation, though at a slower rate than in nerve fibres. The voluntary muscles of vertebrates will not contract unless stimulated by the discharge normally passing through their nerves, or induced to pass by electrical, mechanical, or chemical stimuli. The commonest form of experiment with muscles is the stimulation of the calf muscle (gastrocnemius) of the frog through its nerve (a branch of the sciatic). The Achilles tendon near the heel is severed and attached by a fine thread to a light lever, and the sciatic nerve, still attached to the muscle, is placed over electrodes. The

preparation is firmly pinned down so that movement of the muscle alone works the lever, which is supplied with a writing point that marks smoked paper set on a revolving drum, a "graphic" method invented by Ludwig and Helmholtz. When the muscle preparation is stimulated through its nerve, the nervous impulse travels along the nerve, reaches the end plates in the muscle fibres, leaps from these to the muscle itself, and gradually spreads over the surfaces of the fibres, which then contract. By such a method, muscular contraction can be analysed into a simple "twitch", twitches can be summated to give the maximal contraction, or "tetanus" which is characteristic of the normal contraction in the body, and the effects of fatigue can also be studied. Fatigue is found to be associated with the accumulation of lactic acid.

Towards the end of the nineteenth century this sort of experiment was practised in physiological research laboratories; now it is a commonplace of the elementary classes. Similar methods have been applied during the twentieth century to the study of invertebrate muscles. These often exist in almost equally vast arrays, and they show the same characteristics as vertebrate muscle. Such differences as exist are quantitative, not qualitative. The gastrocnemius muscle of a frog is tetanised by stimulation about twenty times a second (less frequently in "winter" frogs). The muscles of a holothurian pass into the corresponding condition when stimulated once in three seconds. The muscles of insects differ from those of vertebrates in the time scale; the wing muscles of a bee contract several hundred times a second when the insect is in flight. The adductor muscles of bivalve molluscs are of special interest because they comprise slow and rapid components that work harmoniously in shutting the valves of the shell and keeping them closed. Most of the fibres of these muscles are striated, and by their contraction the valves of the scallop's shell are closed in an instant. Some of the muscles are unstriated (but electron microscope studies now reveal submicroscopic striae in some such muscles) and these take about thirty seconds to develop a powerful traction that can be maintained for a very long period—several days under experimental conditions (see A. Bethe, 1911).

A related phenomenon is maintenance of tone in muscles. The legs of a pithed frog do not hang limply, but remain partially flexed. If the sciatic nerve is severed on one side of the body, however, the leg on this side at once falls into a limp posture. Evidently, the muscles of the pithed animal are partially contracted, not completely relaxed, *i.e.* they are in a state of muscular tone, which is probably maintained

by impulses which pass along a few of the nerve fibres that serve the muscle. In the normal animal tonus serves not only to keep the muscles in a prepared state, but also to sustain characteristic postures of the resting animal. Animals at rest are in a state of equilibrium which is preserved by slight contractions of both flexor and extensor muscles, and this condition of tonus ensures that when either set of muscles must contract to produce movement, in an emergency, the efficiency of contraction is much greater than would be the case if the muscles were completely relaxed.

The Chemistry of Muscle

Embden (in Bethe's *Handbuch der normalen und pathologische Physiologie*, 1925) reviewed existing knowledge of the chemical composition of muscle, which is about three-fourths water and one-fourth solids, and contains various substances—proteins, creatine and creatinine, carnosine, carnatine and traces of urea, glycogen, etc. D. M. Needham (1932) wrote a small monograph on the biochemistry of muscle. The two chief proteins of muscle are a globulin known as myosin and an albumen called myogen. The physical properties of myosin were studied by J. T. Edsall (1930). Solutions of myosin are isotropic when viewed by polarised light until they start to flow, when they become anisotropic. This behaviour is characteristic of colloids, so that muscular contraction can be regarded as a problem of colloidal chemistry and physics. The myogens were crystallised by Baronowski (1939) as A and B forms, and muscle also contains a substance known as globulin X of H. H. Weber (1934).

A. von Szent-Györgyi (1948) has made the study of muscle a problem regarding the nature of life itself. He has shown that the shape of colloidal particles may range from the spherical to the thread-like, and their physical properties vary according to shape. Spherical particles show a tendency to remain discrete, giving low viscosity to and promoting high motility in liquids of physiological importance such as blood and serum. Thread-like particles tend to aggregate, imparting high viscosity and low motility to substances that serve the needs of structure in cells. The fibres of striped muscle in mammals are about 0·1 mm. diameter, and each of them is a bundle of fibrils about 0·001 mm. diameter. The electron microscope shows the fibrils to be bundles of still smaller "filaments" many microns in length, which can be shaken apart by supersonic vibrations. These filaments

are the contractile units of muscle, and they are made up of positively doubly refractive protein. The contractile filament is composed of two colloids. One of these is *myosin*—a protein characterised by relatively short rods about 2–4,000 Å long and 25 Å wide, which form a soft plastic mass. The other is the protein *actin*, which exists as long threads. If the two proteins unite, myosin rodlets attach themselves to the actin threads to form the complex known as *actomyosin*, which has powers of contractility that neither of its protein constituents possesses. This was shown by resolving an actomyosin gel into threads, thereby increasing available surface and increasing the penetration of dissolved substances into the gel by diffusion. When the thread is dipped into boiled muscle juice it contracts markedly and rapidly. Increase the salt concentration by adding sodium chloride and the threads relax to their original shape and size. Szent-Györgyi has described the profound impression which this demonstration of the contraction of actomyosin made upon him, and rightly so, because it represents the production of the biological function of motion in a reaction between constituents of the body in the outside world.

It is clearly impossible here to deal even summarily with all the properties of muscle. A tremendous body of work has been done on tonus, the effects of various agents, heat production and chemical changes in muscle. Notable work on the chemistry of muscle began with the observation of W. M. Fletcher and F. G. Hopkins (1907) that lactic acid is produced when muscle contracts. Classical work on the work and heat production of muscle has been carried out by A. V. Hill (1911 onwards; see his paper of 1938) and B. Katz (1939). The changes consequent upon contraction may be considered as electrical, chemical, thermal and mechanical phenomena. The chemical changes are the most complex. Glycogen is broken down to lactic acid through a series of phosphorylated compounds and is associated with the performance of work by adenosine triphosphate. Chain reactions of this kind are exceedingly difficult to work out, but one of the most remarkable discoveries in this connexion was made by Engelhardt and Ljubimowa (1939) and associates the protein myosin with enzyme reactions. This substance is not merely a protein; it is also an enzyme. Some of the qualities of muscle are due to the elongated shape of the myosin molecule and its alteration into a shorter form by various agents such as adenosine triphosphate (ATP), which is dephosphorylated by the action of the enzyme component of myosin.

The Heart and its Action

Cardiac muscle has characteristics not unlike those of skeletal muscle (see A. J. Clark, 1927). Its movement can likewise be analysed into a single twitch, but the refractory period (during which no response to stimulation takes place) is long and the muscle cannot be tetanised. Some of the properties of cardiac muscle nearly approach those of cilia. Like cilia, cardiac muscle is not easily fatigued and it can continue active for long periods without a lowering of performance. The two kinds of tissue also behave similarly to external conditions of acidity and temperature, and they are comparatively insensitive to anions so long as the normal concentration of cations is maintained. Potassium increases the rate of action of both tissues and ultimately produces a prolonged tonic contraction. A deficiency of calcium also produces common effects in the two tissues. These and other similarities between cardiac muscle and cilia lead us to believe, as Gray first pointed out, that either there is some fundamental structural conformity, or else some common property of the cells involved in the two kinds of contractile apparatus.

Isolated fibres of developing heart muscle maintained in suitable culture media will go on beating rhythmically, indicating an inherent property of cardiac muscle (M. T. Burrows, 1912). The excised heart of a frog or tortoise will continue to pump a suitable saline liquid for several days and without any form of stimulation other than that provided by the perfusion liquid. In the living animal, nerves distributed to the heart supply impulses which modify the rate of the beats, slowing down or speeding up the heart-rate as circumstances demand, and the same is true of certain hormones which reach the heart through the blood stream. But the beat of the excised heart shows all the normal characters, because centres of stimulation exist in the tissue of the heart itself. The wave of contraction of the frog's heart begins in the wall of the sinus venosus and spreads to the auricle, ventricle and conus arteriosus in turn. The fragment of tissue at which this wave-like contraction begins acts as the pacemaker of the beat. In mammals, a similar patch of tissue exists between the superior vena cava and the right auricle—the sinu-auricular node—and this acts in the same way.

CHAPTER TWELVE

THE NERVOUS SYSTEM AND CO-ORDINATION

The Nerve Net

THE simplest type of nervous system in multicellular animals is the nerve net, a network of branched nerve cells and their endings underlying the ectoderm. This, in the words of G. H. Parker (1919), "contains the germ out of which has grown the central nervous systems of the higher forms". Some of the cells have two long outgrowths, others several of them, and for this reason they are called bipolar and multipolar nerve cells. The outgrowths branch again and again, and the ultimate endings approach closely to those of other nerve cells and of both receptors and effectors at junctions, or what M. Foster and C. S. Sherrington (1897) called synapses, which may be points of contact, or microscopic gaps that can be jumped by the nervous impulse (E. Bozler, 1927). By this arrangement the impulses set up by stimulation of a receptor are able to spread through the nerve net and influence a number of effector cells, exciting these to give a joint effect. Impulses spread through the nerve net with little impedance because it is not polarised, *i.e.* has no special central region such as occurs in the central nervous system of more highly organised animals.

Nerve fibres were first recognised by Fontana in 1781 and certain corpuscles which later investigation showed to be ganglion cells were first noted by Ehrenberg in 1833. R. Remak in 1838 and A. Kölliker in 1844 realised that there was some connexion between nerve cells and nerve fibres, and this was first demonstrated by H. Helmholtz (1842) for invertebrates and by Kölliker (1844) for vertebrates. In later years the work of F. von Leydig, J. von Gerlach, W. His, S. Apâthy and others proved that in many animals nerve cells and fibres form nerve nets, which were identified in jelly-fishes by A. Bethe in 1903, and in other coelenterates by Wolff in 1904, Hâdzi in 1909 and Groselj in 1909. The coelenterate nervous system "seemed to be nothing but a nerve net", and there was soon evidence that nerve nets are "at least components of the nervous systems of echinoderms, worms, arthropods, molluscs, and even vertebrates", where they are "especially

associated with the digestive tracts and the circulatory system, including the heart" (Parker).

The physiology of the nerve net has been considered in some detail by Parker, and in recent years its study has been taken up by C. F. A. Pantin (1934, 1937, 1950) and others. In some coelenterates the nervous impulse wanes as it passes through the nerve net. Touch the disk of a sea-anemone lightly and the animal reacts by noticeable contraction near the point of stimulation, but to a lesser degree remotely, and not at all on the opposite side of the disk. The stronger the stimulus, the greater the spreading of impulses round the disk, a harsh jab causing the entire disk to contract. The effect of spreading, or "decrement", is noticeable after some kinds of electrical stimulation, as well as mechanical, but a slight electric shock produces a local effect that ends abruptly at some point on the disk, showing that decrement does not occur. When several impulses cross the synapses in quick succession they seem, up to a point, to pass progressively more easily. This phenomenon of "facilitation" is said to be "interneural" when it occurs at the nervous junctions, and "neuromuscular" when it occurs instead at the junctions between nerve endings and muscles. Decrement is the outcome of progressively greater spreading of successive impulses as a result of interneural facilitation.

The rate of conduction of the nervous impulses varies in different regions of a sea-anemone—from 4 cm. per second through the wall of the column to 10 cm. per second along it, and 15 cm. and 100 cm. per second round its base and head. The rate may even reach 120 cm. per second in the mesenteries which support the intestine. This variable rate of conduction through the nerve net allows impulses to travel more rapidly along routes that are not the shortest distances between a receptor and an effector—for instance, through the mesenteries instead of the wall of the column. The nerve net has no centralised regions, but impulses can pass more readily in some directions than in others, indicating that the net is polarised.

When part of a tentacle is snipped off a sea-anemone the muscles contract only in the part which is connected with the body, showing that impulses do not pass in an outward direction; this centripetal polarity is probably due to the existent structural arrangements. Physiological polarity arises, however, when volleys of impulses pass through the nerve net by predominant facilitation in particular directions. The relative slowness of conduction in the nerve net as compared with other forms of nervous system is partly due to delay

at the numerous synapses. But in spite of the fact that facilitation is greater in the nerve net than in other kinds of nervous system—in which decrement does not occur—the essential principles of nervous conduction are the same in all animals, the differences being quantitative rather than qualitative.

The Nervous Impulse

Some early opinions on nervous transmission were outlined by R. S. Lillie (1929) and Heilbrunn (1945). According to the membrane hypothesis of nervous conduction, which has been described by E. D. Adrian (1932), a resting nerve fibre is enclosed by a polarised membrane. Negative ions are aggregated inside and positive ions outside the protoplasm of the fibre. When the nerve is stimulated this polarity is lost at the point of stimulation, where ions penetrate the fibre as a result of decreased permeability and create an electrical discharge, which affects near-by parts in such a way that similar changes occur in them. By the spreading of the discharge in this way an impulse is propagated along the nerve fibre. One of the most useful forms of experimental stimulation is a brief galvanic current, though chemical and mechanical agents will excite the nerve equally well. A very weak current, or a very brief one (passing for less than 0·00001 sec.), fails to generate an impulse or cause any significant change in the nerve fibre. Before it can excite the nerve, the stimulus must inaugurate certain minimal changes in the nervous tissue, and not until the critical strength and duration of stimulation has been reached is the impulse generated and propagated along the nerve. The response is "all or nothing", because the nerve fibre has a "threshold" of excitability.

The impulses that travel along a motor nerve fibre do not follow one another at exactly the same rate, but they keep sufficiently together to form a single volley, and as this reaches any point on the nerve fibre the electrical disturbance that is set up can be measured by a suitably sensitive galvanometer (Einthoven's string galvanometer was developed about fifty years ago, and more sensitive forms are now used in conjunction with valve amplification, which was developed after the 1914–18 war). When two electrodes are placed on the nerve and coupled with the instrument, action-currents pass through the circuit, and as the volley of impulses travels along the nerve the electrically active (negative) region also moves, coming to lie under the two electrodes in turn, with the result that the galvanometer needle is deflected first in one direction and then the other (Fig. 19). This is a

diphasic response, which lasts for only a few one-thousandths of a second. If the nerve is damaged slightly, it remains electrically

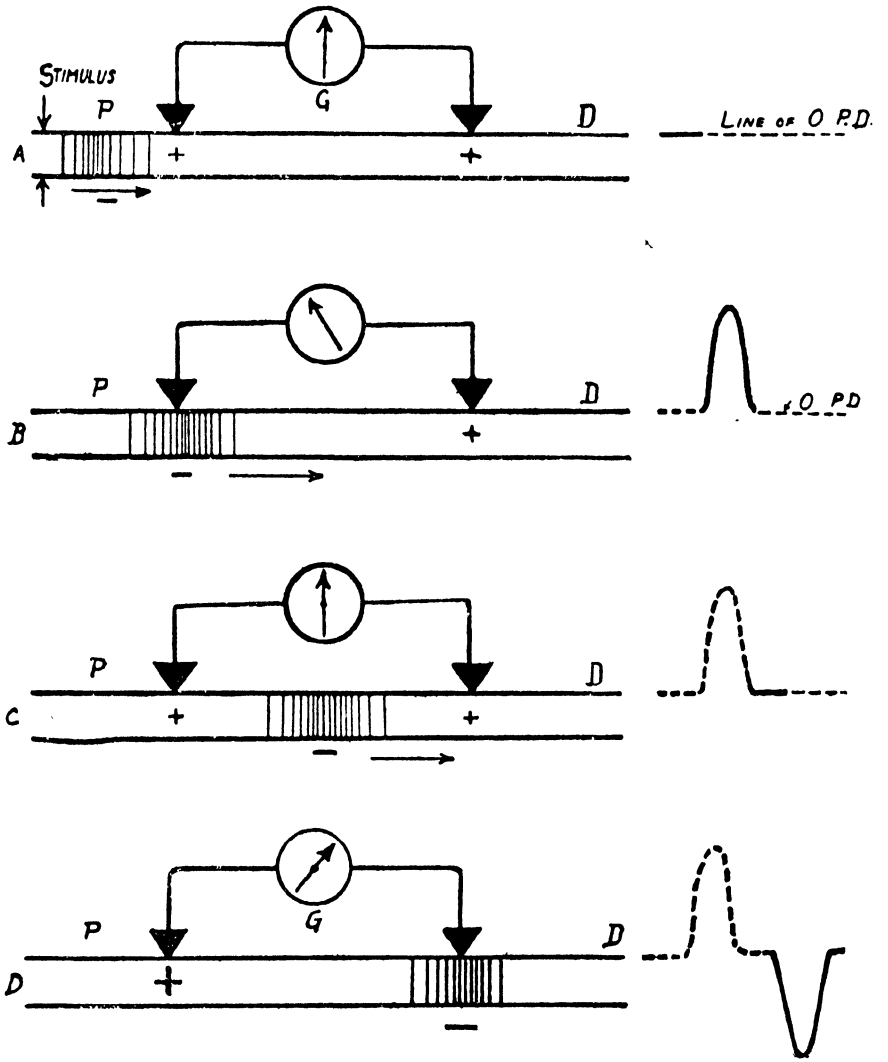


Fig. 19. Scheme showing a recording by a galvanometer (*G*) of the electronegative zone transmitted along a muscle fibre or nerve as a "diphasic" change of potential. In successive intervals of time (*A*, *B*, *C*, *D*) the zone passes beneath the two electrodes in turn. Note: if the left electrode were placed on an injured region (permanently negative zone) the recorded response would be "monophasic". From Winton and Bayliss, 1948. (J. & A. Churchill.)

negative at the damaged point, and if one electrode is placed here the recorded curve has one component instead of two components—*i.e.* the result is monophasic.

When the nerve is stimulated twice in rapid succession it responds to the first stimulus, but not to the second. While the electrical response due to the first stimulus is in progress the nerve is in an inexcitable, or refractory, state and this is at first absolute but later becomes relative. During the relatively refractory state the nerve can be excited only by a more powerful stimulus than the one which previously excited it. A nerve from the frog remains in the absolute refractory state for 0·002–0·003 second and it has almost completely recovered in 0·02 second. One effect of this refractory condition is to limit the discharge of successive impulses along a nerve to a certain minimal frequency. Adrian likens the discharge, not to a stream of water issuing from a hose, but to the stream of bullets issuing from a machine-gun.

There is no significant difference between the discharges that pass along sensory and motor nerve fibres. Impulses travel along the phrenic nerves to the human diaphragm at the rate of seventy per second, resulting in the rhythmical movements so necessary to respiration once every second. The impulses set up in sensory nerves by various means —tapping the skin of a frog to stimulate the cutaneous nerves, applying light pressure to the pad of a cat's foot, distending the aorta to stimulate the cardiac depressor nerve, or firing a gun to stimulate the auditory nerve—last about one-fifth of a second. Though the impulses do not differ, however, the effects produced by them may be extremely different, as Langley showed more than fifty years ago by joining the central end of one nerve (the vagus) to the peripheral end of another (the cervical sympathetic), stimulation of the first nerve then producing the characteristic effect normally produced by stimulation of the second.

Impulses pass along a nerve at rates determined by the intensity of the stimulus. By pruning an already delicate muscle-nerve preparation over and over again, E. D. Adrian and Y. Zotterman (1926) succeeded in isolating a fragment of muscle and nerve which conducted a single set of impulses at rates of 5–100 per second. The impulses were generated by the stretching of the muscle fibres, and the intervals between them varied according to the intensity of stimulation; when the muscle was stretched with weights of 1·0, 0·5 and 0·25 gm. respectively, the frequencies of the impulses fell from 290 to 200 and to 150 per second, although individual impulses remained of the same magnitude.

In 1852 Helmholtz found that impulses pass along a frog's nerve at

a rate of 20 metres per second. Later work has shown that the velocities of the nervous impulses vary in different animals and in different parts of the same animal (see A. V. Hill, 1932), but in all instances the frequency of impulses traversing the same fibre increases with increase in the intensity of stimulation. In some animals there is a relationship between the diameter of the nerve fibre and the velocity of the nerve impulse; the greater the diameter, the quicker the impulse travels (see H. S. Gasser and J. Erlanger, 1929; L. Lapicque, 1939). Another factor related to the speed of the impulse is the nature of the nerve sheath. In medullated nerve of mammals impulses may travel at a rate of 100 metres per second; in non-medullated nerves (without a fatty sheath) only 1 metre per second (Table 10). Similar differences, if somewhat smaller ones, exist between the impulses that travel along

TABLE 10.—THE RATES AT WHICH NERVOUS IMPULSES PASS ALONG THE NON-MEDULLATED AND MEDULLATED NERVES OF SOME ANIMALS. (From Heilbrunn, 1943. *After* various writers.)

Animals	*Medullated (M) or Non-medullated Nerve*	*Rate of Impulse in Nerve* (metres per sec.)	*Temperature*
Pond mussel (*Anodonta*)	N	0·05	...
Portuguese man-o'-war (*Physalia*)	N	0·12	26
Pike (*Esox*) (olfactory)	N	0·2	20
Mammal	N	about 1	37
Crab	N	5 and 1·5	22
Prawn	M	18–23	17
Squid	M	3–23	21–22
Earthworm	M	7–25	10–12
Frog	M	about 30	20
Dogfish	M	about 35	20
Mammal	M	about 100	37

the giant fibres and the ordinary nerve fibres in worms, crustaceans and cephalopod molluscs. In the cuttlefish and squid, contractions of the siphon, through which a jet of water is ejected during swimming movements, are brought about by impulses that travel along giant fibres at a rate of about 10 metres per second, as against a rate of about 1·2 metres per second for the impulses passing along ordinary nerve fibres (R. J. Pumphrey and J. Z. Young, 1938).

Nervous Mechanisms in Ringed-worms and Arthropods

The nervous system of ringed-worms, which are the simplest coelomate animals, is formed mainly out of an inner nerve net, for the plexus of fibrils found underneath the integument of some worms is probably formed by outgrowth from the deep nerve cells. The most evident part of the nervous system is a double nerve cord in the lower part of the body. In each segment two ganglia are united by fibres, both with one another and with ganglia lying in adjacent segments. From each pair of ganglia three pairs of segmental nerves extend outwards into the integument. The ganglia of a particular segment receive impulses from receptors in that segment and they control the muscles in it, but both the sensory and the motor nerve fibres extend into the two adjacent segments, so that there is some overlap of control in small groups of segments. The anterior end of the body is specialised and in this region the nervous system is modified. The first ganglia (cerebral) are the main receptive centres of the worm, for they are associated with abundant receptors in this region, but they play some part in maintaining muscular tone in other parts of the body, and they are associated with tonicity in other parts of the nervous system.

Co-ordination in this type of nervous system is affected by relaying impulses along the sensory fibres of the segmental nerves to nerve cells in the cord, and thence to the motor fibres of the segmental nerves, but this effect is extended by the spreading of the paired nerves into adjacent segments, and by the passage of impulses from cell to cell along the cord. The impulses have to pass numerous synapses and the rate of conduction is not high—about 25 cm. per second—but in the main nerve cord more rapid conduction is brought about by the action of three giant nerve fibres that traverse the entire cord, for in these fibres motor impulses pass at the rate of 15–45 metres per second (references in B. T. Scheer, 1948, p. 253). Unusually powerful stimuli bring these giant fibres into play, and they result in very rapid responses such as may be seen when the worm suddenly contracts, or when it jerks backward with swift spasmodic movements.

Two other influences are at work in the worm's nervous system which must be mentioned. The first concerns a plexus of nerves located at the base of the gut epithelium; it communicates with the nerve cord by six pairs of nerves issuing from the nerve collar, the anterior region of the cord passing on either side of the oesophagus. This arrangement forms a rudimentary type of visceral or autonomic nervous system, concerned with the control of the viscera. The second

concerns the influence of mechanical effects of adjacent structures. The body wall of the worm contains an outer layer of circular muscles and an inner layer of longitudinal muscles. These are segmentally arranged, but connected with one another by the septa between the segments, so that concerted action is possible. When the worm creeps along the surface of the ground, ripples of contraction pass along the body, mainly due to the stimulation of successive segments coming into contact with the ground. Similar movements occur, however, when the worm is suspended in air, and thus slightly stretched. When the muscles of one segment contract (or are stretched) those of an adjacent segment are subjected to a tension that stimulates their proprioceptors, with the result that the corresponding muscles contract. This effect is transferred farther back in the body as more and more segments become involved in succession. The impulses set up by the proprioceptors may also be relayed to the nerve cord and spread by the special arrangements of the segmental nerves, as must happen to produce the rhythmical movements of the worm when attempting to creep over a slippery surface. One effector may thus directly affect another through its proprioceptors, but the same effect may be produced by an alternative means, illustrating the principle of "double assurance" that characterises many other physiological effects (J. Gray and H. W. Lissmann, 1938).

The nervous system of a crayfish has much in common with that of a worm. Each segment has a pair of ganglia, and the segmental control of effectors still prevails. Moreover, the nerve cord has the same general character but is more clearly double. The behaviour of arthropods is on a much higher plane, however, than that of any worm, and the reason for this lies partly in the specialisation of some segments of the body, but mainly in the greater degree to which impulses are conducted up and down the nerve cord. In consequence, reflexes spread through many segments, not just two or three, and sometimes throughout the entire length of the body. The association neurones in the nerve cord traverse many segments, making this spreading easier to achieve, for larger nerve cells mean less delay at fewer synapses. In walking, segmental reflexes may suffice even for an insect which has three pairs of legs, and when walking keeps three legs on the ground at any instant. The first and third legs on one side move forward simultaneously with the second leg of the opposite side, a kind of co-ordination which suggests that reflexes entail three segments. The insect may thus walk as absentmindedly as any pedestrian, but it is not

committed to its reflexes, for if it loses a leg it may show an entirely different gait, and make just as much headway as usual.

Nervous Adjustments in Vertebrate Animals

Backboned animals have a very elaborate and specialised nervous system, but there are central and peripheral parts. The central part (C.N.S.) is a hollow tube composed of nerve cells and their axon fibres. It is dorsal in position and is marked out into brain and spinal cord. The central cerebrospinal canal extends along its entire length. The more elaborate brain region controls both the head and some distant parts of the body, the less modified spinal cord retains its primitive segmental nature, as indicated by a paired series of nerves emerging from it. The cranial nerves have their topographical relationships disturbed by differential growth of the head. Fishes and amphibians have ten pairs of cranial nerves, other vertebrates twelve pairs. The spinal nerves, of which there is one pair to each segment, arise by dorsal and ventral roots, the former bearing a ganglion. The impulse which traverses the sensory process of the receptor cell is relayed to a sensory nerve situated in the dorsal root ganglion and thence to nerve cells in the upper part of the spinal cord, whether it comes from a visceral or a somatic receptor. The ventral root is made up of motor fibres, some of which pass directly to somatic effectors, while others link up with the autonomic nervous system—a chain of ganglia from which nerves pass to internal organs of the body. The nerves arising from the spinal cord are thus of four kinds, named according to the source, direction and ultimate destinations of the impulses which pass along them; "somatic sensory", "visceral sensory", "visceral motor", and "somatic motor" fibres are associated in the cord with nerve cells arranged in this order from above (dorsal) downwards (ventrally). The visceral nerves are specially concerned with the control of internal organs, and they function independently of the animal's will; the somatic nerves control less "vital" parts of the body, and they are under the control of the will. The nerve cells of the central portion of the nervous system are called "association neurones"; their axon fibres constitute the "grey" and "white" matter of the brain and spinal cord.

Adjustment and Correlation Centres of the Brain

Arrangements exist in the grey matter of the brain for relaying impulses from the sensory to the motor nerve fibres. Some adjustment

centres of this kind are concerned with impulses travelling from the nose, eyes, ears and skin, which are transmitted through association neurones to motor neurones and thus complete various "reflex" arcs. The "primary" adjustment centres are segmentally arranged, the centre for smell existing in the fore-brain, that for sight in the mid-brain, and the centres for hearing and the cutaneous senses in the hind-brain, regions established early during development. Superimposed on these centres are subsidiary regions in which "correlation centres" are established in order to unify the components of various reflexes.

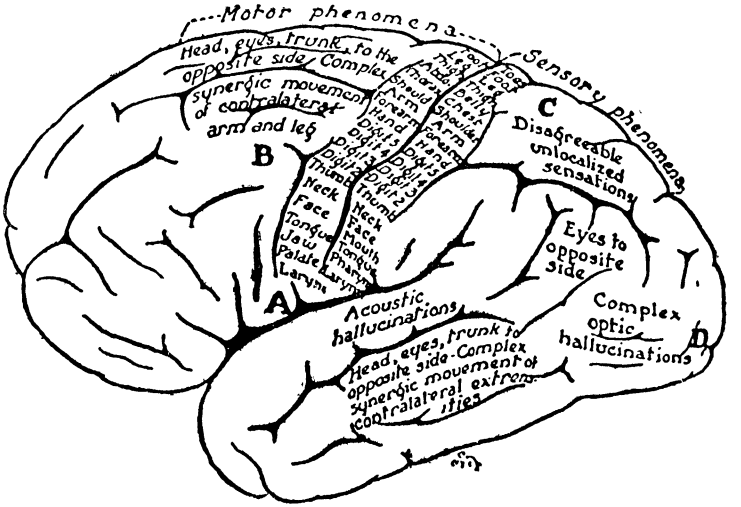


Fig. 20. Diagram representing the chief cortical areas in the human brain showing the main excitable areas as determined by direct stimulation of the brain under local anaesthesia. From Winton and Bayliss, 1948. (J. & A. Churchill.)

In fishes very little adjustment of this kind occurs; the various primary centres are rather self-contained and concerned with their own receptors and effectors. This is indicated by the preponderance of reflex responses to simple stimuli seen in their behaviour. Correlation centres have been established, however, and they are located in secondary enlargements of the main regions of the brain. One such region in that part of the hind-brain, the "cerebellum", is concerned with adjustments made as between vision, hearing and balance. In consequence, this part of the brain has come to control the posture and movements of the body and to regulate muscular tone in widely separated parts of it. In more highly organised vertebrates correlation

centres which are not very well developed in fishes are elaborated in a part of the fore-brain, the "cerebrum". Methods of locating these are difficult and tedious, but a stage has been reached in which it is possible to map them out and show them in a model of the brain of man and animals. These "higher centres" are distinct from the primary centres, and are not monopolised by particular senses. A centre situated in the thalamus is adjusted to most of the sensory centres and is concerned with sensory impressions associated with the sensations of pleasure and pain, so that it plays a large part in conditioning behaviour. A centre in the corpus striatum is mainly concerned with stereotyped responses; it is well developed in birds and other vertebrates that form complex patterns of "instinctive" behaviour.

The Higher Centres of the Brain

In vertebrates the higher nerve centres have been progressively developed in that part of the fore-brain which is called the "cerebral cortex". They are groups of neurones that form the grey matter of this region, and they are concerned with sensory impulses which have already passed through correlation centres. The importance of such centres lies in their making possible various alternative systems of relays. In most fishes they are comparatively simple, but in birds and mammals they are large and important. As the neurones multiplied in numbers in such highly organised vertebrates their maintenance became precarious, but it was assured by relative increase in the amount of brain surface. The cerebral hemispheres became enormous hollow lobes nourished by the blood on the outside and by the cerebrospinal liquid on the inside. Of these two liquids blood is undoubtedly the more important, which may explain why the neurones came to occupy a superficial position just underneath the vascular membranes, not only in this but in other regions of the brain as well. As the cerebrum enlarged, the higher centres came to be arranged in definite geometrical patterns, and this had much to do with increased powers of discriminating between the dispositions of external things in space and time. The establishment of higher centres also helps to explain how animals became able to select from several possible responses those which represent higher forms of control by the subordination of responses of a reflex nature. A dog which fails to remove a "tickling" agent by a "scratch" reflex and brings teeth and tongue to bear on the problems of removing it is overriding reflex behaviour by the use of centres in the brain. The cerebral cortex of man is elaborated out of all propor-

tion to the remainder of the brain, and it contains many millions of neurones by means of which many different kinds of adjustments can be made. The formation of habits probably results from repeated use of correlation centres that are nevertheless sufficiently complicated to allow of such notable behaviour as learning poetry or music "by heart"; but the highest form of behaviour—such as solving a problem in higher mathematics—involves the use of nervous centres and conduction paths seldom used in an entire lifetime. For an elaborate exposition on the physiology of the nervous system (with historical notes) see J. F. Fulton (1949); for a popular article on the function of the central nervous system, J. Z. Young (1945).

Chemical Co-ordination

This type of co-ordination is effected largely by means of endocrine secretions. Most kinds of chemical co-ordination depend to some extent on the nervous system; the pituitary gland is stimulated by direct nervous action, and the thyroid is activated by pituitary hormones, and therefore indirectly by the nervous system. Some hormonal effects last only for short periods of time. The liberation of adrenaline into the blood produces the emotions of fear or anger, and effects a redistribution of the blood to parts such as skin and muscles, but these phenomena may last for only a few minutes. The maintenance of sexual rhythms by humoral action may last for weeks and even months. Another type of co-ordination—by chemical transmitters, or "neurocrines"—may last for only a small fraction of a second, though achieving effects of inestimable value to the organism. This takes the form of chemical secretion at motor nerve endings.

The most important chemical transmitters are the "sympathins" and acetylcholine, which respectively simulate the actions of the sympathetic and parasympathetic components of the autonomic nervous system. The sympathins form a group of substances—of which adrenaline is one—formed and liberated at the endings of the sympathetic motor nerves, which are thus named "adrenergic". They are responsible for characteristic effects of sympathetic stimulation—a redistribution of blood by constriction of the arterioles in the skin and viscera, increase in the rate and force of the heart-beat, dilatation of the pupils of the eyes, the relaxation of the bronchial tubes, and many others. Acetylcholine is liberated at the endings of the parasympathetic and other motor nerves, which are said to be "cholinergic". It is a nitrogenous base and it is prevented from accumulating in the body

by control with an esterase. It exists in both vertebrates and invertebrates. The importance of these and other chemical transmitters has been realised through the researches of R. Hunt and R. de M. Taveau (1906), A. J. Ewins (1914), R. Hunt (1918), O. Loewi (1921), O. Loewi and E. Navratil (1926), H. H. Dale (1934) and others; it lies in their power to react with some constituents of the effector organs and set in motion series of chemical changes that lead up to the contraction of a muscle or the act of secretion by a gland. Their rapid disappearance is due to extreme lability and sensitivity to antagonistic substances, and their equally rapid reappearance at the moment when a nerve impulse reaches them is another factor that tends to promote an almost instantaneous reaction when this is necessary for the integration of the nervous impulse. The interesting stages of research on this aspect of nerve physiology have been described historically by W. H. Newton (1936), F. R. Winton and L. E. Bayliss (1948) and other physiologists.

Chromatic Responses

The colours displayed by some animals may be due not to pigment but to structural peculiarities. The iridescent green colour of a budgerigar's feathers disappears in transmitted light, a dull grey colour taking its place; the green colour is due to interference phenomena. Pigments of many kinds do exist, however, in the skins of many animals, generally in the form of granules in colour cells, or "chromatophores". Pigment cells of this kind may be regarded as "effectors", for by means of them an animal may completely alter the tone and colour of its skin so that it accords with the general appearance of the background against which it is seen. Colour changes may occur in response to stimulation by light falling directly on the body, or by light reflected from other external objects. We must distinguish between chromatic responses of this kind and gross seasonal colour changes in the plumage of birds or the coat of a mammal. They occur in many vertebrates—fishes, amphibians and reptiles—and also in prawns, shrimps, woodlice, cuttlefishes and other invertebrates.

The most widely known type of chromatophore is that containing the black pigment melanin, namely "melanophores", which are very numerous in the skin of a frog or a minnow. When the granules of melanin are dispersed through the branched processes of such cells the entire skin of the animal appears dark, but when the granules are massed in the central regions of the pigment cells the animal appears

pale. Pallor and darkening of the skin are generally attributed to the movements of pigment granules in the cytoplasm of the pigment cells, but there is a possibility also that some synthesis and degradation of pigment occurs under various conditions (B. Dawes, 1941 *a*, *b*). The condition of the pigment granules in melanophores depends to some extent on external conditions; pale frogs occur in bright, dry and warm situations, dark frogs in dark, wet and cooler situations. Pale frogs are common in summer, dark frogs in winter. The tone of the background and the incidence of light are important factors in deciding what the tone and colour of the skin will be. When light falls from above, a dark background produces darkening of the skin, a white or light background paling of the skin. A normal frog or minnow changes the tone of its skin according to that of the background. In some leeches, fishes and reptiles chromatophores are stimulated by the direct action of light, and in some such animals the cells are supplied with nerves, the severing of which produces local changes in skin tone. All efforts to discover similar nerves in frogs have failed, and it is fairly certain that they do not exist. In frogs the chromatic responses are produced by hormones circulating in the blood. If the posterior lobe of the pituitary is removed from a frog, the animal remains pale irrespective of the type of background or light incidence. Injection of an extract of this gland will, however, bring about a marked darkening of the skin, and subsequent intravenous injection of adrenaline will again blanch the skin.

A tremendous literature has arisen on the problems of colour change; but it has been reviewed extensively by G. H. Parker (1948). The experiments of L. T. Hogben and many others have proved beyond doubt that the "pars intermedia" of the pituitary complex secretes some substance that causes darkening of the skin by the dispersal of melanin in the pigment cells. The real nature of this substance is at present unknown, and it is generally called the "B-substance" (B for black). The agent which produces pallor of the skin—the substance "W" (for white)—is secreted either by the pars tuberalis or else by some other part of the pituitary complex. Darkening and pallor are thus due to the antagonistic action of these two substances, B and W, on the melanophores. Their secretion is evoked through the agency of the eyes. The substance B is secreted in vertebrates when light falls on a particular region of the retina in the lower half of the eye, W when it falls on a region in the upper half. The dark-background response is a reflex which works between the eye and the pituitary gland, but the nature

of the white-background response is not clear, for it varies in different classes of vertebrates. In fishes and reptiles direct nervous control of the melanophores has arisen as an independent method; but in bony fishes it has been superimposed on a more primitive humoral method like that used by a frog.

There are various reasons why many vertebrates which possess pigmentary effectors fail to display chromatic responses. The axolotl remains dark under ordinary conditions of life, but it becomes yellowish-white when the pituitary gland is removed and then darkens when pituitary extract is injected into its body. Clearly, the axolotl has powers of colour control that it does not normally use. The failure to change colour may in other instances be due to a loss of sensitivity of the effectors, to subnormal concentrations of hormones in the blood, or to an inability on the part of the animal to adjust or orient the eyes in relation to external sources of illumination which bring about the reflex liberation of the hormones concerned.

Invertebrate animals also make use of hormonal control of chromatic responses. In crustaceans there are two or more hormones, one of which is secreted by a gland in the vicinity of the eye (eye-stalk hormone). The work of E. B. Perkins (1928) is notable because the first of its kind in regard to such animals, and also because of the manner in which his experiments were carried out, to indicate the effect of blood-borne substances. Both B and W substances are involved in colour control, just as in vertebrates, and these are liberated into the blood by means of a reflex acting through the eyes. The substance B is liberated when light falls on particular groups of ommatidia, in the compound eye, the substance W when it falls on certain others. Double humeral control of the chromatophores is a widespread phenomenon, therefore, and it depends partly on nervous mechanisms. The type of adjustment indicated has been called "neuro-humoral"; it is a further example of that type of co-ordination which depends on reciprocal reactions that are commonly spoken of as "antagonistic", and would be better called "complementary".

CHAPTER THIRTEEN

BEHAVIOUR

THE behaviour of animals—the sum of all their activities as living organisms—is not easy to analyse. Every species of animal has its own way of satisfying the everyday needs of life and living, and behaviour may seem to be simple and stereotyped when conditions remain uniform. Ciliated Protozoa may swim continuously for many hours, bivalve molluscs maintain their feeding currents incessantly, and even man is guilty of monotonous conduct under the pressure of dreary conditions of life. Man and animals alike behave in all the ways possible to them only under the wide range of conditions encountered during their whole lifetime. A part of behaviour may consist of many trivial activities, but exceptional responses are often evoked by conditions that arise in special circumstances, and it is the uncertainty of an animal's reactions to highly irregular events in the environment that gives the study of animal behaviour its delightful attributes.

The subject of animal behaviour has a vast literature. N. L. Munn (1933) gave a list of 670 works on the behaviour of the rat—which was first used in such work at the end of the nineteenth century—and well over 300 "selected" references dealing with other animals. Even a short list of well-known treatises indicates not only the progressiveness of the subject but also the diversity of types studied. H. S. Jennings (1906) was mainly concerned with Protozoa and other "lower" animals, W. Köhler (1925, 1927), and R. M. Yerkes and A. D. Yerkes (1929) with the great apes. The early work of G. J. Romanes (1883, 1885) was largely anecdotal, but J. Lubbock (1888) mainly concerned himself with insects and devised many new methods of experimentation, proving himself to be a pioneer of the newer animal psychology. The work of L. T. Hobhouse (1901, 1915) was important because it antedated by two decades the work of the Gestalt psychologists, and that of E. L. Thorndike (1911) indicated new ways of studying the learning process of fishes, chicks, cats, dogs, monkeys and other animals. The work of I. P. Pavlov (1910, 1911) on the formation of conditioned reflexes in dogs was revolutionary in its

methods of measuring accurately the quantity of salivary flow in experimental animals; his work has been discussed in different ways by W. M. Bayliss (1927), C. Singer (1931) and J. F. Fulton (1949). During the present century this sort of work has been extended to include fishes, the series of papers by O. W. Bull being notable in this respect. A well-documented account of the general methods and results of animal psychology was given by M. F. Washburn and the first book on behaviourism was that of J. B. Watson (1914). These and other notable books are cited in the list at the end of this book.

The simplest forms of behaviour in multicellular animals having a nervous system can be represented as reflex acts; impulses are generated in receptor cells and transmitted through more or less simple nervous channels to effectors that make some characteristic responses. Protozoa without any trace of a nervous system make somewhat similar responses, and we cannot logically set their behaviour apart from that of other animals on the grounds of quality. At the other extreme, highly organised animals with a nervous system not unlike our own may behave in ways that we are tempted to interpret subjectively, as if their experiences and our own were identical. The chief difficulty of the student of animal behaviour is carefully to avoid anthropomorphic interpretations and overstatements about mental activities associated with any non-human nervous system. Animals cannot describe their feelings to us, yet some of them lead us to suppose that they have minds. The capacity to think and act with the help of higher mental faculties is granted to animals, however, only when no other explanation of their behaviour can be given.

Behaviour in Protozoa

Unicellular animals may respond to the same external conditions in various ways and to different conditions in the same way (see H. S. Jennings, 1906). A proteus amoeba may react to contact with some solid object by forming a number of blunt pseudopodia, clinging to the object and finally creeping over it; or it may react by dividing to form many amoebulae. Under ideal conditions the amoeba will pursue other organisms and devour them, though unfavourable conditions will cause it to shrink and encyst. When a moving amoeba comes in contact with some obstacle, the advancing protoplasm flows in a new direction, and the degree of turning is determined by the size of the object, which is circumnavigated if small but avoided if large. The presence of a solid object is not necessary to produce this turning

response, for a region of high temperature or chemical substances in solution in the water will also evoke it. Highly illuminated localities have the same general effect on the animal, causing the pseudopodia to retract and fresh processes to be extended in a new direction, only to be retracted in turn if they encounter bright light. This kind of behaviour may persist for some time, but if bright conditions prevail the protoplasm may finally flow in reverse, the amoeba then retracing its former path. Moreover, if such conditions repeatedly confront the same amoeba, the reversal of movement occurs after fewer entries into the light, the behaviour of the animal indicating some degree of learning by experience. When the animal is feeding it may fail to display the turning response, which leads us to suppose that the reaction is not perfectly automatic but has some internal as well as an external cause. As a rule the behaviour of an amoeba is apparently conducive to beneficial effects. When it is suspended in the water it protrudes rather longer pseudopodia than usual, as if seeking an anchorage, and if the pseudopodia encounter a solid object they do not avoid it but instead adhere to it.

Tropistic Behaviour

The term "tropism" was invented in 1832 by A. P. de Candolle with reference to the movement of a plant towards a source of light (heliotropism). In the past one hundred years it has been used in many different senses, but it is usually taken to mean the compulsory (involuntary) orientation of an organism in relation to such stimuli as light, the force of gravity, a current flow, and some other factors of the environment; also to a galvanic current. Such orientations can be studied only in the simpler animals, for conscious volition comes into play in more highly organised forms. Botanists largely stick to the term "tropism", but for animals the alternative term "taxis" is generally used.

The most useful summary of tropistic behaviour is J. Loeb's *Forced Movements, Tropisms and Animal Conduct* (Lippincott, 1918). Some critics have described it as rather one-sided, failing to take into account many controversial matters and considering only behaviour which can be tested by quantitative experiments. It has also been suggested that the whole problem of tropistic behaviour has less significance to-day than it had twenty or thirty years ago, resolving itself (as far as animals are concerned) into problems of nerve physiology and animal psychology. On the other hand, W. J. Crozier and

other biologists have maintained that the study of taxes may furnish valuable information about central nervous states and conditions which is unobtainable by other means. The whole field has been reviewed in recent years by many writers, notably M. Rose (1929) and G. S. Fraenkel and D. L. Gunn (1940). The early literature was extensively treated by J. Loeb, whose list of references numbered 554; Rose listed nearly 3,000 original papers.

The principal taxes of animals include: phototaxis—the behaviour shown by many animals (*e.g.* various Protozoa, coelenterates, worms, molluscs, crustaceans and insects) which move towards or away from a source of light; geotaxis—orientation with respect to gravity—shown by most animals; galvanotaxis—orientation in regard to the path of a galvanic current; rheotaxis—orientation in regard to the direction of a stream of water—shown by fishes and many other aquatic forms; and chemotaxis—movements determined by chemical substances in the environment—shown by many animals and also isolated cells such as sperms, leucocytes and bacteria. Some authors list many more; *e.g.* stereotaxis (thigmotaxis)—orientation in respect of contact or the sense of touch; hydrotaxis—the turning towards water, shown by snails and by eels migrating overland to the sea; hygrotaxis, or the tendency to select regions of moist atmosphere, shown by many insects; vibrotaxis—the response to vibratory disturbances seen in spiders when the web is shaken, and in man when he turns in order to locate the source of sound; and histotaxis, the response shown by parasites which wander through the tissues of an animal. Not all such responses are of real importance.

According to Loeb, the symmetry relations of the body play a large part in the orientations of animals. In bilaterally symmetrical animals the sense organs are distributed equally on the right and left of the median plant. Loeb argued that symmetrical spots on the body surface of a bilaterally symmetrical animal are chemically identical. Eyes are generally symmetrically arranged, and each contains the same photochemical substances in equal amounts; hence, if two eyes are illuminated equally, the products of photochemical reaction must be the same in each. Not so if they are illuminated unequally. A superimposed head-tail relationship imparts on the animal a more dynamic polarity, however, and this is associated with forward and backward motion. Loeb refused to believe that animals go towards or away from a source of light because they like or dislike it; in his view, the unequal illumination of the two eyes established unequal

tensions in symmetrical muscles of the body, with the result that when the animal moves the unequal pull of such muscles turns the animal automatically till its plane of symmetry is in the direction of the light rays. This is what is meant by a "forced movement". Animals which turn into the light are said to show positive phototaxis, those which turn away from it negative phototaxis. That animals do not seek light because they like it is proved by experiments. A negatively phototropic form such as a blowfly larva can be induced to move from weak to stronger light by conditions which determine that both sides of the body are equally illuminated. The converse is true for some positively phototropic forms.

Loeb's proof of the muscle-tension theory was to some extent based on the fact that when the positively heliotropic water-scorpion (*Ranatra*) is illuminated from one side, the limbs on this side are partially flexed while those of the opposite side are fully extended. Such a difference of muscular tone on the two sides of the body determines the swing of the moving insect's body. This happens also if one eye of an insect is blackened (or covered); the animal shows "circus movements", travelling in a rough circle instead of a straight line. This result has been challenged (by L. B. Clark and others). S. O. Mast (1924) believed that orientation in this case is the result of a series of reflexes specifically related to the location of the stimulus in the eyes. Stimulation of a different region in either eye causes different series of reflexes in which all the legs are involved; light orientation is thus taken to be a complicated response or a series of responses determined by reflexes initiated in a complex sense organ.

Rheotaxis

It is well known that some fishes go upstream to spawn. The salmon moves in this way four to five miles per day at breeding time. Rheotaxis is not confined to fishes, however, but is shown by many invertebrates, and also by spermatozoa. In fishes, such movements may be partly due to visual reactions. A parachutist would be unconscious of the direction of wind unless he happened to note the apparent movement of the ground beneath him. Similarly, a fish may judge the direction of a water-current by noting the apparent movement of the river bank or bed. E. P. Lyon (1904) placed a fish in a bottle of water and towed the sealed bottle in water; whichever way he towed the bottle, the fish turned round and tried to swim the other way. The same biologist noted that blinded fish, or fishes kept in the dark, did not

respond to water-currents unless they lay on the bottom; irregular upward currents such as might be produced by stones on the river-bed may become evident to a fish because of the tilting of its position in space.

R. S. A. Beauchamp (1933) devised a special rheostatic trough in which a current of water could be caused to flow, to stop, and to flow in the opposite direction; using this device he demonstrated positive rheotaxis in the turbellarian *Planaria alpina*, though not in all his experimental animals. Starved and nearly mature individuals displayed negative rheotaxis. This fact he applied to the natural movements of the animal. In streams, a whole population of *Planaria* moves against the water-current as development occurs. Upstream overcrowding leads to a shortage of food, and individuals which are not quite sexually mature move downstream. If such individuals find food, the gonads mature, and migration upstream takes place once more. Temperature and the presence or lack of food are most important factors controlling sexual developments, and they determine the movements of the animal up or down stream.

Kühn's Classification of Tropistic Responses

According to A. Kühn (1919) animals may reach a destination without being oriented. Such undirected reactions are termed "kineses"; there is no orientation of the body axis in relation to a stimulus. This can happen in two ways: some stimuli have a "kinetic" effect causing the animal to move at random till it enters by chance a region where the stimuli are lacking, and there it stops; or an animal moving at random meets adverse stimuli, displays an avoiding reaction, moves again at random and continues this trial-and-error response, or "phobotaxis". The responses in which the animal is oriented ("directed reactions") also fall into two groups; "tropotaxis" is the term used to denote the instances cited by Loeb to illustrate the muscle-tension theory; "telotaxis" is the term used to denote all those responses in which the animal "fixates" one source of stimuli with its sense organs, and orients in relation to it, disregarding other sources of stimuli. All these types of orientation can be brought about through the agency of various sense organs; thus, responses to light may be kinetic, phobotaxes, tropotaxes, etc., and to smell chemophobotaxes or chemotropotaxes. An example of a photokinetic response is the behaviour of the Hydrozoan *Gonionemus murbachi*, which collects in the shaded region of an illuminated tank because of decreased activity.

Euglena viridis displays phobotaxis; it collects in the lighted regions of an aquarium, because of avoiding reactions displayed when it happens to enter a shaded region. This holds good also for various negatively phototropic Protozoa and Metazoa, and also *Bacterium photometricum*: such different organisms all display shock reactions when entering the lighted regions of an aquarium. True topotaxis is shown by many copepods in the sea, and by the larvae of crabs and some polychaete worms (see G. M. Spooner, 1933).

Co-ordinated Behaviour

It has often been argued that in experiments on orientation the animal is subjected to only one type of stimulus at a time, whereas in the wild the animal is exposed to a great variety of stimuli, which vie with one another in the production of a response. The "Gestalt" school (of which E. S. Russell is a notable exponent) claims that the organism responds to changes in the whole pattern of stimuli, and that reliable results cannot possibly accrue if only single stimuli are employed. Others hold, however, that the study of behaviour is analytic, and that an animal's behaviour can be resolved into a succession of orientations. In nature simple responses are often shown. Newly hatched *Lymantria* larvae displays positive phototaxis and negative geotaxis, and the orientated larva comes easily to the leaves on which it regularly feeds. Phototaxis is the stronger response, however, and if in experiments light is thrown upwards from below, the larva moves down the plant, fails to obtain food and dies of starvation. Many insects show rather more complex "light-compass" movements. Orientation is at an angle to the source of light, so that one side of the body is the more strongly illuminated. This was first observed in ants, which move in the wild along a straight course by maintaining a constant angle to the sun's rays. If the insect be allowed to move for some time, is then imprisoned for a period, and finally released, its subsequent path is inclined to the primary path by an angle which can easily be shown to equal the angle of apparent movement of the sun during the period of imprisonment. Such phenomena are known in many insects.

The term "menotaxis" has been used to denote orientation to somewhat complex patterns of stimuli, and the basis of the response is the maintenance of a constant visual pattern. If the insect is placed on a turntable it moves round as the table rotates, continuously facing conspicuous objects. Aquatic forms will swim round inside a rotating glass vessel having vertical stripes, keeping in line with a particular

stripe. Still more complex types of behaviour are seen in insects which forage at a distance from their nests. The ant utilises many factors in the environment, and its responses are compounded of light-compass movements, the odour of trails, topochemical scents, the tactile sense and the proprioceptive sense, fatigue also playing some part. Such insects have been a rich source of experimental results. Bees also use many factors, but the sun's rays are of considerable importance. Over familiar ground, however, bees use landmarks, and seem to memorise the angles through which the body is turned at some points during flight. Bees can be induced to follow artificial landmarks and they have been the subjects of many researches. They seem to have some appreciation of time, and they can be trained to come and get food at any hour of the day, and even to come at certain times for larger amounts of sugary substances. By some biologists they have been credited with "memory", at any rate for short periods of up to twenty-four hours, which may be correlated with the way in which some plants proffer nectar or pollen at particular times of the day.

Chain-like Patterns of Behaviour

The behaviour of some animals seems to be made up of a sequence of actions each of which leads on to another, and this to others, till a chain-like pattern is completed. A hydra makes looping movements along the stem of some water-plant which seem to originate spontaneously in the general behaviour of the animal. The tropical, swamp-dwelling oligochaete worm *Aulophorus* builds itself a tube from the spores of water-ferns in an interesting way. The worm extends its body in front till it is able to grasp a spore, which is then coated with a sticky substance and deposited on top of others in the partially built tube as the worm retracts its body, behaviour which is continued till the tube is complete.

Some solitary wasps select a site for a nest, then excavate a hole and finally carry out an even more complex chain of reactions. The wasp sets out in quest of caterpillars, which are stung into a state of paralysis, dragged back to the nest and thrown into it. Finally, the wasp lays an egg on top of the food and fills in the nest. Such behaviour continues, oft-repeated, to the end of the reproductive period. Birds also display elaborate chain reactions when sexually mature. A couple will choose a site for the nest, embark on a complicated courtship, perform the sexual act, build the nest, incubate the eggs and rear the young, making innumerable journeys from the nest in order to obtain food and bring

it back. Some fishes make extensive spawning migrations; before the eel sets out on its long journey into the Atlantic it undergoes structural and functional modifications in keeping with future life in the depths of ocean—enlargement of the eyes, silvering of the skin and internal changes of a physiological nature. We can hardly credit wasp or bird or fish with an awareness of the ultimate ends to be gained by their chain-like patterns of behaviour, but they all express the urge to follow characteristic lines of conduct and every link in the chain of reactions leads inevitably to the next.

The "Gestalt" Theory; "Holistic Behaviour"

Some opponents of mechanistic biology, or causal-analysis, object to tropistic interpretations of animal behaviour because they seem to suggest that an individual animal does nothing of its own accord in the sense that human beings do. It is true that many of the more complex reactions of animals cannot in the present state of our knowledge be explained in terms so far discussed, and much can be learned by studying animals in the field. E. S. Russell is the author of several delightful and instructive books and an advocate of this method, preferring to regard behaviour as the response of the organism as a whole—the outlook of the "Gestalt" school. Animals are regarded as superior to living machines whose actions and perceptions are fully explicable in physiological terms. E. S. Russell (1930) has described his point of view as "organismal" or "holistic", and he approaches the study of animal behaviour by asking himself such questions as "what is the animal doing, or trying to do?" and "how does its behaviour develop through maturation and experience?" The aim is to ascertain whether or not an animal's behaviour is modifiable or adaptable. Every animal lives in a perceptual world of its own, and this is simpler than our own and has different focal points of interest. Some critics might be disinclined to agree, for it is difficult to gain any insight into the possible perceptual world of an amoeba or a flatworm, but the holistic approach has much to commend it in regard to the more highly organised animals, and some of Russell's points are here noted gratefully.

Behaviour and Ecology

Most marine animals live in situations (habitats) that can be defined by the kind of substratum, the depth of water and other factors in the environment; in short, in what is called a precise ecological "niche".

Shore-living forms segregate themselves in definite zones, and it is pertinent to inquire how they find their ecological niche at the end of larval life in the plankton, as well as how they find their way back to it if inadvertently dislodged from it. Chance may play a large part in the settling-down of some shore animals. By a hit-or-miss method, some molluscan larvae (periwinkles and such-like) may find the zone proper to them, but many fall in unsuitable places and die. The larvae of the American oyster tend to float in rising flood tides and to sink when the tide ebbs, thus being carried into estuaries and settling there; salinity differences and water-currents are thus involved in the processes of dispersal and spat-fall.

Some larval polychaete worms seem to choose the situations in which they will settle down, metamorphosis being conditioned by a particular kind of substratum. According to D. P. Wilson (1932) *Owenia fusiformis* will not metamorphose in a glass vessel devoid of sediment, or in a dish containing fine mud; but if suitable fine sand like that which shelters its parents is available the young worm proceeds with its metamorphosis. Chemical factors can hardly be held responsible in this instance, as in the case of earthworms that refuse to burrow into damp sawdust unless decaying organic matter is added to it. Russell's suggestion is that such phenomena are due not so much to tropistic behaviour as to an attempt on the part of the animal to reach or get back to a normal environment; the various taxes or other responses involved seem meaningless apart from the end achieved by the whole activity. Animals spend much of their lives in winning a livelihood from a hostile environment and ensuring their own preservation. But the animal is not necessarily conscious of working towards self-preservation; its behaviour stands at a level such that action follows close on perception. It has needs to satisfy, and it sets to work on their satisfaction in order to maintain itself. Many of the maintenance activities of animals are associated with the finding of food and the avoidance of enemies. The medusa *Gonionemus* "angles" for food with a fringe of tentacles in what seems to be a purposeful way, rejecting useless particles accidentally acquired. Some larger dragonflies hunt only on the wing, requiring a "sign-stimulus" from their normal prey, and many vertebrates, from fishes to frogs and toads, and various cats, similarly take their prey only when it is in motion. One of the most formidable means of defence in the animal world is remaining perfectly still! Escape calls for swift action, however, and entails the use of every kind of receptor and effector.

Instinctive Behaviour

This type of behaviour consists of a sequence of actions that do not need to be learned, but follow an inherited pattern. It is therefore in contrast with the adaptive or intelligent behaviour of mammals such as rats, monkeys and apes, which modify their reactions according to experience. Instinctive behaviour gives an observer the impression of clever action, but this is generally as stereotyped and specialised as it is automatic. An animal may perform the most intricate tasks automatically, but when confronted with a novel situation it may behave with incredible stupidity. Fabre linked up the two ends of a column of caterpillars that normally walk in single file on pine-trees, with the result that they paraded round the lip of a vase for a whole week! Certain dung-beetles spend much time rolling a ball of dung of their own shaping to some convenient burial-place, and they reject a ready-made ball unless this is proferred to them in exchange for the one they are moving: they are unable to break the sequence of chain reactions at one point and start again anywhere except at the beginning. Instinctive behaviour is orderly but inflexible, or not very flexible. The instinctive animal is nonplussed by novel circumstances, and even birds —which display some intelligence—may make no attempt to feed their nestlings when these do not display the normal reflex of opening the mouth, and they may take no steps to assist the fledgeling that falls out of the nest but is easily retrievable.

Conditioned Behaviour

Some animals which act instinctively for the most part can learn by experience and modify their behaviour accordingly. If an earthworm is placed in a T-shaped tube so that it must move up the long arm, it will turn as often to the left as to the right. If electrodes are so arranged that on entering the left arm the worm receives a mild electric shock, it soon learns (after about twelve trials) to turn to the right arm, and it will continue to do so after the electrodes have been removed. If the electrodes are then moved to the right arm, the worm may similarly be trained to alter its choice, but more trials will be necessary because there is the difficulty of breaking the first formed habit (R. M. Yerkes, 1912; L. Heck, 1919–20). Learning in such animals does not depend on stimuli having an unpleasant effect on the animal. The ragworm (*Nereis*) will live in an open tube immersed in sea-water, coming to one end of the tube for food. If the worm is kept in dim light, but given food in bright light, the worm soon learns to come to the end of the

tube in response to the light alone; it has learned to associate food with light, or has become "conditioned" to light (M. Copeland, 1930). The classical experiments of this kind were those of I. P. Pavlov on the dog. The experiments of O. W. Bull using various fishes and of many other biologists using other animals have clearly indicated the value of such conditioning in animal behaviour generally. Even human behaviour is largely built up of conditioned responses. The human infant at birth shows fear responses to loud noises, but not to darkness, though it may be accidentally conditioned to fear the dark by the association of loud noises with darkness. The only other fear responses of the newly born human infant are evoked by tending to fall and by hurtful stimuli acting through the sense organs of the skin. Later developed fears are therefore "conditioned".

Intelligent Behaviour

This type of behaviour is the result of a power to learn by experience and to profit by the solving of unusual problems of life. It is often built on a foundation of instinctive reactions. Of all animals whose instincts are modified by learning as they grow up, mammals are by far the most teachable. Kittens hunt moving objects and kill mice without any preliminary training, but they can easily be brought up on friendly terms with rats and mice by learning which overrides their instincts. Apes and monkeys are just as adaptable as kittens, and the chimpanzee is of all animals the one best equipped to profit by "insight", for it is able to see the solution of a problem when this can only be achieved by roundabout methods. W. Köhler (1927) tested the capacity of the chimpanzee to learn by devising simple problems that could not be worked out in a straighforward way because of obstacles of some kind. To the chimpanzee a bunch of bananas just beyond reach outside the cage and a stick left apparently carelessly inside the cage soon acquire related significance, and the animal quickly learns to reach the food and draw it through the bars of the cage with the stick. Once having learned the trick, the animal will try to use all sorts of objects—bits of straw or wire, or even a blanket—in lieu of a stick. When fruit is suspended from the ceiling of the cage out of reach, the animal soon learns to fit together two pieces of bamboo rod, and even to gnaw the end of one piece so that it fits snugly into the other, and to use the lengthened rod to knock down the fruit. It will also learn quickly to pile boxes to form a means of getting at the fruit. Often the solution of a problem becomes apparent to the animal suddenly, thus indicating

some power to reason and to profit by past experiences of both success and failure. According to the Gestalt theory the elements of behaviour are not distinct and separate events, but are inseparable from whole behaviour, just as the pattern of stimulation by light and shade of innumerable rods and cones in the human retina is inseparable from the whole image formed. Confronted with a situation comprising a number of stimulating elements the animal may focus its attention on those most closely related to its immediate needs, ignoring others till fresh needs arise. In our own perceptual world we are inclined to regard many things with unseeing eyes, and to turn a deaf ear to many sounds, unless experience prompts us to give them significance and attention. So it is with many animals also, for each of these lives in a world of its own and one that is appropriate to its zoological status and grade of experience.

CHAPTER FOURTEEN

EVOLUTION

THE concept of organic evolution is not a theory but a fact. The publication of Darwin's *The Origin of Species* was followed by a period during which the proofs of evolution steadily arose out of studies in palaeontology, comparative anatomy, embryology, taxonomy, physiology and geographic distribution.

THE EVIDENCES OF ORGANIC EVOLUTION

Palaeontology

That conditions favourable to living organisms have prevailed on earth for many millions of years is proved by the study of fossil-bearing rocks. The sedimentary series—which consist of the compounded fragments of older volcanic and plutonic rocks—contain the hard remains, shells and bones, for the most part, of many generations of animals and plants. These fell to the bottom of seas, lakes and swamps, mingled with silt and were incorporated into various strata, often crushed and defaced, but sometimes undergoing molecular replacement with lime or silica and preserved without alteration of shape or structure. [For an interesting account of processes of fossilisation see the article by G. Thomas (1950)]. As the strata were formed during successive periods of the earth's history, characteristic groups of fossils were laid down during various periods of sedimentation. Biology owes much to the early pioneers who were interested in such remains—to Nicolaus Steno and Martin Lister of the seventeenth century, to Scheuchzer, Baron Cuvier and William Smith during the eighteenth and early nineteenth centuries, and to those who followed—W. Phillips, Conybeare, Sedgewick, W. Buckland, de la Beche, Fitton, Mantell, Webster, Lonsdale, Murchison, J. Phillips and others. The publication of Charles Lyell's *Principles of Geology* (1830–33) destroyed the catastrophic theories of the earth's history and prepared the way for the theory of organic evolution. Once the theory had been established the proofs of its validity were produced by men such as E. D. Cope and O. C. Marsh, who established whole orders of fossil forms, H. F.

Osborne and his colleagues, who described nearly 300 species of ancestral or near-ancestral horses, and Stensiö, who elucidated the relationship between the early jawless vertebrates, or Ostracodermi, and the existing lampreys and hag-fishes (Cyclostomata).

The study of fossils soon showed that organisms have multiplied abundantly in the past, both numerically and in the numbers of their species. The oldest sedimentary rocks (Cambrian) contain few fossils, mainly the remains of trilobites, graptolites, brachiopods and other invertebrates. The absence of vertebrate fossils from such rocks can have one meaning only—vertebrates did not exist when these rocks were formed. These animals appeared for the first time in Silurian rocks, the earliest of them being shark-like forms and Ostracoderms. The remains of vertebrates other than fishes are not found in Silurian rocks, for they had not yet come into existence. The Devonian rocks contain abundant remains of bony fishes that lived in coastal waters; the Osteolepids moved from pool to pool in shallow sea-water lagoons that tended to dry up periodically, and the evidence of their skull structure shows them to have been the ancestors of the Amphibia (D. M. S. Watson, 1926). Mixed with such remains are the remains of various invertebrates, for spiders and insects had already conquered the land and the air respectively. Indubitable amphibian remains first appear in the Carboniferous rocks; most of the early Amphibia were heavily armoured Labrinthodonts, and some of these gave rise during the Permian to reptiles that flourished during the Triassic, Jurassic and Cretaceous epochs of the Mesozoic era. The viviparous fish lizards (Ichthyosaurs) hunted schools of fishes and were hunted in turn by the long-necked Plesiosaurs which outmanœuvred them as swimmers. The true land reptiles (Dinosaurs) were already diverse in habits, rather like mammals to-day, and at least two races of carnivorous crocodile-like forms ran separate, almost parallel courses in evolution. Flying dragons (Pterodactyls) appeared also during the Mesozoic era, arising in all probability from the same ancestors as birds, but along a different line. The earliest bird-like vertebrate was *Archaeopteryx*, which left its remains in the Upper Jurassic rocks of Bavaria. About as large as a crow and a good flier, it was still a flying reptile, having teeth lodged in sockets in both jaws, three clawed fingers not yet merged into a proper wing, an ill-developed breastbone, and a long tail with steering feathers set in its lateral edges.

We do not know how the enormous Mesozoic reptiles came to be extinguished, but their downfall was probably brought about by the

predations of some early mammals then appearing. Mammals originated in the Triassic epoch, and their warm-bloodedness and superior brains gave them immediate advantages over the reptiles from which they arose. They were small, bloodthirsty creatures, and some of them undermined specialised reptilian stocks by preying on their eggs. Well endowed from the start, the mammals soon branched out into the three main lines—monotremes, marsupials and eutherians—and in that order. Monotremes did not go far but they are still represented by the platypus and the echidna. Marsupials became numerous and diverse but they succeeded mainly in Australia in the absence of competitors. Early eutherian mammals, no larger than a rat, could deal with various kinds of food, and they soon became recognisable as Insectivora, Rodentia and members of other orders. From small and primitive mammals hosts of more specialised forms gradually arose, and the dog-like Creodonts gave rise to the ancestors of modern Carnivora, the totally different Condylarthra and Amblypods to the Ungulata.

Many gaps appear in the fossil record, but in spite of them we can recognise certain sequences of animals that arose during the course of evolution. The first amphibians arose from fishes, the earliest reptiles from Amphibia, and both the first birds and the first mammals from Reptilia. The sequence fishes, amphibians, reptiles, birds and mammals was a succession in time and also a series of trends in evolution. Man appeared comparatively late during the story of evolution, for the Primate stock arose from arboreal insectivorous mammals only about sixty million years ago. Before man had his opportunity to populate the earth many other mammals had already run their evolutionary course, the fossil record providing very convincing and now familiar evidence concerning the evolution of horses, elephants and camels (see R. S. Lull, 1936).

Many efforts have been made to estimate the ages of various geological eras and epochs, always with considerable difficulty. During the past twenty years, however, the method of measuring geological time by means of radioactive lead has come into use, and this refinement has called for twenty-fold increases of older estimates (see A. Knopf, 1949). The age of the earth is now generally accepted to be at least two thousand million years, for the oldest minerals are of about this age. B. B. Boltwood (1907), who first proposed this method of determination, based his conclusions on the amount of lead generated in radioactive minerals by atomic disintegration. More recently it

has been disclosed that most radioactive minerals contain three radioactive elements—U^{238}, U^{235} and thorium—all of which produce lead of different atomic weights at different rates. From one mineral sample, therefore, three determinations can be made, one serving as a check to the others. Modern estimates allow about 1,500 million years for Pre-Cambrian history, about 300 million for the Palaeozoic Age, about 130 million for the Meozoic, and about 70 million for the Caenozoic. The Tertiary estimates are made up of about 20 million for the Eocene, 11 million for the Oligocene, 17 million for the Miocene, 11 million for the Pliocene and about 1 million for the Pleistocene. For the checking of such estimates there is no objective evidence available; the task of checking, according to Knopf, has yet to be carried out.

Taxonomy and Comparative Anatomy

The basis of the classification of animals, as has been stated, is the best attempt we can make to construct a genealogy of animal life out of the resemblance and differences between animals. Convergence and divergence may hinder our efforts, but we can generally put them in their proper place. Comparative anatomy is concerned with numerous interrelated characters of animals, and when we refer to the similarity between the arms or legs of an ape and man we take into consideration not merely superficial characters but also the similar arrangements of all the bones and muscles, blood vessels and nerves, and other tissues that go to make up the limb. When we extend the comparison to include the limbs of dogs, sheep, horses, frogs, newts and such-like the general resemblance is there, but we are perhaps more concerned with the differences, and we find that they occur about a mean type of structure, embodied in the concept of the typical pentadactyl limb. Coincidence might explain superficial resemblance between the limbs of various vertebrates, but it cannot be held to account for the general patterns of complicated parts that run through the entire series.

We need not stop at the limbs. Notable similarities exist in the structure of the skull and backbone, the brain and nerves, the heart and blood vessels, the kidneys and their ducts, and other systems of complicated organs and parts. Numerous characters of vertebrates fit together into a fundamental plan of structure that indicates bonds of affinity, and it is incredible that they could have arisen independently in such precise combinations. And we need not stop at vertebrates. Greater degrees of contrast come into focus when we compare these

with invertebrates, but many organs of similar general pattern are common to both these large divisions of the animal kingdom. More variable patterns of structure imply more attenuated bonds of affinity, not lack of affinity. The relationship between all living animals cannot be denied, because it is based on many characters that could not have arisen in such formidable conjunctions fortuitously. Comparative anatomy is the study of structural evidences of evolution.

Embryology

During the course of its development an animal passes through a sequence of stages during which the various organs arise as microscopic rudiments and then enlarge and alter into the definitive form and structure. The fanciful idea of *emboîtement*, according to which an egg contains a miniature model of the adult, was long ago discarded as ludicrous. Development entails epigenesis, not preformation, and one striking feature about it is the close resemblance between the early stages of related forms, and particularly the resemblance between the young stages of some animals and later stages or the adult state of others. To account for this fact, Haeckel made his generalisation that ontogeny recapitulates phylogeny. K. E. von Baer was more guarded in his generalising, stating merely that the embryos of all vertebrates are so much alike as to be indistinguishable. It soon became apparent that many embryonic stages could not possibly represent ancestral animals, for some organs disappear long before the adult stage is reached and can be regarded as embryonic additions to the original ancestral type. We are now familiar with numerous embryonic and larval adaptations (*caenogenetic characters*) that tend to falsify the ancestral record, notably the placenta and embryonic membranes of the amniote vertebrates (see G. R. de Beer, 1940).

In a different category are *palingenetic* characters such as the visceral clefts that arise during the development of reptiles, birds and mammals—animals that never breathe by means of gills. These are transitory structures, marking a stage of development now almost lost, but they are common to numerous vertebrates and they strengthen rather than weaken the doctrine of evolution. Many vestigial structures belong to this category, the rudiments of teeth that arise in the foetal baleen whale or the duck-billed platypus, the lanugo or fine hairs on the human foetus and the third or pineal eye of vertebrates. Perhaps the most remarkable vestiges are the tiny wings under which the kiwi is reputed to endeavour to tuck its head when roosting, circumstantial

evidence at any rate that this vestige was once a wing and indicating the evolutionary truth to the sceptic.

Physiology

Many physiological and structural characters of animals run parallel with one another, though some of the former are not obviously related to morphology. The tissue liquids of many different animals are remarkably similar in chemical composition and not fundamentally different from the sea-water which is the mother-of-all-media. Regulation of the concentration of ions and salts in these tissues depends on the rates of ionic penetration, and similarity of chemical composition thus implies some fundamental agreement in structure between the membranes of cells in different organisms. The blood of animals also provides evidence in support of evolution, notably differences between the red pigments (haemoglobins) which may be arranged in series that parallel the taxonomic arrangement of species and genera. The precipitin reactions of blood serum also show parallel arrangement with the phylogenetic series; there is less difference between these reactions in man and the anthropoid apes than in apes and monkeys (or primates as a whole) and other animals. The blood sera of mammals show even greater differences from those of other vertebrates.

Hormones generally produce characteristic effects, but they are not specific in their action. The thyroid of an ox can be used to make good the deficiency of thyroxine in some human beings, or in the tadpole of a frog. The endocrines have a common mode of origin in vertebrates, but the resemblance goes further than this in those instances where a vertebrate hormone will produce its characteristic effect in an invertebrate—for instance, where pituitrin from an ox will darken the skin colour of shrimps and prawns. Neurocrines also exert a common effect and further illustrate the truth of evolution. Similarly digestive enzymes, which are strikingly specific in their chemical action on the food of all animals, whether amoeba or men. Physiological mechanisms in general show that the structural plan according to which the body of an animal is built is not merely a set of architectural elements, but chemical entities with relatives ranging throughout the animal kingdom.

Geographical Distribution

Various writers (J. A. Thomson, 1899; H. Gadow, 1909, and others) have discussed the work of early pioneers who studied the distribution of animals and plants long before Darwin appeared on

the scene. The older naturalists collected specimens on a large scale and some facts of distribution inevitably emerged. To discover organisms in unexplored territories, however, is one thing; to explain the anomalies of their distribution quite another. Without the concept of organic evolution to serve as a guide little progress was made, so that, just before *The Origin of Species* appeared, Semper referred to zoogeography as "nothing more than a great mass of material thrown together without thought". A. Wagner (1844–46) divided the earth's surface into circumpolar zones in relation to the distribution of mammals. A little later (1845–54) L. Agassiz worked on the same lines, likewise E. Forbes and J. D. Dana, who mainly studied molluscs and crustaceans respectively. In 1858 P. L. Sclater published his scheme dealing with the distribution of birds, and in 1866 A. Murray's scheme for animals appeared. This gave the lead to others by seeking the clue to present distribution in past earth history. In 1868 T. H. Huxley divided the earth's surface into two main divisions transversely: the North World (Arctogæa) included Sclater's Indian, African, Old World (Palaearctic) and New World (Nearctic) regions; the South World (Notogæa) included Austro-Columbia (the neotropical region) and also Australasia and New Zealand. The great work of A. R. Wallace was published in 1876, since when there have been many studies of the distribution of special groups of organisms and the collections of many expeditions. In regard to animals, existing schemes divide the earth into six great regions: the Nearctic and Neotropical in the New World, and the Palaearctic, Ethiopean, Oriental and Australasian in the Old World. Each of these regions has its own more or less characteristic fauna (see M. I. Newbigin, 1936).

Geological changes during the past epochs of the earth's history have restricted considerably the distribution of certain species of animals, notably in those instances where peninsulas have been converted into islands. A few miles of sea may be an effective barrier to the migration of land animals. The early marsupials migrated into Australia when this continent was connected to Asia by a land bridge, becoming isolated when this bridge was broken. On the mainland of Asia and elsewhere marsupials fell in competition with the eutherian mammals, but in isolation these animals were not only able to survive, but were able to radiate to yield a number of highly specialised forms paralleling eutherian cats, dogs, wolves, rats, bats, and many other types.

Zoologists have asked many questions regarding the peculiarities

of geographical distribution. Why are the faunae of comparable regions of the earth—Japan and Britain, for instance, or the tropical rain forests of Africa and South America—so different from one another? Why do polar bears exist only in the Arctic, penguins only in the Antarctic, and why are island faunas so different from one another? What is the explanation of the marked difference between the animals found in Africa north and south of the Sahara? How can we explain the discontinuous distribution of animals such as the lung-fishes or elephants? Why are edentates and humming-birds restricted to South America; lemurs to India, North Africa and Madagascar; and the bison to North America? Why is the distribution of genera generally broader than that of species, or that of families wider than that of orders? Why is there any need to recognise the various zoogeographical regions at all? The answer is to be found in the populating of the world by descendants of animals of long ago and the migrations of animals from one place to another, undergoing modification as they moved, certainly not that all the various species were independently created and placed where we now find them. The evidence from palaeontology supports such ideas, for the ancestors of marsupials, lemurine types, elephants and many other animals were much more widely distributed over the earth long ago than are their descendants to-day. As living animals evolved, the earth suffered many changes—seas have cut off some land masses and engulfed others, mountain ranges have been thrown up, treeless plains and deserts have arisen and some regions of the earth have become localities of tropical heat or polar cold. No locality has long persisted in the state in which we find it to-day, and most localities have suffered change time and time again. All these changes have tended to provide obstacles to the movements of animals in certain directions, but have actually prompted them in others (see H. Gadow, 1913). Taken in conjunction with other kinds of evidence, the geographical distribution of animals clearly shows that evolution has assuredly taken place and, moreover, has provided a far more exciting spectacle than one or even a number of separate acts of creation ever could have provided.

THE MECHANISM OF ORGANIC EVOLUTION

The Struggle for Existence

The teeming abundance of living things in all sorts of situations is a most impressive biological fact. Life is frequently renewed in the sea,

on land and in the air. Two parents of some species of animals may produce a swarm of young, and sometimes only one parent is needed to give rise to a brood, or clone. Instances of great fecundity have been given already. The herring lays fifty thousand eggs in one season, though to perpetuate the species only two individuals are required to take the place of the parents when they die. In spite of such productivity, populations rarely increase significantly and, in spite of periodic fluctuations, they may indeed remain surprisingly constant. Nature puts a low premium on life, and the odds against survival may in some instances be several millions to one. Impressed by such considerations as these, Darwin was led to deduce the fact of a "struggle for existence", which he applied not only to the life of the individual, but also to "success in leaving progeny". Most animals tend to increase their numbers geometrically, but limitations of space, food and shelter hold most animal populations in check. The more prolific the animal, the greater is the mortality amongst its young in order to preserve the balance of nature.

Animal stocks may be thinned out accidentally. Some thousands of copepods die every time a baleen whale takes in a mouthful of water, and no matter how perfectly these crustaceans may be adapted to planktonic life the coincidence of the whale's coming determines their fate. Apart from such accidents, and in general, the offspring of two parents differ in certain characters and even slight variations may make all the difference between survival and extinction in a competitive struggle for existence. Many animals must die, but those "fittest" to survive under the prevailing conditions of life will be favoured by natural selection. This so-called Darwinian factor determines what variations shall be conserved and what eliminated from individual and racial characters by extinction. Individuals will survive or not according to the degree of harmony or disharmony between each one of them and its environment. The elimination by natural selection of unsuccessful competitors in the struggle for existence is a fundamental factor in evolution.

There are several aspects of this "struggle". An organism may live in strenuous competition with its own kind, as house mice compete for scraps of food in some cellar. This "intraspecific" struggle may in crowded communities be more intense than the "interspecific" struggle—*i.e.* that between unrelated forms such as cats and mice—and more significant than that against adverse conditions in the external world. The threat of extinction does not come from one factor alone,

or one set of factors, however; animals have to cope with predators, parasites, drought, floods, extremes of heat and cold and natural calamities such as earthquakes and hurricanes. Mankind is not absolved from any of the three aspects of the struggle for existence, for war is intraspecific, the fight against organic disease is interspecific, and famine is a threat from the environment. In human affairs it has often been said that the "fittest" to survive is the first to fall, but taking the broadest view of nature the converse is generally true.

Variation

This term denotes the means whereby an organism comes to differ from its parents, but it has also come to mean the actual structural, physiological, or psychological difference or differences involved. For many years it was customary to classify variations according to their apparent nature, and also the methods used in analysis. "Meristic" variations are differences in the number of repetitive parts—for instance, thirteen pairs of ribs in man instead of the normal twelve; "substantive" variations concern structure or size, including such characters as height and weight in man, and the colour of his eyes; and "physiological" variations concern function—for instance, the egg-laying capacity of fowls and the milk-producing capacity of cattle. Variations may also be "congenital" or "acquired" during the lifetime of the animal; the former are a part of the inheritance and must be handed on, while the latter are not known to be transmitted. The existence of an extra digit in the hand or foot is a congenital variation; the hypertrophy of one kidney when the other has been excised is an acquired variation, or modification. To distinguish between the two kinds of variation may be impossible unless breeding experiments can be carried out, and sometimes it is difficult even then.

Both germinal and acquired variations may be "indeterminate" or "determinate", terms which imply that changes do not tend or tend to accumulate along definite lines. Acquired variations of both types are common, but determinate germinal variations are rare, though they are the mainstay of one theory of evolution, namely orthogenesis. Variations have also been classified as "continuous" or "discontinuous"; the former are slight changes having a directional trend, the latter more considerable changes, or mutations, in any direction. Most variations are independent of the inheritance, but they may in one sense affect the next generation. Embryos crowded in the uterus of a

rat compete for nutrients located in the mother's blood, and some may fare better than others, become larger and stronger by the time they are born and more fitted to survive. Mutations are brought about by some change in the protoplasm of the germ-cells, notably to genic alteration. Because they are generally recessive in the inheritance, mutations are more frequently expressed in the rare homozygous condition than in the commoner heterozygous conditions, and hence they come under the influence of natural selection less frequently. Mutations expressed as dominants may give rise to favourable or unfavourable characters which are either conserved or repressed by natural selection. Partially recessive mutant genes may produce differential effects in the heterozygous condition, and the advantageous or disadvantageous nature of these will decide whether they are conserved or not. Mutational effects may be modified by factors in the environment but not suppressed by them, for they are the outcome of particulate inheritance; like modifications they indicate that the developing organism is affected by the interplay of two sets of conditions, one germinal and the other environmental. Interference with either of the sets of conditions may modify development, but if any evolutionary effect is to be achieved variations must be heritable. New species of organisms often display inherited variations of a mutational character. Mutations and recombinations of genes produce characters that come under the influence of natural selection and provide what J. S. Huxley (1942) referred to as the "raw materials of evolution".

The fossil record contains many examples of evolution by gradual change in a particular direction. This process of orthogenesis has been conspicuous in some phyla of animals (molluscs, brachiopods, echinoderms and vertebrates). Orthogenetic trends have been disclosed in primitive amphibians (Labrinthodonts) by D. M. S. Watson (1926), in horses by W. D. Matthew (1926) and R. A. Stirton (1940), and in the large, hooved mammals known as Titanotheres and in elephants by H. F. Osborne (1929, 1936). Huxley has remarked that the phyla in which orthogenetic evolution has been observed are important, but they do not constitute the entire animal kingdom. Other facts gleaned from ecology and comparative physiology lead us to suppose that evolution has proceeded by hosts of adaptations whose origin provides the key to the problem, and in some instances this is true, though many exist in which it is not. The truth of the matter seems to lie in the fact that the origin of species has come about not in one way but in many ways.

Some Trends in Evolution

Some species of animals consist of numerous individuals widely dispersed in large areas, others of relatively few individuals thinly scattered in small groups that tend to become isolated in specific regions. It has been argued that there is generally variety in numbers, and that species having many widespread individuals provide a greater aggregate of inheritable variations than is found in species with few individuals, and this increases the tendency to differentiate into subspecies (species-in-the-making), though slight migrations may facilitate interbreeding and the mingling of hereditary units between these groups and thus tend to eradicate them. In different localities various adaptations will tend to arise and mask the taxonomic differentiation, but intraspecific competition will be relatively acute and it may give rise to novel evolutionary achievements. Rarefied species will tend to split into distinct subspecies and then new species, within which there will be little competition. The origin and nature of species may therefore be affected by numerical and geographical factors.

In other instances evolution seems to have come about by means of long-sustained trends towards specialisation, sometimes of that kind which is called "degeneration"—intense simplification by pruning parts unnecessary to a simplified mode of life. Long-sustained trends in different directions have produced many instances of divergent evolution, but minor changes have occurred as parts of a larger trend, or to form the bases of a number of distinct groups that have arisen out of a single species. Minor systematic changes are heterogeneous. Oceanic islands and other isolated situations in which only a few animals have come to live have given relief from competition, which has resulted in radiant evolution into many highly distinctive species with rather trivial characters that would not have been conserved in intensive competition. Evolution has not been a standardised process; differences in the mode of life, environmental conditions and the hereditary mechanism have produced various agents of evolution that can work alone or jointly to produce new species of animals.

Adaptation

Many differences between animals can be related to special modes of life. The wings of birds, bats and insects promote aerial life, the streamlined shape of many fishes facilitates swift movement, and the cylindrical form of worms is well suited to burrowing life. The

relationship between the structure and functions of the body and the special conditions and states which constitute the environment is called "adaptation". Because of adaptation, unrelated animals may have certain characters in common, giving the impression of relationship where this does not exist; bats and birds thus show "convergence" in having organs of flight. On the other hand, closely related animals having different modes of life may come to differ so much as to suggest lack of affinity between them; bats and whales are mammals which show "divergence" as a consequence of totally different modes of life. All animals are modified by the circumstances of their lives, and convergence and divergence are the alpha and omega of adaptation. Some adaptations are obviously morphological; others are physiological and sometimes without obvious morphological equivalents. They are often related to physical and chemical conditions in the environment—changes of temperature, humidity and salinity—and to the pursuit and capture of special prey, also to efficient escape from enemies.

The principal types of adaptation were discussed by R. S. Lull (1936), who also gave references to the literature concerning them. So adaptable are animals that few situations on earth are uninhabited by them. Marine animals may drift near the surface of the sea, swim in midwater, walk on the bottom, attach themselves to rocks and weeds, penetrate into crevices, or dig in sand or mud. Oceanic forms tread treacherous oozes in inky darkness, though some of them illumine the darkness by means of special luminescent organs. On land, Arctic cold, tropical heat, deep swamps and arid deserts have not proved too forbidding to some animals. The mammals adopted all sorts of conditions. Some entered fresh water or returned to the sea, a few were content to amble along on the soles of their feet, but many learned to run nimbly on the tips of the toes, some inhabited the trees, others to dig into the ground or hide in caves. These and other modes of life have been associated with so many and such varied adaptations as to defy classification. Adaptations for swimming, walking, running, burrowing, climbing, planing and flying do not complete the list. Some animals are adapted to a parasitic mode of life.

In some schools of biological thought it has been fashionable to condemn the study of adaptation and even to deny that it is a fact. J. S. Huxley (1942) has said that an alleged teleological flavour was supposed to put the study of adaptation beyond the pale of scientific inquiry, and its consideration stood in the way of mechanistic analysis. He also showed that both forms of condemnation were unnecessary. In

his words, the "teleology of adaptation is a pseudoteleology, capable of being accounted for on good mechanistic principles, without the intervention of purpose, conscious or subconscious, either on the part of the organism or of any outside power". To the second objection he merely remarked pungently, "since adaptations are facts, it is the business of biologists to study them". Every biological problem has evolutionary and immediate aspects, a functional meaning as well as a mechanical basis, and both sides call for study.

Physiological Adaptation

What is meant by the term "adaptation" was made clear in the definition of E. J. Allen (1929): "By an adaptation we mean nothing more than a character of an organism which has enabled a species to survive itself as such, or to survive until it is transformed into another species. It is survival that gives the measure of adaptation." This is a simple and precise statement; a character is adaptive so long as it increases the chance of survival, even when it does so under unusual circumstances which the organism could never have been prepared to meet. Proceeding from this definition, C. F. A. Pantin (1930–32) stressed that in considering adaptation we must take the environment carefully into account. Adaptation to conditions that cannot be specified cannot be discussed. In comparing the physiological mechanisms of different animals correlations are often found which do not seem to have any functional explanation—for instance, the presence of certain respiratory pigments in the organs of some invertebrates. In some instances physiological adaptation seems clear. The oxygen-carrying properties of haemoglobins in some fishes which live respectively in stagnant and running water are sometimes very different and markedly correlated with the oxygen content of the surrounding water.

Pantin distinguished carefully between the structures, processes, states and properties of living organisms. The molecules of respiratory pigment are "structures", the changes taking place in metabolism are "processes", the maintenance of a definite ionic concentration of the blood is a "state", and the ranges of pH and temperature which define the limits between which an organism can live are "properties". Structures and properties have, of these things, been most considered. Physiological structures are material things, whether of molecular dimensions or larger; they differ from morphological structure mainly in the matter of size. Such things do not have the plasticity generally

attributed to morphological characters, however, because they are formed of smaller units. Proteins are composed of amino-acids, which are of very limited number, and—according to T. Svedburg (1930)—their molecular weight seems to be some multiple of 34,500, each protein being an aggregate of units each containing about 350 amino-acids, the molecular weight of which is 90–100. An almost infinite gradation of protein structure is possible, but the nature of the molecule is limited because composed of such units. Limitations are evident also in the case of respiratory pigments, substances of unique function. When animals develop such pigments they are usually restricted to one of four kinds of molecules—haemoglobins, chlorocruorins, haemerythrins and haemocyanins. The first three contain iron, the last copper. Such pigments have been independently evolved in distinct animal groups and they are characters of great adaptational significance which could not have emerged gradually, for oxygen-carrying properties emerge only in the complete molecule. Presumably, such structures are evolved by natural selection operating on abrupt variations, or Mendelian mutation. Pantin's main point seems to be that the evolutionary and adaptive significance of physiological processes and of the states they maintain differ from that of molecular or gross morphological structure. Only the latter can evolve and become adapted in the ordinary sense; processes and states exist at any moment only in consequence of structure, and to say that the ionic composition of an animal's blood is adapted to the maintenance of tissue-cells usually means that the surface membranes and excretory organs have undergone adaptation. In consequence, it is not permissible to speak of the adaptive significance of blood composition until sufficient knowledge has been obtained about the "structures" which maintain it.

Adaptations and Selection

Several main kinds of adaptations come under the influence of natural selection. Organisms may be fitted for a new mode of life by having already certain structural and physiological characters which predispose them to survive under the new conditions; because they are "preadapted" to them. Interspecific adaptations may also arise during the normal mode of life as protective devices against enemies, parasites and disease, or new ways of capturing prey and using it as food. The recognition marks and scents in gregarious birds and mammals are intraspecific adaptations of a co-operative or competitive value. Some animals are doubly adapted for a complex mode of life, birds to life in

the air and life on land or in water. Internal adaptations lead to a better functioning of digestive, excretory and reproductive viscera, to greater perfection of nervous action and endocrine co-ordination, and to new functions in an enlarging and more complex body. Like Pantin, J. S. Huxley has stressed the need for caution in assigning adaptive significance to bodily functions, for adaptations are ubiquitous and difficult to overlook but easy to misconstrue. The bright colours of male birds may be regarded as an adaptation for stimulating the female, but may be a warning threat to territorial rivals of either sex.

Adaptive Radiation

We have already commented on the phenomena of convergence and divergence in evolution. Adaptation to similar modes of life may lead in unrelated animals to parallel (convergent) evolution, and, conversely, related animals which migrate into regions where environmental conditions differ may be expected to adapt themselves and show divergent evolution. Osborne (1910) and many others have shown that large groups of related forms have become adapted to various mutually exclusive modes of life and have undergone adaptive radiation. J. S. Huxley cited the placental mammals which from the end of Cretaceous times gave rise to many divergent evolutionary lines. Some of these animals reverted to aquatic life, giving rise to carnivorous whales, porpoises, seals and sea-lions and to the herbivorous sea-cows and manatees. Terrestrial forms radiated into a number of branches represented by the carnivores, rodents, elephants and ungulates, but some took to aerial life and gave rise to bats, and others to arboreal life and gave rise to the primates. Intensely specialised forms also arose, splitting up to form the stocks of armadillos, sloths and ant-eaters, but unspecialised mammals gave rise to the South American edentates. Some lines became over-specialised and were extinguished, notably the carnivorous creodonts and the herbivorous amplypods and titanotheres. Persistent lines often radiated into many subsidiary branches, and bats became differentiated into fructivorous, insectivorous, piscivorous and sanguinivorous forms.

The trends of adaptive radiation can be attributed to the influence of natural selection on progressive variations that proved advantageous to forms developing along certain lines. Selection has the effect of encouraging further variation in particular directions till some limit is reached—for instance, in horses till the digits had been reduced to one. This type of change has been regarded as orthogenetic, but

Huxley has suggested that orthoselection—that form of selection which favours the continuance of an adaptive trend—may produce effects that resemble orthogenesis; such trends are determined less by one-sided germinal change than by factors influencing the functional lives of organisms. The term "orthoselection" was invented by L. Plate (1913), and R. S. Lull (1917, 1929, 1936, 1945) applied it to those instances where modifications had resulted from the elimination by selection of all other kinds of variation, and where the resultant lines of evolution were not predetermined as they are in orthogenesis. As examples of the way in which orthoselection operates, J. S. Huxley cited special features in the evolution of the elephant. First, the muzzle was lengthened and both the upper and lower jaws and the upper and lower tusks were enlarged till a limit was ultimately reached beyond which enlargement could not go without interfering with function. In later evolution, however, the jaws were shortened and the lower tusks were abolished, but the muzzle was lengthened to form the trunk; the same result—a long prehensile organ—was attained by completely different means in different periods of the elephant's evolution. Reversal of evolution in the mechanical sense cannot, it is claimed, be explained by orthogenesis. Positive evidences of orthogenetic evolution do exist, however. Lull cited analogous or parallel variations—modifications of similar characters that exist in both related and unrelated groups of animals—and several other categories of facts. An animal's body is so constituted that changes can occur only in certain directions; limitations are set by the physical, chemical and mechanical nature of the body.

Consequential Evolution

Huxley also showed that certain trends in evolution may be the direct consequence of types of structure and function that are handed on from some ancestor at a much earlier stage of evolution. Salamanders are land animals, but they had a piscine ancestry and their manner of walking bears close resemblance to the swimming movements of a fish, the trunk and tail forming similar undulations. Land forms seem to have made use of mechanisms primarily associated with aquatic locomotion in learning to walk over solid ground. The structure of the body in man and other primates is really conducive to a mode of progression on all-fours, and the adoption of a bipedal gait has tended to upset various internal adjustments related to a creeping mode of life, calling for counter-adjustments. These are

examples of what Huxley called "consequential evolution". The development of sex also had its consequences in evolution, for characters are often sex-linked, but they are sometimes acquired by one sex and transferred to the other, so that selection acting on one sex only may have an indirect effect on the other and may increase specific diversity.

Other trends in evolution cited by Huxley have their basis in differential development. The effect of the crowding on embryos in the uterus of the polytocus mammals has already been mentioned (p. 273). In this instance, a premium is put on rapid early development during foetal life. In monotocus mammals, however, pre-natal competition is abolished and in consequence development and growth can be slower. The relative rate of human development has undergone great reduction, both in pre-natal and post-natal life, and this has provided longer youth and better conditions for learning. What L. Bolk (1926) called "foetalisation"—the persistence of certain embryonic characters in the adult condition as a result of retarded development—is evident in many human characteristics, notably comparative hairlessness and the Mongolian eye-fold or epicanthus. The condition of neoteny—sexual maturity associated with a larval condition of the rest of the body—also seems to be due to a lowering of the rate of development. It is best known in the case of the Mexican axolotl, but is not confined to amphibians, occurring also in some beetles—and probably in man.

The rates of development of embryonic parts are controlled by the action of genes. Rate genes may thus determine the relative rates of growth of organs and parts and therefore the proportions of the body. They also effect reduction in the size of vestigial organs, which are originally of normal size in the embryo but which lose growth intensity as development proceeds. By producing and maintaining even a slight degree of negative allometry rate genes may produce substantial ultimate effects. The full suppression of growth in some organ or part is conceivable as a result of mutation during the phylogeny of a race of animals; an inherited alteration of the mechanism of growth.

Rate genes may also speed up development, so that the life-span of an animal provides time for the addition of new (hypermorphic) characters beyond what would otherwise have been the end of development. If the rate of development is constantly increasing, characters will tend to be compressed in the ontogeny. If, on the other hand, the rate of development is constantly diminishing there will be an anti-recapitulatory instead of a recapitulatory effect, for the life-span will

not permit of the full expression of certain characters as indicated by phylogenetic considerations. Mutations that tend to lower the rate of development may therefore obliterate some of the characters of previous life-histories.

We have already noted that the larvae or embryos of animals may show adaptations which are not projected into adult life. In such instances a study of the adult would not reveal the existence of such "caenogenetic" characters. Even if such characters appeared regularly in the ontogeny, the morphologist who studied only adults would be entirely unaware of their existence. A slowing-down of development, or the establishment of neoteny or foetalisation, would have the effect, however, of forcing the novel characters into adult life, phylogenetic change then becoming evident to him. Examples of this factor—which de Beer (1940) called "clandestine evolution"—seem to have affected the evolution of some animals, notably amphibians, beetles, molluscs and vertebrates.

One other consequential trend in evolution is related to increase in total size of the body, for positively allometric organs and parts then become progressively relatively larger. Increase or decrease in total size must have produced many correlated changes in the proportions of the body, and mutations that tend to alter existing degrees of allometry may produce greater evolutionary effects than the primary cause would seem to warrant. The same is true of hormonal effects. Without a thyroid, or with a deficient thyroid, the aquatic larval amphibian cannot qualify for adult terrestrial life, for metamorphosis then does not take place. Similar loss or deficiency in a mammal implies change of proportions and also errors of metabolism. Other endocrine glands are similarly important in the ontogeny of vertebrates, and as all such organs display correlated activity it is likely that they have played important parts in phylogeny. Their secretions have set up definite patterns of evolutionary change in vertebrates, and probably in invertebrates also.

Evolutionary Progress

J. S. Huxley has indicated that the term "progress" is difficult to justify in regard to evolution. We may refer to "higher" and "lower" animals but at the same time admit that animals of all grades of structure may be equally well adapted to their particular modes of life. Perfect adaptation means ensured survival, which has real biological value, but adaptation is universal and therefore cannot be used as a criterion

of progress. Neither does specialisation indicate progress, for it may imply perfect adaptation, though it has often led to extinction because adaptation was one-sided and related to a specialised mode of life, whereas progress implies improvement in the efficiency of a broader and more generalised existence. Huxley regarded the emergence of dominant types as the most salient fact in evolution, and he distinguished between forms only temporarily dominant and ultimately extinguished, and forms that remained dominant more or less permanently. The success of such forms was due either to a high degree of control gained over the environmental conditions, or else to the attainment of comparative independence of such factors. The first stage in overcoming the difficulties of enlarging size was the attainment of the metazoan type of body. This brought about the development of mesoderm and the coelom and many improvements of structure and function consequent upon this. Dominant types then acquired bilateral symmetry, and the consequent evolution of a head followed. Some successful types of animals failed to make a conquest of the land as the most highly organised animals of to-day succeeded in doing. Molluscs succeeded in a watery medium, and arthropods limited themselves by developing tracheal respiration and a cuticle that had to be moulted periodically, consequently remaining of small size. According to Huxley, vertebrates alone became eligible for unlimited progress because they mastered the conditions of structure and function that allowed size to increase and activity to become intense in terrestrial life. The development of lungs and the attainment of warm-bloodedness increased the scope of life and led on to the development of intelligent behaviour. Many such dominant types avoided over-specialisation, one method of escape being to accelerate sexual development relative to general development. This abolished the specialised adult stage and provided a more generalised structural condition for further progressive evolution. Physical characters remained important, even in the most progressive types, for the human hands are the most efficacious tools which emerged in evolution; but mental characteristics became at least as important, and they extended the human potentiality for evolutionary progress beyond the level reached by any other organism.

NOTE. The literature on the subject of organic evolution is very extensive and no effort has been made here to review even a small part of it. In writing this chapter I have drawn substantially from J. S. Huxley's book *Evolution, the Modern Synthesis* (1942), which is the

most recent British work on the subject and perhaps the most comprehensive ever written by one person. C. L. Hubbs (1943) spoke of it as "the outstanding evolutionary treatise of the decade, perhaps of the century". About 950 books and original papers are referred to in the 35-page list of literature, and this is not exhaustive. T. Dobzhansky (1941) referred to about 900 books and papers in writing his book on the relation of genetics to evolution. The futility of attempting to compress existing knowledge concerning evolution into one short chapter of a book will be evident. Huxley's book has already become out of date, and it may mark the end of a phase in which it was possible for one person to review so many fields of study. The problems of evolution are deepening rapidly and future summaries will call for specialists, both in the writing and in the reading. Dobzhansky (1949) has stated that the conventional biological disciplines are in process of dissolution. In 1943, however, the National Research Council in the U.S.A. established a joint Committee on Common Problems of Genetics, Palaeontology and Systematics and the outcome of this has been the publication of a *Symposium* edited by G. L. Jepsen, E. Mayr, and G. G. Simpson (1949). Jepsen, in the Foreword, referred to the book as "a compound of data, of ideas, and of conclusions". A number of prominent biologists (five of them British, namely, D. M. S. Watson, T. S. Westoll, D. Lack, E. B. Ford and J. B. S. Haldane) have dealt with special topics, such as geological time, the viewpoints of geneticists, morphologists and palaeontologists on evolution, evolutionary rates and trends, speciation, adaptation and human evolution. To the distinguished geneticist H. J. Muller fell the task of redintegration of the *Symposium*. To consider the findings and opinions of these writers is clearly impossible here, but the reader who is interested in modern trends in the study of evolution will need to consider their work carefully. Other notable books on the subject are mentioned in the list which follows, and the recent work of G. G. Simpson (1944, 1950) is worthy of special attention. The earlier book was a blending of the evolutionary data derived from palaeontology and genetics, and the later book builds on the earlier foundation and propounds an evolutionary philosophy of existence which Dobzhansky (1949) typified as the "most daring which ever challenged the creative imagination of a biologist". In the future it seems inevitable that the symposial treatment of this, as of other subjects in biology, will be more necessary than ever. At present there is a concentrated effort to study evolution by specialists in comparative anatomy, taxonomy, embryology, genetics,

physiology and palaeontology, and in even more specialised fields such as physiological genetics and population genetics. Another Darwin will apparently be needed to extract the essence from the results now coming to light concerning the details of evolutionary mechanisms. G. S. Carter (1951) has, however, attempted a summary of recent views.

CHAPTER FIFTEEN

MARINE BIOLOGY

Life in the Sea

OCEANS and seas cover about seven-tenths of the earth's surface and lodge representatives of nearly every class of animals and many kinds of plants. Much of the sea's fitness for supporting life depends on the exceptional properties of water and its great bulk (see L. J. Henderson, 1913). The high specific heat of water and the vastness of oceans explain why the temperature of the sea rarely extends beyond the range -2 to 32° C. in polar and tropical regions and why local changes rarely exceed about 5° C. The viscous nature of water and the great depth of ocean ensure comparative freedom from mechanical disturbances, except near the surface of the sea and the shores of the continents. The sea also contains more than forty chemical elements, and its saltness is of such variety as to provide an ideal medium for the maintenance of life. Living things are teemingly abundant in the sea, which is something more than salt water and can be regarded as a regulated liquid containing dissociated salts, or ions, in almost precisely the amounts present in the tissue liquids of animals. In fact such liquids have been regarded as samples of some primeval sea which have become incorporated in the animal's body. The sea is also a vast pasturage for herbivorous animals, and a well-stocked larder for marine carnivora of all sorts. J. Colman (1950) has pointed out that "in 1870 man's knowledge of the sea below a depth of about 100 fathoms was to all intents and purposes *nil.* By 1914 he knew the main depths of all oceans, the nature of their bottom deposits, the distribution of temperature, salinity and oxygen in a general way at all depths, and above all he had worked out and described all the main groups of animals and plants to be found in the sea; in this last field only details have since had to be filled in." In early attempts to explore the sea, chemistry and physics were outstripped by biology, though after the First World War physicochemical investigations were both comprehensive and detailed. Nowadays the three sciences work together harmoniously in thrashing out the complex problems of marine research. This is admirably shown in the published lecture on

Pure and Applied Science of the Sea by F. S. Russell (1948) and the extremely valuable book by H. U. Sverdrup and colleagues (1942).

Life on the Sea Shore

Life on the beaches is made precarious by the ebb and flow of tides alternately draining and flooding the shore, by the intense heating of shallow waters by the sun's rays during the day and rapid cooling at night, and by waves that break with great force over the homes of many animals. Certain advantages outweigh these disadvantages, however, for near the shore food, light and oxygen are abundant. The student of marine biology must consider these facts very carefully in regard to the inhabitants of various regions of many kinds of shores, and also deal with estuarine life which occupies the gateway into fresh water, with life in sea-water pools and marshes in which water may stagnate with dire consequences. Life in all such situations is faced with hazards which do not exist in the sea offshore, and the hardy organisms which survive the high degree of exposure to be found in them have been the main interest of many pioneers of marine biology.

Little can be said here about the difficult subject known as the ecology of the seashore, but mention must at any rate be made of some of those who have made valuable contributions to our knowledge of it. C. M. Yonge (1944, 1949) has not only paid tribute to early workers in this field but has also provided delightful accounts of life on the seashore. In the later of these two works he has given an account of the extensive literature on this subject. In the earlier of them he has shown how considerable is our debt to George Johnston, John Ellis and others of the eighteenth century, and to Philip Henry Gosse and many others who worked out the structure, life-histories and habits of marine animals during the nineteenth century—to Edward Forbes, G. H. Allman, Thomas Hincks, Thomas Bell, Michael Sars, C. S. Bate, J. O. Westwood, T. R. R. Stebbing and many others who studied invertebrates, and to William Yarrell, Frank Buckland and others interested in the lives of fishes. Buckland, who became an Inspector of Salmon Fisheries, was a pioneer in the methods of rearing and culturing young fishes which were practised extensively later on, and used for the establishment of commercial fisheries in many parts of the world. These and many other biologists, who cannot be specified by name, have made very substantial contributions to our knowledge of life in the sea and, incidentally, to many other aspects of biology.

Yonge has also written (1950) an up to date article on life on sandy shores.

Other Aspects of Marine Biology

In addition to the drifting, swimming and creeping forms of life on the seashore and the sea-floor, many animals which bore into piers, groynes and ships claim the interest of some marine biologists. For an elementary account of the biology of ship-fouling see K. A. Pyefinch (1947). Wood-borers such as the shipworm (*Teredo*) and the gribble (*Limnoria*), respectively a bivalve mollusc and a crustacean not unlike a wood-louse, do serious damage to submerged timbers, and, strange though it may seem, stone-borers are of greater variety, if less efficient than wood-borers, belonging to such diverse groups as sponges, worms, molluscs and crustaceans. Marine biology is concerned with the mode of life of such organisms and also with methods of protecting timber and stone from their ravages. It is equally concerned with the "synthetic" activities of corals in the production of reefs and it has many other concerns—the colour and phosphorescence of the sea and creatures that live in it, ocean seasons, symbiotic, commensal and parasitic relationships between organisms, the feeding of marine animals, the shellfish industries, sea-fisheries, whaling and seal fisheries, and all aspects of fishery research. It is interested in the preservation of fish and in fish and whale products, pearls and shells, precious corals, turtles, sponges and seaweeds and, in fact, with all products of the sea. Nothing is too academic and nothing too industrial or economic for the marine biologist to tackle in this enormous field. He may devote his energies to the evaluation of biological communities on some jetty, or he may range the oceans in a quest for data bearing on one or many aspects of marine life. If necessary he will enlist the services of many experts on various subjects in the interests of accuracy of results, or he will apply himself diligently to the counting and measuring of numerous things and dimensions, realising that knowledge is never wasted and that an apparently insignificant fact may find a key position in the oceanographical scheme of things.

Marine Biological Laboratories

Progress in marine biology has been due largely to the rise of marine laboratories in various parts of the world. In these establishments the most varied researches have been carried out on an international scale. The first marine biological laboratory was founded by

P. J. van Beneden at Ostend in 1843. About five years later Valenciennes began to collect marine specimens on the coast of Brittany, and this led to the foundation of the first marine biological station at Concarneau, Finistère, in 1859. The famous biological station at Naples was set up by the German zoologist Anton Dohrn, who, in 1873, spoke of it to the British Association (1874) as "a battlefield where all the different zoological armies (systematists, anatomists, physiologists and embryologists) may meet and fight their common adversaries (error and ignorance)" (quoted by H. A. Jack, 1945). The first American marine station was established in 1873 by Louis Agassiz on the tiny island of Penikese, about a score of miles from Woods Hole. At Annisquam, Massachusetts, a small laboratory was set up in 1881 to replace that abandoned at Penikese after 1874. By 1886 this had grown so much that it was moved to Woods Hole, an ideal location on Cape Cod. Adjoining this laboratory at the present time there is both the U.S. Bureau of Fisheries Station and an Oceanographical Institute. Many other stations now exist in U.S.A. In 1888 the first marine biological laboratory was set up in Britain, at Plymouth. Similar but smaller laboratories have been established at Bergen and Trondheim, Kristineberg and Göteberg, Copenhagen, Helder, Helsingfors, Roscoff and Banyuls. British University laboratories are located at Port Erin, Millport, Cullercoats and Bangor, Government laboratories at Lowestoft, Aberdeen, Conway and elsewhere. Fresh-water biological stations eventually established in various countries extended ecological work to inland waters; the laboratory of the British Fresh-water Biological Association is at Windermere. Reviewing the biological stations of the world, C. A. Kofoid (1914) listed twenty-four in America plus three in Canada, and seventy-six in Europe; E. J. Allen (1928) listed one hundred and five marine stations; and H. A. Jack (1945) gave a complete directory, indicating an enormous increase in their numbers later on. Up to 1880 there were in all sixteen biological field stations dispersed in several countries, but in the single decade ending in 1930, when the number of foundations was greatest, about seventy new stations were established.

The Plymouth Laboratory of the Marine Biological Association

The history, aims and achievements of this laboratory, which for forty-two years was directed by the late Dr. Edgar Johnson Allen, and later came under the direction of Dr. Stanley Kemp, have been described by the present Director, Dr. F. S. Russell (1947). As a

result of the avowed aims of the Association, the early work centred on "the habits of fishes, shellfish and other products of the sea, and the collection of information on the methods and results of commercial fishing", but the results of a detailed study of the flora and fauna of the south-west coast of England made by the staff and other workers was set down in the *Plymouth Marine Fauna* (1904, 1931). After he 1914–18 war, when the Ministry of Agriculture and Fisheries had taken over fisheries research, the work at Plymouth "became for the greater part fundamental in its nature". Emphasis rested on the study of chemical and physical conditions of life in the sea, and the life-histories, development and distribution of marine organisms. Some research continued to deal with the biology of fishes such as the mackerel, the bionomics of the oyster and the distribution of seals. In recent years most of the researches carried out by the staff "can be built around two main underlying themes. The first is how much living matter can the sea produce, what are the variations and causes of variation in productivity, and how do the organisms obtain the materials necessary for life? The second is how do marine animals in general live, how do they fit their various individual environments, and what alterations in their environment can they appreciate?" The sea "contains all the ingredients necessary for the successful growth and development of the living organisms; in so far as the general biology of the animals is being studied it is the conditions in the sea-water which determine their distribution, habits and migrations".

From this it will be clear that the staff of the laboratory is concerned with much fundamental research on the physics and chemistry of the sea, and particularly with the determination and estimation of nutrients which form the basis of marine life. Unicellular plants which constitute the herbage of the sea depend on nitrogen, phosphorus and other elements, the annual cycles of which are determined afresh each year. Photo-electric methods specially devised by W. R. G. Atkins for measuring the degree of penetration of light into the sea have been applied to the problem of photosynthesis in these microscopic plants, which are eaten by adult fishes such as the mackerel and hosts of minute larval fishes which cannot feed on anything larger than diatoms. The populations of plants and animals which make up the plankton have been the subject of studies on distribution, both horizontal and vertical, and the development, growth and habits of many of the organisms have been worked out. The relationship between the plankton and the main water masses around the British coasts has also

been studied in detail. Some planktonic forms such as the arrow-worm (*Sagitta*), unusually interesting because characteristic of certain types of environment, have become important indicators of the movements of these water masses.

What Dr. Russell has called "the second major line of research, the biology of marine animals", is extremely varied. The sea maintains a wider variety of animals than are found in any other environment. Only the insects of all animal groups are poorly represented in the sea. There is thus plenty of scope for many types of workers in biology—whether systematists, morphologists, embryologists, physiologists, or geneticists. Once the systematists have made a broad survey, "research has chiefly been directed towards the description of the life-histories of animals important in the general economy of the sea, of their food and methods of feeding, of their breeding and rate of growth, their parasites, and of their relationships with their animate and inanimate environment". Research on the biology of crabs and lobsters, oysters, mussels and other shell-fish is of great practical importance; likewise that concerned with boring organisms that damage submerged timbers or sedentary forms that foul the hulls of ships, for these organisms involve the nation in tremendous annual losses. The problems of preventing the fouling of marine structures by living organisms have lately been the concern of other departments, but the earlier fundamental work carried out at Plymouth provided a sound basis for further study. Methods for the preservation of fishing nets of all kinds have been determined. The laboratory also plays an important part in the development of the broader field of oceanography. Methods which are eventually used on the oceanic scale are planned and developed in the laboratory and put to preliminary tests in the Association's vessels at sea. The laboratory has also attracted visiting researchers from all parts of the world, and the results of their work is difficult to evaluate because often not published in the Association's journal, which has nevertheless run to about thirty volumes. Such work has been of immense value not only to the development of marine biology, but to that of biology in the widest sense of the term. An earlier description of the laboratory was published by E. J. Allen and H. W. Harvey (1928) along with a list of many publications issued between 1886 and 1927. The list contains the titles of about 300 original works of economic importance and more than 600 which are concerned with morphology and other biological matters; all these were the results of work carried out at Plymouth or on the North Sea coast under the auspices of the

Marine Biological Association. E. J. Allen (1926) published a bibliography on marine bionomics and fishery investigations, which was "intended as a guide only to the complete literature". The first part contained nearly 500 titles of original works bearing on the investigation of the physical and biological conditions in the sea; publications dealing with the physics and chemistry of sea water, ocean currents and their measurement, light, colour and transparency in the sea, the vertical movements and geographical distribution of planktonic organisms, the conditions of productivity in the sea, the bottom fauna and deposits. The second part contained more than 400 titles of publications dealing with fishery investigations; these concern the plaice, sole, flounder, witch, halibut, cod, haddock and whiting, herring, pilchard, sprat and anchovy, mackerel, gurnard, eel, skates, rays and dogfish, and invertebrates such as the oyster, mussels and other molluscs, lobsters, crabs and shrimps.

Oceanic Exploration

A progressive eighteenth-century innovation which benefited biology was the inclusion of naturalists in the personnel of ships making voyages of discovery. Joseph Banks sailed with James Cook in the *Endeavour* in 1768, taking with him Linnaeus's pupil Solander and the artists who helped with the drawing of specimens collected during the voyage. The ship made innumerable deep-sea soundings and temperature records during the next three years, and Banks and his assistants collected many data regarding fishes and birds, as well as plants. There were many such voyages during the nineteenth century. Robert Brown sailed in the *Investigator* in 1801, Darwin in the *Beagle* thirty years later. Joseph Dalton Hooker went with the *Erebus* and *Terror* to the Antarctic (1839–43), T. H. Huxley with the *Rattlesnake* (1846–50) and G. C. Wallich with the *Bulldog* (1860). During this period Johannes Müller, Michael Sars and his son (G. O. Sars) and others were accumulating knowledge about marine organisms, and Matthew Fontaine Maury was compiling his *Physical Geography of the Sea*. The experience of laying the transatlantic cable in 1866 resulted in the improvement of equipment used for exploring the sea, and the cruises of the *Lightning* (1868) and the *Porcupine* (1870) secured new biological data from the Atlantic and the Mediterranean. Oceanographic investigations on the grand scale were instituted in December 1872 when H.M.S. *Challenger* left Portsmouth, taking Charles Wyville Thomson, John Murray, H. N. Moseley and Willemoes-Suhm with

her. The corvette covered 69,000 miles during a three-year cruise, crossing and recrossing the Atlantic and proceeding to the Pacific. The vast reports of this expedition, taking up more than thirty large folio volumes, secured the foundations of oceanography. Other notable expeditions include the cruises of the *Blake* and the *Albatross* under Alexander Agassiz, on which wire rope replaced the more cumbersome hempen ropes formerly used, the deep-sea expedition of the *Valdivia*, the voyages of the *National* and the *Deutschland* from Germany, and the Dutch ship *Siboga* in the East Indies, the cruises of the *Michael Sars* under the direction of Hjort and Murray from Norway and the voyage of the *Tuscarora* from the U.S.A. These and other enterprises such as Nansen's voyages in the *Fram* to the Arctic led on to the modern expeditions of the barque *Discovery*, the *William Scoresby* and *Discovery II* to Antarctic waters for the study of whales, and to the voyages of the U.S. ships *Atlantis*, *E. W. Scripps* and *Catalyst*.

The founding of the International Council for the Exploration of the Sea in 1901 had for its prime objective planned experiments on a grand scale for the improvement of the fisheries of the North Sea and surrounding waters, to which end delegates from Norway, Sweden, Denmark, Finland, Germany, Great Britain and Ireland, France, Belgium and Holland have pooled their knowledge to the great benefit of all branches of marine biology.

A new development in marine biology was initiated in 1828 when the British naturalist Vaughan Thompson towed his fine-meshed nets through the surface waters of the sea south of Ireland (see A. C. Hardy, 1948). By this means he captured hosts of new microscopic organisms which form the great populations of drifting life, or plankton. To capture the smallest planktonic organisms you need something better than the finest silken net, and filter-feeding animals have a much finer pharyngeal net of their own, which can also serve the marine biologist. The name plankton was invented by Hansen to distinguish this multitudinous floating and drifting life from larger forms, the nekton, which move by their own exertions. Microscopic plants (diatoms) form a significant fraction of the plankton. The Dane O. F. Müller, who invented the naturalist's dredge, was the first to describe diatoms in 1773, and the Swedish biologist C. A. Agardh gave the first systematic account of them in 1824, describing forty-nine species. During the next fifty years the number of known species increased to about 4,000 and by this time many planktonic animals were also known.

No hard-and-fast limits can be drawn between planktonic and

nektonic forms; planktonic forms may be able to make some little headway in the sea by their own efforts and nektonic forms may be held back by strong oceanic currents. We generally understand by the term plankton any small organisms that can be captured with fine silk nets at or near the surface of the sea. The most familiar animals of the plankton are certain free-living oar-footed crustaceans which Milne-Edwards (1830) named copepods. According to F. S. Russell, the Norwegian bishop Gunnerus (1765) described the most important species, *Calanus finmarchicus*, which forms the principal food of many animals, notably the herring and the rorqual whale. When the herring is too small to capture and devour *Calanus* it feeds on small forms such as *Pseudocalanus elongatus*, but when fully grown the fish will eat large copepods such as *Temora longicornis*. For the elaborate "food-chains" which link planktonic forms and herring see Fig. 21. Much of our knowledge of the marine free-living copepods goes back to the monograph written by C. Claus in 1863. Their value as food for whales was clearly realised by Roussel de Vauzeme (1834) when he used the name *Cetochilus* for some of them. Countless generations of fishermen, noting the varying colour of the sea in relation to their activities, have used the terms "red-feed" without realising that the red colour was due to species of *Calanus*, *Temora* or *Pseudocalanus* in immense shoals. The study of the food of fishes has been a difficult one, and few realise how much research has been carried out by such men as K. A. Möbius (1878), G. Brook and W. L. Calderwood (1886), H. F. Moore (1898), R. Collet (1886) and many others during the nineteenth century. This work formed the basis for the studies of G. E. Bullen (1908, 1912) on the food of the mackerel, H. Swithinbank and G. E. Bullen (1913) on the food of the pilchard, A. C. Hardy (1925 onwards) on the food of the herring, and J. Hjort and J. T. Rudd (1929) on the food of whales. For a long list of the results of fishery and other investigations see Allen (1926) and also the publications of the Ministry of Agriculture and Fisheries and the Fishery Board for Scotland, which are listed concisely. Related studies such as that on the food of various young fishes made at Plymouth by M. V. Lebour (1916–20) are supplemented by the study of the food and feeding habits of the copepods themselves. Miss Lebour (1922–23) referred to three types which eat diatoms, or other copepods, or else are mixed feeders. Importance also attaches to the chemical composition of copepods, which serve to transfer valuable substances, notably vitamin A, from diatoms to fishes and to mankind.

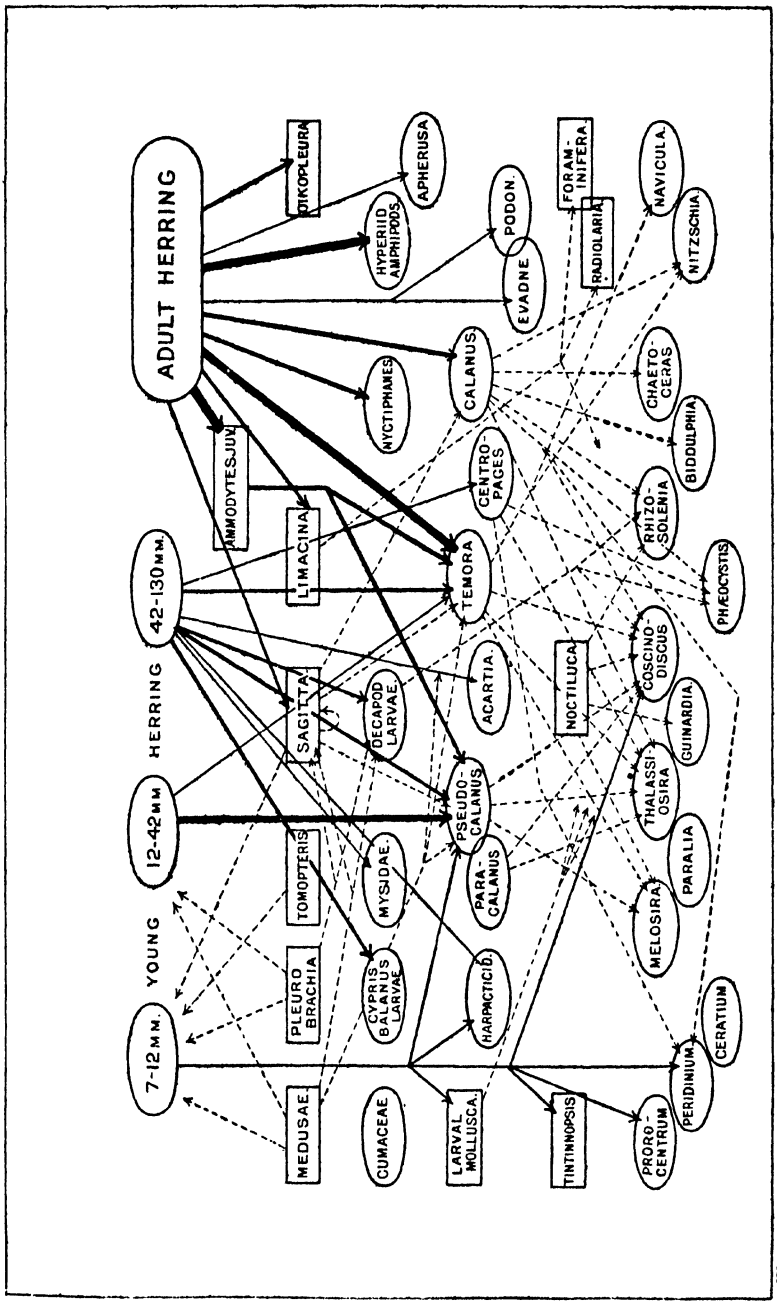


Fig. 21. Diagram representing the relationship between herrings of various ages and the plankton as a whole. The arrows link animals with their prey, their heads indicating the latter. The lowest stratum in the scheme is made up of plants, and copepods figure prominently above these. Notable enemies of the herring are indicated. From Hardy, 1924. (H.M. Stationery Office.)

The Discovery Committee

This Committee is named after its first research ship, the refitted *Discovery* of Captain Scott. It was set up under the Colonial Office in 1923, and in 1925 it began a scientific survey of the Antarctic from a marine biological station set up at Grytviken, South Georgia. In 1926 the *Discovery* was replaced by *Discovery II*, a larger ship with a greater cruising range, and since this time the *William Scoresby* has also played an important part, notably in the "marking" of whales. It is interesting to note that an undertaking to improve the economic resources of a small group of remote islands (the Falkland Island Dependencies) should have the effect of enriching marine biology. Whaling is the chief industry of these islands, and its betterment called for a study of the biology of whales and a determination of the effects of whaling on existing whale stocks. Essentially the work of the Committee concerns the feeding, wanderings and reproduction of whales, and at first whale carcasses had to be brought laboriously ashore, though when whaling factories were instituted the bulk of the work was carried out at sea. Much systematic and morphological work has been carried out at the British Museum (Natural History) and elsewhere by specialists on various groups of animals and plants. Already twenty-five large quarto volumes have been published as Reports, and much collected materials and data have still to be studied. Whales feed largely on "krill"—swarms of the small crustacean *Euphausia superba*—which are dispersed in the plankton by ocean currents, so that the study of plankton became an important part of the project, much credit for which goes to the late Dr. Stanley Kemp and his colleagues. In April 1948 the first Annual Report of the Advisory Council on Scientific Policy recommended that oceanographical research should be extended from public funds and that the Discovery Committee should be reconstituted as a chartered body. On April 1st, 1949, the Committee came to work under the Admiralty with a view to its ultimate reorganisation as part of a National Institute of Oceanography, the aim of which would be to deal with "every branch of oceanography in all the seas of the world" (*The Times*, March 30th, 1949).

Planktonic Organisms and Fishery Predictions

Some planktonic organisms have proved to be valuable indicators of currents in the sea. F. S. Russell (1935) gave a list of such forms and

showed that around the coasts of Britain one species of arrow-worm, *Sagitta elegans*, is an oceanic form which is common in the western part of the English Channel, while the neritic species *S. setosa* lives in the Channel itself and in the North Sea. When Atlantic water flows strongly round the coast of Scotland into the North Sea the *Sagitta* populations in the Channel move to the westward. Observations made over a long period show that the populations "swing to and fro off Plymouth". The diatoms *Rhizosolenia* and *Biddulphia* also serve as indicators of water movements, and in British seas their movements generally conform with those of *Sagitta*. When *S. setosa* appears near Plymouth, *Rhizosolenia* becomes abundant in the southern part of the North Sea. These and other members of the phytoplankton may form dense masses which discolour the surface waters of the sea, as R. Brown (1875) first showed in regard to diatoms in Arctic seas. Herring fishermen try to avoid such "stinking water", which indicates poor fishing. Adult herrings dislike diatoms as much as their larvae fear arrow-worms. Miss M. V. Lebour (1925) made a special study of the enemies of some young fishes, including *Sagitta* among them. R. E. Savage and A. C. Hardy (1935) investigated phytoplankton concentrations in the southern area of the North Sea, and they thought it likely that the herring will not swim in areas of dense phytoplankton, and concluded that change in the position and density of such concentrations might influence the great autumn fishery. The shoals of herring that form the basis of the fishery are spawning individuals migrating inshore, and these may be diverted and prevented from reaching the spawning grounds by dense aggregates of diatoms. E. S. Russell (1935) described how at the commencement of the herring season of 1933 W. C. Hodgson at Lowestoft predicted fair fishing in the North Sea. Fisherman could not locate the shoals, however, and the research vessel of the Ministry of Agriculture and Fisheries was sent out to try to locate them and to determine why they had not appeared as usual. Extending across the entrance to the southern part of the North Sea an enormous belt of phytoplankton mainly consisting of *Rhizosolenia* and *Biddulphia* had formed an effective barrier to the migrating fishes. In quest of high concentrations of the copepods, on which it feeds, the herring definitely avoids areas densely populated by diatoms.

It may seem a long call from diatoms and copepods to the herring on the breakfast-table, but in the economy of the sea these three forms are closely linked. Where copepods abound, herring fishing is generally

good; where diatoms abound, it is poor. A. C. Hardy (1937) has described the momentous steps taken in such investigations during

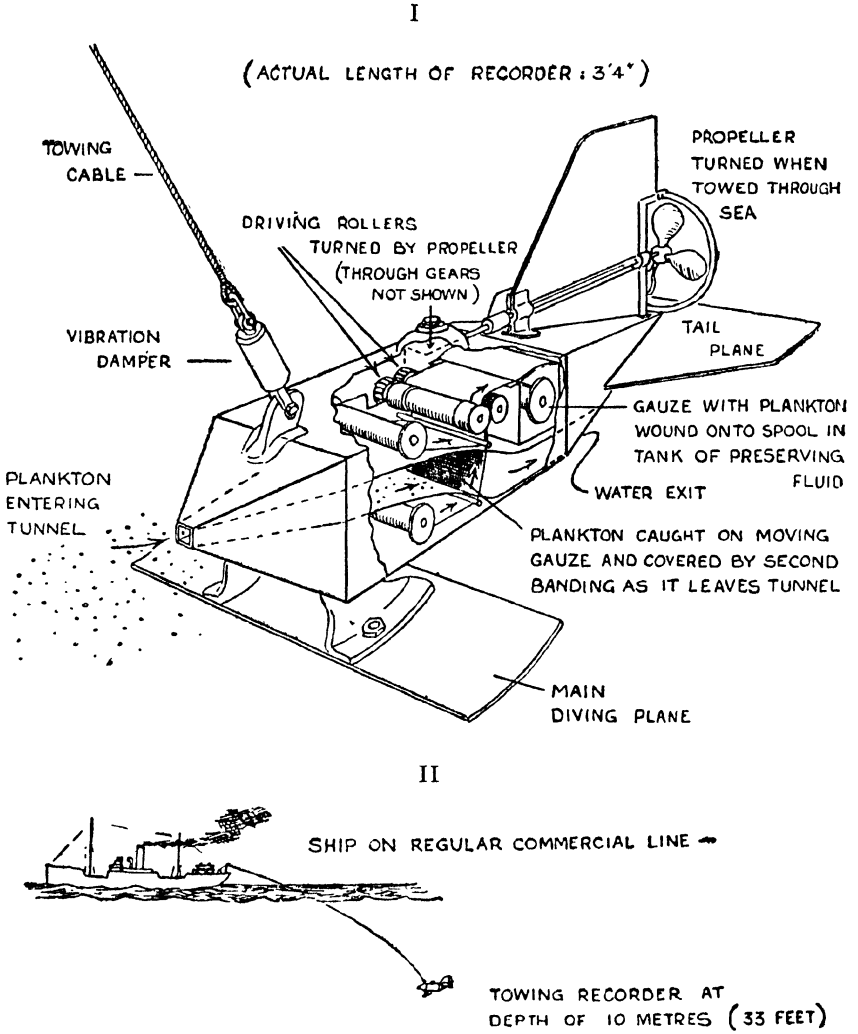


Fig. 22. I, Diagram of the Hardy continuous plankton recorder, with part of the casing cut away to show the internal mechanism. Catching gauze ruled in numbered divisions, each of which may represent one or more miles of sea according to the setting of the propeller blades. II, Towing the recorder. From Hardy, 1944. (*Hull Bulletin of Marine Ecology.*)

the period 1931–36, and he has stated: "Once we could establish beyond doubt the reality of the positive correlation of the herring with its food *Calanus* and the negative correlation with the dense plant

plankton we could place in the hands of the fishermen a means of sampling the water as they went out to fish and so enable them to fish in the more profitable waters." This marked the beginning of the period in which the "plankton indicator" came into use. It is a small, torpedo-like object carrying a gauze disk, and as it is towed through the sea it sieves the plankton through the disk. In practice, the instrument was towed for about one mile and then hauled, the gauze disk being removed and preserved. Details of time and position and also of catches of fish were also collected, and in the initial experiments thirty-five different drifters played their parts well. In 1932 a number of steamship lines traversing the North Sea towed behind them a rather more complicated instrument in which a moving band of gauze replaced the sampling disk, collecting plankton continuously and rolling it up in a precise position on the gauze in a preserving chamber. These machines were called Continuous Plankton Recorders, which were towed to the Skagerrak, Bremerhaven, Rotterdam and other North Sea ports abroad. At the end of a voyage the gauze is unrolled under the microscope and varying quantities of different kinds of planktonic organisms can be examined. Marked divisions on the gauze correspond to specific distances along a definite course at sea, and as a single spool will cover 400 miles, the plankton can be mapped out over extensive areas by the marine biologist on shore. Even the simpler recorders act as a third eye for the fishermen, who are often unable to appreciate visually where diatoms or copepods abound, and where fishing is likely to be poor or good accordingly. By towing a plankton indicator for a short distance on a prospective fishing ground and then hauling it for scrutiny of the gauze disk a decision can be reached immediately; diatoms form green or black accumulations on the gauze, copepods red or orange-red accumulations.

Fish Culture

The two main lines along which the culture of marine fishes have been carried out has been outlined by the late Fabius Gross (1941). The eggs of fishes such as cod, plaice, sole and turbot have been collected and placed in hatcheries ashore, and the larval fishes derived from them have been returned to the sea later, just before the young fish has used up its store of yolk. Young plaice have also been taken from inshore grounds and transplanted on rich feeding grounds only thinly populated with fishes. The method of hatching eggs has been carried out on a grand scale in U.S.A. and Norway, and also in the Isle

of Man and in Scotland. In such methods of culture millions of larval fishes have been liberated annually. The transplantation experiments carried out by Dannevig for the Scottish Fishery Board were discussed by T. W. Fulton (1909), who concluded that the liberation of more than 142 million baby plaice in Loch Fyne during the period 1896–1901 substantially increased the plaice population. Intensive growth of plaice followed the transplanting of young forms from the coasts of Denmark and Holland to the Dogger Bank during the period 1904–8 (see W. Garstang, 1905; and J. O. Borley, 1912). Young fishes about 8½ inches long increased their length by about 5¼ inches as against about 2 inches on the inshore grounds, and their weight by nearly 400 per cent. as against 100 per cent. inshore. Since 1908 Danish fishery experts have transplanted many millions of young plaice annually, and these growth data have been largely substantiated (see H. Blegvad, 1933). Gross has argued, however, that to stock the sea with millions of delicate larvae is to try to increase the harvest of the sea by increasing the number of seeds sown. In Loch Fyne the experiment did lead to an increase in the population of plaice, but the loch had its own plaice population and this "did its best to grow in numbers". Only a small fraction of the 142 million forms placed in the loch was able to survive because no special steps were taken to provide food for an increased population of baby fishes. Animal life in the sea largely depends on phytoplankton for food and "the bulk of animals maintained is roughly proportional to the bulk of vegetation on which they directly or indirectly graze". Gross (1937 *a*, *b*) has shown that many species of marine diatoms and autotrophic flagellates can be cultured in the laboratory for long periods, populations becoming much denser in culture than in the sea—500 million cells per litre as against 25 million per litre in the spring plankton, in which they are more numerous than at other times (S. M. Marshall and A. P. Orr, 1930). Attempts to culture planktonic organisms on a large scale were made at Göteborg by H. Pettersson, F. Gross and F. Koczy (1939) with some success.

In 1941 a group of British biologists conceived the idea of increasing the harvest of the sea by adding artificial fertilisers to it, thus supplementing the amounts normally present. In 1942 experiments were started in Loch Craiglin—a small arm of Loch Sween, Argyll—with the aim of enriching the plankton, obtaining a better population of bottom-living animals, and providing more food by means of which fishes could be expected to grow both more rapidly and to a larger size (see F. Gross, 1947, 1949, and J. E. G. Raymont, 1947 *b*). In the

first year about 600 pounds of sodium nitrate and two-thirds as much superphosphate were put in the loch—which covers an area of about eighteen acres and is about two metres in mean depth. In 1943 the same amount of nitrate was put in the loch and half as much superphosphate again. These added substances were rapidly utilised by diatoms and other microscopic plants, and the plankton of the loch became one of the richest known. The growth of bottom-living animals was studied throughout this two-year period by J. E. G. Raymont (1947 *a*); it showed a great increase during the first summer and a much greater increase during 1943. But the experiments were not an unqualified success in regard to plaice growth. Small fishes removed much greater quantities of food than the flat-fish consumed, and the latter did not make such good growth as they might have made. The experiments have been criticised rather adversely (L. H. N. Cooper and G. A. Steven, 1948) and it has been argued that we shall never be able to farm the sea in this way, but F. Gross (1948) replied to the criticism and it seems too soon to decide whether or not the application of agricultural methods of this kind to marine pisciculture will or will not benefit our fisheries by increasing the harvest of the sea.

In an important and stimulating paper, H. W. Harvey (1950) has tried most carefully to evaluate the production of living matter in the sea. His first considerations were the conditions of growth, the standing crops, the annual yield and the rate of production of planktonic plants. Eight interdependent factors were shown to affect the production of plant tissue in the sea. The continuance of plant growth depends on the rate of regeneration of nutrients from dissolved organic matter in the photosynthetic zone and the quantity of organic matter which is raised into the zone by turbulence of the water. The size of the growing stock of plants (quantity of photosynthesising phytoplankton) depends on the population density of animal planktonic forms which eat the growing plants, the rate of loss of stock due to sinking out of the photosynthetic zone, and the mean depth of this zone (which varies according to the amount of light penetrating the surface of the sea and the transparency of the water). This last factor also influences the rate at which the stock of plants grows, which is also modified by temperature effects on plant respiration, the concentration of nutrients (ammonia, nitrates, nitrites, amino-acids and phosphates), and perhaps also by the concentration of other constituents of sea-water. From these and other determinations—concerning the zooplankton and its food, fluctuations in population

density, the quantities of pelagic and demersal fishes, bacteria in suspension and on the sea-floor, and the bottom-dwelling animals—Harvey provided estimates (intended as pointers, not conclusions) to show that the sea maintains "an average of 1000 pounds of animal tissue per acre" and that "with a better 'balance of life' there is reason to suppose that the sea could maintain an almost phenomenal quantity of animals compared with cattle on land". He mentioned Chinese methods of banking off shallow sea areas to form sea-water ponds, which are freed of predatory animals and—after algal growth has started—stocked with quick-growing herbivorous fish fry. The enormous yields—5,000–7,000 pounds of fish per acre annually—achieved by the use of this system in the Philippines and on the coast of India have been described by D. Frey (1947). After two years of service such ponds are drained, the mud bottom is sun-baked and ploughed, and the water is then replaced; this treatment increases the passage of nutrients from the bottom to the water, thus preserving the fertility of the pond fishery.

The Life-history of the Herring

The remark which was passed in a previous section about a forecast of "fair fishing" calls for amplification. How can the fisheries naturalist prophesy that herring fishing will be good, bad, or indifferent in any season? This question can be answered by a few remarks about the life-history of the fish. Most of the food fishes lay their eggs in the plankton, but the herring deposits her eggs on the sea-floor, and the localities in which they are laid can be determined by various methods. Likely places can be dredged with suitable nets in the hope of finding the eggs, the localities in which spawning females are caught can be noted and the sea here can be swept with plankton nets in a quest for the larvae, or the localities in which haddock are caught can be searched —for the haddock feeds voraciously on the herring's eggs. The first method is not very practicable, because the eggs often lodge in crevices so that the dredge misses them, but the other methods have helped to solve the problem. Adult herring go year after year to the same localities to spawn. Coastal and offshore spawning grounds exist in the North Sea, and the most important ground in the northern region is off the Dogger Bank. Later on, autumn spawning occurs off the Lincolnshire coast farther to the south, and in late November the shoals appear near the estuary of the Thames, though the biggest shoals appear off the coast of Kent during January.

The newly hatched herring lives for a time on the yolk provided by the parent, but as soon as the mouth opens it begins to eat copepods. During spring and summer the young fish feeds on rich animal plankton, but in autumn appetite falls off and during the winter the fish hardly feeds at all. At first, the shoals of young and of older fish mingle, but when the fish is about three years old—and age can be determined readily by the rings of summer and winter growth in the scales—the fish leaves the herring community and moves inshore along with the shoals for the execution of the spawning act. During the early years of its life, therefore, the herring feeds hungrily and stores up in its tissues deposits of fats and other nutrients, on which it lives during the spawning period. Later on, if the fish avoids the fishermen's nets, there is a period of recovery from the physical strain of spawning. The shoals are closely studied by naturalists of the Ministry of Agriculture and Fisheries from year to year, and samples of the annual broods are submitted to quantitative analysis. A good spawning year indicates the probability of good fishing two years later, and this chance can be tested by further analysis of the larval stocks in ensuing years. The movements of the shoals are carefully charted and any influence which may mar the predictions of time and place are noted. As the fisheries naturalist acquires the relevant ecological data, his predictions become remarkably reliable, unless untoward events arise in the form of swarming phytoplankton.

The Life-histories of other Food Fishes

The movements of food fishes other than the herring have also been closely followed in Britain and elsewhere during the twentieth century, and their various life-cycles have likewise been determined. Plaice thickly populate the North Sea, and they lay their eggs in winter in the warm waters of the Southern Bight. The eggs float in the plankton and develop as they drift towards the coasts of Denmark and Holland. At hatching time the larvae feed on plankton, and for some time they are bilaterally symmetrical like most other fishes. Eventually they seek the sea-bottom in shallow coastal waters, where they metamorphose into baby flat-fishes. They feed henceforth on bottom-living animals, and as they grow they slowly migrate towards their birthplace in the Southern Bight, where at last they spawn (E. S. Russell, 1937).

The cod also inhabits the North Sea, and the shoals assemble early in the year—February and March—north and west of the Dogger

Bank. Spawning takes place mainly in March, when a single female lays several million eggs. At the conclusion of the spawning period the shoals disperse and the adult fishes hunt the herring, some of them appearing as far south as Flamborough Head. The eggs drift in the plankton, however, and the larvae, which hatch out within a fortnight, are scattered to the east and south of the Dogger Bank. For four years the young cod feed voraciously—now on crustaceans and then on fishes—and gradually they work their way to the ends of the Bank. By the end of this period they become mature and join the spawning shoals, though how they find their way to the spawning grounds is still something of a mystery. A great stock of cod also swarms in northerly waters between Norway and the Arctic, feeding in the comparatively shallow water between Spitsbergen, Bear Island and Novaya Zemlya, mainly eating crustaceans and lamellibranch molluscs. These fishes become mature when about eight years old, after which they make extensive migrations towards the west coast of Norway, where the largest shoals exist. From January till April the Norwegian line fishermen take great toll of the spawning fishes, notably in the Löfoten Isles, catching an average of about 20 million fishes each season. Enormous numbers of eggs are laid, however, and these develop as they drift in the strong northerly current that carries them to the main feeding grounds, and spent fishes that escaped the fishermen's nets travel in the same general direction. We see, therefore, that the life-history of the cod and the plaice show the same general features; spawning fishes swim against prevailing currents away from the feeding grounds, towards which the developing eggs and young later drift.

Perhaps the most remarkable piscine life-history is that of the eel, which has been so brilliantly investigated all over the world by Johannes Schmidt (1908–31). The adults go down the rivers and move off to the westward into the Atlantic Ocean, travelling several thousand miles to spawn in the deep waters of the Sargasso Sea. Schmidt discovered the true breeding place in 1922, solving what had hitherto been a complete mystery. The larvae (strap-like leptocephali) which hatch from the eggs later drift eastwards in the warm waters of the Gulf Stream, taking about three years to reach the coasts of Europe. By the end of this time they have developed into tiny glass eels, or elvers, and these aggregate in myriads in river estuaries and eventually move into the rivers. In the estuary of the Severn they are nowadays trapped in large masses by specially trained biologists, and dispatched by rail and other forms of transport to various parts of Britain and

Continental countries, there to stock the rivers. There are many ways in which fishes benefit mankind; but this is one way in which a reciprocal effect is achieved, for the elvers are more certain of survival and have an easier journey to their future homes than was formerly the case.

The life-history of the salmon provides a further contrast. In both Europe and North America the eggs are laid in some river bed in very shallow water far up-stream, where the young fishes live for about two years. The partly grown salmon then migrate down to the sea and for two years they feed on marine animals and grow rapidly. By the end of this period they are almost mature, and then move back towards the coast and ascend the rivers, making very determined efforts to reach the shallows where spawning later takes place, though now greatly helped by ingenious man-made easy steps. Sometimes immature fishes "run" in the spring, but this generally happens in the autumn when the gonads are ripe. The adults often return to the precise spots where they spent the early part of their lives, thus displaying a remarkable "homing instinct". Whether or not some form of "inherited memory" or an ancestral habit is involved we do not know, but experiments in America have proved beyond doubt that individual feats of memory come into play. Eggs spawned in one tributary of a particular river have been transferred to some other locality, so that the young grow up away from their "birthplace", and when marked fishes from such transplanted stocks return from the sea they settle down to spawn not in the stream in which they were spawned, but in that where they spent the early part of their lives.

Bottom Deposits

As is well known, the shells of various Protozoa which abound in the surface waters of seas and oceans fall to the bottom after the death of the animal and contribute there to sediments which form the basis of geological formations such as the chalk of southern England, which consists of the remains of Foraminifera. Marine sedimentation has been extensively studied (see Sverdrup *et al.*, 1942). Various methods have superseded the method of taking a small sample of the bottom on a piece of tallow set at the end of a sounding "lead". Various methods of sampling bottom-living populations by means of a mechanical grab have also been used with great success in Plymouth Sound and other localities. Mention must be made of a new method of bringing to light data which promise to advance marine zoology considerably,

particularly in relation to geological changes which have taken place in the past history of the seas. This is the method of obtaining drillings or "cores" by various means devised in Sweden. In 1942 Kullenberg and Pettersson invented a vacuum core sampler, and with it raised an undisturbed core fifteen yards long from the bottom of Gullmar Fjord. Three years later a piston sampler invented by Kullenberg raised a core nearly twenty-four yards long. Other methods of determining the nature of the sea-floor—and several have been described by H. Pettersson (1949, 1950)—include the determination by sounding of the thickness of the "carpet" sediment, by echo-sounding devices which reflect sound waves from the surface of the "carpet" of mud and also from the "bottom below bottom", or underlying rocks. The new methods were tested on the cruise of the *Skagerak* in the western Mediterranean during 1946, and in 1947 the 1,450-ton motor-schooner *Albatross* started out on July 4th on the First Swedish Deep-Sea Expedition sponsored by the Royal Society of Göteborg. The ship was a floating laboratory carrying core samplers weighing up to 1½ tons and 4,400 fathoms of steel cable, and in a cruise lasting fifteen months a continuous record was kept of bottom profile along a course 20,000 sea-miles long, registered by an ultrasonic echograph made by a London firm. The expedition brought back in cold storage 200 long cores from a depth of 2–4,000 fathoms, totalling one statute mile, also some 4,000 water samples (some of them large enough for radioactive determinations) and 10,000 temperature records.

This expedition has provided materials and data which will occupy physicists, chemists and biologists for a long while, but remarkable results have already become clear. In the Pacific and Indian Oceans the carpet sediment is less than 1,000 feet thick, whereas in the Atlantic it is more than 12,000 feet thick. Mid-Atlantic sediment cores consist of homogeneous red clay, but compacted below. The cores are being examined by radioactivity methods in order to establish the time-scales of sedimentation, by mineralogical methods to gain some idea of composition, and also by biological methods for identification of remains in the sediment. Results obtained by F. B. Phleger Jr. with a core 15·4 metres long, taken from a depth of 4,900 metres in the Caribbean Sea, show a very complicated pattern of remains, and this indicates considerable temperature fluctuations in the surface waters during the period of sedimentation, which is believed to cover the whole of the Pleistocene period. The remains of Foraminifera that have been identified are the shells of animals which lived in localities where the

temperature varied as considerably as it does between tropical and arctic seas, and they are being used to throw light on the problem of submarine geochronology. Identifiable pollen grains of various species of *Pinus* have also been recovered in cores taken from a great depth in the sea, and also burrows of mud-eating organisms which delve into such deposits at great depths have also been identified. It was formerly possible to examine fossil remains in land masses thrown up out of the sea by earth movements, and this new line of investigation of rocks in process of formation in the depths of ocean promises valuable results for various sciences, not least for biology.

CHAPTER SIXTEEN

PARASITES AND PARASITIC DISEASES

PATHOLOGY was defined by J. R. Reynolds (1866) as "the scientific study of any condition of the organism which limits life in either its powers, enjoyment or duration". More recently, G. Payling Wright (1950) has defined it as "the science concerned with abnormal states of the body, the functional disorders that accompany them, and the causes that bring them about". Aetiology is the name given to the study of the causes of abnormal states, which are diverse and complex, involving both hereditary and environmental factors—that is to say, both nature and nurture. The congenital condition known as haemophilia and the deficiency disease called rickets are due to these respective factors, and something has already been said about them. Other environmental factors arise because of the action of external agents, and notably of parasitic organisms such as viruses, bacteria, Protozoa and helminths (flatworms and roundworms).

The most distinguished pathologist of the nineteenth century was Rudolph Virchow, founder of the *Archiv für pathologische Anatomie* (later known also as Virchow's *Archiv*). His great work *Cellular Pathology* (1858) brought about the fall of the old "humoral" pathology and the rise of new conceptions of morbid structures as cellular things. Virchow's contemporary Louis Pasteur, who is universally recognised as the outstanding figure in medical history, solved one problem after another and brought lasting benefits to agriculture, industry and medicine with results of experiments won in various fields. His work on putrefaction and fermentation, silkworm disease, anthrax, chicken cholera and rabies have been described over and over again. Along with Robert Koch, Pasteur has the honour to be the founder of modern bacteriology. Others who acquired fame during the last century include Élie Metchnikoff, Russian pupil of Pasteur and Nobel Prizeman, who founded the doctrine of phagocytosis, and Émile Roux, assistant and successor of Pasteur as Director of the Pasteur Institute in Paris. Roux developed methods for preparing anti-diphtheria serum, and Emil von Behring developed serum treatment

and discovered the diphtheria antitoxin. The work of these men, and a dozen others who laid the foundations of bacteriology, has been sketched by various writers on the history of medicine and of bacteriology (see D. Guthrie, 1946).

Kinds of Parasites

The researches of innumerable biologists during the past hundred years have shown parasites to be unevenly dispersed in the animal and plant kingdoms. Some animal phyla contain very few parasites, others none. Parasitic Polyzoa, Brachiopoda, Echinodermata and Protochordata are unknown, and there are but few parasitic Coelenterata, Annelida, Mollusca and Craniata. Plant parasites also are relatively few. That well-known semi-parasite the mistletoe obtains only water and salts from its host, making food by means of its own chlorophyll. The truly parasitic dodder (*Cuscuta*), which forms luxuriant growths on many plants, is a typical seed plant, but it has neither roots nor chlorophyll: "haustoria" take the place of roots and enable the plant to extract nutriment from the host. Relatively few seed plants have acquired the parasitic habit, which is largely confined to the fungi, but many members of the Orobancaceae are parasites, notably the beechdrop (*Epiphagus*).

Parasites are sometimes classified as "permanent" or "temporary" parasites. The trypanosomes and malarial parasites have no capacity for free life; blood-sucking leeches and ticks leave their hosts when gorged with its blood, and return to it only when hunger returns. Some forms are parasitic only as larvae, others only as adults. The glochidium larva of the pond mussel (*Anodonta*) buries itself in the integument of a minnow for several weeks, but later emerges to lead an independent life; conversely, the fleas that infest dogs and cats are blood-sucking adults, their larvae dwelling in cracks and crevices on the ground. Some forms are classified as "obligatory" and "facultative" parasites. Many flukes, tapeworms and roundworms must have one host and sometimes they require several. Conversely, the roundworm *Leptodera appendiculata* can live and develop either in damp earth or on the body of a slug, though it grows to a larger size and lays more eggs when nurtured on a host. Perhaps the best rough method of classifying parasites, however, is to separate such as live on the outsides of animals (ectoparasites) from those which penetrate more deeply into them (endoparasites).

The Origin of Parasitism

All parasitic animals are presumed to have arisen from free-living forms. Flimsy associations were no doubt formed during the early stages of parasitism, perhaps merely the sharing of food and shelter. Under such conditions of *commensalism* some turbellarians live on the lower surface of king-crabs, between the valves of the oyster's shell, in the burrows of pagurid crabs, and in the mantle cavity or on the gills of various molluscs. Turbellaria are typically free-living, but parasitic forms exist in the gut of many echinoderms, in worms and molluscs, on the body and the eggs of crustaceans and attached to the skin of skates. Every order of the Turbellaria contains some commensals or parasites, so that the origin of the parasitic habit in the Platyhelminthes is not very obscure. The fluke-like Temnocephalids live attached to fresh-water crustaceans, and are passengers rather than parasites, for they feed on small aquatic creatures that live in the water around them. But they have learned the first trick of the parasite: they have won attachment to some animal and have gained the ability to hold on. The ectoparasitic trematodes (Monogenea) have better developed organs for this purpose, suckers or clamps strengthened by firm skeletal parts (sclerites), and some of them have acquired the habit of entering the host, thus qualifying for the title of endoparasite. The endoparasitic trematodes (Digenea) show varying degrees of penetration into the host. Some of them lodge in the buccal cavity and pharynx, others pass down the oesophagus and remain in the stomach or intestines, and others again enter the lungs, liver, kidneys, or body cavity, even the heart and the blood vessels. Intestinal flukes mostly live on the predigested food of their hosts; but it was no very great step from such food-stealing habits to the more drastic procedure of eating the lining of the host's intestines and bile ducts, a step which many roundworms and flukes were able to take.

The Effects of Parasitism

The parasitic habit has effects on both the host and the parasite. A tapeworm several yards long may seriously impoverish the nutrition of a sheep or a man, and the excretory products of the worm may exert a mildly toxic effect. Hookworms severely damage the intestinal mucosa of the host, and produce more serious toxic effects; moreover, the wounds which they make in the tissues may become infected with micro-organisms that cause disease. Even immature parasites may

produce serious effects in the host if they happen to lodge in unusual situations. The condition of "staggers" or "gid" is caused in sheep by the bladder-worm (cysticercus) stage of a tapeworm lodging in the brain. Microscopic parasites may block blood vessels or lymph channels. The microfilariae of man permit lymph to enter a limb but prevent it from flowing away, and the limb steadily enlarges to an enormous size. Isle-of-Wight disease in bees is caused by mites of the species *Acarapis woodii* blocking the air tubes, or trachea. The spiny eggs of some blood flukes (Schistosomes) harm the host; they work their way through the wall of the bladder or intestines, lacerating the tissues and causing serious loss of blood in the urine or faeces. Heavy infections with some parasites may be very harmful to the host, whereas light infections do little harm; this is true of the malarial and many other parasites.

By comparing parasites with their nearest free-living relatives we find, as a rule, a certain simplification of structure, though hardly the degeneracy which is sometimes attributed to parasitism. The animal may, in the long run, lose certain organs that were essential to free life and are not required for a parasitic existence, but what organs remain ensure success in life and may be improved to bring this about, notably so in the case of adhesive organs. Whatever simplification of structure is found in some organ systems, the reproductive organs are usually well developed, for fecundity is one of the outstanding characteristics of parasites. Hermaphroditism is common and a single tapeworm may possess more than one thousand sets of male and female reproductive organs. Countless young forms must be produced to counterbalance the risks associated with the transference to a new host during early life. The pork tapeworm (*Taenia solium*) can produce fifty million eggs and the beef tapeworm (*Taenia saginata*) three times as many. These remarkable figures do not do full justice to the fecundity of some parasites, for the egg of an endoparasitic trematode, or that of some tapeworms, will produce not one adult but thousands of adults, because of asexual multiplicative stages in the life-cycle. To consider the recent advances in our knowledge of the life-histories of parasites would call for a whole book in itself, for many biologists have disclosed striking adaptations for the successful propagation of the species. Readers interested in such work will find much information in the books recommended for further study.

To summarise the parasite and host adaptations, we can say that even when a parasite spends part of its life in freedom, the remaining

part of the life-cycle is full of difficulties for host and parasite alike. The parasite often has the task of finding and penetrating a particular species of animal; the host or hosts have to bear the burden of nutritional, histological and toxicological disturbances. A close relationship has grown up over a long period between the parasite and its host, perhaps out of continual association in the same habitat. The host's presence in this habitat may be determined by factors such as warmth, moisture and food, but the simultaneous presence of the parasite is largely fortuitous. The eggs of the liver fluke *Fasciola hepatica* are shed in the droppings of the sheep, and the larvae (*miracidia*) which hatch out can live no longer than twenty-four hours in freedom. In less time than this the successful larva will have found its snail host, and the unsuccessful one will have perished. The later larvae (*cercariae*) which emerge from the snail must somehow find their way back to the sheep. This is achieved—as A. P. Thomas in Britain and R. Leuckart in Germany showed independently in 1881—by the agency of a protective cyst fixed to herbage bordering some pool, provided that the sheep actually crops that sample of herbage. The larvae of hookworms, schistosomes and some other parasites seek out the final host and actively penetrate it by their own efforts. The cercariae of some blood flukes of birds are sensitive to shadow stimuli, rising in swarms in the water when a swimming bird passes over them, then penetrating the host by way of the legs. Even when the right host has been found and penetrated, the larvae must find the proper location in the body, which sometimes involves an intricate and extensive migration through the tissues. Ideally, the host must not be overburdened with parasites, for this would threaten the parasite's own existence.

Viruses

The name virus has had several meanings. It has been used to denote "poison" and even "moral turpitude", and K. Smith (1948) has indicated that in the modern sense it still has two meanings, for in one sense it is "nothing more nor less than a protein of high molecular weight", while in another it implies a filter-passing micro-organism. The difficulty lies partly in the fact that a virus which can be analysed as being a crystalline nucleoprotein still has the capacity to reproduce itself after the fashion of a typical organism. The discovery of the virus may be said to have arisen out of the methods perfected by various biologists for the filtering of bacteria from solutions.

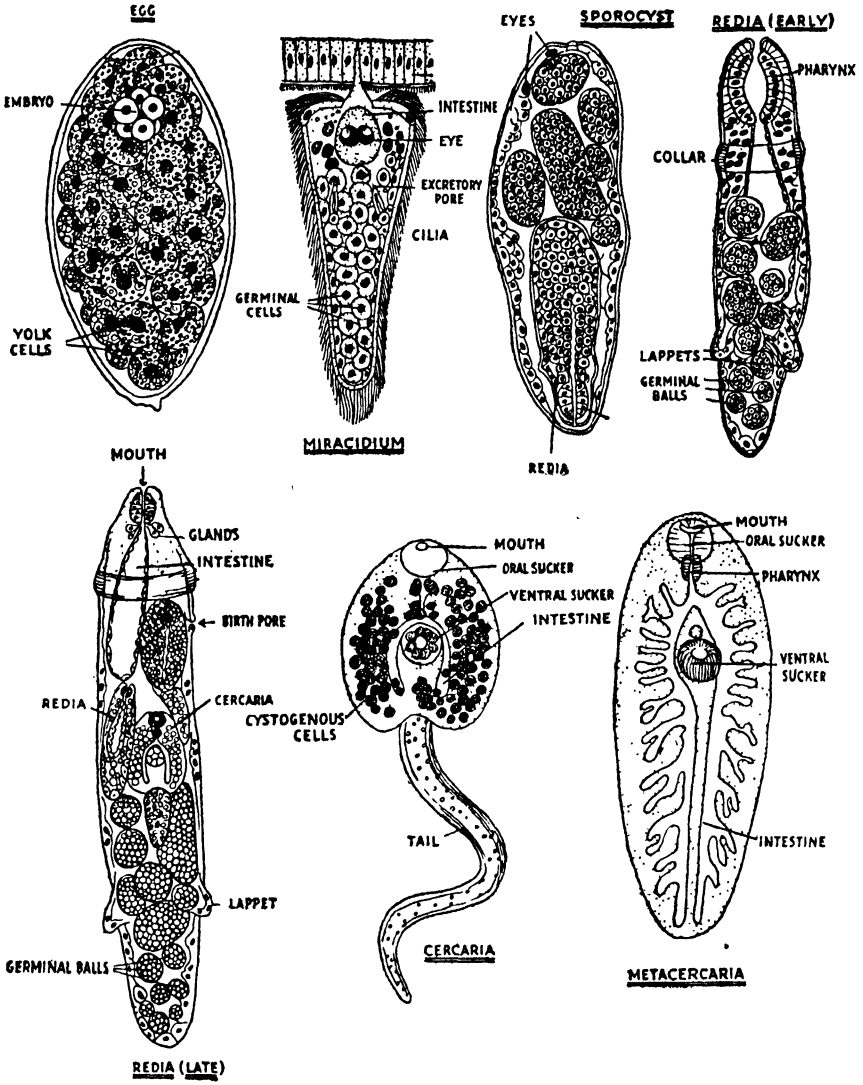


Fig. 23. Stages in the life-cycle of the liver fluke, *Fasciola hepatica*. The embryo in the egg develops into a larva (the miracidium), which penetrates a snail of the species *Limnaea truncatula*. Inside the snail's body this larva is transformed into a sporocyst, the germinal cells forming germinal balls, which give rise to other larvae (the rediae). A second generation of rediae may arise, but ultimately the tailed larva (or cercaria) is formed. This encysts on herbage which may be eaten by a sheep or ox or rabbit. The tail-less larva (or metacercaria) migrates through the wall of the intestine and penetrates the liver, becoming mature in the bile ducts. Note that a "germinal continuity" runs through all the larval stages, during which the progeny of the fluke are multiplying. From Dawes, 1947. (*Monthly Science News*, No. 1; British Council.) After Thomas, 1883.

Tiegel (1871) handled anthrax liquids and used filters of unburned clay, while Pasteur and Joubert (1877) separated anthrax germs by means of plaster-of-Paris filters. Unglazed porcelain candles were the discovery of Chamberlain, who worked in Pasteur's laboratory, and the Berkefeld filter of infusorial earth known as Kieselguhr was invented by Nordtmeyer (1891). Liquids passed through a Berkefeld filter are completely freed of bacteria and therefore from the bacteriologist's point of view are quite sterile.

Pasteur was aware that the infective secretions of rabid animals though free of bacteria might contain agents of infection which were beyond the resolving power of the microscope, but the first demonstration of a virus was that of the Russian botanist D. Ivanovsky (1892). He showed that the clear, filtered sap of tobacco plants having leaf-mosaic disease will cause the disease to develop in healthy plants when injected into them. About seven years later Beijerinck rediscovered this fact, but in the meantime Loeffler and Frosch (1898) passed the vesicular liquid from cattle having foot-and-mouth disease through a Berkefeld filter and obtained a clear filtrate which was just as infective as unfiltered liquid. The real importance of virus bodies was not appreciated, however, until the nineteen-twenties and subsequently the determination of one of the characteristics of a virus—its size—was made by the use of filters having pores of known dimensions. The same thing can now be done also by means of the ultra-violet microscope, the electron microscope and the ultra-centrifuge. The largest known virus is that which causes psittacosis (parrot disease), the smallest that of foot-and-mouth disease; the respective diameters of these viruses are 275 mμ and 10 mμ, figures which are interesting because indicating overlap with bacteria on the one hand and protein molecules on the other. More than thirty human diseases are ascribed to viruses, some of which are practically confined to man; for instance, smallpox, epidemic poliomyelitis, chickenpox, measles, common wart, denge, mumps, influenza, the common cold, infective hepatitis, glandular fever, etc. Others, such as vaccinia, rabies, yellow fever and psittacosis occur in man and also in animals, and others still are confined to animals as is foot-and-mouth disease, dog distemper, swine fever, cattle plague and fowl pest.

In general, viruses are susceptible to the same adverse factors as bacteria; for instance, the effects of heat, ultra-violet radiations and antiseptics. They increase in the tissues of organisms and therefore have reproductive capacity. They display variation, becoming

modified in virulence under certain conditions, and serological specificity. They share with bacteriophages the capacity to proliferate only inside living cells. Some plant viruses are undoubtedly rods or crystals of nucleoprotein, though this feature has not been proved for animal viruses. They show no evidence of metabolic functions and in one view they represent an extreme example of parasitism, being absolutely dependent on the synthetic products of cells. Their investigation has revived the idea of spontaneous generation, or the origination of a living thing from something unlike itself, which is very nearly what the chemist says when he regards viruses as the products of autocatalytic processes, for this means that a virus can transform a substrate into virus particles.

Bacteriophages

The discovery of a "bacteriolytic agent"—a living enemy of bacteria and even smaller than they are—was announced in the *Lancet* in 1915 (ii, p. 1241). It was known to be exceedingly small, and it invariably appeared in an active state in the clear liquid obtained by passing infected micrococci through a porcelain filter. F. W. Twort (1949) has told us that his discovery was made as a result of an idea which occurred to him in 1909, that a study of the needs of growing micro-organisms might throw some light on the problem of infectious diseases of animals, plants and man. His chief concerns were the physical conditions necessary to stimulate micro-organisms, the chemical background which they needed for cultivation, and the reactions of one living form to another. First consideration was given to the diseases leprosy, tuberculosis and Johne's disease of cattle, all these diseases being known to originate from infection with bacilli belonging to the same biological group, though at that time only one of the three (the tubercle bacillus) had been cultured on artificial media. According to F. d'Herelle (1949), who has greatly extended our knowledge of the agent concerned, the name bacteriophage first appeared in a note presented to the Academy of Sciences on his behalf by Roux on September 15, 1917 (vol. 165, p. 373); the note was entitled "On an Invisible Microbe, an Antagonist of the Dysentery Bacillus". Since that time, we are informed, more than 6,000 scientific notes and papers on the bacteriophage have been published in journals all over the world. Yet the full importance of the bacteriophage has not yet been realised, though it is now clear that it plays an active part in all phenomena which affect microbes. For concise general accounts

of the nature of bacteriophages see A. D. Gardner (1931), R. W. G. Wyckoff (1949), and C. H. Browning and T. J. Mackie (1949).

The Conquest of Parasitic and Viral Diseases

Heroic stories of the conquest of disease have often been told, but some points may be mentioned briefly concerning the parasitic diseases elephantiasis and malaria and the virus disease yellow fever. The first of these, now known as filariasis, is caused by roundworms once called *Filaria*, and is a hideous disease in which a member of the body—arm or leg or other part—becomes enormously inflamed and swollen with congealed lymph, its skin and tissues thickened and coarsened. The elucidation of the causes of this disease earned for Sir Patrick Manson the title of Father of Tropical Medicine, though the research by which this distinction was gained may fairly be described as biological (dates and details by Sir M. Watson, 1936).

In 1866, one year after graduating at Aberdeen University, Manson went to Formosa and in 1871 to Amoy, a most uncongenial place, where elephantiasis was rife. With poor laboratory facilities and little help he searched the blood of patients in a quest for the probable cause of the disease. Some years before, in Cuba, J. N. Demarquay (1863) had discovered a minute larval roundworm in the milky dropsical liquid of a patient, and in 1866 O. Wucherer had found a similar organism in the urine of one of his Brazilian patients. In India T. R. Lewis (1870) made a similar observation, and two years later came to regard human blood as the normal habitat of this minute worm, which he called *Filaria sanguinis hominis*. We now know that the worms mature in the lymphatic glands, their larvae migrating into the blood vessels after liberation from the parent. In 1876, at Brisbane, Australia, T. L. Bancroft discovered the adult female form, which Cobbold (1877) called *Filaria bancrofti*. This name was changed by L. G. Seurat (1921) to *Wuchereria bancrofti*. The adult male animal was discovered by A. G. Bourne in 1888.

Meanwhile, Manson had made great strides in his investigations. Becoming suspicious of the larval roundworm, he was nevertheless puzzled, because samples of blood from sufferers with elephantiasis did not always show it. He eventually discovered that the minute worms disappeared from the finger blood of patients during the day, but reappeared in tremendous numbers at night. In fresh blood the embryos were invariably enclosed in a loose sheath, and as the blood cooled on the microscope slide the worm pushed its way through the

sheath and became more active than ever. To Manson this suggested an attempt to find a fresh host, and he soon came to suspect night-flying mosquitoes. Putting his idea to a test by feeding mosquitoes on a parasitised Chinese boy, he dissected the insects after a few days and found the parasites multiplying considerably in the haemocoele, or blood space round the gut, through which they had penetrated. In 1879 he perfected the hypothesis of nocturnal microfilarial periodicity. In the insect's blood he found and studied the growth stages of the parasites, but unfortunately he was denied his final satisfaction because of the difficulty of keeping mosquitoes alive in the laboratory, and it was for Dr. George Carmichael Low, who took up the work at Manson's suggestion, to discover, in 1900, that the worm finally leaves the insect as it entered, along the proboscis, but in the reverse direction. Not having actually seen this final migration, Manson, who published the results of his work in 1878, was uncertain about the mode of human infection. But later he not only formulated the mosquito hypothesis of filarial transmission, which soon became fact, but applied his discoveries to the problem of malaria, and was the first to suggest that this disease also is spread by mosquitoes.

Malarial fevers were known to ancient Chinese physicians, and Hippocrates recognised the types now called quotidean, tertian and quartan. In Peru, the Countess de Chinchon, wife of the Viceroy, was cured of malaria in 1638 by concoctions of the bark of quinine-producing trees, afterwards called *Cinchona*. Biologists just over one hundred years ago were applying their microscopes to the study of the disease. Meckel (1847) first noted the dark colour of the organs of malaria victims and R. Virchow (1848) found pigment in their cells, but it was A. Kelsch (1875) who discovered pigmented bodies in the blood. At this time malaria was regarded as a bacterial disease, but in 1880 the French army surgeon C. L. A. Laveran, working in Algeria, discovered and described the malarial parasite (*Plasmodium*), and two years later E. Richard confirmed the discovery. Two years later still C. Gerhardt (1884) transmitted malaria experimentally by inoculating blood containing the protozoan parasite, and in 1885–86 C. Golgi differentiated between the forms causing quartan and tertiary fevers and described their cycles of asexual reproduction (schizogony) in human blood. In 1885 E. Marchiafava and A. Celli named the quartan form *Plasmodium malariae*; in 1890 B. Grassi and R. Feletti named the tertian form *P. vivax*; and in 1897 W. H. Welch described and named the third species *P. falciparum*. More than a dozen species

exist in birds and the first of these was discovered by Grassi and Feletti (1890), while spore-formation (sporogony) was described in one of them (*P. praecox*) by Ronald Ross (1898). In 1891 D. L. Romanowsky devised an improved technique which enabled better-stained preparations to be made, and in 1912 C. C. Bass and M. Johns devised methods of culturing the parasites *in vitro*, another aid to further research.

After twenty-five years of work in China, Manson retired in 1889 and came to London. In 1890 he started work again and soon afterwards became Medical Adviser to the Colonial Office, an event which led to the foundation of the London School of Tropical Medicine and Hygiene. In his research on malaria, Manson was soon impressed by the development of the peculiar crescent-bodies, which were unrelated to the regular bouts of fever that came on with great regularity after 24, 48 or 72 hours and, as in the case of larval filariids, he soon noted that they become more active in cooling blood on a microscope slide. Such bodies were then believed to have no special significance, but Manson's insight suggested them to be the first stage of the parasite's life-cycle outside the body of man. Living in London, Manson was unable to test his idea, but he had the good fortune to meet Ronald Ross, who went to London in 1894 fresh from a study of malaria in India. Manson suggested that Ross should feed mosquitoes on blood containing crescents—bodies which threw off minute writhing filaments in what seemed to be their death agonies.

On his return to India, Ross studied these peculiar flagella and found them to develop more quickly in the juices taken from the mosquito's stomach than in human blood. But he discovered the fate of the flagella only after making a tremendous effort. For two years he dissected mosquitoes and searched their viscera without finding any trace of malarial parasites, and the clue which led finally to the elucidation of the life-history was just a few clear cells in the wall of the mosquito's stomach which contained grains of black pigment. We now know that the flagella are sperm-like bodies (microgametes) which fuse with egg-like bodies (macrogametes) to form the zygote. This gives rise by asexual reproduction to many thousands of sporozoites, the forms which infect human blood corpuscles. So, in a malarial district Ross toiled to elucidate that stage of the malarial parasite's life-history which takes place in the body of the mosquito.[4] The crescents turned out to be developing gametes. The mosquito, receiving these in a droplet of blood, becomes the nursery of the sexual reproductive stages and is also the vector that spreads the disease. To

complete the proof, two volunteers (Dr. L. W. Sambon and Dr. G. C Low) lived for the three most dangerous months of the year in another malarial district (Ostia), but in a mosquito-proof house, and did not contract malaria, and two more in London (Manson's son, Dr. Thornburn Manson, and Mr. Warren of the London School of Tropical Medicine) were bitten by mosquitoes previously fed on malarial patients in Rome and contracted the disease. In 1948—and after much experimental work had been carried out on the malarial parasites of birds—the important exo-erythrocytic forms of malarial parasites were discovered in the liver of monkeys and man by workers at the London School of Tropical Medicine. These forms arise when experimentally inoculated sporozoites disappear from the peripheral blood and when the parasites leave the blood corpuscles and inhabit the liver during the period between relapses, later producing erythrocytic forms (Fig. 24). For an account of this work see the papers of Shortt and colleagues (1948 *a*, *b*, *c*).

The discoveries of Manson and Ross in relation to filariasis and malaria had important repercussions in America. In 1881 the Cuban Carlos Findlay had suggested that the yellow-fever germ is transmitted by a mosquito, but he was unable to obtain proof of this. In 1885 the French failed to build the Panama Canal largely because of the ravages of this disease, and in 1889 Walter Reed was chosen to investigate outbreaks of yellow fever which were sapping the strength of the U.S. Army of Occupation in Cuba. At this time there were nearly two thousand cases, and more than two hundred had been fatal. Working with Reed on the Yellow Fever Board were three other doctors, J. M. Lazear, J. C. Carroll and A. Agremont. Quite early during the work Lazear died of experimentally induced fever and Carroll suffered a severe attack which shortened his life. Experiments at Camp Lazear, Cuba, started in 1900, and on the last day of that year Reed was able to report (to his wife) that his mission had been accomplished. The experiments formed three series. In the first, three men lived for twenty-one days in a mosquito-proof hut and wore the clothing of yellow-fever victims; no case of yellow fever developed. In the second, a building was divided, one part being netted and the other not, and volunteers lived in both halves; the man (John J. Moran) who slept with mosquitoes (*Aedes aegypti*) had fever, the others not. In the third, blood and filtered serum was injected into volunteers, all of whom developed the fever, showing that the disease was due to something carried in the blood, though no living organism had been seen.

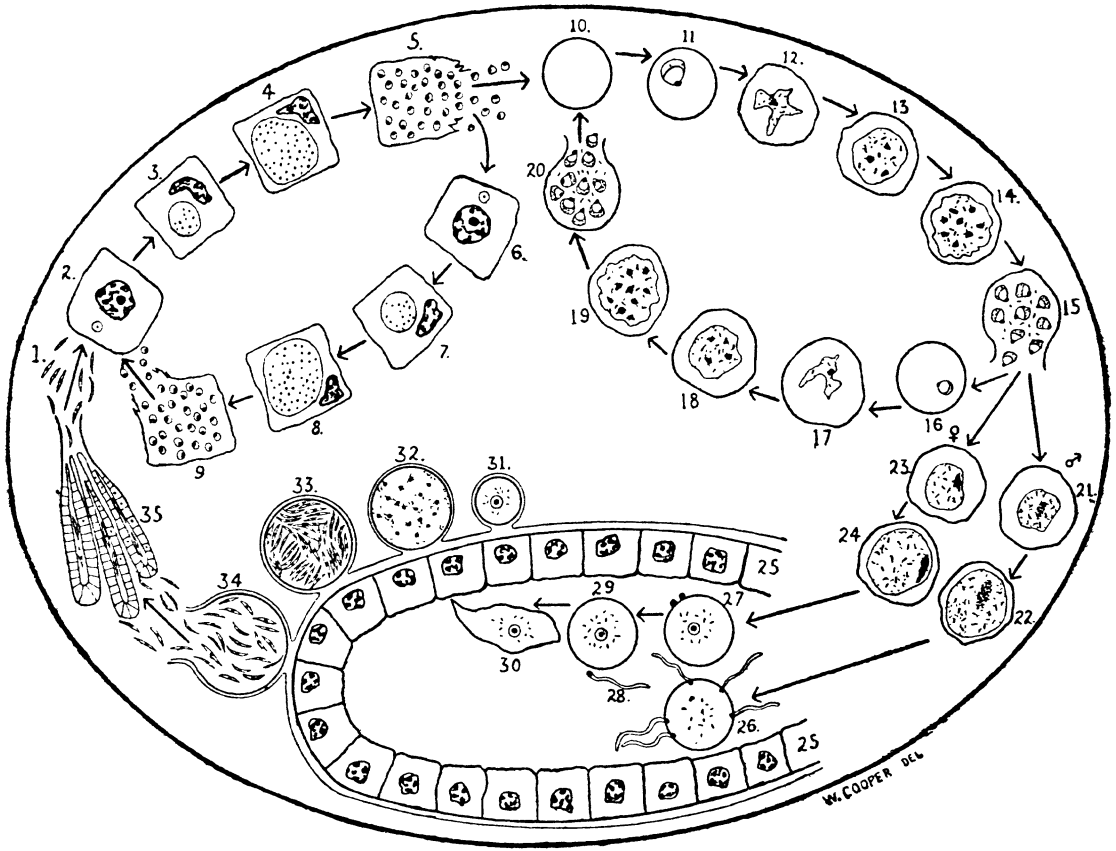


Fig. 24. Diagram to illustrate the complete story of a malarial infection. 1, Sporozoites from the saliva of a mosquito enter the liver cells of the monkey; 2, 3 and 4, stages in pre-erythrocytic schizogony in the liver cells; 5, release of pre-erythrocytic merozoites; 6, 7, 8 and 9, repetition of cycle in liver cells and production of second generation of merozoites; 10, red blood corpuscle; 11–14, schizogony in blood corpuscles; 15, release of erythrocytic merozoites; 16–20, repetition of schizogony in blood corpuscles; 21 and 22, development of male gametocyte; 23 and 24, development of female gametocyte in blood; 25, wall of mosquito's stomach; 26 and 27, development of microgametes and macrogametes respectively; 28 and 29, impending union of gametes to form the zygote; 30, oökinete about to penetrate wall of mosquito's stomach; 31, oöcyst on outer surface of stomach; 32 and 33, development of oöcyst and production of sporozoites; 34, rupture of oöcyst and dispersion of sporozoites, most of which penetrate the insect's salivary glands, 35. From Shortt, 1948. (*Trans. Roy. Soc. Trop. Med. and Hyg.*)

In 1900 two doctors went from England to Peru to study the disease. Both contracted it, and in January 1901 one (Walter Myers) died. In 1901 the city of Havana was cleared of mosquitoes and yellow fever wiped out. In Panama the Canal was built in record time and here too fever was eradicated. Yellow fever broke out elsewhere, however, and in 1926 there was a swift development which took severe toll of life, including several investigators (Dr. A. Stokes in 1927, Drs. H. Noguchi and W. Alexander in 1928). But Stokes and his colleagues had shown that the Indian monkey was susceptible to the disease, and Theiler, who showed that mice can be infected, devised a test to determine whether or not a person's blood contained the causal agent, a virus, and from this work arose the preparation of vaccine against it.

Trypanosomes

The first haemoflagellate was discovered by G. G. Valentin (1841) in the brown trout, and two years later D. Gruby established the genus *Trypanosoma* for similar parasites living in the blood of frogs. The first trypanosome to be discovered in a mammal was the well-known species *T. lewisi*, which T. R. Lewis (1879) discovered in the rat in India. In 1880 G. Evans found another species, *T. evansi*, in the blood of horses in India and ascertained later that it occurs in the camel, elephant and buffalo (also the dog) and is the cause of the disease known as "surra", which for very many years before had been ascribed to some agent associated with certain biting flies. In 1894 J. Rouget found another species, *T. equiperdum*, in horses in Algeria and this was associated with the disease known as "dourine". Some four years earlier Nepveu had found haemoflagellates in human blood during the course of researches on malaria in Algeria, and in 1895 D. Bruce showed that "nagana", a disease of horses and cattle in Africa, can be attributed to another species, *T. brucei*, and that it is transmitted by the bite of the tsetse fly, *Glossina palpalis*. In 1901 H. Vogel obtained the species *T. equinum* from horses suffering from *mal de caderas*, and in the same year Forde observed the first trypanosome from human blood, apparently associated with some non-malarial fever. He showed this parasite to J. E. Dutton, who (1902) recognised it as a trypanosome and called it *T. gambiense*. At this time A. Castellani was studying sleeping sickness in Uganda and in 1903 he found *T. gambiense* in the cerebrospinal liquid of patients with this disease. By this time, Bruce and D. Nabarro had confirmed that this species is the causal agent of sleeping sickness, and they and others had proved

beyond doubt that *Glossina palpalis* transmits it. A few years later C. Chagas (1907) discovered the species *T. cruzi* in Brazil, and J. W. W. Stephens and H. B. Fantham (1909) described *T. rhodesiense* in Rhodesia (D. L. Belding, 1942). The conquest of trypanosomiasis is a subject which cannot be discussed here; C. H. Browning and T. J. Mackie (1949) have dealt with the modern aspects of it, and K. R. S. Morris (1949) has described the science of tsetse-fly control.

Helminths and Mankind

Many human factors are involved in the spreading of human parasites. Hookworms were carried from Africa to America by the slave trade, and schistosomes are widespread because of the rice farmer's use of human excreta containing their eggs to fertilise the land. Other insanitary habits also create reservoirs of larvae, and imperfect culinary treatment of food may result in much unnecessary infection. The notorious lung fluke *Paragonimus westermani* is acquired by eating imperfectly cooked crayfish containing late larvae (*metacercariae*), the Asiatic liver fluke *Clonorchis sinensis* by eating undercooked fish, which are reservoirs of such larvae. As a rule, there is a simple method of breaking the links in the chain of forms which make up the life-cycle of a parasite, though more often than not human ignorance, prejudice and habits prevent this from being achieved, except when drastic measures are adopted.

A very striking world analysis of human infection with helminths (trematodes, cestodes and nematodes) has been worked out by N. R. Stoll (1947). Taking available figures from the *Statistical Yearbook of the League of Nations* and other sources, Stoll estimated the world population as 2170 millions and human infection with helminths as 2257 millions, the mean figures suggesting that every human being carries at least one helminth in his body. The truth is, that while some human beings are free of parasites, many carry more than one species. Nematodes most affect human well-being, *Ascaris* claiming 644 million human hosts and the hookworm 457 million, the two together accounting for more than one-half of human helminthiases. The notorious roundworm of children, *Enterobius vermicularis*, claims nearly 209 million victims, the whipworm *Trichuris trichuris* 355 million and the filariid *Wuchereria bancrofti* and *W. malayi* 189 millions. Other filariids which are spread by *Simulium*, *Culicoides* and *Chrysops* (genera of insects), namely *Monsonella ozzardi*, *Loa loa*, *Acanthocheilonema perstans* and *Onchocerca*, represent 67 million human

infections, and the dreaded guinea-worm *Dracunculus medinensis* 48 million. Hookworms are the world's most pathogenic helminths, but in the U.S.A. an average of one person in six (21 million infections in a population of 131 millions) harbours "garbage worms", the notorious *Trichinella spiralis*. Of the remaining kinds of helminths three species of blood flukes claim 114 million human victims. Of the cestodes, the beef tapeworm, *Taenia saginata*, claims twenty-five times as many victims as the pork tapeworm, *Taenia solium*, nearly 39 million infections as against 2½ million. The notorious tapeworm of children, *Hymenolepis nana*, finds more than 20 million human hosts and the broad tapeworm of fish-eating peoples more than 10 million (see Table 11). A few comments about such important helminths as these are clearly required.

TABLE 11.—CALCULATED NUMBERS OF HUMAN INFECTIONS WITH HELMINTHS. Numbers in millions. (*After* STOLL, 1947.)

NEMATODES		
Roundworm:	*Ascaris lumbricoides*	644·4
Hookworm:	*Necator* and *Ancylostoma*	456·8
Whipworm:	*Trichuris*	355·1
Pinworm:	*Enterobius vermicularis*	208·8
Filarial worms:	*Wuchereria bancrofti* and *W. malayi*	189·0
	Loa loa	13·0
	Acanthocheilonema perstans	27·0
	Onchocerca volvulus	19·8
	Strongyloides stercoralis	34·9
Garbage-worm:	*Trichinella spiralis*	27·8
Guinea-worm:	*Dracunculus medinensis*	48·3
CESTODES		
Beef-tapeworm:	*Taenia saginata*	38·9
Pork-tapeworm:	*T. solium*	2·5
	Hymenolepis nana	20·2
Broad-tapeworm:	*Diphyllobothrium latum*	10·4
TREMATODES		
Blood-flukes:	*Schistosoma japonicum*	46·0
	S. haematobium	39·2
	S. mansoni	29·2
Liver-flukes:	*Clonorchis sinensis*	19·0
	Opisthorchis felineus	1·1
Intestinal fluke:	*Fasciolopsis buski*	10·0
Lung-fluke:	*Paragonimus westermani*	3·2

Estimated world population	2,170
Calculated infections by nematodes	2,000 plus
,, ,, by cestodes	72
,, ,, by trematodes	148
Total helminthic infections	2,257

Ascaris lumbricoides has been known since ancient times, but was named and characterised by Linnaeus (1758). The adults live in the intestines, and they adhere to the mucosa periodically but obtain most of their nourishment from the intestinal contents. The eggs are unsegmented when they leave the host's body in the faeces and they develop in moist soil for about two weeks. The mode of human infection is by eating food contaminated with the eggs. The larvae hatch out in the small intestines and undergo a remarkable migration through the body, which F. H. Stewart (1916) worked out in laboratory rats and mice. The larvae penetrate the wall of the intestines, traverse the body cavity, pierce the lungs and get into the bronchioles, pass up the bronchi and are coughed up into the mouth, having developed considerably meanwhile. They are swallowed in sputum and return to the intestines, this time to settle down and become mature. During the transit of larvae through the lungs, the host may develop a fatal broncho-pneumonia.

Hookworms parasitic in man belong to three species, *Ancylostoma duodenale* (the Old World form), *Necator americanus* (the better-known New World form) and *Ancylostoma braziliense*. All three species exist in America, Africa and the Far East. Hookworm disease probably existed in ancient Egypt, and it was known in Italy, Arabia and Brazil much more than a hundred years ago. A. Dubini described *A. duodenale* in 1838, and named it in 1842 when a second infected individual was discovered, and not long afterwards other human infections became evident. In 1866 O. Wucherer found hookworms in Brazil, and in 1878 B. Grassi and E. Parona were able to diagnose infection by identifying eggs in the faeces of infected persons. The impression that the disease ancylostomiasis was confined to tropical and subtropical regions was dispelled when an epidemic broke out among miners constructing the St. Gotthard Tunnel (Switzerland). After the completion of the tunnel labourers returning to their homes spread the disease to many countries (Germany, France, Holland, Belgium, England, Spain and Sicily). Between 1877 and 1881 several Italians studied the disease. The transformation of free-living larvae into infective larvae was described by E. Perroncito (1880), but not till 1896–97 was the manner of penetration through the skin made clear by A. Looss, who accidentally infected himself, suffered a dermatitis of the hand and found eggs in his own faeces. In 1911 Looss described in detail the route taken by the larvae of the dog hookworm, *A. caninum*, through the skin, to the lungs, trachea and glottis in turn, and then along

the alimentary canal to the final location, the intestines. In America hookworm disease was first recognised in 1845 and observed in 1893. The New World form was not definitely identified as such till C. W. Stiles described it in 1902. The Brazilian form was described by G. de Faria in 1910. The pathology includes a dermatitis at the site of infection, inflammatory reactions in the air-sacs of the lungs and an ulcerated condition of the intestines due to the adult's habit of feeding on blood and torn mucous membrane, sometimes complicated by bacterial infection. There is usually chronic infection and the listlessness of infected persons may characterise large communities.

The whipworm *Trichuris trichura* was first described by Linnaeus in 1771. The common name denotes the long and whip-like body, the "lash" being the anterior region, which is usually embedded in the wall of the human caecum or colon. Infection is by the accidental ingestion of eggs, which are laid at the rate of about 2,000 a day and which hatch in the small intestine. The young worms then migrate into the large intestine and give rise to a severe form of septicaemia, and other inflammatory conditions are brought about if penetration is deeper. The much smaller pinworm, *Enterobius vermicularis*, was described by Linnaeus in 1758 and is very common in children all over the world. The adults live in the caecum and the females commonly emerge from the anus at night and wander about in its vicinity laying their eggs. The irritation set up by the worms leads to the contamination of probing fingers, which transfer ova to the mouth, bringing about re-infection. Otherwise, contaminated food may establish fresh infections. *Strongyloides stercoralis* was first observed by A. Normand (1876) in Cochin-China and described by A. Bavay in the same year. This worm causes a severe form of diarrhoea. There are reasons for supposing that larvae may reproduce parthenogenetically, though both parasitic and free-living males and females are known. Larvae hatching outside the host give rise to infective forms which penetrate the human skin, and, as many workers (P. van Durme, A. Looss, B. H. Ransom, F. Fülleborn) showed during the period 1902–14, make a comprehensive migration through the body; they enter the circulatory system by some vein, pass through the heart and on to the lungs, penetrate the air-sacs, enter the bronchioles, bronchi and trachea in turn, and eventually reach the glottis and the mouth, only to be swallowed with mucus and pass down the alimentary canal to the final location.

Trichinella spiralis is an unusual roundworm in that man, the pig

and other mammals can serve as both intermediate and final hosts, though change of host is necessary for completion of the life-cycle. The disease it causes is brought about by eating infected pork, imperfectly cooked. The muscles harbour encysted larvae. The only method of prophylaxis is cleaner pig-feeding. *Dracunculus medinensis* —the once-dreaded guinea-worm and the fiery serpent which afflicted the Israelites—was defined as a species by Linnaeus in 1758. H. Bastian (1863) described the structure of the worm. The eggs hatch in water and the larvae are eaten by a water-flea (*Cyclops*). The final host is infected by inadvertently ingesting infected water-fleas along with drinking water. The young worms take about one year to reach the final location of the host, the subcutaneous tissues, and the adult female liberates toxic substances and causes ulcers through which she protrudes part of her body in order to lay eggs.

Taking into consideration a predicted increase in world population, amounting, according to F. W. Notestein (1945), to more than 50 per cent. by the end of the twentieth century, N. R. Stoll suggested three possibilities which might reduce upwards of 3,000 million human helminthiases that can be anticipated. First, improving teaching in the field of parasitology of principles which should be known by all world citizens; second, doing all that is possible to shorten the period which is taken up in applying acceptable improvements when they will do most good and being less tolerant when the lag is unnecessarily long; and third, sharpening the tools already furnished for attacking the problem of human infection with helminths. This last includes better education, improved sanitation and up-to-date treatment. Methods of soil sterilisation are needed to protect human life and health in some districts and regions. New chemotherapeutic preparations are needed to break the life-cycles of parasites. The best agents so far have proved to be tetrachlorethylene against hookworms, hexylresorcinol against ascarids in children, gentian violet against the pinworm and other nematodes. These and other agents leave something to be desired, and in many cases of human parasitism there is no really good prophylactic or remedy—for instance, against whipworms. The solution of these problems calls for much more research and many more workers, both in the laboratory and in the field.

CHAPTER SEVENTEEN

ANTIBIOTICS

Immunology

NOT the least aspect of Pasteur's greatness was his will to press on beyond the discovery of a microbe and the demonstration of its pathogenicity and to find ways of counteracting its virulence. Pasteur rationalised the principle of vaccination, which Jenner first used empirically in 1796, and from his work arose that branch of biology and medicine which is known as *immunology*. He showed that when an animal is inoculated with microbes of reduced virulence it acquires a benign illness, but henceforth is safeguarded against serious illness as a result of infection with similar microbes in full virulence. The child given an injection of the comparatively innocuous liquid from cowpox pustules (*Vaccinia*) gets a mild form of smallpox but is protected from the more serious form subsequently. This disease is caused by a virus which when transferred from man to cattle, and back again, somehow loses much of its virulence; it has become what is called an "attenuated" virus.

Many other vaccines arose out of subsequent work by Pasteur and by Koch. In 1880 Pasteur discovered that the fowl can be protected against chicken cholera by inoculation with bacilli that have lost much of their virulence because they have been kept for several weeks in a culture. The bird develops a mild attack of the disease, but afterwards even virulent strains do it no harm. The loss of virulence in this case seems to result from an ageing of the bacteria. The anthrax bacillus loses its virulence when it is cultured at 42° C., the virus of rabies when it is dried.

Von Behring (1890) discovered that the immunity observed in guinea-pigs recovering from diphtheria was conferred on the animal by virtue of something in its blood serum, something which, though without effect on the diphtheria bacilli themselves (they will grow in it), in some way counteracts the effect of the poisons (or what Roux called *exotoxins*); and this something he called an *antitoxin*, though the broader term antibody is now used to denote any one of various entities

which act in somewhat similar ways. "Antitoxins" are antibodies which act on proteinaceous poisons such as snake venom, neutralising their action. "Agglutinins" act on suspensions of bacteria, causing them to become clumped or agglutinated, subsequently to settle and lose their potency. "Precipitins" are antibodies which react with foreign proteins that may enter the body of an animal, and "lysins" are agents which tend to dissolve or disintegrate bacteria. Some authorities are sceptical about the existence of so many kinds of antibodies, but such varied activities as these are best segregated for study. One outcome of this work was to show that the concept of antibodies can be brought successfully to bear on diseases such as tetanus, scarlet fever and gas gangrene; another was the discovery that vaccination is a method of evoking in the animal's body a natural response to foreign bodies by the production of antagonising agents. This is *active* immunisation as distinct from the passive form which characterises the inoculation of antibodies as such.

For some diseases neither toxins nor antibodies have been found, but the body of an animal has other defences, as the work of E. Metchnikoff at the Pasteur Institute, Paris, has shown (1901); notably the continual warfare which is waged between invading micro-organisms and certain white blood corpuscles, microcytes and macrophages. A win for the microbes spells susceptibility to disease; a win for the blood cells immunity. Metchnikoff watched the ingestion of minute particles by the amoebocytes of sea-urchin body liquid, and later on the ingestion of the spores of yeast cells which sometimes aggregate in the gut of *Daphnia*. If these spores penetrate the gut they develop in the haemocoele of the water-flea into yeast plants, which threaten the life of the animal, but they are effectively removed by phagocytic ingestion. Invading bacteria are likewise treated in the blood and tissue liquids of vertebrate animals, including man, and the leucocytosis which accompanies severe infection is to be regarded as a mustering of phagocytic reserves. J. C. H. Ledingham (1912) showed that any agent which makes adhesion more certain aids phagocytosis. Recent work on immunity has proceeded along various lines, and one important line concerns precipitins. Following up the work of von Behring (1890) on diphtheria immunity and P. Ehrlich (1891), who was the first to regard precipitins as specific entities, G. H. F. Nuttall in 1901 proceeded to collect blood samples from as many species of animals as he could get hold of. Then he tried to determine from precipitin reactions the degrees of relationship between various animals

—for instance, man and other primates, concluding that the Old World primates are more closely related to man than are the New World primates. In his book *Blood Immunity and Blood Relationship* (1904) he applied serological methods to taxonomy, and introduced chemical instead of morphological differences and resemblances into tests of animal relationships; literally a working out of "blood-relationship (see W. C. Boyd, 1949). This was the basis of modern classification of the blood groups (see p. 170).

A. Tyler (1942) introduced the methods of immunology into the field of embryology. More than twenty years earlier F. R. Lillie (1913, 1919) studied the penetration of the sea-urchin's egg by the sperm, and postulated the existence in the egg of a substance, *fertilisin*, which combines with another substance, *antifertilisin*, much as the participants of an antigen-antibody system operate. In this case the result which follows the entry of one sperm is the production of the fertilisation membrane, thus debarring entry to other sperms. Tyler suggested that fertilisin occupied a part, and possibly the whole, of the gelatinous covering of the egg, and is of the nature of a glycoprotein. Antifertilisin found on the surface of the sperm (and in the deeper part of the egg) has the property of being able to neutralise the sperm-agglutinating action of fertilisin. In short, the deeper parts of the egg contain a substance which acts as an antibody to the surface substance (see M. R. Irwin, 1949). Tyler later (1947) projected his ideas into an auto-antibody concept of cell structure, growth and differentiation. In 1948 he put forward the idea that the living cell is a mosaic of substances which are mutually complementary, *i.e.* are able to combine in the same manner as antigen and antibody, where they come close together. The result of their combinations is to produce structures such as the plasma and nuclear membranes, vacuolar membranes and such-like, which tend to keep the complementary substances apart under normal conditions. This is not as far-fetched as it may at first sound, for the close study of blood has demonstrated the presence of many antigens in it. In man, the corpuscles hold A and B substances (which happen to be polysaccharides of the same type as in certain bacteria) and also M, N and Rh antigens, and in birds even more are to be found. According to K. Landsteiner (1945) the specificity of the antigen is determined by particular parts of its molecule, and according to L. Pauling *et al.* (1940, 1946) the antibody molecule is of protein type and similar to the gamma-globulins of blood serum, the essential feature being appropriate folding of the peptide chain.

F. Haurowitz (1949) has shown that it is in such foldings that the complementary surfaces of antigen and antibody molecules is achieved. Antigens are visualised as substances which are deposited in locations where protein synthesis is proceeding, a process which they disturb. Protein synthesis takes place in two steps. First there is the formation of a two-dimensional layer and then a folding of this into a globular, three-dimensional figure. Antigens interfere with the latter process, with the result that the globular particle formation is complementary to that of the antigen molecule; as it were, moulded to an antigen template. If this modified protein passes into the blood serum it can act there as an antibody; if it remains in the cell it produces a condition of allergy in the cell. The function of nucleic acids in protein synthesis is believed to be to make the mono-molecular layer of peptide which serves as the template relatively insoluble and rigid (see Haurowitz, 1949). Alternatively, E. M. Burnet and F. Fenner (1949) regard antibody formation as an "inherited" mode of globulin synthesis which persists for many cell generations after the disappearance of the antigen.

Chemotherapy

The name "chemotherapy" was invented by Ehrlich to denote the freeing of an organism of its parasites by means of chemical substances of relatively low molecular weight. H. H. Dale reviewed the progress and prospects of chemotherapy up till 1924 in his Presidential Address to the British Association at Toronto. An interesting review of the history and the principles of the subject may also be found in the paper by Professor Adrien Albert (1946). Paul Ehrlich's interest in the subject arose in 1899, when he became Director of the Institute for Experimental Therapy in Frankfurt. Influenced no doubt by the great progress then being made by the application of organic chemistry to the science of medicine he set out in quest of chemical entities simpler than antigens which could be applied to the conquest of parasitic diseases. He worked along the right lines from the start, as is now evident in the fact that therapeutic agents discovered are all of much lower molecular weights than the protein derivatives known as antigens, mostly a few hundreds as against tens or even hundreds of thousands. Ehrlich was also looking for substances with two types of atomic groupings, one intended to exert the requisite toxic effect on the parasite and the other to have a chemical affinity for certain atomic groups which would form a "chemoceptor" in the body of the parasite.

The fundamental idea was to concentrate the drug where it would do most harm to the parasite and least harm to the host. Ehrlich never succeeded in identifying definite atomic groups with chemoceptors, but he worked on the assumption that certain specific groupings in protoplasm received arsenical drugs and certain other groupings antimonial drugs, and also that their normal function was related either to nutrition or to respiration of the cell. Albert has stressed that Ehrlich's concepts of active atomic groups in the molecules of drugs and of atomic groupings in cells which serve for their reception represented an enormous advance in biological thought and are "essentially compatible with present-day knowledge".

Ehrlich's opinions were criticised, notably by H. Uhlenhuth, who denied that drugs could have any direct effect on parasites, but served instead to heighten the natural resistance of the host. In 1907 Uhlenhuth found that trypanosomes were not harmed in the test-tube either by atoxyl or by trypan red, two of Ehrlich's most potent therapeutic weapons. Ehrlich and his Japanese assistant K. Shiga introduced trypan red in 1904, and it had been the first therapeutic agent to kill invading organisms without also killing the host. This took place in laboratory animals, but in 1905 H. W. Thomas had used atoxyl, which was discovered by A. Béchamp in 1863, for the cure of trypanosomiasis, the first clinical application of a chemotherapeutic agent. C. Levaditi (1908) tried to combine the opinions of Ehrlich and Uhlenhuth, suggesting that drugs have a chemical action on a parasite only after they have been modified in some way during their passage through the body of the host, a view which, according to Albert, is true to-day for some drugs such as prontosil but not for others such as sulphanilamide. Not till 1920–21 was trypan red superseded by the less toxic drugs tryparsamide and that form known as "Bayer 205" in the treatment of sleeping sickness.

E. Franke and W. Roehl (1907), working with Ehrlich, discovered the important phenomenon of drug-resistance, which may arise when the drug is taken in doses that are too small to kill all the parasites and so cure the disease. After a relapse, fresh treatment may fail to kill the micro-organism because in some way resistant strains have arisen and may require several hundred times the usual concentration of drug to kill them, a more massive dose than the host can in fact tolerate. Ehrlich himself encountered such resistance in trypanosomes, and found it possible to develop experimentally strains which were resistant to only one or to several classes of drugs, a fact which perhaps

encouraged him to develop his opinion regarding chemical specificity in the parasite.

Ehrlich lived to see the success in 1910 of "Salvarsan" (which he and his chemist F. Bertheim synthesised in 1912) in the treatment for syphilis, the application by L. Rogers (1912) of emetine, the active principle of ipecacuanha, to the cure of amoebic dysentery, the discovery by his pupil C. H. Browning of the first antibacterial therapeutic agents acriflavine and proflavin and their application in the treatment of sepsis in wounds. But Albert has written of the somewhat lean years between 1910 and 1919 when chemotherapy declined, and has stated that not till 1935 when G. Domagk used "Prontosil" for the control of certain bacterial infections "did chemotherapy recover its former position in the eyes of the medical world". But the years between the wars produced many notable discoveries. R. Sazerac and C. Levaditi (1921) applied bismuth compounds to the treatment of syphilis, and this was followed in 1932 by the use of "Mapharsen" by A. Tatum and G. Cooper. The scourge of malaria was combated by the use of "Plasmoquine" by W. Roehl (1926) and "Atebrin" by W. Kikuth (1932), amoebic dysentery by the use of "Carbasone" by C. Leake, D. Koch and H. Anderson (1930). Research on parasitic amoebae was facilitated by methods of culture *in vitro* discovered by P. P. Laidlaw, C. Dobell and Ann Bishop (1928), and by the culture *in vitro* of trypanosomes by W. Yorke, A. Adams and F. Murgatroyd (1929). During this period, as Albert has shown, much progress was made on the scientific side of chemotherapy, with complete vindication of Ehrlich's opinion that parasites can be eradicated by the use of chemical substances of low molecular weight and the establishment of chemotherapy on a sound theoretical basis. During these years the sulpha drugs were perfected in a series which included sulphanilamides, sulphapyridine and sulphadiazine in the treatment of bacterial sepsis. During the recent war years came the perfection of chemotherapeutic remedies for malaria, leading up to the use of "Paludrine" in 1945, but this period has been remarkable for the introduction of the agents known as antibiotics, the most notable of which are penicillin and streptomycin.

The term "antibiotics" has been applied to the chemotherapeutic substances which some moulds and bacteria normally produce and use to keep down their biological competitors. The modern conception of these substances has developed rapidly since Professor Andrew Fleming, working at St. Mary's Hospital, London, made the

chance discovery of penicillin by following up the spoiling of bacterial cultures by the spores of moulds in 1929. Professor H. W. Florey saw the clinical possibilities of their use in 1938 when in the Sir William Dunn School of Pathology at Oxford there followed team work which led up to the commercial production of penicillin. Florey had the assistance of Dr. E. Chain and others. N. G. Heatley devised methods of assay for penicillin and constructed the first laboratory plant on a large scale, A. G. Sanders devised apparatus on a still larger scale. C. M. Fletcher assisted Florey in the clinical work and E. P. Abraham assisted Chain in studying the chemical composition. Professor A. D. Gardiner studied the bacteriological aspect of penicillin problems and M. A. Jennings worked on other biological aspects (see G. S. Ranshaw, 1946; and E. S. Duthie, 1946).

These discoveries had several forerunners which are of some historical interest. In 1877 Pasteur and Joubert discovered that a culture of one species of bacteria could be suppressed by the development of foreign bacteria, and within a few years it was suspected that such inhibition must be due to the production of antibiotic substances. The early treatment of diphtheria and of septic wounds by means of pyocyanase, an autodigested culture of the microbe of blue pus, *Pseudomonas pyocyaneae*, met with a certain amount of success, and more recent work has shown that various bacteria can be combated by antibiotics produced by similar organisms. The antagonistic action of crystalline products of certain moulds on bacteria was studied before the end of the nineteenth century, and in 1910 A. Vaudremer suggested that substances produced by the mould *Aspergillus fumigatus* could be used to combat the tubercle bacillus.

Since the discovery of penicillin an intensive search has been made for new antibiotics, involving experiments with many hundreds of moulds, bacteria and other plants which have revealed very many examples of antibacterial action, though only a few substances of much value. By means of X-rays and radium it is now possible to produce mutating stocks of moulds and bacteria, thus increasing the potential number of antibiotics available. In this way it is possible to aim at producing the ideal antibiotics for certain specific purposes. An ideal antibiotic substance will be lethal to bacteria, not merely inhibitory, will resist chemical alteration in its passage through the blood and tissue liquids of the host, and will be tolerated by the host even in large therapeutic doses and harmless to its leucocytes; it will be applied to just those diseases which do not respond to treatment with

simple chemotherapeutic agents. The most useful antibiotic since penicillin is streptomycin, which was obtained in 1944 by S. A. Waksman and other members of the Mayo Clinic in America and which has been used in the cure of typhoid and tuberculosis (see Waksman, 1945). At Oxford several other antibiotics have been produced, notably pro-actinomycin and helvolic acid, but as these attack the same bacteria as penicillin and are more toxic than this substance they are not likely to have a very wide application in chemotherapy. The biologists and chemists of Parke Davis & Co. have recently investigated the newer antibiotic chloromycetin, which is effective against scrub typhus and similar infections. For the first time chemotherapy is thus brought to bear on a disease caused by a Rickettsia and the way is opened up to control diseases caused by viruses.

Selective Toxicity

The broader aspect of chemotherapy is now called "selective toxicity", which Adrien Albert (1950) has defined as "the science of injuring certain kinds of living cells without harming other kinds of cells in the vicinity". In practice the aim is to kill uneconomic cells or organisms so as to promote the survival of economic cells or organisms. By the use of selectively toxic agents such as weed-killers or insecticides the farmer or horticulturist is able to increase his harvests by the suppression of those forms of life—fungi, weeds and insects—which cause havoc to his crops. Such agents also have their use in animal husbandry for the control of external and internal parasites which threaten domesticated animals, and also in medicine for the same purpose in regard to man. Selective toxicity is a branch of biology which includes chemotherapy, and also pharmacology in as far as this subject concerns itself with the eradication of uneconomic cells. One of the most notable selectively toxic agents discovered in recent years is dichlor-diphenyl-trichlorethane, now better known as DDT. Not the least remarkable thing about this substance is that it was synthesised as long ago as 1874, by Othmar Zeidler, who recorded his discovery in a few lines of text (*Ber.*, **7**, 1181) and who died without seeing the fruits of his discovery, which was neglected for more than sixty years. During the nineteen-thirties the substance claimed the attention of various chemists and biologists. In 1939 a DDT compound made by the firm of Geigy, and later sold as "Gesarol", saved the potato crop of Switzerland from the threat of colorado beetle, and two years later the Swiss notified Geigy, New York, of developments,

though this action produced little response. In 1942, however, Geigy of New York received a quantity of DDT from Switzerland and the notice of the U.S. Department of Agriculture was directed to tests on various insects, which soon produced spectacular results bearing on the lousicide properties of the compound. Patents were taken out in Britain during 1942 and production began soon afterwards.

During the war DDT proved invaluable for ridding the body of lice and for combating malaria-carrying mosquitoes. It was first tried out on a large scale in the typhus epidemic of Naples, 1943–44, with complete success, the destruction of human body-lice resulting in an immediate decline of the epidemic. It was applied as a dust, enabling the body and its clothing to be treated in about two minutes. More than 70,000 individuals were cleared of lice by this means in a single day. Several methods were used against mosquitoes; a thin film was sprayed on the interiors of houses and huts, or on the surface of pools in which mosquitoes bred, and larvae live. Aircraft were used for spraying extensive tracts of country. P. A. Buxton (1945) has reviewed the relation of DDT to tropical medicine. Also used for the same purposes is Gammexane (known also as 666), the γ-isomer of hexachlorocyclohexane (other isomers are non-active), which was discovered by Faraday in 1925. Like DDT it is toxic to man and domesticated animals if taken orally in large amounts or applied to the skin in strong solutions, a drawback which is not involved in the use of another powerful insecticide dimethyl phthalate, which can be applied to the skin and will keep mosquitoes at bay for several hours, and for several days if sprayed on clothing. Other insect repellents are indalone and Rutgers 612. The interested reader will find much information regarding DDT in the monograph *Some Properties and Applications of DDT*, published by the Ministry of Supply (H.M. Stationery Office, 1946: price sixpence). It contains many references of historical significance.

J. E. Webb (1949) has shown that insects are killed when some insecticide interferes with one of the vital centres of the body after penetration by way of the mouth, or the openings of the respiratory system (the spiracles), or through the cuticle. Insecticides thus fall into three broad categories: stomach, respiratory, and contact poisons. Stomach poisons are used to deal with insects having biting mouth parts. Respiratory poisons are of great efficaciousness with some insects but insecticidal dusts may be kept out of the tracheal system of other insects by filtration at the spiracles.

According to Albert (1950), we cannot yet profitably classify selectively toxic substances according to physical or chemical action. The action of most of them depends on specificity of structure. Substances with molecules of a certain shape and with certain chemical groups characteristically disposed enable the specifically toxic substance to combine with certain cell constituents. Physical properties are important for the accumulation in some vitally important part of a cell of substances which seem to disorganise the respiratory processes of the cell. This is true for hydrocarbons, alcohols, ethers, ketones and non-ionised bases or acids, all of which have the same degree of biological action when "proportional saturation" is the same, even when the concentrations are far from equimolar.

With structurally specific toxic agents the degree of specificity is very great, as is shown by "metabolic analogues", substances which operate by blocking the natural receptors for substances used in metabolism (metabolites), and prevent these from exerting their normal biological action. According to P. Fildes (1940) and D. D. Woods (1940) sulphanilamide destroys bacteria because it is a metabolic analogue of *p*-aminobenzoic acid, which plays an important part in the metabolism of the bacteria. The subject was reviewed in detail by R. O. Roblin (1946). By the study of metabolites and their antagonistic analogues it is possible to discover valuable new selectively toxic agents. D. W. Woolley (1947) made a list of forty substances, notably vitamins and amino-acids and their analogues, two of which became recognised as valuable drugs by such considerations of antagonistic blocking of metabolites. The degree of ionisation may also be an important feature in selective toxicity; of the many known acridines the most markedly antibacterial are those which are highly ionised, the least so those which are little ionised. Another important consideration is the possibility of selectively toxic action by increasing the concentration of elements which are present only as traces, or by lowering the concentration so that the necessary trace is denied to the uneconomic cell or organism (see H. N. Rydon, 1949). W. A. Sexton (1949) has reviewed the organic chemist's approach to antibiosis and R. A. Peters (1949) the idea of selective toxicity to enzymes.

CHAPTER EIGHTEEN

AGRICULTURAL BIOLOGY

THE importance of biology in agriculture is bound up with its relation to the breeding of animals and plants, the study of the soil, and the cultivation of crops. From the eighteenth century onwards, British cattle, horses and sheep have been much improved, and this had gained world-wide recognition much more than one hundred years ago. Among the early pioneers were Robert Bakewell, who bred Longhorn cattle and Leicester sheep; Charles Colling, who bred Shorthorns; and the Davy family, who bred Devon cattle. The Hereford Herd Book was established in 1846, the Devon Herd Book in 1851, and by 1880 the books of many other breeds had been set up (T. Bedford Franklin, 1948). Advances in plant breeding were more retarded, the major developments coming with the advance of genetics during the twentieth century.

During the early nineteenth century agriculture was in a sorry state in Britain, but in 1838 the Royal Agricultural Society gained its Royal Charter and in 1840 began to publish its own journal. In the first volume of this (1840, p. li) the nine main problems of agriculture were defined (see Sir E. J. Russell, 1932). As new knowledge was gained, farmers were encouraged more and more to utilise biological discoveries for the improvement of their craft. In 1840 Justus von Liebig began to investigate soils in relation to the nutrition of plants, and in 1843 the oldest and finest agricultural research station in Britain was founded at Rothamsted. The Cirencester Agricultural College was founded in 1842, and in later years plant breeding was taken up at Cambridge, and other establishments were set up at Wye College and elsewhere. The Board of Agriculture was founded in 1889, Bangor College in the same year. The twentieth century has seen the foundation of various related institutes and colleges—for animal nutrition at Cambridge, for dairy research at Reading, and for agricultural economics at Oxford. Eighteen agricultural institutions existed in 1900. Biology has played a large part in these developments and others which came later, and it has been advanced substantially by the work carried out in them. In 1905 an International Institute of

Agriculture was founded at Rome, and by 1910 forty-two countries had joined the organisation.

Soil Science

Soil science is a development of the twentieth century. J. Hendrick (1936) pointed out that there were no British text-books on the subject in 1900, though there were a few American books. Biologists interested in problems connected with the soil began to hold international conferences soon afterwards, the first of them (on "Agro-Geology") at Budapest in 1909. A series of such conferences led to the foundation at Rome in 1924 of the International Society of Soil Science. The Proceedings of this Society took the place of the earlier *International Mitteilungen für Bodenkunde*, and the activities of the Society led to the appearance of a new journal, *Soil Research*. In 1916 the related American journal, *Soil Science*, appeared.

The soil is something more than a medium in which plants can grow; biologically speaking, it is a complex world of living things competing with one another for limited amounts of food under a special set of physical and chemical conditions. The organisms are the chief concern of soil microbiology, their background that of agricultural chemistry. Both of these special aspects of biology have arisen since the time of Liebig and are products of nineteenth-century progress. S. Winogradsky (1949) has reviewed fifty years of progress in soil microbiology. The organisms in soil range from virus particles to voles. Bacteria exist in tremendous numbers in some soils, being reckoned in thousands of millions per gram. Protozoan animals may number one million per gram of soil, and other simple organisms such as algae and fungi though not present in such prodigious numbers nevertheless loom large in bulk. If we add to this welter of primitive life the products of life and death of innumerable worms, arthropods, molluscs and other animals we are inclined to agree with the soil chemist and the soil biologist that complexity exists in the medium in which plants grow. One phenomenon is nitrogen fixation, whereby free gaseous nitrogen is bound to other elements to form compounds that are useful to plants, notably amino-acids. From these substances the plant builds up proteins which come to be used in nutrition by animals. The plants themselves are ultimately either eaten by animals or else they die and decay. Animals in their turn produce nitrogenous waste materials which are returned to the soil and, like animal remains, are broken down by bacteria and fungi, decay and putrefaction leading

to the production of ammonia and ultimately to free nitrogen. This constantly recurring process whereby free nitrogen is temporarily abstracted from the funds provided in nature, utilised for a time by organisms and finally returned to the common fund, is known as the *nitrogen cycle*, which takes place in lakes and the sea as well as on land.

The fixation of nitrogen by micro-organisms is essential for the maintenance of life on the earth. All the nitrogen which is found in various nitrogenous compounds originated from the atmosphere. Most of it results from the activity of micro-organisms. The use of industrial nitrogenous fertilisers accounts for only one part in two hundred of the nitrogen harvested annually in the world's crops. J. G. Lipman and A. B. Conybeare (1936) estimated that cultivated land in the U.S.A. gains 16·45 million tons of nitrogen per year, nearly three-fifths of this (9·83 million tons) from micro-organisms and about one-third (5·46 million tons) from the bacteria associated with leguminous plants. By contrast, industrial fertilisers and manures used annually contain only about three million tons of nitrogen. For a recent discussion on the nitrogen cycle in nature see G. R. Clemo and G. A. Swan (1950).

Nitrogen Assimilation

The problems of nitrogen fixation are fundamental in agriculture and research on them dates back at least to 1837, when Boussingault showed that it is achieved by some plants but not by others. Clover, peas and other leguminous plants achieve it, but wheat and others do not. Liebig (1846) did not accept the view that free nitrogen was involved, suggesting that the essential substance needed by plants was ammonia, but about 1866 botanists began to notice again the nodules which Malpighi saw in 1686 on the roots of leguminous plants, and these were soon shown to contain colonies of bacteria. After sustained research for about ten years Berthelot in 1886 proved that it is these bacteria which "fix" free nitrogen, and showed one year later that such organisms contribute nitrogenous matter to the soil by their own syntheses. In 1888 Hellriegel and Wilfarth proved that the bacteria infect the nodules and suggested that they live in a mutually beneficial (symbiotic) relationship with the plant. In the same year Beijerinck made pure cultures of the bacteria and in 1890 Prazmovsky gave them the name *Bacillus radicicola*, of which a number of strains have since been recognised. The bacteria, which are now known as *Pseudomonas radicicola*, enter the plant through the root-hairs, which have some sort of attraction for them and which become deformed by substances

produced by the organisms. Once established in the plant they evoke cell multiplication (proliferation) and this leads to the production of the nodules by irregular growth. In 1920 Bewley and Hutchinson showed that the bacteria pass through various stages—coccus, flagellate form, unbanded rod-like form and banded rod-like form—whether living in the soil, in the plant, or in cultures. Some leguminous plants (*e.g.* wild senna) do not have root nodules, and some non-leguminous plants (*e.g.* the alder) do have them. In some non-leguminous plants the leaves show small swellings harbouring other nitrogen-fixing bacteria (*Mycobacillus rubiacearum*). Certain soil bacteria also have this power, notably *Clostridium pasteurianum*, which was discovered and named by Winogradsky in 1893, and *Azotobacter chroococcum*, which was discovered by Beijerinck in 1901. The former is aerobic, the latter anaerobic. Both assimilate (fix) nitrogen in proportion to glucose utilised: on the average 1 gm. glucose corresponds to 2–3 mg. and 10 mg. nitrogen. Other bacteria and moulds such as *Aspergillus* and *Penicillium* may also play a part in nitrogen fixation, which can also be brought about by the oxidative effect of lightning (products brought down in rain satisfy 1–2 per cent. of the plant's needs). The great nitrogen-fixing industries produce ammonia in tremendous quantities, either by passing an electric spark through a mixture of nitrogen and hydrogen, or else by catalytic action at high pressures and temperatures (200 atmospheres and 500° C.). As yet there is no knowing how plants achieve this effect. But, as Winogradsky proved (1895), ammonium nitrogen is converted into nitrites by the specific action of bacteria known as *Nitrosomonas* (*Nitrosococcus* in America), and these are further oxidised to nitrates by the bacteria known as *Nitrobacter*. Both kinds of bacteria are anaerobic forms which use the energy released by the oxidative changes for their own metabolism, building up their own carbon compounds from carbon dioxide and water as do other autotrophic organisms.

It is now well known that green plants build up amino-acids and proteins from ammonium compounds, nitrites and nitrates (see Petrie, 1943). This process, which will take place in the dark and in isolated roots, is independent of photosynthesis. The chemical reactions involved are unknown, though some experiments have shown that amino-acids are derived from keto-acids (such as pyruvic acid) and ammonia. In recent years some attempts have been made to follow the process of nitrogen assimilation by means of radioactive tracers, using heavy nitrogen (N^{15}). When plants are grown in solutions of

ammonium compounds containing heavy nitrogen the roots seem to be most active in nitrogen assimilation, but heavy nitrogen is found in protein molecules widely distributed in both the growing and the mature plant. In sunflower-plants there may be as much as 12 per cent. replacement of protein nitrogen in less than a fortnight (see Hevesy *et al.*, 1940) even in old leaves which are not growing. It seems that nitrogen atoms are continually entering and leaving the very labile protein molecules of the plant, so that we have a dynamic and not a static condition. In the green alga *Chlorella*, according to Warburg and Negelein (1920), nitrogen assimilation involves enzymes containing heavy metals and is dependent on manganese, as is true also for wheat plants, though in the absence of this element other catalysts which do not contain it can be used.

In a recent review A. I. Virtanen (1947) claimed that the effectiveness of legume bacteria in nitrogen fixation depends to some extent on the host. The invasion of the roots by the bacteria leads to the formation of nodules, but not necessarily to nitrogen fixation. Changes which take place in the nodule decide whether or not it will become effective. Beijerinck in 1888 first demonstrated the change of the rod-shaped bacteria of nodules into swollen and irregular "bacteroids". In 1893 Nobbe and Hiltner suggested that unchanged bacteria are ineffectual as nitrogen fixers, and Virtanen and his colleagues, who found bacteroids in effective but not in ineffective nodules, have revived this view.

Mothes and Pietz in 1937 and Pietz in 1938 studied the red pigment found in the nodules of leguminous plants. In 1939 Kubo extracted such pigment from soya bean and watery extracts of it gave a haemoglobin spectrum. The war prematurely stopped this research, but Virtanen and his colleagues in the Biochemical Institute, Helsinki (in 1944), confirmed the work of Kubo. By 1945 Virtanen had traced the relationship of the pigment to nitrogen fixation in a series of experiments with pea plants. Root nodules containing effective bacteria invariably produce red pigment under conditions of nitrogen fixation. Nodules which contain ineffectual bacteria neither produce red pigment nor achieve nitrogen fixation, and this is true of nodules with effectual bacteria if oxygen is not present in the substrate. When normal plants are kept for some days in the dark their red pigment becomes altered to green and henceforth they cannot fix nitrogen, even in light. Burris and Haas in 1944 showed that the red pigment is a haemoprotein; Keilin and Wang in 1945 that it is a haemoglobin.

For it Virtanen suggested the name *leghaemoglobin.* The green pigment which is derived from the red when plants are kept in the dark contains iron but no longer gives the spectrum of haemoglobin. Interestingly, the red root nodules regularly turn green when the pea-plant is flowering. After the last flower has appeared and the last growing point gone most of the root nodules have become green and very soon all are green. After this, nitrogen fixation no longer takes place. Virtanen (1947) considered that the red pigment may be a store and a carrier of oxygen, taking no part in nitrogen fixation; or, it may participate directly in the first stage of nitrogen fixation: or, it may instead catalyse further changes of the primary product of nitrogen fixation. Of these three possibilities he preferred the first. Many experiments have established that the passage of organic nitrogen to the plant is a form of excretion. The fixed nitrogen is transferred to the cytoplasm of the nodule cells, thus becoming available to the plant. When nitrogen fixation ends the bacterial mass in the nodule decomposes and the products may also be used by the plant.

Ecology

The study of organisms in relation to their environment was at one time known as natural history, which dates back to antiquity. It is now called ecology. The exploration of the sea is one aspect of it, but other aspects have arisen out of botanical studies made on land, and animal ecology arose when zoologists followed the example of early plant ecologists such as E. Warming (1895), who dealt with the ecology of plant associations. The first text-book of animal ecology was the *Guide* written by C. C. Adams (1913), the first comprehensive work on animal communities that of V. E. Shelford (1913). W. C. Allee *et al.* (1949) gave an outline history of ecology up to the twentieth century and during the first four decades of it. This book is concerned mainly with principles, but it contains about 2,500 references to the scientific literature. This is a field which calls for knowledge of a wide range of subjects (see C. Elton, 1933). The ecologist must be a map reader, something of a geologist and a student of soils and climate. He must be aware of influences such as grazing upon agriculture and the modifying influences of vegetation upon animal life. Whenever man comes into contact with animals and plants in the wild state ecology becomes vitally important, consequently the rise of civilisation and repeated conquests of new territories to provide fresh areas of cultivation have created biological problems. The cultivation of land reveals the pests

of crops and stored products, the planting of forests brings the menace of many enemies of timber, the herding of animals is accompanied by the spread of disease. Wherever man comes into contact with nature at the economic level he finds problems by the score, and many of these are still unsolved. The control of locust and lesser agricultural pests such as the codlin moth, cotton boll weevil, and the pear slug—these and many other problems still await a solution. Various writers have given accounts of the biological control of insects—a subject of considerable importance which cannot be discussed fully here—notably H. L. Sweetman (1936), A. D. Imms (1937) and H. Nicol (1943).

Plant Pathology

The diseases of plants are of fundamental importance to agriculture. Some early developments in mycology were mentioned on p. 16, and H. S. Reed (1942) has outlined other developments in plant pathology. Many standard works on the subject are now available, *e.g.* F. D. Heald (1933), I. E. Melhus and G. C. Kent (1939), and F. C. Bawden (1948). Notable efforts to investigate the bunt of wheat were made by M. du Tillet (1755) and B. Prévost (1807), and the ancient plague of rust on wheat was one stage nearer control when T. A. Knight in 1804 infected plants experimentally from rusted wheat leaves and also by spores collected from the barberry. Plant pathology first became a science, however, when De Bary had worked out the life-histories of certain notorious fungi. At the turn of the nineteenth century the Tulasne brothers were investigating the origin of smuts and the development of ergot. Soon afterwards (1858) J. Kühn published *Die Krankheiten der Kulturgewächse*, and plant pathology was established on a scientific basis. Other pioneers in this subject were E. Prillieux and A. Millardet of France, J. Eriksson in Sweden, M. S. Woronin in Russia, A. N. Berlèse and others in Italy, A. B. Frank in Germany, and F. L. Scribner, N. B. Pierce and others in U.S.A. Notable books on forest pathology were H. M. Willkomm's *Die Mikroskopischen Feinde des Waldes* (1866–67) and R. Hartig's *Lehrbuch der Pflanzenkrankheiten* (1900) and text-book on the diseases of trees (Eng. trans. 1894; Macmillan).

Bacterial Diseases of Plants

The first instance of the bacterial cause of disease in plants was established in America in 1878 by T. J. Burrill, who discovered (only

two years after Koch discovered the cause of anthrax) that Twig Blight of apple, pear and other fruit trees is due to a bacterium which he called *Bacillus amylovorus*, which destroys the cells of the cambium. At Amsterdam in 1883–84 J. H. Wakker discovered that "yellow disease" of hyacinths is caused by a form which he called *Bacillus hyacinthi*, living chiefly in fibrovascular tissue. In 1893–95 E. F. Smith of the Federal Department of Agriculture, U.S.A., discovered and named the organism causing a wilt disease in Cucurbitas—*Bacillus cucurbitas*, and in 1893 W. B. Pierce the organism causing a blight of cultivated walnuts—*Pseudomonas juglandis*. Early during the twentieth century other bacterial causal agents of disease in plants became known and in 1911 the virulent bacterial disease known as citrus canker was introduced into the U.S.A. from the Orient, being recognised in 1913 as due to *Phytomonas citri*. Reed (1942) has described the remarkable campaign which was waged against this disease. Complete defoliation of infected stocks and subsequent treatment with fungicides were completely ineffectual. Trees were then sprayed with burning oil and four million of them were destroyed, representing damage amounting to $2,500,000; the disease, however, was eradicated.

Virus Diseases of Plants

In 1899—and about seven years after D. Ivanovski's discovery regarding mosaic disease in the tobacco-plant—Beijerinck set up the concept of "a living contagious liquid" carried in the phloem of infected plants. During the first three decades of the twentieth century many virus diseases of plants were discovered and described, but little progress was made in systematically classifying them. Viruses do not produce spores or other bodies which aid diagnosis and classification, and consequently the diseases they cause are better known by the damage done to their plant hosts—such as "leaf-roll" of potato, "curly-top" of sugar-beet and "crinkle" of cotton. The viruses are generally localised in the growing cells of the plant, and less frequently in the root than in the stem. They are often spread from plant to plant by contact—which human agency may aggravate—but the importance of insect vectors is now recognised in the virus diseases of plants as well as of animals. Takami, in Japan, first noted the part played by insects in spreading virus disease. In 1901 he infected healthy rice-plants with stunt disease by the agency of *Nephotettix*, a leaf-hopper. Modern research has revealed many other instances, and virus research now figures prominently in the programme of work

carried out in agricultural stations. F. C. Bawden (1939), J. G. Leach (1940) and others have dealt with modern aspects of such work.

The Biological Control of Weeds

Weeds are plants unwanted for one or more of several reasons. They may occupy space intended for the crops of arable land, reduce the value of pastures and the yield of milk, beef and mutton, spoil economic products as burrs spoil the fleece of sheep, and generally interfere with agricultural practice. They may be poisonous to both man and his domestic animals. Weeds have been able to overcome the natural barriers such as oceans, mountains and desert which prevent their spreading, and they have been carried as seeds to many countries in animal fodder and soil. According to F. Wilson (1950) their control by biological methods has been a development of the last fifty years, and has followed on the similar type of control of insect and other animal pests. Entomologists have searched the world for the natural enemies of insect pests (see A. D. Imms, 1937). In Mexico, A. Koebele found a fly that attacks the seeds of the shrub *Lantana camara*, which became a pest in Hawaii. This discovery led to the use of plant-eating (phytophagous) insects in the control of this and other weeds. Eight species of insects which feed on *Lantana* were sent from Mexico to Hawaii and established there. The shrub was largely destroyed by a fly which, as a larva, ate the berries, a bug which attacked the foliage and damaged the flowers, and the caterpillars of a moth which spoiled stem, flowers and fruit.

The most notable example of biological control of weeds concerns the prickly pear—various species of the genus *Opuntia* (family Cactaceae). About half a dozen species became pests in Australia, after being introduced there from America in 1839. By 1900 this cactus had spread to about ten million acres, and by 1925 to sixty million acres, mostly in Queensland, but also in New South Wales. In 1920 the Prickly Pear Board was set up to deal with this enormous problem. During the period 1920–37 much work was carried out in America on insects which live on cacti, and about 150 species were found. The fifty which held out most promise of combating prickly pear were dispatched to Australia. Here the insects were kept in quarantine for some time and their food habits carefully studied, for there was some risk of the insects themselves becoming serious pests. Some of them were starved and their feeding reaction to various vegetables, fruits and cereals examined. The dozen most promising species were

then liberated and established, among them a moth, three bugs, a cochineal insect and a red spider. The immediate results were good. In 1925, however, a moth (*Cactoblastis cactorum*) which normally lives on prickly pears was sent from the Argentine. This insect lays its eggs in sticks of about eighty in a row and produces two generations a year. The caterpillars penetrate and feed on the tissues of the prickly pear. As fast as they destroy one stem they pass to another and eat that. In 1926 this species was distributed in the egg stage and by the end of 1927 about nine million eggs had been put out at strategic centres. From these more egg-sticks were gathered and further distributed until in 1928–30 at least three thousand million eggs had been disseminated. The result was spectacular; vast areas of prickly pear were devastated and by 1933 the last group in Queensland was destroyed. Swarms of moth caterpillars then wandered about, causing some anxiety until it was ascertained that they merely starved and died. Small outbreaks have since taken place, but as a result of this experiment about twenty-two million acres of prickly pear territory was reclaimed and put under cultivation. The campaign was described in detail by A. P. Dodd (1940).

Wilson (1943, 1950) has described work carried out more recently against the poisonous weed St. John's wort (*Hypericum perforatum*), which has been a particular nuisance in Australia and New Zealand. Five species of insects were carefully studied in England, shipped to Australia and liberated. These insects—three leaf-eating beetles and two moths—at first multiplied, but eventually disappeared, having presumably succumbed to predators and climatic conditions. Further work based on the South of France—which has a climate more like that of Australia—produced two more beetles, *Chrysolina genellata* and the root-boring form *Agrilus hyperici*, which were sent out to Australia, released in 1939–40 and soon established themselves. Meanwhile, the English beetle *Chrysolina hyperici* reappeared, and in the following years this and the related *C. genellata* multiplied abundantly. The beetles produce several thousand eggs in one brood annually, and their larvae feed on the foliage of the weed. Their depredations promise the end of trouble with St. John's wort in the Antipodes.

Wilson gave an outline of the general basis for the biological control of weeds, which is not regarded as the solution to all or most weed problems but one of the chief methods, and an inexpensive method, of eradicating alien weeds. Insects are well-known pollinators of plants but little-known weed-controllers, which is remarkable because

"the world contains hundreds of thousands of kinds of insects that live at the expense of plants, and there is barely a plant species in the world but has its associated complex of insects, enemies that are often specialised to attack it and its near relatives only". He has shown how delicate a balance is set up between weeds, the insects that feed on them and also their predators and parasites, the latter often preyed upon by secondary parasites and these by tertiary parasites. Biological control of plants, as of animals, is not an undertaking to be embarked on without due regard for all the biotic factors involved.

Modern Problems of Agriculture

Sir John Russell (1949, 1950) has vividly sketched out present-day problems of agriculture and has shown how expansion and improvement can be carried out on a world scale. He has a vegetation plan for dealing with the problems of soil erosion and soil conservation. Hilltops and slopes can be protectively covered with trees, and cultivated lowlands guarded against soil movements and erosion by water. Such a plan calls for collaboration between biological specialists—ecologists to determine what plants are best suited to particular types of land, agriculturists and foresters to consider which of these plants are of greatest economic value, plant geneticists to develop varieties of plants ever nearer to what is ideally possible, by the transference of desirable characters from one plant to another. In this way geneticists have already evolved new varieties of wheat to ripen early, produce short stems and heavy ears, resist rusts and other diseases, or withstand frost. Intensification of cropping calls for specialised knowledge concerning fertilisers, and also about the problems of extended irrigation and control of weeds. Other problems which come into the picture concern viral, bacterial and fungal diseases in the field, and the pests which spoil the harvests in storage. Grain crops are preyed on to a serious extent by rats and mice, and by hosts of insects found only in granaries. As new remedies such as DDT or methods of biological control in the field are devised to combat such pests, hosts of fresh problems arise. This is true also of stockbreeding, for the appearance of new stocks may create fresh problems of disease, and these in turn create still other problems such as the perfection and use of vaccines and sera.

As is well known, what may at first seem to be purely academic scientific research sometimes turns out to be of the utmost practical importance. The uses to which plant hormones (auxins) have already

been put far surpasses the wildest imaginings of those who discovered and first worked with them. Fruits may be "set" in tomato, cucumber and other plants without recourse to fertilisation, weeds may be exterminated promptly, root crops prevented from sprouting in storage, harvests may be "staggered" to suit the requirements of the preserving industries, and shoots that would have produced only leaves can be induced to produce flowers and fruits instead. The value of soil organisms in the production of antibiotics such as penicillin has only recently been realised, and may be expected to grow as research proceeds. Hormones from animals can be used to enrich milk or increase its yield in cows, even to induce lactation in virgin heifers and barren cows. The widely used practice of artificial insemination enables the benefits accruing from the work of the animal breeder in producing stocks with desirable qualities to be spread, both at home and abroad. Following the discoveries which made possible dispatch of stocks of sperms through the post comes the transplantation of embryos of live stock into artificial mothers. New methods of feeding can transform the proportions of a sheep or a pig, and yield a more valuable food animal with whatever relative quantities of red meat and fat are desirable. The knowledge won by biological research is never wasted, and there is no telling into what outlying regions of the subject the newly discovered knowledge will spread, or with what effects. The recent trends in biology touch human life in all its aspects, from the purely physical to the psychological. The problems of life merge almost imperceptibly with the physical universe on the one hand and man's mental outlook on the other.

Locusts and their Control

Locusts have been serious agricultural pests from the earliest times and their ravages have created wholesale famine and caused untold human misery. They are exceedingly mobile insects and very numerous, so that a plague of them may descend on a whole country without warning. Most of Europe is safe from their depredations, but Portugal, Spain, Italy, the Balkans, the Ukraine and the Caucasus have all been menaced by locusts at one time or another. According to B. P. Uvarov (1941) "none of the five continents is free from these pests, which in fact are absent only from the forest and tundra belts in the north, from the equatorial forests, and from high mountains". Apart from human misery, sickness and death, locusts cause enormous losses, which have been estimated for the world at about £15 million

per annum. The possibility of reaping some benefit by processing their bodies to form cattle and poultry food, soil fertilisers and even human food has been considered, for some locust swarms represent hundreds of tons of organic materials, but an industry could hardly be based on materials of such sporadic appearance.

Locusts belong to a number of species, eight of which are particularly important. These are the Asiatic migratory locust (*Locusta migratoria migratoria*), the Moroccan locust (*Dociostaurus maroccanus*), the Oriental locust (*Locusta migratoria manilensis*), the desert locust (*Schistocerca gregaria*), the African migratory locust (*Locusta migratoria migratorioides*), the red locust (*Nomadacris septemfasciata*), the brown locust (*Locustana pardalina*) and the American locust (*Schistocerca paranensis*). About seventy-seven separate countries are regularly or periodically affected by locusts, and countries which do not have locusts (*e.g.* Canada) have to reckon with grasshoppers. The two kinds of insects have much in common, and in fact Uvarov informs us that "a locust is nothing but a species of grasshopper, but usually larger in size and characterised mainly by gregarious habits". Both kinds of insects have a fairly simple life-history. The female deposits eggs in packets ("egg-pods") of 30–100 in the soil, where in cold countries they lie dormant during the winter. In spring young locusts ("hoppers") emerge from the eggs and reach the surface of the soil. At this stage, even in large aggregates, grasshoppers lead independent lives, while locusts soon congregate in bands. The hoppers grow, moult several (4–6) times and become mature. [For an interesting account of the transformation from hopper to locust see B. P. Uvarov's article (1947).] One generation arises each year in temperate countries, but in the tropics several generations may appear in one year. The adult locusts form moving swarms, or bands, which sometimes cover large areas of territory; in East Africa one swarm which covered an area of 180 square miles was estimated to contain one million million individuals, and even larger swarms have been recorded. The bands travel very large distances—sometimes more than 1,500 miles in a straight line—in a sequence of migratory flights. Uvarov has stressed that a band does not migrate because food is scarce or in quest of more fertile regions; climatic conditions largely initiate and direct migration, and bad weather may delay its stages.

Some methods of locust control date back many centuries—for instance, digging to kill the eggs, or forcing hoppers into slit trenches there to destroy them. In recent years very formidable weapons

have been brought to bear on locusts: steam-rollers, poison gases, flame-throwers, bacterial diseases, balloon barrages, smoke-screens, artillery, and in fact all the devices of modern war have been called on to serve in locust campaigns. Many of these mechanical things bring maintenance troubles in the field, and after 1944 the comparatively simple method of employing poison baits came into universal use. Locusts will ignore their usual green food in favour of bran containing sodium arsenite, and if the amount of poison is kept low there is no danger to cattle and other grazing animals. Another method widely used is the spraying of locusts with lethal dusts and liquids from low-flying aircraft. The main difficulty of control is the sporadic nature of locust attacks, speedy organisation often failing to keep pace with invasion, but one failure in the past has been "the isolationist policy of practically every country subject to their depredations" (Uvarov, *loc. cit.*). The problem is an international one, and this was generally admitted when in 1920 the delegates at the Rome International Conference pledged their countries' co-operation in the war on locusts. In 1928 an outbreak of desert locust induced the British Government both to adopt defensive measures and to take radical steps to find the cause of swarming, and in 1929 a committee was set up to deal with the problem of locust control. Sir Guy A. K. Marshall took charge of a special Anti-Locust Research Unit based on the British Museum (Natural History) in South Kensington, and B. P. Uvarov undertook its technical direction. By its work the unit soon attracted attention abroad and at the First International Locust Conference in Rome in 1930 it was requested to serve as the International Centre for anti-locust research. It has since received and correlated many thousands of radio and other reports on locust swarms and has become the World Centre for disseminating information regarding locusts and their movements.

During the period 1930–38 there was a concerted scientific effort to investigate locusts in their natural backgrounds. Experts went from Britain, France, Belgium, India, South Africa and Egypt to some of the most inhospitable regions of the earth, there setting up field laboratories where basic researches were carried out. The British Mission in Arabia—where agriculture is hardly practised at all, but where locusts multiply abundantly—used in 1943–44 nearly 400 trucks and nearly 1,000 men like a military force to search out the breeding grounds of locusts and to wage war on these insects. Elsewhere, work was carried out on a similar scale. Uvarov has stated, of the

earlier period: "The results of this team work, which is certainly unique in entomological history, have justified the effort. At the outset of the investigations, practically nothing was known on the distribution of the different species of locusts in Africa, of their seasonal cycle and migration, and particularly, on the origin and the course of their periodic outbreaks. After eight years of intensive work, a clear picture of the whole problem became available, which has made it possible to formulate an entirely new anti-locust policy, aiming at a radical solution of the locust problem." The main point of this policy was to prevent locust outbreaks, not merely to act defensively against swarms. Serious locust invasions arise from small beginnings, which implies that comparatively small areas can be put under permanent observation and incipient swarms destroyed. By 1938 practical plans had been formulated for dealing with the desert, migratory and red locusts, the three main species of Africa and the Middle East. The plans were in the final stages of preparation in 1939, "when the outbreak of war made the locust problem seem insignificant". The scheme was put into action against the red locust in 1940, however, and "the foundation stone of permanent international locust control was laid". A series of international campaigns were started in several countries, and Uvarov (*loc. cit.*) has shown where special credit goes for their establishment and continuance.

The methods used for destroying locusts have been described in detail by D. L. Gunn (1948, *a*, *b*). Hoppers can be poisoned by bran treated with benzene hexachloride ("Gammexane", "Benhex", etc.) and scattered in the path of the migrating bands. The first experiments with aircraft were carried out in the highlands of Kenya in 1944 with the help of the Anti-Locust Flight (R.A.F. and S.A.A.F.) and J. S. Kennedy. The most effective contact locusticide, dinitro-*ortho*-cresol (D.N.O.C.) was scattered in dusts on the desert locust with full success, though locust mortality was low in wet periods, even when much heavier loads of dust were used. After these tests had been carried out, J. S. Kennedy returned to England and worked in the Porton laboratory of the Ministry of Supply on special problems of spraying—determining the lethal doses in terms of individuals and the quantity of spray collected by locusts when at rest or in flight, and obtaining other data required in the field. By August 1945 a programme of spraying trials had been prepared and preliminary tests then being made in Kenya were augmented. In the following year many improvements in both apparatus and chemicals were tried out,

and in 1947 a successful campaign was launched against the red locust. Gunn (1948 *a*, *b*) has stated, however, that no single technique of locust control is entirely satisfactory, and that the use of locusticides is a temporary measure until better methods of control are developed. Uvarov (1948) also regarded the use of such chemicals as palliative only, and he discussed the three most profitable methods of solving the locust problem—direct defence, the suppression of outbreaks, and the prevention of swarming. For direct defence against locusts, chemicals such as benzene hexachloride will protect standing crops reasonably cheaply. Outbreak suppression calls for the mapping and permanent supervision of outbreak areas where the initial solitary phase is transformed into the gregarious phase and where suppression is practicable. The prevention of swarming can be achieved only when control is exercised over phase transformation in the outbreak areas, and this calls for more fundamental research on the biology and ecology of locusts.

The recent report by B. P. Uvarov (1951*a*) gives much valuable information bearing on locust research and control—international and inter-territorial co-operation, the anti-locust campaigns of 1929–37 and 1942–47, the Moroccan locust and grasshoppers, and regional anti-locust organisations—and also both a summary of progress and a statement on future policy. Another article by Uvarov (1951*b*) deals particularly with recent advances in locust research.

Commonwealth Agricultural Bureaux

During the past forty years the establishment of a number of bureaux dealing with various aspects of agricultural research has assisted the progress of pure and applied biology (see P. R. Laird, 1948). The first of these dealt with insects. In 1909 and with funds provided equally by the South African colonies and the United Kingdom, the Entomological Research Committee (Tropical Africa) was set up. This was based on the British Museum (Natural History), South Kensington, and it made the first systematic collection of insects that are injurious to crops, animals and man. In 1911 this successful venture was discussed at the Imperial Conference, and two years later it was enlarged as an Empire organisation called the Imperial Bureau of Entomology, which in 1933 came under the control of the Executive Council. The Commonwealth Institute of Entomology—to use the present name—aims to assist in the identification of injurious insects sent from all parts of the Empire, and since 1913 it has also issued a

monthly periodical—the *Review of Applied Entomology*—summarising current world literature bearing on insects as agricultural pests and agents in the spreading of disease. Agricultural, veterinary and medical workers obtain from the Institute information or assistance in entomological matters related to injurious or useful insects, other arthropods of economic importance, *e.g.* mites, ticks and millipedes, and insects that injure bees, silkworms, lac-insects and their products. The *Review* has sections A and B; the former deals with plant pests, and the latter with beneficial insects and noxious arthropods. The pests of crops are studied in relation to climate, soil, vegetation and other factors; they include arthropods which damage fruit-trees, vegetables and grain crops, and also various special crops such as coffee, tea, cacao, cotton and tobacco. Ornamental plants, stored products, pastures, forest trees and timber also have their pests. All such arthropods are controlled by various methods and are studied in relation to the diseases they transmit to plants. The biology of noxious arthropods is concerned with harmful species and the pathogenic agents they transmit, and also with their natural enemies. Man and domesticated animals may be harmed by the direct attack of pests or as a result of diseases these transmit by contaminating food in warehouse or home.

The immediate success of the Institute of Entomology led to the establishment at Kew in 1920 of the Imperial Bureau of Mycology, which is now called the Mycological Institute. The task of this Institute is to deal with fungal pests, some 25–30,000 species of which are lodged in its herbarium for purposes of reference. The Institute maintains type cultures of all fungi except yeasts, medical species and timber-rotting forms, and it deals with many aspects of plant pathology, notably with disorders caused by viruses and bacteria and by soil deficiency. The monthly periodical *Review of Applied Mycology* maintains records of research dealing with fungal attacks on insects and various sorts of products such as fabrics, electrical and optical equipment, leather, paper, stored foodstuffs and fresh fruit. Various methods of testing fungicides both in the laboratory and in the field also come under review, likewise the apparatus used for applying crop sprays and dusts, and seed and soil disinfectants.

In 1927 an offshoot of the Institute of Entomology was founded at Farnham House, near Slough. With funds provided by the Empire Marketing Board a laboratory was set up to deal with problems of controlling insect pests of agriculture and forest crops by means of predators and parasites—*i.e.* biological control. In 1929 the insect

enemies of weeds also came in for special study. As the Imperial Parasite Service, the laboratory was moved to Canada in 1940, and in 1946 it was renamed the Commonwealth Bureau of Biological Control. Biological control of animal and plant pests means reducing their numbers by the use of organisms such as viruses, bacteria, fungi and both predatory and parasitic animals, particularly insects, which prey on them. The Bureau supplied beneficial organisms for attacking certain pests to Commonwealth countries, and sometimes takes complete charge of biological control projects in these countries. Arising out of this work is both academic and applied research, and also the important task of training future experts who will use the methods of biological control. Substations exist in Europe, the West Indies, south-west U.S.A. and South America, and experts in other countries co-operate in this work.

In 1927 the Imperial Agricultural Research Conference issued a recommendation to set up other bureaux representing eight selected branches of agricultural science, and in 1929 these were set up, getting the name Commonwealth Agricultural Bureaux in 1948. Each covers a fairly definite field of study and issues its own journal of abstracts, which are mostly monthly or quarterly publications. They are variously concerned with agricultural parasitology (St Albans), animal breeding and genetics (Edinburgh), animal health (Weybridge), animal nutrition (Aberdeen), horticulture and plantation crops (East Malling), pastures and field crops (Aberystwyth), plant breeding and genetics (Cambridge) and soil science (Harpenden). In 1936 the British Commonwealth Science Conference recommended the addition of two more bureaux and in 1938 these were founded in relation to dairy science and forestry. In addition to these bureaux and their *Abstracts* the Organisation is responsible for the publication of journals such as the *Bulletin of Entomological Research* (1910—), the *Zoological Record* (Insecta), the *Bibliography of Medical Mycology* (1944—), the *Bibliography of Systematic Mycology* (1947—) and the *Index Veterinarius* (1933—). The Commonwealth Potato Collection is another responsibility. This was first made on expeditions to Mexico and South America in 1938 and 1939. The aim is to use desirable qualities of potatoes from the New World and to establish new varieties that will resist diseases of various kinds. Material is obtained annually and is studied in various ways—described and classified, tested in regard to resistance to blights, viruses, eelworms and frost, and used to provide breeding stocks. The collection now contains about 1,500

samples, which are maintained at Cambridge. A new field station has recently been erected from funds provided by the Nuffield Foundation to guard against viral infection and the laboratories adjoin special insect-proof glasshouses.

The Commonwealth Bureau of Agricultural Parasitology (Helminthology) deals with the diagnosis, taxonomy, biology, pathology, treatment and control of helminths whether these are parasitic or not, and whether they are found in man, animals, plants, soils or water. Much consideration is also given to the hosts of helminths, which include molluscs, arthropods and other animals and also plants. The scope and aims of the Bureau have been outlined by B. G. Peters (1932), who stated that the subject-matter of the Bureau comprises data on "distribution, systematics, life-histories, biology, pathogenesis, therapeutics, prophylaxis and, in fact, most aspects of helminthology except the purely clinical, which is traditionally the affair of the practitioner rather than the scientist". Apart from "domesticated animals" and "farm crops" in the generally accepted sense, the hosts include fur-bearing mammals and various kinds of poultry, and in regard to the Empire as a whole one has to "admit such animals as elephants, camels and reindeer as 'domesticated', and has to consider the whole range of tropical crops in relation to eelworm attacks". "Fisheries and game reserves also contribute their problems." The hosts are generally economic assets and their parasites economic liabilities; but in regard to pests such as the grey squirrel, the locust and agricultural weeds, the parasites may be assets in the sense that they may exercise some degree of biological control over the pests. In some instances hosts of little or no significance may harbour the young forms of important parasites, thus serving as reservoirs or intermediate hosts which may be animals (molluscs, arthropods, earthworms) or plants. Helminthology began as a branch of human medicine and it has developed mainly on this side, so that the Bureau must also keep in touch with medical parasitology. In some instances, one stage in the life-history of a parasite exists in man, and another in some domesticated animal, as for instance with some tapeworms and roundworms. Free-living roundworms exist in tremendous numbers in water, soil and sewage, and also in such products as vinegar and paste; their significance is still doubtful and some attention must be given to them.

Dr Peters also illustrated the difficulties of abstracting and providing bibliographies of important original papers published in zoological,

medical, veterinary, agricultural and horticultural periodicals of the world. In one such issue (1930) a list of 917 titles related to 346 periodicals, though actually 213 periodicals contained only one title each. In other words, to obtain one reference in many instances a whole volume of original papers has to be scrutinised. "The Bureau staff is not proud of having traced so many titles," wrote Dr Peters (though, one might add, they had good reason to be proud!), "but rather anxious to discover how many were missed." A similar bibliography published during the following year (1931) contains records from more than 400 periodicals, some of them journals which published no papers on helminthology during the previous year. This sort of difficulty holds for workers in all the many fields of biology, and the time saved for them by compilations such as the *Abstracts* of the Commonwealth Agricultural Bureaux is incalculably great, a fact which is not always recognised or appreciated.

The Bureau of Animal Breeding and Genetics is largely concerned with animals of economic value and aims to increase productivity by effective breeding. Such work as is recorded in *Animal Breeding Abstracts* (1933—) deals with genetics in its various aspects—evolution, variation and domestication; cytogenetics; selection and breeding; and the history, description, differences, societies and acclimatisation of breeds, races, varieties and strains of animals. This work touches the live-stock industry at many points, for it is concerned with various aspects of reproduction (sex physiology, sterility, artificial insemination, etc.) and growth (meat production), and the production of milk, eggs, meat, skins, fur, wool, feathers and work. Many kinds of animals are included in the term "live stock"—for instance, the buffalo, camel, elephant, llama, reindeer and yak, as well as such "poultry" as the ostrich and also cage-birds, laboratory animals, fur-bearing animals and game animals.

The Bureau of Animal Health has a very broad field dealing with animal health in general. Special reference is made to the prevention, control and cure of disease in animals, to methods of transmission of disease from animals to man, and to the ways in which disease influences production. The *Veterinary Bulletin* (1931—) covers such subjects as infectious diseases brought about by viruses, bacteria, fungi and Protozoa, problems of immunity, helminthic diseases and diseases caused by arthropods, nutritional disorders, the diseases of breeding stocks, toxicological agents, live-stock hygiene, pharmacology and therapeutics. The Bureau of Animal Nutrition deals with one aspect

of animal health in the widest sense, for man is regarded as "animal"; food is considered from every point of view from the processing of it to the physiological effects it produces. *Nutrition Abstracts and Reviews* (1931—) covers information on physicochemical techniques and the chemical composition of foods of all kinds, on vitamins and the physiology of nutrition, and on human diet in relation to health and disease and the feeding of animals. The Bureau of Dairy Science is concerned with, and its *Abstracts* (1939—) record, research on milk and milk products, "though with every kind and aspect of milk (including human), whether from an animal of economic importance or not".

The Forestry Bureau is concerned with the husbandry of forest trees in all its aspects, "not excluding pathology, genetics and the wide field of utilisation, both of timber and of every subsidiary product that forests yield". *Forestry Abstracts* (1939—) deals with forest botany and zoology, various aspects of silviculture, including afforestation, shelter-belts and windbreaks, various aspects of utilisation and technology (for instance, the attack of wood by plants and animals, the manufacture of wood products and by-products, and the preservation and seasoning of timber), and it is concerned also with forest injuries and protection. The Bureau of Horticulture and Plantation Crops covers the field of horticulture from seed to storage and canning, including in its scope border-line crops such as the potato and tobacco. The closely related Bureau of Pasture and Field Crops is concerned with plants that are used as fodder for animals, "from grasses and clovers to shrubs and trees" and (since 1946) with field crops. These two bureaux produce *Horticultural Abstracts* (1931—), and *Field Crop Abstracts* (1948—) and *Herbage Abstracts* (1931—) respectively. The Bureau of Plant Breeding and Genetics is concerned with all plants from its own point of view, and *Plant Breeding Abstracts* (1930—) covers such subjects as the breeding, cytology, genetics, variation and evolution of economically important plants ranging from bacteria and fungi to forest trees, and certain aspects of ecology and plant geography, taxonomy, vernalisation and photoperiodism, and substitute rubber plants. The Bureau of Soil Science deals with "all literature relating to the soil, whether as the nurse of growing crops, as the raw material for a road, or from the purely physical and chemical aspects". *Soils and Fertilisers* (1938—) covers the broadest aspects of soil science and utilisation, and also deals with such miscellaneous subjects as animal diseases in relation to soil, the quality of plant and

animal produce in relation to soil, hydroponics and the growth substances in soils. All the various Commonwealth Agricultural Bureaux are intended to assist agricultural research workers in the Empire, but not "to answer inquiries from the general public or to give advice on the local problems confronting those engaged in agriculture, stock raising or fruit growing". The many occasional publications, some of which are monographs of considerable importance, can be obtained from the various bureaux; they are listed in a booklet (Laird, 1948) issued by the C.I.B.

The Agricultural Research Council

This Government organisation—consisting of fifteen members, ten of whom are eminent persons in some field of agricultural science—was established in 1931 and given the duty of advising the Development Commissioners and the Departments of Agriculture in England and Wales and in Scotland on the financing, planning and conduct of agricultural research. Such work is now largely the concern of the state, but it is administered by the A.R.C. and the two Government Departments mentioned. About £1,600,000 is spent annually out of public funds on the maintenance of agricultural research. About one-fifth of this sum is devoted to the investigation of animal diseases; about one-fifth to researches in animal physiology, animal breeding and genetics, and dairying; nearly one-third to researches concerning plants and the soil, including soil fertility, the nutrition and physiology of crops, plant pathology, plant breeding and genetics, and grass husbandry; and about one-quarter to research on weed control, microbiology, nematology and plant biochemistry. A specially trained scientific personnel of about 700 is needed to carry out all these lines of research.

The A.R.C. maintains close liaison with the Department of Scientific and Industrial Research and the Medical Research Council for the co-ordination of research. Its detailed business is conducted by two Standing Committees (a third will soon deal with agricultural engineering) respectively responsible for botanical and zoological researches. About forty technical committees plan new research programmes and review progress in their various provinces, dealing with animal diseases such as contagious abortion, mastitis and tuberculosis in live stock, and with fertilisers, mineral deficiencies and other problems concerning plants. A Soil Survey Research Board was appointed in 1947 to oversee the soil survey of Great Britain.

Many agricultural research institutes existed long before the A.R.C was established. Some of these were privately owned, others—dealing largely with diseases in animals and plants—were under the control of the Agricultural Departments. Such institutes range from large stations like Rothamsted to small units, and they are now controlled by the Agricultural Departments, by the A.R.C., or by individual governing bodies financed by maintenance grants. The A.R.C. directly controls eight institutes and units—the Experimental Field Station at Compton, Berkshire; the Animal Breeding and Genetics Research Organisation at Edinburgh; the Institute of Animal Physiology at Cambridge; the Poultry Research Centre at Edinburgh; the Plant Virus Research Unit at Cambridge; the Unit of Insect Physiology at Cambridge; the Unit of Animal Reproduction at Cambridge, and the Unit of Plant Biochemistry at Cambridge. The Council also oversees the research programmes, staffs, and budgets of about thirteen English and Welsh institutions and five Scottish institutions maintained by grants from respective Departments of Agriculture. The complete lists of these are as follows:

English and Welsh Institutions

Rothamsted Experimental Station, Harpenden.
Plant Breeding Institute, Cambridge.
John Innes Horticultural Research Station at Bayfordbury.
Horticultural Research Station, East Malling, Kent.
Agricultural and Horticultural Research Station, Long Ashton, near Bristol.
Glasshouse and Experimental Research Station, Cheshunt, Herts.
Welsh Plant Breeding Station, Aberystwyth.
Research Institute in Plant Physiology, London (Imperial College).
National Institute for Research in Dairying, Reading.
Foot and Mouth Disease Research Station, Pirbright, Surrey.
Vegetable Research Station, Charlecote, Warwickshire.
Grassland Research Station, Hurley, Berks.
National Institute of Agricultural Engineering, Wrest Park, Beds.

Scottish Institutions

Macaulay Institute for Soil Research, Aberdeen.
Scottish Society for Research in Plant Breeding, Edinburgh.
Animal Diseases Research Association, Moredun, Edinburgh.
Rowett Research Institute, Aberdeen.
Hannah Dairy Research Institute, Ayr.

The Ministry of Agriculture and Fisheries directly controls the Veterinary Laboratory, Weybridge, Surrey, and the Plant Pathology Laboratory at Harpenden; and the Department of Agriculture for Scotland centres for seed testing, plant registration and plant pathology services. Of these institutes and units, the Field Experimental Station at Compton (established 1937) offers facilities for studying large groups of live stock, and ancillary buildings recently completed will provide for testing vaccines and other work on an even larger scale. This station also breeds animals, large and small, for use at other research institutions. The Animal Breeding and Genetics Research Organisation at Edinburgh (established 1947) is now being supplemented by substations in various parts of Great Britain for more intensive genetical studies and live-stock breeding research. The Institute of Animal Physiology has developed since 1948 on an estate at Babraham. Since the last war the Poultry Research Centre has also developed, and another centre may be set up in southern England soon for research on poultry breeding. The other units at Cambridge have arisen during the same period. The Council also undertakes the co-ordination of research and developments on insecticides. Its scientific personnel is made up of graduates who have specialised in at least one subject, and special training in research is provided by the Council, about thirty Agricultural Research Scholarships being awarded annually.

It is impossible to deal with the work of all the institutions in this place and I have singled out several of them in order to illustrate briefly in the next chapter their aims and some of their achievements.

CHAPTER NINETEEN

SOME RESEARCH INSTITUTES AND THEIR WORK

Medical Research Institutes

SOME institutes which are mainly concerned with the science of medicine have carried out much fundamental biological research. In Britain the Lister Institute of Preventative Medicine, the Wellcome Research Institution and the National Institute for Medical Research are notable, and no account of biological progress would be complete if it did not say something about their aims and achievements.

The Lister Institute

In 1889 the Lord Mayor of London, Sir James Whitehead, visited Paris to consult Pasteur about his records on rabies. He went at the suggestion of the distinguished zoologist Sir Edwin Ray Lankester, who shared the opinion with some others that the muzzling of dogs would do more to eradicate rabies than any biological measures. This prophecy turned out to be correct, but the Lord Mayor's visit produced one valuable result: it led to the establishment in 1891 of the *British Institute of Preventative Medicine*, which was later called the *Lister Institute*. Work began in 1894 at the College of State Medicine and at a small farm at Sudbury, near Harrow (the present premises in Chelsea Bridge Road were partly built in 1898, additions being made in 1910). Dr. A. N. Drury has described (1948) how, during about fifty years' research, workers at this Institute have published about two thousand scientific papers on medical subjects and related topics, many of them representing marked advances in their own fields.

For about five years Dr C. Martin studied the spread of plague in India, where, with two colleagues, he proved that the rat flea (*Xenopsylla cheopis*) carries the plague bacillus, and is in turn carried by the wild rat, *Mus rattus*. During the 1914–18 war Ledingham discovered that the causal organism of trench fever is a *Rickettsia*, and perfected a technique which was later applied to the study of the viruses of vaccinia and fowl-pox. Sir Joseph Arkwright and other bacteriologists for many years investigated variation in bacteria, and Ledingham and

Penfold observed that modification of the characters of cultured colonies of many pathogenic bacteria involves corresponding modification of virulence. After P. Buchner's discovery (1897) that fermentation can proceed in the absence of living cells, A. Harden proved that if the enzyme zymase is to convert sugar into alcohol a co-enzyme must be present. Warburg and H. von Euler determined the nature of this co-enzyme (adenine pyridine diphosphonucleotide) and Harden and von Euler shared the Nobel Prize in chemistry. Robison discovered the enzyme phosphatase in the bones of young animals. He also inferred how calcium is deposited in bone during growth and eventually he developed his own theory of bone-formation, which involves a complex system of enzymes, and not phosphatase only.

The later biochemical work of the Institute was concerned with the chemical nature of certain bacterial antigens, and in 1939 the purification of dysentery and typhoid group antigens was speeded up. In 1942 volunteers were successfully immunised against the dysentery bacillus discovered by K. Shiga. The effects of blood transfusion provided an important task for the department. Specific substances were isolated from human blood of the groups A, B and C, and the biological implications have called for their study by genetical methods. The investigations of the toxins produced by *Clostridium welchii*, the causal agent of gas gangrene, have led to the development of new ways of studying bacteriological poisons.

In the pathological department the work has been just as varied. Leathes investigated the metabolism of fatty substances; J. S. Haldane, Boycott and others studied physiological adaptation to increased and lowered atmospheric pressure. Experiments carried out in a specially constructed pressure chamber have shown what precautions must be taken by divers both during and after diving operations, and how the breathing apparatus used for rescue work in mines should be constructed. Research on nutrition became concentrated on the vitamins, and a peak was reached after the 1914–18 war when a team spent three years in Vienna investigating rickets and scurvy. During the last war investigations centred on the storage of vitamins and the nutritive qualities of various kinds of flour.

The study of Protozoa was taken up by E. A. Minchin who, in 1906, investigated the life-history of the sleeping-sickness parasite, *Trypanosoma lewisi*. The late Dr Major Greenwood applied statistical methods to the study of disease. In 1911 A. W. Bacot started research on the bionomics of fleas and lice. Some time later he collaborated

with Sir J. Arkwright in a study of typhus in Egypt; both biologists took the disease, and Bacot died. Since the 1914–18 war, and in conjunction with the Medical Research Council, a collection of organisms of special interest in medical biology has been built up, and the National Collection of Type Cultures now forms a fund drawn on by certain research workers all over the world.

Biophysics research has been concerned with vaccinia, antitoxins, and both normal and pathological sera, and since the last war new methods of ether extraction have been developed in the large-scale preparation of blood plasma for storage and transport. With suitable methods good supplies of pure fibrinogen, prothrombin and *beta-* and *gamma*-globulins can now be prepared from human plasma and serum. These have important uses in surgery and medicine. A suitable mixture of fibrinogen and thrombin will provide a clot that assists nerve-suture and skin-grafting. Treated fibrinogen yields a special fibrin foam which arrests bleeding and can be left in a wound because slowly absorbed. The *beta*-globulins contain the blood group agglutinins and the *gamma*-globulins the natural antibodies against disease, some of which have already been sucessfully applied to the prevention and mitigation of measles. The work of the Lister Institute illustrates the way in which biology now demands the co-ordinated participation of the chemist and physicist.

The Wellcome Research Institution

The history of this Institution has been outlined by its Director-in-Chief, Dr C. H. Kellaway (1948). The name indicates an assemblage of museums and research undertakings under the Wellcome Foundations Limited, a company set up in 1924 and a development of Burroughs Wellcome & Co. (1880). The first London laboratory was founded in 1895 to manufacture diphtheria antitoxin, which had just come into use. The Institution has many notable successes to its credit, particularly in physiological research. In 1904 George Barger was conducting chemical studies on ergot (*Claviceps purpurea*). Very soon the fungus had yielded new drugs such as ergotoxine and histamine, as well as other amines which simulate the action of the sympathetic nervous system of animals. A. K. Ewins discovered the drug acetylcholine, and H. H. Dale determined its nicotine-like action. This work was related to that of Otto Loewi, who gave us the conception of chemical transmission at nerve endings. In 1913 Dale, Barger and Ewins joined the staff of the Medical Research Council (see below),

but the tradition was carried on and during the period 1910–14 fewer than a dozen scientists published about one hundred papers, many of them representing marked advances in physiology.

During the 1914–18 war members of the Institution prepared large quantities of tetanus and diphtheria antitoxins, antigangrene sera and typhoid vaccines. In the period between the wars more than 300 original papers were published by a staff not exceeding twenty-eight persons. The pharmacologist O'Brien, who succeeded Dale, was the first in Britain to carry out the Schick testing and a pioneer of active immunisation against diphtheria. T. Dalling successfully controlled a form of dysentery which was killing thousands of lambs annually, and also found means of providing immunisation against dog distemper. Hartley developed a medium which gained a world-wide application for the production of diphtheria serum. During the last war heavy demands for tetanus and gas-gangrene antitoxins and other agents for the prevention and cure of disease were met by still greater efforts. More than one thousand horses were maintained for the production of various types of sera. The production of penicillin and streptomycin came later, and more recently new studies have concerned immunity, toxins of the *Clostridium welchii* group, the pharmacology of "Sulphitrone" and streptomycin, the production of diphtheria toxin by the method of deep culture, new methods of refining antibacterial sera and the new antibiotic "Aerosporin". This last affects bacteria which are unharmed by penicillin and streptomycin, and does not permit resistant bacterial strains to develop.

In the Wellcome Laboratory of Tropical Medicine C. M. Wenyon, later Director-in-Chief of the Institution, worked on Protozoa, A. C. Stevenson on pathological problems and M. E. MacGregor on the study of insects. In 1927 Hoare was engaged at Entebbe in investigations on trypanosomiasis. G. M. Findlay visited various parts of the world investigating yellow fever, which Hindle also studied. In 1932 the London premises in Euston Road were built and work began on virus diseases and leptospiral infections. Findlay started the manufacture of yellow-fever vaccine, using methods devised at the Rockefeller Institute. During thirty-four years the workers in this laboratory published eight books and nearly six hundred original papers bearing on tropical diseases. In later years the laboratory has been concerned also with research on bacteriophages, the tissue culture of protozoan forms, the serology of leptospirosis and the chemotherapy of tropical disease. The scourge of scrub-typhus in the Burma campaign led to a

great demand for the protective vaccine, large-scale production of which was devised by Fulton and Joyner at the National Institute for Medical Research. In the six months beginning in May 1945 sufficient had been prepared to protect 100,000 men, and by a hazardous method which involved collecting vast numbers of lungs from the cotton rat after inoculation with *Rickettsia tsutsugamushi.* Workers were vaccinated beforehand and special methods of air-sterilisation and ventilation protected them. Four infections resulted despite these precautions, but in every case recovery followed.

The National Institute for Medical Research

The work of this Institute has been described by Sir Charles Harington (1949) and by C. H. Andrewes (1950). In 1913 the Medical Research Committee was set up to administer the fund for research collected under the provision of the National Insurance Act of 1911. Seven years later it was granted a Royal Charter and became the Medical Research Council. The present location at Mill Hill was acquired in 1921 and temporary laboratories were built to cope with work on viruses that could not be carried out at Mount Vernon Hospital, Hampstead, where some earlier researches were conducted. New buildings were completed in 1940, but the use of the building by the Admiralty delayed the inauguration of the National Institute at Mill Hill till May 5, 1950 (see *The Times*, April 21, 1950). Consequently, early work was carried out in various laboratories—bacteriology by Sir Almroth Wright and S. R. Douglas at St Mary's Hospital, pharmacology by Dale, Barger and Ewins at the Lister Institute, and applied physiology by Leonard Hill, Benjamin Moore and Martin Flack (later on L. Colebrook and Sir Alexander Fleming as well) at the London Hospital.

Dale and colleagues investigated shock and trinitrotoluene poisoning, C. Dobell worked on amoebic dysentery. One of the earliest types of research, the study of virus diseases, has remained the main theme of the Institute. Laidlaw and Dunkin studied distemper in the dog, using ferrets for the production of effective vaccines, and in a few short years they showed how the disease can be prevented. In 1933 the ferret again proved to be a useful laboratory animal, this time for the cultivation of the influenza virus. Later on, the method devised by Goodpasture in U.S.A. for cultivating the virus in developing hen's eggs was improved at the Institute by F. M. Burnet. Dr W. E. Gye studied the viruses involved in the production of transmissible tumours,

work which has a direct bearing on cancer research. Elford developed the standard collodion membranes, which have pores of definite sizes and can thus be used for determining the sizes of virus particles. Sir J. E. Barnard, as already mentioned, developed ultra-violet microscopy at the Institute.

The study of chemical control and co-ordination of function in animals was extended by the use of the newly discovered drugs histamine and acetylcholine. Methods were devised for the purification of insulin and the sex hormones came in for close study. Vitamins were also studied, and vitamin D_2 was discovered at the Institute. The department of applied physiology has been largely concerned with a study of the factors of the environment in their relation to human health and bodily activity, but also with the physiological effects of ultra-violet light and raised and lowered atmospheric pressures. One other important undertaking by the Institute is the maintenance of biological standards. This involves the setting up of standard preparations of antitoxins, vitamins, hormones and drugs of various kinds and the definition of their biological activity in terms of known amounts of the standards. Since the Therapeutic Substances Act was passed in 1925 the Institute has been responsible for issuing samples and standards to manufacturers so as to ensure that marketed products satisfy the requirements laid down by law. The value of much scattered biological research in colleges, universities and institutes in which such substances are frequently used depends to a large extent on the accuracy of the work done at the National Institute. Sir Charles Harington stated that during its development the Institute "has come to lay emphasis on biochemistry and biophysics, the broadening of biological research through endocrinology and the more general aspects of experimental biology".

Dr C. H. Andrewes has dealt with the latest developments at Mill Hill. Work in the biological chemotherapy laboratories has included the use of a newly discovered malarial parasite (*Plasmodium berghei*) for carrying out tests with antimalarial substances. Laboratory mice have now to some extent taken the place of young birds for the cultivation of the parasite. At Mill Hill, however, research on chemotherapeutics is "tending to swing a little away from malaria and trypanosomiasis (sleeping sickness) to the study of schistosomiasis, filariasis and other worm infections", but *Leishmania* and *Entamoeba histolytica* "get their share of attention". The department now has an insectarium in which mosquitoes in particular are reared. Related

to chemotherapy is the work on the metabolism of bacteria carried out by a team of researchers formerly employed at the Lister Institute. In the division of experimental biology, which is a widened department of endocrinology, Dr A. S. Parkes directs research on "the fertilisation and cultivation of mammalian ova *in vitro* and of the behaviour and preservation of mammalian and avian sperm *in vitro*". Dr C. H. Andrewes himself is in charge of the division of virus research, at present specially interested in "virus infections of the respiratory tract". The Common Cold Research Unit at Salisbury is based on Mill Hill, which also contains the laboratory of the World Influenza Centre. This maintains contact with laboratories all over the world, gathering information and virus strains and trying to improve our knowledge of the global epidemiology of influenza. The division of biological standards holds forty-five international or British standards.

The Royal Botanic Gardens, Kew

In 1840 the gardens at Kew passed over from private to public ownership, mainly as a result of the efforts of John Lindley. In 1841 they came under the direction of Sir William Hooker. During the next five years the gardens were extended almost to the present limits —a total area of about 300 acres plus a pinetum of 50 acres at Bedgebury, Kent. More than one-half of the staff of about 270 are concerned with the culture of living plants, the scientific staff numbering about 40, plus visiting scientists. The institution consists of four departments—the Herbarium and Library, the Museums, the Jodrell Laboratory and the living collections. The history and the work of the institution has been described by Sir Edward Salisbury (1948). Nearly six million specimens are lodged in the Herbarium. One person would require forty full years to work through the collection, which contains about 200,000 types and grows at the rate of about 50,000 specimens per year.

About thirty major floras and monographs have been prepared at Kew, notably Bentham's *Flora Australiensis* (1863–78), the *Flora Capensis* (1859–1900) and the *Flora of British India* (1872–97). Each of these comprises seven volumes, and the last alone is a description of more than 15,000 species. The ten volumes of the *Flora of Tropical Africa* deal with 18,000 species. Another notable publication, *Index Kewensis*—a catalogue of all the flowering plants described since 1753—was begun in 1893 and contains 375,000 citations. Each quinquennium a supplement is added. The periodical *Icones Plantarum*, which is

published at Kew, contains illustrated descriptions of more than 3,000 new and rare species of plants. The *Botanical Magazine* of the Royal Horticultural Society is also prepared at Kew; since 1787 it has issued illustrated accounts of more than 8,000 species of plants. The *Kew Bulletin* is another medium for the dissemination of botanical knowledge. Salisbury has stated that during the first thirty years (1841–70) about 460 scientific papers were published and during the next thirty years about 1,400. Since 1900 about 50 books and papers have been published annually.

In addition to maintaining numerous notable trees, shrubs and herbaceous plants, and managing more than 2,000 species of plants of more than 500 genera, in the largest glasshouse in the world, Kew has played an important part in the development of economic botany. Plants dispatched in the Wardian case (a kind of travelling glasshouse) have helped to establish rubber plantations and the industries based on cinchona, coffee, pineapples and breadfruit. Considerable exchanges of seeds have also been made with various scientific institutions. More than 10,000 botanical enquiries are dealt with by experts every year. In the Jodrell Laboratory the main emphasis is on the anatomy and taxonomic characters of plants, but the abundant materials at Kew are the subject of continual investigation by cytologists and physiologists as well as taxonomists and morphologists, and it was in this laboratory that Scott worked assiduously on fossil plants.

Rothamsted Experimental Station

This research station was founded in 1843 by Sir John Lawes, then a young landowner, and a young chemist—(Sir) Henry Gilbert—who had studied under von Liebig, directed the scientific work, which for the first eight years was conducted in a converted barn. This, the first laboratory in Britain to be devoted to agricultural science, soon offered farmers a cheap, manufactured powder as an alternative to farmyard manure for the enrichment of the soil. Faced with the question as to why the bones of animals will improve some soils but not others, Lawes began a study of the phosphate problem by treating bones with sulphuric acid, and he obtained a soluble phosphate which plants can utilise readily. The new product, which is now called superphosphate, was tested for several years at Rothamsted, and the factory opened at Deptford in 1841 for its production marked the beginning of the great fertiliser industry. In 1889 the Lawes Agricultural Trust was founded, though annual Government grants supplemented

the Trust funds, and the station is now largely financed by the Ministry of Agriculture and the Agricultural Research Council. Lawes died in 1900, Gilbert in 1901, and in 1902 Sir Daniel Hall became Director of the station. In 1912 Sir E. John Russell took over the Directorship, and in 1943 Sir William G. Ogg succeeded him. Less than eighty years ago the station had a staff of twelve workers; now it employs more than three hundred persons in various departments: Chemistry, Biochemistry, Physics, Botany, Soil Microbiology, Plant Pathology, Entomology, Insecticides and Fungicides, Nematology and others. The present laboratory was built in 1914, but additions have been made to it several times since then, and the station also has an experimental farm of 250 acres and the Classical Fields, where crops have been cultivated experimentally in a continuous series since 1843. The station runs an electron microscope, has a photography section and a Pedology Department, where X-ray, spectrographic and other methods of analysis are employed. A Statistical Department was developed by R. A. Fisher between 1919 and 1933, and the Library contains 30,000 volumes.

Since its origin in 1906 the main concern of the Botany Department has been with plant nutrition, especially the importance of micronutrients such as Boron to plants and the relation of Molybdenum to nitrogen metabolism in the lettuce and red clover. Water-culture methods of rearing plants have been developed, and weeds have been closely studied in relation to problems of cultivation. Soil microbiologists have dealt with the ecology of soil organisms since 1907, studying the micro-populations in experimental plots variously manured. Incredible numbers of micro-organisms exist in the soil, one gram of which may contain three thousand million bacteria, up to one hundred yards of fungal mycelium, several hundred thousand Protozoa, and also many other organisms. Special groups of soil organisms which attack bacteria (notably Myxobacteria and Acrasieae) have been studied, as have the nitrogen-fixing nodule bacteria of leguminous plants. The Plant Pathology Department, started by W. B. Brierley in 1918, has been concerned with the viral and fungal diseases of plants. Annual crops of potatoes may be spoiled by leaf-roll viral disease. In 1949 the crop of sugar-beet was reduced by more than a million tons by disease caused by the yellow virus. Of the viruses transmitted by insects, some soon lose infectiveness while others retain it for long periods. Other viral diseases are spread by man, tomato mosaic by contact between diseased and healthy plants.

The virus X of potatoes is spread by root- as well as leaf-contacts. Field experiments conducted at Rothamsted are concerned with the rate of spread of such diseases and the factors that influence it. Some viruses have been isolated as crystalline nucleoproteins containing ribose-nucleic acid.

Fungal diseases studied at the station include the footrots of wheat. One of these, "eye-spot", causes the straws to fall over before the crop is harvested, thus reducing the yield; it is commonest on heavy ground, especially in wet seasons, when wheat and barley are grown after short intervals. The fungal disease known as "take-all" attacks the roots and produces various effects which may lead to the death of the plants; this is commoner in light soils. Both diseases have been reduced on experimental plots by spraying the crops with strong ($12\frac{1}{2}$ per cent.) sulphuric acid before mid-March. Epidemic diseases of arable crops, such as the rusts and mildews of cereals and potato-blight, are transmitted by spores that drift through the air, and spore-traps are used to determine the numbers disseminated under certain conditions. The club-root disease of brassica crops is caused by a fungus that penetrates the root-hairs of plants; the spores arise in galls on the roots, and any which may escape into the soil may remain viable for many years, though modern study aims at expediting their destruction.

The Entomology Department at Rothamsted, started in 1918 by the late A. D. Imms, wages war on the insect pests of farm crops. The Department of Insecticides, founded by F. Tattersfield in 1918, assists in this work, aiming at direct control. The entomologist uses special traps to capture numerous insects under various conditions of temperature, air-flow, humidity and rainfall, all of which affect fecundity and behaviour. In south-east England insects multiply after wet days in summer and warm days in winter, and the larger insects deliberately migrate, while smaller forms such as greenfly drift on the wind, both methods of dispersal taking insects scores of miles from the place where they emerged. By means of nets slung on the cables of barrage balloons, many small insects may be commonly found at a height of two thousand feet. Other work concerns the gall midges which damage crops everywhere, notable soil insects such as wireworms and cockchafer grubs, and those destructive molluscs, slugs. Earthworms are also studied in relation to the fertility of the soil; they are useful in grassland for maintaining tilth and draining, but are much less important in arable land.

The Insecticide Department (with chemistry and biology sections)

deals with the effects of known insecticides rather than the discovery of new ones, but the ultimate aim is to find basic principles and determine what is required in a new insecticide and how the best results can be obtained with it. The chemists have discovered that the effectiveness of a suspension of insecticidal spray depends on the size of the particles in it, and also on wetting agents. They have investigated the relationship between insecticidal activity and chemical constitution, and later work has dealt with the difficult problem of synthesising pyrethrins. The biologists have ascertained that the toxicity of an insecticide is correlated with the temperature at which insects are maintained after spraying. Differential effects have also been noted in relation to nutrition; the pea-aphid is more resistant to some insecticides when fed on clover than when fed on broad-bean plants. Natural fluctuations in resistance to some insecticides have also been noted, likewise variations which are due to the stages of growth reached by the insect. After spraying insects with insecticides, resistant strains may be found, and an enquiry is being made as to how these arise. Biochemists investigating the effects of insecticides have noted that DDT and the pyrethrums heighten respiration temporarily, but many other insecticides depress it from the start. Some concern is felt about the action of insecticides on beneficial insects such as the bee, and the question of protection for such insects will have to be carefully dealt with. The Bee Department, founded in 1922, is concerned with pollination studies, the breeding and husbandry of bees, the effects of various environmental factors on bees, the behaviour of these insects both in the hive and on foraging expeditions, and (since 1934) with the diseases of the honey-bee and her brood. Bees are the most important agents of pollination, and as they affect fruit and seed crops their importance extends to horticulture and agriculture. One aim of the Bee Department is to raise a strain of bee which can pollinate the red clover.

The special concern of the Nematology Department is eelworms—a highly successful group of roundworms, or nematodes, which cause great damage to various plants. Some eelworms are free-living in soil and water, others live in decaying vegetation, and many feed on bacteria and even on other eelworms; but the most destructive ones are parasitic species which attack different parts of plants—the roots, stems, leaves, or flowers. One species may be confined to one or two kinds of plants; another will parasitise many kinds of cultivated plants and affect common weeds as well. The two main divisions of eel-

worms affect either the root or the stem and other parts. The stem eelworm (*Ditylenchus dipsaci*) is a well-known pest on many crops—oats, beans, parsnips, red clover, strawberry and bulb crops such as hyacinths and daffodils. Various races now being investigated are morphologically indistinguishable but physiologically adapted to different kinds of plants. Another stem eelworm, *Ditylenchus destructor*, attacks the potato tuber, causing it to rot, and this persists in the field long after the remnants of the crop have been gathered in. Eelworms of the genus *Aphelenchoides* attack the leaves and buds of the strawberry and blackcurrant, chrysanthemums and ferns. The root-infesting forms of the genus *Heterodera* attack plants such as sugar-beet, cereals, peas and brassicas, and the potato. The control of all such forms is sought and is often difficult to achieve for two main reasons: the worm and its egg are protected by materials that resist the action of disinfectants, fumigants and other chemical substances; and the worm often passes into a resting phase which persists for several years, so that the rotation of crops and fallowing will not get rid of it. Experiments on chemical control have produced one method of trying to kill the resistant stage of *Ditylenchus dipsaci*, namely treatment with methyl-bromide vapour. The possibility that eelworms thrive or not on various kinds of manures is being tested at present with *Heterodera schachtii*, the well-known parasite of sugar-beet and mangolds.

Lastly, Rothamsted has contributed to biological progress by helping in the training of graduates. Special courses of instruction are not given at the station, but as many post-graduates as can be helped are assisted, and "it is not uncommon to find men and women of ten or more different nationalities working harmoniously side by side. Many of the present Directors and leading members of staff of Empire and other overseas stations have had part of their training at Rothamsted" (Sir E. John Russell, 1946).

East Malling Research Station

This horticultural station was founded near Maidstone, Kent, in 1913 as a branch of Wye College, with one scientific member of sta and twenty-three acres of fruit-growing land. The first buildings were completed in 1914 and equipped by donations from fruit-growers. In 1926 a membership scheme was introduced and two years later the Empire Marketing Board also donated funds and enabled the station almost to double its previous output of work. In 1929 East Malling was chosen as the home of the Imperial (Commonwealth) Bureau of

Horticulture and Plantation Crops, which began to issue its quarterly periodical, *Horticultural Abstracts*. In 1932 the Ministry of Agriculture assumed responsibility for the staff and enabled the station to maintain its increased activity, and 160 acres of land had been planted with fruit-trees by 1938 and the buildings had become overcrowded. Soon afterwards the near-by property of Bradbourne and an additional 200 acres of unplanted land became available for experimental work. During the war the staff were concerned largely with horticultural work of national importance. A Fruit Farm Survey covered more than 25,000 acres in Kent and 1,000 acres in Norfolk; work was carried out on defects in food crops as a result of mineral deficiency in the soil, and on the maintenance of soil fertility in orchards. Since the end of the war the station has been reorganising, and the Ministry of Agriculture has now assumed complete financial responsibility for it. In 1946 the National Agricultural Advisory Service was formed and members of the staff have thereby been somewhat relieved of routine advisory work and given more time for research.

The central theme of the station's research programme is the fruit plant in relation to its environment, and the original staff of pomologists has been supplemented with chemists, statisticians and biologists, so that its problems can be attacked from all sides. In the early years, fruit-trees root stocks were collected, classified and planted, and some of these have been growing under the eyes of the experts since 1920. Two series of apple stocks have been raised from plantings made in 1945, and they are now on trial in the plantations at Bradbourne. One of them is immune to the woolly aphid, and the other has the good qualities but not the faults of existing stocks. At the end of the war another method of propagation—by cuttings—was brought into use in order to hasten rooting. Trenches having glass sides have been erected to facilitate direct observation of root growth, and special instruments have been employed to measure temperature and moisture of the soil in contact with the roots. Even dwarfing stocks have been found to spread their roots widely and deeply in the soil. As regards soil fertility, it was soon found that treatment with nitrogen, potash and other minerals does not necessarily yield healthy trees; the soil must be in "good heart", which can best be achieved by cover cropping and the use of leys. Long-term trials with various kinds of manure have disclosed the main nutritional requirements of fruit-trees. The effects of various kinds of grafting and pruning have also been studied; framework grafting can change the variety of a fruit-tree rapidly, and

pruning is used to control "biennial training"—*i.e.* the production of a heavy crop one year and a light crop the next. Plant breeding has produced apple varieties similar to, but maturing earlier or later than, Worcester or Cox varieties, *e.g.* Tydeman's Early Worcester, which is a cross between a Worcester and McIntosh Red. The injury caused by frost to fruit blossoms has been carefully studied since the heavy frost of 1935; attempts have been made to determine injurious low temperatures for different varieties and blossom at different stages by means of special low-temperature chambers.

The pests and diseases of fruit-trees have provided problems for the specialists. Plant pathologists at East Malling have studied diseases such as apple and pear scab, canker, brown rot, silver leaf and bacterial canker of stone fruits. Control measures against such diseases are now widely used, but efforts are still being made to improve them. Entomologists concerned with the life-histories of insect pests of fruit-trees have determined methods of control for aphides, caterpillars, capsid bugs, sawflies, codling moth and apple-blossom weevil. Recent attempts at controlling fruit-trees red spider have also met with some success. In these attacks on agencies which do serious damage to fruit-trees and fruit the pathologists, entomologists and chemists work together to determine the relationship between pests, diseases and tree condition in relation to its variety, root stock, type of soil and manner of cultivation. During the last ten years a Plant Protective Chemistry Section has been set up to deal with spraying materials. A special team is in quest of better methods of using existing spray chemicals and of new substances that can be used. Work on the possible correlation between chemical structure and toxicity to pests and disease organisms is in progress, and it is hoped to find the ideal sprays which will keep fruit free from blemishes. One new fungicide which has emerged from this work—phenyl mercury chloride—is now used by growers, though still on trial. As a result of successful work on root stocks, manuring, pruning and spraying, Cox's Orange Pippin, once difficult to grow, is now widely grown in this country; when the remaining problems of "biennial training" and frost injury have been solved the growing of this variety of apple will rest on a sound commercial basis.

Work on soft fruits has paralleled that on top-fruits, and its results have been just as remarkable. The virus diseases of soft fruit have created problems of varying magnitude. Blackcurrants are affected by only one virus, reversion, but strawberries and raspberries may carry

more than one, even when the plant appears to be healthy. By dint of team work, however, new strains free of viruses can now be selected from the chief varieties of strawberries, and some of these are now grown commercially under conditions which ensure that they shall remain free of viruses which cause disease. Entomologists have discovered that the strawberry aphid transmits a virus from diseased to healthy plants, and they have also devised methods of eradicating the insects in the field by the use of nicotine vapour. Similar work concerning the raspberry has lately been carried out by a team working at Dundee. All such work aims at determining the relationship between one virus and another and the reactions of different varieties of fruit plant to various combinations of viruses.

Much progress has been made in the control of pests such as the raspberry beetle and raspberry-cane spot. Cane blight of raspberries was once regarded simply as a disease but is now known to be a combination of pest and disease, the trouble being started by the raspberry-cane midge. Control of the midge will probably bring about the eradication of the disease. Other work on soft fruit includes the breeding of new varieties such as the blackcurrant Wellington XXX and the raspberry Malling Promise, which have been released for temporary use until established varieties can be reared free of their viruses. Other research concerns hops and is mainly cultural but also concerns diseases such as Verticillium wilt, which is caused by soil fungi. This disease was first noted in 1924, but not till ten years later did it cause serious concern, then breaking out and very quickly spreading through the largest British hop area. The disease is being controlled by the use of resistant varieties, four of these reared by Professor Salmon at Wye showing promise.

The planning of the experimental plots at East Malling is carried out by statisticians with the help of data gained in experiments on growth, size and the cropping of plants. Wasted effort is thus minimised and the value of different methods of experimentation is assessed scientifically. Another important concern at the station is the maintenance of close contact between grower and horticultural research worker. Growers can learn from the Annual Report of the station the results accruing from recent work, and on members' days they can visit the station to see experiments then in progress. They can also view by special arrangement at any time any work of special interest to them. This important function of the station is the special concern of the Scientific Liaison Officers, who also maintain contact

with other stations and researchers both at home and abroad. The organ of this and the Long Ashton station, the *Journal of Horticultural Science*, circulates the latest information on horticultural research throughout the world. The reader who desires further information should consult leaflet T6 of the Kent Incorporated Society for Promoting Experiments in Horticulture; *General Development and Activities.* The work of the Long Ashton Research Station—the study of micronutrient deficiencies by sand-culture methods, of plant hormones, of virus diseases of tree fruits, etc.—has been outlined by G. T. Spinks (1950).

The National Institute for Research in Dairying

This Institute, the aims and history of which have been outlined by Professor H. D. Kay (1950), was one of the centres set up under the Development and Roads Improvements Funds Act of 1909 for the promotion of research in agriculture. It was established in 1912 at University College, Reading, with a staff of three—the bacteriologist Stenhouse Williams, the chemist John Golding and a boy (W. A. Hoy) —in quarters which comprised an attic and a cellar in an old house. More suitable quarters were obtained in 1920 at Shinfield (three miles from Reading), where a herd of dairy cows was established on the Manor Estate (350 acres), and laboratories were set up in the Manor House. In 1924 three departments (Bacteriology, Chemistry and Dairy Husbandry) began researches on the problems of milk production and the chemistry of milk and milk products, the rearing of calves and the nutrition of dairy heifers. The "drive and determination" of Mr Williams (who died in 1932) eventually led to further enlargement of the scope and activity of the Institute, and by April 1950 there were seven main departments (Dairy Husbandry, Feeding and Metabolism, Physiology, Bacteriology, Chemistry and Physics, Dairy Engineering, and Nutrition) and a smaller section dealing with Statistics, an experimental Dairy and a Library. The total staff is now 220, mostly farm workers and skilled tradesmen, but including 51 trained graduates with scientific or experimental officer grade.

During the period of great development (1933–39) the Institute was concerned with many problems, only a few of which can be mentioned. Dairy cows were found to require for milk production only four-fifths of the protein previously believed to be necessary; calves, rats and children were found to grow equally well on either raw or pasteurised milk; the nutritive values of sterilised, condensed and

dried milk were determined; and the discovery was made that ordinary daylight rapidly destroys vitamin C in milk. Studies were commenced on the precursor substances of milk in the blood of dairy cows, and the discovery was made that feeding thyroid gland or administering thyroxine to dairy cows increased the milk yield and the butterfat content of milk. The milk of defective cows was also studied. Attempts were made to determine the period of survival of the tubercle bacillus in infected pastures and in dairy products made from infected milk. For a popular account of the formation and secretion of milk see the article by F. H. Malpress (1948).

After the outbreak of war in 1939 urgent matters which had to be dealt with as a matter of routine did not stop the flow of fundamental research at the Institute. The enzyme rennin was purified and crystallised, iodinated proteins were fed to dairy cows to increase the milk yield, and sterile or virgin heifers were treated with synthetic oestrogens so as to induce lactation artificially. Methods were devised to indicate whether or not the cow is ripe for fertilisation ("on heat") and active oestrogens were discovered in some British grasses and clover. An artificial insemination centre was set up at Shinfield in 1942 at the request of the Ministry of Agriculture as a prelude to the nation-wide scheme adopted in 1944. In England and Wales in 1949 nearly half a million dairy cows (one-seventh of the total population) were inseminated artificially, about 21,000 of them at Shinfield. Research on the biochemistry of milk formation was continued and it was discovered that one of the main sources of milk fat is acetate circulating in the blood of the cow. The condition of "let-down" in dairy cows was found due to tactile stimuli of the teats, or other stimuli which the cow associates with milking, evoking the liberation of a hormone from the posterior lobe of the pituitary gland. A bacteriophage was found to cause difficulty in cheese-making and the new antibiotic nisin was isolated from cultures of lactic acid streptococci, purified, crystallised and tested *in vitro*. The work of the Institute at Shinfield thus touches biology at many points and has produced advances worthy of note.

For information on developments in dairy hygiene in Great Britain see the article by W. R. Wooldridge (1949–50).

The Department of Scientific and Industrial Research

In 1915 the Government appointed an Advisory Council for Scientific and Industrial Research and in 1916 established a separate

Department. This covers a very wide field of research and has been responsible since 1918 for the National Physical Laboratory, and since 1919 for National Surveys of coal and other fuels, also various Testing Centres. It has also established various research institutes in which biology figures prominently—for instance, the Food Research Stations, the Forest Products Research Laboratory, and the Water Pollution Research Laboratory. In regard to the first of these, the Cold Storage Board was set up in 1917 and in 1918 it became the Food Investigation Board under the chairmanship of (Sir) William B. Hardy. Its chief concern was research in the preparation and preservation of food, particularly the refrigeration of fresh foods. The aim envisaged was prevention of wastage of valuable food materials in the field, during transport, and in warehouses, markets, shops and the home. In 1919 a laboratory was erected at Cambridge and in 1922 the Low Temperature Research Station was completed. Ten years later the station was enlarged, and soon afterwards the Ditton Laboratory was established near East Malling for experimental work on large-scale storage of fruit. In 1929 the Torry Research Station was established at Aberdeen for research on the freezing and smoking of fish and fish products. In 1935 the D.S.I.R. took over from the Ministry of Agriculture responsibility for the Chipping Camden Research Station of the University of Bristol, where research was carried out on the canning of fruit and vegetables. Small laboratories were also established for fruit and meat examination respectively, one in 1926 near Covent Garden Market, and another in 1938 near Smithfield Market. The work of the Food Investigation Board was therefore extremely varied, but its chief concern was to keep alive or to preserve satisfactorily the tissues of various organisms used as food. In the words of Sir William B. Hardy, the science of food preservation "is essentially a biological industry. Biological thought and biological research fix the conditions necessary for successful storage, and to the cold storage engineer is left the duty of realising these conditions in practice. Logically, biology has precedence". The change of outlook which all these types of applied biology brought about has been discussed by D. W. Hill (1947). In regard to results, the layman can now procure at small cost Government leaflets dealing with fruit, vegetable and fish preservation by freezing or cold storage, and the specialist can study detailed reports on such subjects as microbiology in the preservation of animal tissues or eggs, and the changes produced by bacteria in meat extracts.

In 1921 the Forestry Products Research Board was established for

the purpose of setting up and maintaining research on timbers and other forest products, and the concern with national housing problems has thus benefited biology. A timber-seasoning plant was secured at Farnborough and a Forest Products Laboratory was set up at Princes Risborough under the direction of (Sir) Ralph S. Pearson. Later on the scope of this venture was extended, and extra-mural work was carried out at the Imperial College, South Kensington, at Oxford and at St Andrews. In addition to many technical problems which do not specially concern biology, the Laboratory and other centres have dealt with the problems of insect infestation of timber and forest products.

The Water Pollution Research Laboratory was set up in 1927 by a Board under the chairmanship of Sir Robert Robinson, the Government Chemist. This arose out of investigations made by the Ministry of Health and the Department of Agriculture and Fisheries on the damage done to fresh-water fisheries by sewage disposal, and at once a biological and chemical survey was made of the River Tees, into which many types of effluents were discharged. In 1927 the effects of effluents from beet factories were investigated, and in 1933 an inquiry into the effect of discharging crude sewage into the Mersey estuary. These investigations have established knowledge which can be applied to the clearing of all contaminated rivers and tidal basins, and they have shown how "process waters" of beet and other factories can be purified by means of biological filters and reused, thus avoiding pollution to streams and rivers. This work was largely carried out at Rothamsted during the period 1927–30, and at the same station the results of an investigation of methods of treating waste waters from dairies and factories of the milk industry were published in 1941.

Food Infestation by Arthropods

Many kinds of stored foods are infested by insects and mites, notably wheat and maize seeds (the cores of which are eaten away) and sultanas and other dried fruits (which are "spoiled" by larvae living in them). Infestation becomes an economic problem where large stocks must be warehoused for long periods, for heavy losses accrue. In the period 1930–35 the Australian Dried Fruit Board made strenuous efforts to control one insect pest—the moth *Plodia interpunctella*; about £30,000 was spent on research, but by 1939 five times this sum had been saved. During the 1914–18 war the Royal Society Grain Pests (War) Committee was set up to advise on methods of protecting warehoused grain, and about ten reports were made (see J. W. Munro, 1940, 1947).

In 1927 the staff of the Entomology Department at the Imperial College, South Kensington, began a study of the insects infesting various foodstuffs in warehouses at the London docks, mainly cocoa. The Empire Marketing Board, and later the Imperial Agricultural Bureau, supported and helped to finance such work in relation to tobacco and dried fruits, as well as cocoa, and the University Grants Committee enabled the college to carry out its work on a permanent basis. In 1935 industrial interests (represented by W. McA. Gracie) and the professor of entomology at the Imperial College (J. W. Munro) suggested that the college should conduct an extensive survey of problems concerning the infestation of stored products, and in 1939 a college report indicated serious and widespread effects. The D.S.I.R. thereupon set up its own research organisation and based it on the Imperial College Biological Field Station at Slough. During the 1939–45 war the Infestation Branch of the Laboratory (established 1941) greatly assisted the Ministry of Food in control of pests of grain, other cereals and various other stored products. For a relevant report see J. W. Munro (1940, 1947). Thus the biologist became involved in the broader problem of grain contamination. Impurities such as foreign seeds can be removed from grain by means of sieves and aspirators but there still remain biological problems due to weevils and other insects which live and multiply in the stores. Information bearing on the control of such insects, the principles of fumigation to get rid of them and the biology of mites and other arthropods can now easily be obtained at small cost from Government publications. For popular accounts of food infestation by insects see J. W. Munro (1929) and J. A. Freeman (1948).

Other Institutions

It is not possible to give details of the ways in which other institutions have furthered biological research, much of which is carried out in the British Isles in universities, polytechnics and colleges. Special schools have been set up for certain fields of research—Brewing at Birmingham, Leather at Leeds, and Textiles at Leeds, Manchester, Glasgow and Nottingham. The British Council has in recent years attempted to outline the main trends in research in the universities and to get detailed information one would have to consult the journals of relevant scientific societies. Old establishments such as the Royal Society of London, the Royal Institution and the British Association

for the Advancement of Science have made invaluable contributions to biology, as well as to other sciences. The Corporation of the City of London and various Companies have done much for education and nearly as much for research: *The Clothworkers* in regard to research on textiles at Leeds, *The Drapers* by way of grants to various colleges of the University of London and *The Fishmongers* by grants to various marine and fresh-water biological laboratories (at Plymouth, Millport and Ambleside). These researches have rarely been strictly biological, but fundamental discoveries have sometimes been made which have advanced biological thought considerably—for instance, the results of research on protein fibres at Leeds.

Co-operative industrial research has extended throughout the British Empire and it seems to have originated in the U.S.A. in the late eighteen-eighties, mainly in connexion with the sugar industry. Various Government laboratories in the U.S.A.—the Fish and Wild Life Service, regional establishments for dealing with research on various agricultural products (cotton, sweet potatoes and peanuts at New Orleans, for instance), the Rockefeller Institute for Medical Research in New York, the Bureau of Agricultural Chemistry, and many trade organisations—are world-famous, as are the various organisations dealing with cotton (for instance, the National Cotton Council of America, the Textile Research Institute, the Cotton Textile Institute and the Textile Foundation, and more recently the Calloway Institute and the Institute of Textile Technology). For an account of these and others, see D. W. Hill (*loc. cit.*).

Pure Chemicals and Biological Progress

Much progress in biology has been made because of the availability of chemical substances derived from animals and plants and produced on an experimental or commercial scale. Modern biological research is continually calling for pure preparations of hormones, vitamins and other pharmaceutical substances and, in spite of advances in synthetic chemistry, these must often be obtained from organisms in which they originated. Some commercial firms regularly manufacture such substances and I should like (without invidious intent) to mention just one of them—the Armour meat-packing firm in Chicago, which has access to inexhaustible supplies of raw materials and has both the scientific personnel and the facilities for dealing with these. Some Armour developments have been described by

Laurence L. Lachat (1948), who has also kindly given me a statement (*in litt.*, July 1950) on which I draw gratefully. During the 1939–45 war a pressing need arose for a cheap, effectual and safe substitute for human blood plasma, and an attempt was made to meet this by adapting to pilot-plant operation an experimental method—devised by E. J. Cohn of Harvard University—for the separation and isolation of protein fractions from human plasma. After the war, the chemical fractionation of human plasma was discontinued, but the experience gained was applied to the isolation of components from the plasma of animals, mainly the ox. Using the new technique, animal fibrinogen, fibrin films and foams, *gamma*, *beta* and *alpha* globulins, and albumin were manufactured in relatively pure and undegraded forms on an experimental basis, and distributed to the scientific professions as a public service. Such products found many general applications. Albumin is used in hospitals as a diluent in Rh typing sera, in tuberculosis clinics for the culture of pathogenic organisms, and in university and other research centres as a standard reference protein.

Other developments included the isolation of fractions from the pituitary glands of animals, notably the adrenocorticotropic hormone (ACTH), which has shown wide effects in a variety of diseases and is now used for the therapeutic treatment of rheumatoid arthritis, gout, lupus erythematosus, and pathological conditions involving secretions of the adrenal glands. Intensive research on this compound has revealed many new facts useful in medicine and related fields. Other hormone preparations now available include growth hormone, thyrotropin and gonadotropins. Still another development is the manufacture of enzymes in a relatively very pure state. Without specially purified pepsin, trypsin, chymotrypsin, ribonuclease and lysozyme many types of biological research would be retarded and progress in medicine impeded. The important muscle constituent adenosine triphosphate—from which in the living muscle energy is transferred to the muscle protein myosin, with resultant contraction of the myosin molecule—is also being produced in a specially purified form, and will surely be in great demand by the muscle physiologist. Important compounds are also being isolated from the liver, which for some years now has been a dependable source of the anti-anaemic principle otherwise known as vitamin B_{12}, and there is the possibility that other and equally valuable principles will be recognised, produced and investigated further. Speaking on behalf of his firm, Dr Lachat has said: "With passage of time we can organise production by wise,

efficient, and co-operative effort to draw out ever more of these materials from the animal and apply them beneficially"—a sentiment which will no doubt be echoed by other workers in the same or similar fields.

Government Publications

Many students and teachers know the value of summaries of researches published by H.M. Stationery Office. The Ministry of Agriculture and Fisheries List of Agricultural Publications is a bibliography of expert work on the many problems of agricultural science. Bulletins deal with such subjects as bee-keeping and the diseases of bees, the raising of vegetables, fruit and live stock, the pests and diseases of farm animals, the principles of rabbit and poultry feeding, and such miscellaneous topics as edible and poisonous fungi, the cultivation of medicinal plants, and the destruction of rats. For a short account of the war on rodents, with references, see A. Barnett (1941). There are several hundreds of brief and simply-worded Advisory and Animal Health leaflets on live stock and dairying, the pests and diseases of fruit, flowers and vegetables, weeds, birds, and various subjects which range from grey squirrels to the mole, and from soil analysis and seed-testing to orchard renovation and the storage of fruits. Animal Health leaflets deal with the diseases and disorders of domesticated animals—*e.g.*, coccidiosis in poultry, fluke disease (liver rot) in sheep, mastitis in cattle, and nutritional anaemia in young pigs. These elementary leaflets are not primarily intended for students, who will however get useful information from the other publications, and possibly from some of these.

The Forestry Commission List likewise enumerates sets of reports, bulletins, booklets and leaflets which contain reliable information on such varied subjects as woodland mosses, bark-beetles and forestry practice, as well as general statements on various pests of conifers and other trees. The D.S.I.R. List covers work dealing with food investigations, forest products research, road research (which includes soil-survey procedure, etc.), and water-pollution research. The Ministry of Food List covers much work which is not biological, but it includes circulars on the insect pests of food, the control of rats and mice, a manual of nutrition, and a report on the chemical composition of foods. The Ministry of Health circulars, reports on Public Health, and medical subjects also cover a wide field, but also include biological matters. The Medical Research Council War Memorandum Series largely covers certain medical and surgical subjects, but the biologist

will find much to interest and instruct him in the memoranda which deal with such subjects as the determination of the blood groups, the use of sulphonilamides and penicillin, environmental warmth and its measurement, food yeast, etc. The results of intensive research planned and fostered by Government Departments through their committees form an invaluable source of information which the student of biology will be unwise to ignore or neglect in the future.

Natural History Publications of the Trustees of the British Museum

These publications range from very technical reports written by specialists for specialists to economic leaflets which can be read by boys and girls, and they form a monument to the process of gaining and spreading biological knowledge. They include the large volumes of the National Antarctic Expedition of 1901–4 ("*Discovery* Reports"), the British Antarctic ("*Terra Nova*") Expedition of 1910, the Great Barrier Reef Expedition of 1928–29, the John Murray Expedition to the Indian Ocean (1933–34), the British Graham Land Expedition of 1934–37, the Rumenzori Expedition of 1934–35, and the South-West Arabia Expedition of 1937–38. Additional publications take the form of numerous catalogues on various mammals, birds and fishes, and also on representatives of nearly all the invertebrate phyla and classes, notably insects. These are taxonomic works of some importance. Special lists of British animals form another series, and other publications deal with plants and fossils. The "Guides" to the various galleries of the Natural History Museum will be known to many visitors. The Economic Series deals with many animals of some importance in human affairs—the housefly, the bed-bug, lice and fleas, mosquitoes in relation to disease, marine boring animals, furniture-beetles, the cockroach, clothes moths, and common insect pests of stored products. One recently revised booklet deals with the biology of water supply in many of its aspects. The Economic leaflets are concerned with such subjects as the danger of disease from flies and lice, and with animals such as the furniture-mite, silver-fish, book-lice, crickets, earwigs and carpet-beetles.

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II. SOME TECHNICAL ADVANCES

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Note.—O. W. RICHARDS of the Research Department, Scientific Instrument Division, American Optical Society, wrote a valuable paper (*Trans. Amer. Micr. Soc.*, **68**, 1949, 55–57; 206–207; 275–276) giving many other references, mentioning 25 books, 32 essential papers and 24 papers dealing with recent trends in microscopy. In regard to phase-contrast microscopy, the American Optical Society has published a list of 135 papers up till March 1949. This list is supplied gratis on request. A selection of references appears below, mainly those mentioned in the text.

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Note.—DARLINGTON and MATHER (1950) include a list of 217 books on the subject of genetics, which can be grouped as follows:

Up to 1899 . . .	15
1900–9	14
1910–19	36
1920–29	50
1930–39	60
1940 onwards . . .	42
Total	217

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