UNIVERSAL
LIBRARY
OU_162645
UNIVERSAL
LIBRARY

OUP—23—4-4-69—5,000.

OSMANIA UNIVERSITY LIBRARY

Call No. 573 B98M Accession No. 241

Author Butler, J.A.V.

Title Man is a microcosm.

This book should be returned on or before the date last marked below.

MAN IS A MICROCOSM

MAN IS A MICROCOSM

by

J. A. V. BUTLER

Man is a microcosm, or a little world, because he is an extract from all the stars and planets of the whole firmament, from the earth and the elements; and so he is their quintessence.

PARACELSUS

LONDON
MACMILLAN & CO. LTD
1950

This book is copyright in all countries which are signatories to the Berne Convention

Stone walls do not a prison make,
but scientific terms do.

O. St. J. Gogarty in
Tumbling in the Hay

PRINTED IN GREAT BRITAIN

FOREWORD

In this book I have attempted a broad survey and interpretation of present knowledge of the nature and basis of life, which will, I hope, be of interest to the general reader as well as to scientists. I have avoided using technical expressions as far as possible. In the earlier chapters a few chemical formulae are shown, but their understanding is not necessary to the argument and I trust that readers, who are not technically equipped, will not be unduly frightened by them. They are only the exhibits in the case, samples of the evidence which is available for the scrutiny of experts. While I hope that they will be of interest to those who know how to interpret them, the less expert can look upon them merely as the footprints which scientists have used in finding their way along the roads on which we shall travel, in our voyage of exploration towards the almost "undiscovered countries" of the mind. My aim has been to explain what science has found out about living things, and also to bring out the repercussions which this knowledge has had on the thought of recent times and on the picture which ordinary people have of life and human nature. The influence of science in forming the human outlook is very great and deserves a closer study than I have been able to give it. Unfortunately much of the information which reaches the public, even when it is not incorrect, is without a sufficient background to enable them to judge its importance in the whole scheme of things. The man in the street does not merely see science through a glass darkly, but reflected in distorting mirrors which magnify some features out of all proportion and suppress others. He reads about wonder

drugs, test-tube babies and electronic brains and is impressed. He is hardly to be blamed if he thinks that what remains to be found out will be found out very soon. My object has been to put the scientific discoveries into a reasonable perspective ; to show what has been achieved and how much remains.

ACKNOWLEDGEMENTS

CHAPTERS II-IV are based to some extent on my Cantor Lectures to the Royal Society of Arts (1947) and I am indebted to the Council for permission to make this use of them and also for the loan of some of the blocks. I wish also to express my gratitude to A. J. V. Gale, Esq., for reading the MS. and giving me advice and suggestions which greatly improved it, and to Dr. K. A. Smith for reading the proofs. I am also indebted to Prof. G. A. Baitsell and Dr. Edith Sitwell for permission to quote from their works, and to all the following who have generously given me their beautiful photographs and drawings and permission to reproduce them: Plate I (*upper*), Prof. H. Neurath; (*lower*), Dr. D. Glick; Plate II (*upper*), Dr. J. H. Northrop and the Columbia University Press; block by courtesy of Butterworth's Scientific Publications; (*lower*), Dr. M. F. Perutz and Butterworth's Scientific Publications; Plate III, Dr. M. Kunitz and Columbia University Press; Plate IV, S. H. Revell, Esq.; Plate V (*upper*), Dr. P. C. Koller; (*lower*), Dr. A. F. Hughes; Plate VI, Drs. Chu, I. M. Dawson, and W. T. Elford and the Editor of the *Lancet*; Plate VII, Dr. R. W. G. Wyckoff; Plate VIII, Dr. Max Hartmann and Messrs. Gustav Fischer, Jena; Fig. 10, Prof. G. W. Beadle, Prof. G. A. Baitsell, the Yale University Press and Oxford University Press; Fig. 14, W. F. Floyd, Esq.; Fig. 15, Dr. Lorenté de Nó, Prof. John F. Fulton and the Oxford University Press.

CONTENTS

		PAGE
	FOREWORD	v
	ACKNOWLEDGEMENTS	vii
I.	LIFE IN THE UNIVERSE	1
II.	THE BUILDING STONES AND THE FABRIC	11
III.	MEDIATORS BETWEEN THE LIVING AND THE NON-LIVING	21
IV.	HELPERS AND HINDERERS OF VITAL PROCESSES	29
V.	HOW PROTEINS ARE MADE	45
VI.	LIFE GOES ON	51
VII.	INSIDE THE CELL	64
VIII.	CHEMICAL CONTROLLERS OF THE BODY	77
IX.	DEVELOPMENT AND GROWTH	88
X.	HOW DID IT ALL BEGIN?	96
XI.	MUSCLE AND BRAIN	105
XII.	ACTION AND FREE WILL	117
XIII.	SPEECH AND THOUGHT	128
XIV.	IS THE BRAIN A CALCULATING MACHINE?	135
XV.	THE STATURE OF MAN	142
	INDEX	151

LIST OF TEXT ILLUSTRATIONS

FIG.		PAGE
1.	How the fabric of life is woven	14
2.	Some of the smallest living things and the molecules they are made of	17
3.	An example of the possibilities of pattern in the proteins	18
4.	How an enzyme breaks a compound	26
5.	Structural formula of co-enzyme — a detachable bit of an enzyme	34
6.	Some of the vitamins — substances essential to life in large and small organisms	35
7.	A vitamin — and an antagonist to it	37
8.	How an enzyme might be made from its gene and how the enzyme might become changed so that it will fit a particular molecule	56
9.	A nucleic acid	57
10.	How mutants of the fungus *Neurospora* are made and tested for their nutritional requirements	61
11.	Diagram of the contents of a cell (after Lazarow)	66
12.	Relative sizes of virus particles and bacteria	69
13.	Some of the hormones	80
14.	Electrical oscillations in the brain, recorded through the skulls of human beings	111
15.	Typical neurones and their branching connections found in different layers of the cortex of an ape	137

LIST OF PLATES

PLATE		FACING PAGE
I.	(*upper*). Model of a peptide (Neurath) (*lower*). The distribution of a single enzyme (a phosphate-splitting enzyme) in the tissues of a plant	20
II.	(*upper*). Crystals of the protein pepsin (*lower*). An X-ray diffraction photograph of a single wet pepsin crystal, by Dr. M. Perutz	21
III.	(*a*). Crystalline ribonuclease, a digestive enzyme (Kunitz) (*b*). Crystalline hexokinase (Kunitz and McDonald)	36
IV.	Chromosomes in the nucleus of cells from the growing tip of the onion root at various stages of the process of cell division	52
V.	(*upper*). The effect of a chemical substance (a nitrogen mustard) on the chromosomes of a tumour cell (*lower*). Photograph of a living cell	53
VI.	Electron micrographs of Influenza A virus adhering to a red fowl cell	68
VII.	Two pictures of bacteriophage attacking a bacterium (*B. coli*), taken with the electron microscope by Dr. Ralph W. G. Wyckoff	69
VIII.	The miracle of growth. Early stages of the development of a sea-urchin from a single fertilized egg cell (from Boveri)	88

I

LIFE IN THE UNIVERSE

'Tis surely a most shabby thinker
Who, looking on Nature, finds not the reflection appalling.
ROBERT BRIDGES

Sheer multitudinosity has power to oppress the mind.
R. KNOX in *Let Don's Delight*

WHAT is life? A little scum of no importance on the surface of an unimportant globe circling round a second-rate star? An accidental conglomeration of atoms which have come together by an odd chance, the result of an exceedingly improbable happening? That is what some astronomers would have us think. Looking out into the depths of space, they have discovered a universe of unthinkable dimensions. A billion suns in our own galaxy, beyond it perhaps a billion galaxies, only revealed to us as tiny smudges on a photographic plate. No wonder they are impressed by the enormous disparity between the scaffolding and the result. Life seemed to be, as Jeans said, " an utterly unimportant by-product " in " a universe which was clearly not designed for life, and which, to all appearances, is either totally indifferent or definitely hostile to it ". It seemed " incredible that the universe can have been designed primarily to produce life like our own; had it been so, surely we might have expected to find a better proportion between the magnitude of the mechanism and the amount of the product ".

It also used to be thought that the conditions under

which life could possibly arise in the universe were not likely to occur frequently among the stars. Life, as we know it, requires water, light, a moderate temperature neither too hot nor too cold, and a variety of chemical elements. It is not at all certain that these conditions are to be found, in our own solar system, except on the earth. Planetary systems, probably the result of a near encounter of two stars, were believed until recently to be of comparatively rare occurrence. This view was based on calculations of the chance of stellar encounters. The stars are separated by enormous distances, and though they are in motion, the chance of a close approach of two stars is comparatively small. When such an encounter takes place, enormous tides in the liquid or gaseous surfaces of the stars are set up, which may result in large masses of material being pulled away from them and, condensing, giving rise to planets.

These calculations have had to be revised in some respects. According to the recent theories of Hoyle and Lyttleton, the planets originated in the break up of a companion of the sun in a tremendous explosion. Explosive stars, called *supernovae*, are not at all infrequent and it has been estimated from such occurrences that at least a million planetary systems may have been produced in our own galaxy.

If this is so, it is not unlikely that in many of them there will be planets in which the essential requirements of life are present. All we know about the material universe suggests its great uniformity. We know from the light they emit that the stars contain many of the elements we have on the earth. There is nothing whatever to indicate that our present world is unique, or even exceptional. Should we not expect that conditions which have produced life on the earth will operate wherever similar conditions exist? There is no reason why we should not be willing to think that life may exist in great profusion in other worlds.

If this is so, we must not expect that evolution has followed similar paths everywhere, or has gone on at the same speed. There may be worlds in which life has not yet produced thinking and reasoning creatures like ourselves; there may be others in which organized rational societies have existed for many millions of years. Life may also have developed other and perhaps fantastic forms. Some worlds may be completely covered by the oceans, and have developed fishy societies. In worlds which are much greater than the earth, the greater intensity of gravitation will have forced living things to solve quite different structural problems. A man's limbs would not be strong enough to support his weight on a larger planet, where the force of gravitation is considerably higher.

Since we have no prospect whatever of exploring these other worlds, these are idle speculations at the present time. All we can find out about life, we must discover from what we see in our own world. We must turn away from the macrocosm to look at the microcosm, which exists everywhere around us and within us. At the same time as telescopes were being constructed to look into space, microscopes in the hands of Robert Hooke and A. van Leeuwenhoek began to reveal the complexity of living things. John Ray described the revelations of the microscope as follows:

"Our sight doth not give us the just Magnitude of Things, but only their Proportion; and what appears to the Eye as a Point, may be magnified so, even by Glasses as to discover an incredible Multitude of Parts; nay some animals there are, so small, that if a Grain of Sand were broken into 8,000,000 of equal Parts, one of these would not exceed the bigness of those Creatures, as Mr. Leeuwenhoek affirms. And Dr. Hooke proceeds farther, and says, that he had discovered some so exceedingly small, that Millions of Millions might be contained in one Drop of Water. If these whole Creatures be so incredibly little

what shall we think of their Parts, containing and contained, their Entrails and Muscles, their Ovaries and Eggs?" [1]

The world was found to be teeming with microscopic life wherever there was water and warmth. A drop of water taken from a pond was seen to contain creatures of many kinds all engaged in complex modes of living. The larger organisms were found to be not unitary, but societies of cells, each possessing its own life to a limited extent, co-operating in a common purpose.

Notwithstanding all this diversity of size and form, it has been suspected for a very long time that all kinds of life had an underlying similarity. About 500 B.C. the Greek philosopher, Empedocles, is reported to have said that "Hair and leaves and the thick feathers of birds and the scales that form tough limbs are all the same thing", — a fairly accurate statement of what modern chemistry has found. Detailed study has in fact disclosed an extraordinary similarity in the underlying chemical constitution of all living things. Whether they are microscopic organisms, tiny blobs of jelly, or large animals, they are, as we shall see, all made of very much the same substances.

In earlier times, when every substance was believed to have its own qualities, there was no difficulty in believing that some substances were endowed with life, others not. Wood was wood, and water water; and though transformations did occur, as in the disappearance of wood in the fire, they were not surprising in a world where the most miraculous changes were taking place under everyone's eyes every day. There was nothing but

> doth suffer a sea-change
> Into something rich and strange.

A seed put into the ground became in a short time a plant with leaves and flowers; the white and yolk of an egg

[1] *Three Physico-Theological Discourses.*

turned into the flesh and bones and feathers of a chicken, which, no sooner was the shell cracked, jumped out and started running about.

Chemistry emerged as a science when it was understood that all substances are combinations of the same primary elements, which are to all intents and purposes indestructible (except under such violent actions as occur in the atomic bomb). Wood turns out to be a combination of carbon, hydrogen, and oxygen, and when it is burnt the carbon is turned to carbon dioxide and the hydrogen to water, and one can make an accurate balance sheet accounting for everything originally present in the wood. The first stage of scientific chemistry, which was begun by Lavoisier with the correct account of combustion, was guided by the atomic theory of Dalton, which served to explain the facts of chemical combination in simple compounds. It was concerned with the elementary composition of substances. This was understood when it was expressed in an atomic formula. NaCl stood for the combination of one atom of sodium (Na) with one of chlorine (Cl), forming sodium chloride or common salt. Water was H_2O, the combination of two atoms of hydrogen (H) and one of oxygen (O). These formulae were based on the facts of chemical combination, but they have stood the test of time and the more powerful physical methods which later became available, and undoubtedly represent the real structure of the molecules, *i.e.* the smallest natural unit of these substances. The great profusion of substances which come from living things, like alcohol, oils, fats, sugars, waxes, resins, rubber, cellulose, starch, were originally called *organic* compounds and thought to be entirely different from the *inorganic*. Although they were compounds of carbon, hydrogen, oxygen, etc., chemists thought they were an entirely different class of compounds from those which they had managed to prepare. But the distinction broke down when a German

chemist, Wöhler, prepared urea, which had previously been regarded as a typical product of life.

For a long time chemists could not see how so many different compounds could be formed from the same elements. The secret of their mode of combination was not discovered at first, but eventually it was found that the carbon atom can combine with itself, as well as with other elements, to form an enormous variety of chain and ring structures.

This discovery opened up the road to the synthesis of large numbers of organic compounds, many of them the products of life, others types which have not been found in Nature.

The success of organic chemistry in making these compounds — natural and artificial colouring matters, drugs, solvents, essential oils, etc. — has given rise to an exaggerated idea of its capabilities. It is true that some types of compounds, such as the more complex carbohydrates like cellulose, and also proteins, still resist the efforts of chemists. But perhaps it will only be a matter of time before all these compounds can be made. Will it then be possible to create a living system by putting together all the compounds which make up a living organism? Shall we be able to create life in a test-tube?

I do not think there is any scientific knowledge which leads to a certain answer to this question; we can only explore what has been found out about the chemical basis of life, and my readers can judge for themselves how far chemists have progressed on the long path of its reconstruction.

We will enquire, then, just what is involved in reconstructing living things, starting with the simplest we can find. It might be thought that this is a technical question of no great human importance. If this achievement is in any case very remote, does it matter very much what progress has been made or how distant is the goal? You are

willing to agree that the achievements of chemists are impressive and that living things are also very complex. No doubt scientists will continue to make discoveries, and some day they may manage to make a microscopic spot of jelly which, they will tell us, is alive. Does it really matter very much? Are not the real problems of mankind elsewhere, in politics, in personal relations, in artistic endeavour, in finding out how the human population of the earth can agree to share it and to make the most of it, or in avoiding a world-wide famine?

A little reflection will convince most people that what we think and do are greatly influenced by our conceptions or misconceptions of the nature of life. The cosmology of Galileo did more than displace the earth from its pre-eminent position in the centre of the universe. It entirely changed the world picture of Western man and his estimate of himself as the lord of creation, " the master work, the end of all yet done ", made to rule

> Over the fish and fowl of sea and air,
> Beast of the field, and over all the earth
> And every creeping thing that creeps the ground.

He became an insignificant inhabitant of an unimportant planet. Newton extended the rule of law from the earth to the planets, which moved no longer of their own caprice but in orbits determined by the laws of gravity. Darwin's theory completed the picture. It brought the origin of species within the realm of natural law. It was " blind forces, blindly acting " which had brought human beings out of the primeval slime. Man was not only of less significance in the universe than a grain of sand on the seashore, he was also the result of the operation of the laws of chance, operating under the sole criterion that only that which is efficient can survive.

This was the picture most scientists had towards the

end of the nineteenth century, and though many of them were aware of its limitations and were willing to exercise the suspense of judgement which a consciousness of their great ignorance required, it became in a debased form the popular picture of life and man. The prevalent view of man is in fact very low. He is a mere unit of man-power, a cog in a machine. Even scientists are referred to to-day, in Government reports, as so much scientific man-power. Much of the conflict of the present-day world is due to this belittling of man. No doubt industrial civilization, which made men the servants of machines, and was contemptuous of the aspirations of ordinary men to live a good and satisfying life, is partly responsible; but it could only arise in a society where a low view of the value of human beings was taken for granted.

Because they had learnt a little about living things, uninformed people jumped to the conclusion that what was still to be learnt was unimportant. Because they were impressed by machines, they assumed that human beings were like them, only a little more complicated. The mechanical concept of life runs through innumerable books and newspaper articles and has done much to produce and foster this low opinion of human ability. A calculating machine is called a mechanical " brain ". It is true that these machines are wonderful pieces of mechanism and ingenuity, but the operations they perform are really rather limited. Their main value is to carry out quickly certain repetitive operations which human beings find tedious and time-consuming. To call them " brains " is a gross libel on real brains, the fantastic operations of which, as we shall see, are quite beyond our understanding even in comparatively unintelligent animals.

The idea of a " mechanical man " is another sign of the times. " Rossum's Universal Robots " have had plenty of successors, which have spilled over from literature into the

films and comic strips. The popular magazines of " science fiction " are full of them. The girl in the mass-production factory takes them for granted; but it is not surprising that she should think that an automaton could put a squiggle on the chocolates nearly as well as she can, and if an automaton could do that, she might easily imagine there was little difference between it and her.

The ultimate horrors in this direction are the grotesque representations of the human body, which are supposed to be educational and have been seen in exhibitions — a crude human shape, with a few lamps that go on and off and perhaps a coloured liquid circulating through some pipes; the ability to perform a few simple movements and perhaps respond to one or two words of command.[1] This is supposed to represent what science has learnt about man and what it can do to re-create him! It is significant that in a mechanical age people should be willing to accept such a crude model as something even vaguely human.

Scientists themselves are turning away from the cruder mechanical ideas. Their exploration of living things has revealed an extraordinary complexity. Whatever life is, we shall see that it is certainly not a simple phenomenon and cannot be described in simple terms. Scientists of many kinds: biologists who study intact organisms and their mode of life, physiologists who study the mechanism of action of the various organs, biochemists who study the constituents of living things, physicists who bring their powerful instruments to the study of living matter: all find that their work reveals an ever-increasing complexity, the bottom of which has not been reached. The fact of this complexity, alone, means a revolution in our assessment of life and its significance, which must have great implications when it is more widely known and understood. Nineteenth-

[1] The New York Fair of 1939 had one; so did the Paris Exhibition of 1937. It is still on view, I believe, in the Palais de la Découverte.

century science, being concerned with the elemental forces, sought and found simplicity in the universe, a simplicity which Eddington brought to its ultimate conclusion in his view that all the physical quantities such as the size of the universe, the number of particles in it, and the mass of the electron could be derived from a few inter-relations between the ultimate physical constants.

A simplicity of the ultimate particles is not incompatible with an extreme complexity of the patterns they make. The main emphasis of science is now changing from the study of the elementary forces and simple particles to the complexities of living textures. This may bring about a revaluation of man's estimate of himself. For although the austere and noble studies of astronomers, mathematicians, and physicists, which have revealed the foundation stones and dimensions of the universe, have enriched mankind by their demonstration of the power and sweep of the human intellect, they also left them a little naked, exposed, and insignificant in the chilly vaults of space. The balance may be redressed by the complementary studies of living structures, which, by revealing a world as rich in texture as the other is vast, may make men feel again that they are not out of keeping with the splendour of their setting.

II

THE BUILDING STONES AND THE FABRIC

> We shall con the grammar, the material alphabet of life,
> Yea, ev'n more from error to preserve our inquisitive mind,
> Than to secure well-being against adversity and ill.
>
> ROBERT BRIDGES

HALF A DOZEN elements form the greater part of the substance of living things. Others occur in smaller proportions and are necessary to life; for example, calcium in bones, iron in the pigment of blood, iodine in thyroxine, a product of the thyroid gland. But the fabric of living structures is normally made of carbon, oxygen, hydrogen, nitrogen with smaller proportions of sulphur and phosphorus.

A great many compounds of these elements have been found in living things and many of the simpler ones have been synthesized by chemists in their laboratories. Many of the more complex have not, as we shall see, been made artificially so far.

In Nature it is the function of plants to build up organic compounds, and they do it most profusely, producing a host of compounds which we use for food or in other ways — sugars, starches, rubber exudations, drugs like atropine and quinine, essential oils like turpentine, dyes and perfumes. What purpose many of these substances serve in the plant we do not know. It is easy to understand why a flower has a colour in its petals, or an odour to attract insects, but we do not know what is the usefulness of the poisonous alkaloids in the berries of deadly nightshade, of the caffeine in the

coffee berry or the rubber in the sap of the rubber tree. They may be essential substances for the life of the plant, or mere by-products.

What ever may be their use, organic compounds are produced by plants in a fantastic variety. But light is necessary for their formation. In darkness all this activity comes to an end and plants, as is well known, become pale and wither away. When exposed to light, plants take carbon dioxide from the air and liberate its oxygen. The carbon which is left is united with oxygen and hydrogen in the proportions of water, to give carbohydrates. The first recognizable products of this process are simple sugars like glucose, which contain six of the units CH_2O, arranged in a ring. At the next stage come the ordinary sugars, like cane sugar, which have twelve units in two rings.

Out of these materials the plant makes its structural constituents: the starches, which are composed of many rings of this kind, arranged either in long straight chains or with branching chains; cellulose, another still more complex molecule of the same type, the structural component of plant life and the principal constituent of wood and paper.

The animal is differently constituted. It lives by eating plants. It cannot absorb energy from sunlight; it gets what it requires by burning the carbohydrates which the plants have made. It also obtains the nitrogen compounds it needs from plants and builds up from them *proteins*, the most characteristic compounds of the animal organism — hair, wool, muscle, red blood corpuscles, nails, skin, the white of eggs, the casein of milk are largely made of proteins. They are not, however, peculiar to animals. All plants, and in fact every living cell, contain them. No organism has been found which does not contain proteins in every part and all living processes involve proteins at some stage or another. Protoplasm, the jelly-like substance inside living cells, is largely made up of proteins and water.

What are these proteins? By chemical analyses it was found that they are made up of substances called *amino-acids*. These are compounds which have what we can call a Jekyll and Hyde nature. They possess both acidic and basic parts. Acids and bases have the power of neutralizing each other by combination. The acidic group of one amino-acid can combine with the basic group of another. The amino-acids have, as it were, two hands — an acidic hand and a basic hand. The acidic hand of one amino-acid clasps the basic hand of the next, and so we get long chain-like molecules built up by the repetition of this process.

Fig. 1 shows what this process looks like to a chemist. The symbols on the left are some of the amino-acids, and the chain formed from them is on the right. The acidic hand is the group —COOH, and the basic hand, the group $-NH_2$; these combine together, forming what is known as a *peptide link*. A model of the molecule obtained in this way is shown in Plate I.

The formation of long chains of amino-acids in this way is the whole basis of protein structure. Most protein molecules are, however, much more complicated. They usually contain several chains which are held together by "bridges" between them, which are not very well understood.

There are about twenty-five different amino-acids which have been found to occur in proteins. It is easy to see that the number of different ways in which these can be arranged in chains of this kind is almost endless. In football pools you have to decide the result of ten or twelve separate matches. Everyone knows what a large number of combinations there are of all the possible results. If you have a protein chain with ten different amino-acids only, the number of possible ways of arranging them is given by the number of ways in which you can fill ten places with ten different things: a problem in permutations and combinations which any "pool" expert can understand. The simplest

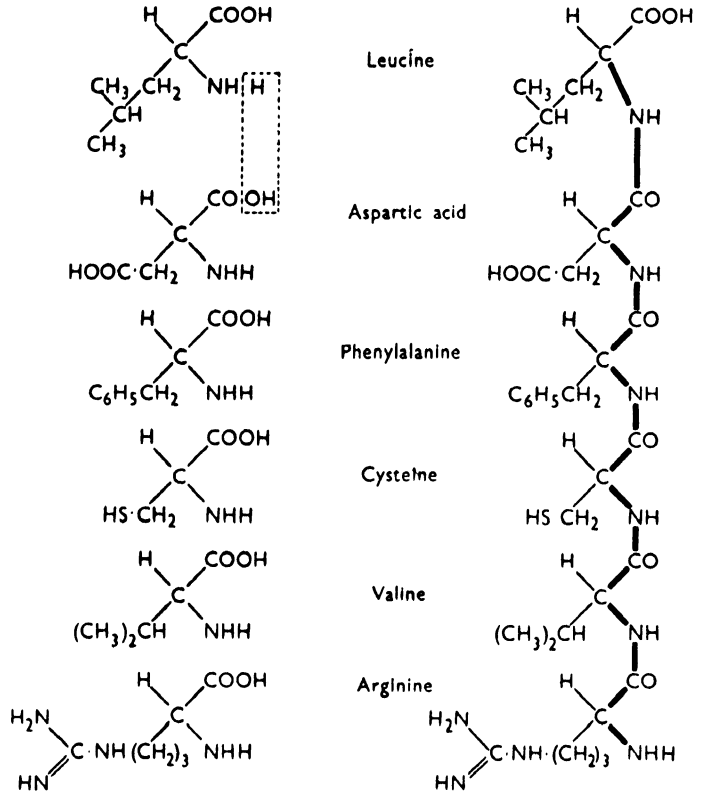


FIG. 1.—How the fabric of life is woven. The chemical formulae of a number of amino-acids and the peptide chain formed from them. Proteins are constructed out of much larger patterns of this kind (see Fig. 3)

protein has at least a hundred places to be filled and usually about twenty different amino-acids to put into them! It does not require any calculation to see that a very great number of arrangements is possible.

It is this possibility of making an endless number of different patterns which accounts for the great variety of naturally occurring proteins. Life, we shall see, requires a

large number of highly specific proteins — with different sizes, shapes, and patterns. In peptide chains constructed from a limited number of amino-acids, it has found an economical way of providing for a great variety of patterns out of a limited number of building bricks. The problem is that of an architect who is building a new town on mass-production lines. His machines will turn out bricks of standardized sizes and shapes. How many standard bricks is he to have? The most economical solution from the point of view of the manufacturer is to make them all the same; but this will result in a very ugly town. The architect will have to decide on the most convenient number of types of bricks to use, and this is what living things have done. They find they can make all the protein structures they need out of about twenty-five kinds of bricks and, so far as we know, every living thing contains the same twenty-five kinds of bricks, or at least most of them.

That was about as far as our knowledge went twenty years ago. It was known that proteins were very complex — more complex than any substances of which the structure had been worked out. But were they made up of definite molecules, all the same size, or were they just an indefinite assemblage of peptide chains of various lengths?

This question was answered in two ways. It was found that some proteins could be crystallized. Egg albumen, for example, which makes up the greater part of the white of egg, was crystallized many years ago by Hofmeister — although the importance of the observation was not noticed at the time. The haemoglobins of the blood of many animals can also be crystallized by very simple means.

In a crystal the molecules of a substance are lined up in rows according to a definite pattern. They can only do this if they are entirely, or at least mainly, of one kind. If we take a strong salt solution and evaporate off the water, we shall eventually reach a point at which crystals of salt

are formed and more soluble impurities are left behind in the liquor. This is what happens when a protein is crystallized; the crystal will be a comparatively pure protein and "impurities" (protein molecules of other kinds) are left behind in the solution.

This is not quite a true picture, because protein molecules of similar sizes and shapes will often crystallize together. It is then a very difficult matter to separate them; some of the earlier protein chemists despaired of ever getting *pure* proteins — in fact they doubted if such a thing existed in Nature. They argued that what we call a single protein is made up of a variety of molecules varying in size, and as more refined methods are applied, we may get specimens in which the molecules are more and more alike, but we shall never get a really pure substance in which all the molecules are the same. But this has been disproved. A number of proteins have been made which answer all the tests of purity that can be applied.

The first thing scientists try to find out about molecules is their size and weight. There were no practicable methods of finding the weight of very large molecules until Professor The Svedberg of Uppsala, Sweden, invented an instrument called the ultra-centrifuge. A small tube containing a solution of the protein is whirled round at a very high speed — about 1000 revolutions a second. Just as when you throw a handful of dirt into a pond the heavier particles settle down first and the lighter ones follow more slowly, so in the ultra-centrifuge the heavier particles are driven outwards by the centrifugal force more quickly than lighter ones. The rate of settling is observed by means of complicated optical arrangements, and from it the weight of the molecule can be calculated. In this way it was found that the molecules of proteins were much heavier than the molecules which organic chemists had hitherto been accustomed to. When they measure the weights of molecules, scientists

take the weight of the hydrogen atom as the unit. Simple organic substances like sugar and aspirin, to name only two common ones, have molecular weights of only one or two hundreds. The simplest real protein so far found (ribonuclease) has a molecular weight of about 17,000. Most proteins have much bigger molecules than this — the soluble proteins frequently weigh from two to four times as much, but others have molecular weights up to a million or more. The comparative sizes of some protein molecules, in relation to some of the larger particles, are shown in Fig. 2.

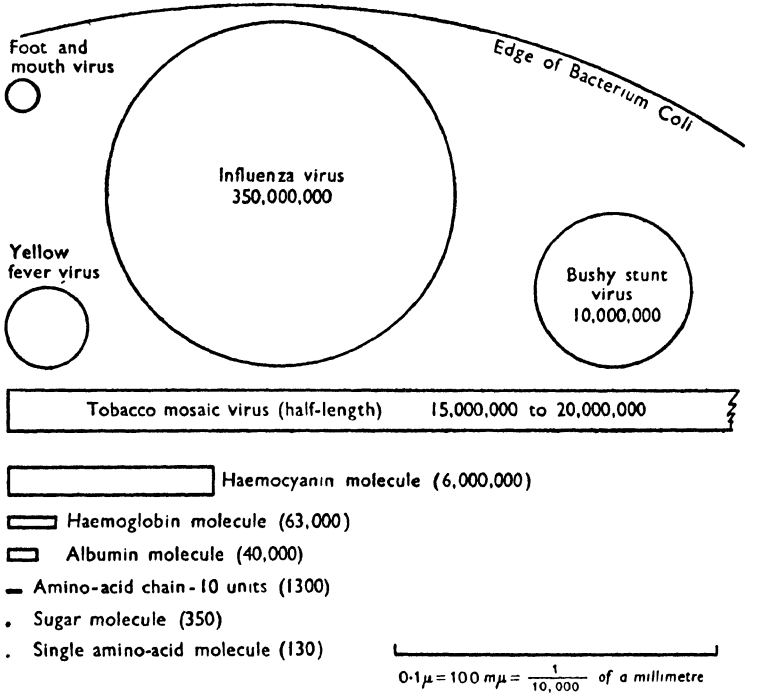


FIG. 2.—Some of the smallest living things and the molecules they are made of — an illustration of the complexity of life

These molecules contain a large number of atoms. Let me try to give an impression of the construction of one of the simpler ones, insulin, a protein which is so involved in the utilization of sugar in the animal body that a deficiency of it causes diabetes, a disease produced by the inability of the tissues to make use of sugar. Its molecular weight is about 40,000, but this is believed to be made up of three similar units with weights in the neighbourhood of 12,000-13,000 each. It has been shown by Professor A. C. Chibnall that this *sub-molecule*, as it is called, contains 101 amino-acid units of fifteen different kinds, and Dr. Sanger has shown that these are arranged in four distinct chains, united by six strong links, which are formed between the sulphur atoms of cystine. Fig. 3 shows one of the many possible ways in which these 101 amino-acid units could be united. Work is being done which may in time enable the actual order to be determined.

Very little is known about the internal organization of protein molecules, especially the larger ones. They are undoubtedly very precise and orderly structures. Crystals of pepsin, haemoglobin, and other proteins have been examined with X-rays and the results indicate a great degree of regularity down to atomic dimensions (Plate II). They are therefore not irregular arrangements of the amino-acids, but exactly built structures. The long amino-acid chains of the protein molecules are not, as was thought at

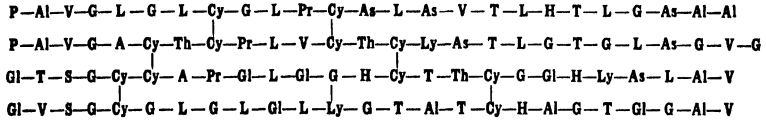


FIG. 3.—An example of the possibilities of pattern in the proteins. How the 101 amino-acids of the insulin sub-molecule might be arranged. The actual order is largely unknown. The insulin molecule is composed of three of these grids

A = arginine; H = histidine; Ly = lysine; G = glutamic acid; As = aspartic acid; Cy = cystine; T = tyrosine; Al = alanine; V = valine; P = phenylalanine; S = serine; Th = threonine; L = leucine; Gl = glycine; Pr = proline.

one time, collected into loose heaps, like a pile of girders, but they are built into exactly engineered and highly organized structures.

While we do not know at present on what plans these structures are built, we do know that they are very easily damaged. Everyone knows what happens to the white of egg, when it is heated. The protein becomes insoluble and forms a hard mass. Proteins in this state are said to be " denatured ". They cannot be crystallized and, in fact, they have lost most of the useful biological properties they may have possessed. The amino-acid chains are now in disorder. Some proteins are very easily damaged; they are highly delicate structures, like a house of cards, which comes to pieces under slight stress, such as gentle heat, contact with acids and alkalis or organic liquids. Others are comparatively robust.

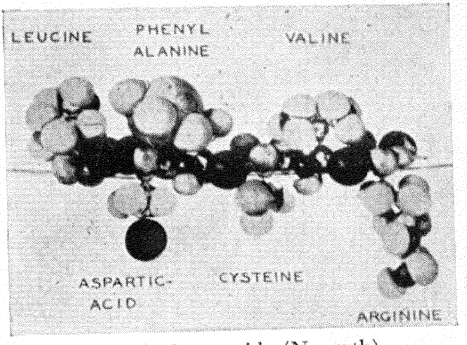
When they have been broken down in this way, nothing we can do, so far as our present knowledge goes, will put them back into their original condition. Like Humpty Dumpty, the protein molecule is an unrepairable structure.

Chemists are able to synthesize chains of amino-acids containing ten, or perhaps more, amino-acid units in any order, and there is no real reason why, if sufficient effort is expended, considerably longer chains could not be made. It is not unlikely that ways of joining these chains together may be found and we may thus get something resembling a denatured protein. But making the highly organized structure of a native protein is something different. How it is achieved in the living organism is still one of the secrets of Nature, and scientists do not know how to set about doing it. The methods of the chemist are rough and his reagents powerful. They will put together the parts of a complicated molecule in the correct order, but no way has been found — unless it occurs by the natural process of crystallization — of fitting molecules together into a structure highly organ-

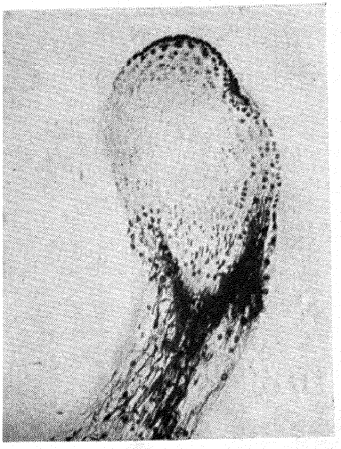
ized in space. The chemist can prefabricate the parts and can sometimes make little houses from them, but sky-scrapers or Crystal Palaces are beyond his powers.

Schoolboys in their chemistry classes often mix two solutions which react with each other to form an insoluble substance, which appears in the tube as a flocculent precipitate, in which the separate particles are obviously very small. When this is kept it sometimes becomes crystalline. This is because the forces between the molecules are so strong that they pull the atoms into the regular orderly structure of the crystal, which really represents the most stable state of the substance. We have seen that the native protein molecule is not a stable state, because under a slight stimulus it passes into the " denatured " state. We may liken the ordered arrangement of a protein molecule to a crystal; but it is clearly an *unstable* crystal and this is something which cannot be formed simply by bringing its component parts together. It can only be formed from a still less stable state — but what that is we have no knowledge at present.

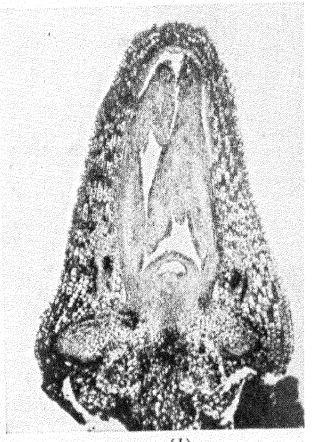
So even at the start of our study, we find in proteins structures which seem to be peculiar to life; which require for their formation something more than the present equipment of the chemist provides. It may be that in time they will find out how to make these regular and unstable structures; but at the present time they are beyond their ability not merely because the molecules are large and complicated, but also because they involve a new idea which is not encountered in the simpler creations of organic chemistry.



Model of a peptide (Neurath)



(*a*)



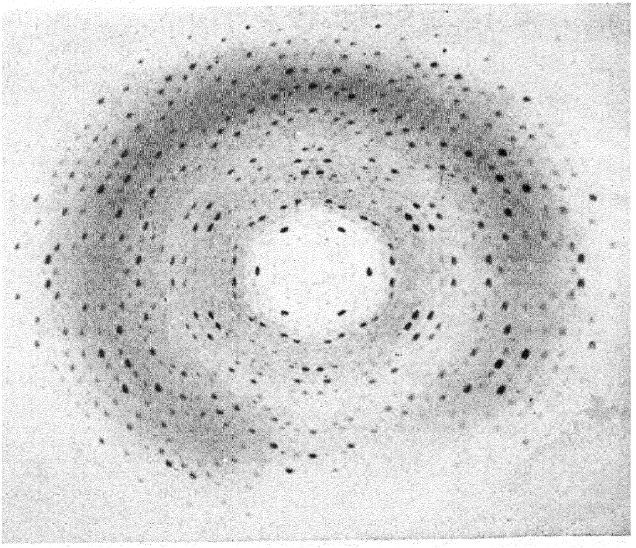
(*b*)

The distribution of a single enzyme (a phosphate-splitting enzyme) in the tissues of a plant (D. Glick)

The enzyme is made to write its own autograph by a chemical process which reveals its whereabouts in a thin section of the plant. (*a*) is a longitudinal section of the tip of a wheat root; (*b*) a section of the growing shoot

PLATE II

Crystals of the protein pepsin (Dr. J. H. Northrop)



An X-ray diffraction photograph of a single wet pepsin crystal, by Dr. M. Perutz

Each spot comes from an orderly repetition of atomic patterns in the crystal and their clarity and symmetrical arrangement indicates a perfectly orderly arrangement of the atoms in the crystal, down to atomic dimensions

III

MEDIATORS BETWEEN THE LIVING AND THE NON-LIVING

> The sovereign Alchemist that in a trice
> Life's leaden metal into Gold transmute.
>
> OMAR KHAYYÁM (trans. of FitzGerald)

WE have learnt a little about what living things are made of, but nothing about their activities. The living cell is not a static thing; it is the scene of tremendous transformations. Living cells, of course, grow and sometimes reproduce themselves, but even when they are merely living they are usually the centre of much chemical activity. In order to live they must have food, which enters into the cell and is transformed in various ways. It may be burnt to provide energy or changed into substances needed for growth, and the products which are not wanted are given out. In large organisms great numbers of cells work in co-operation and divide the labour of the whole organism between them. Some help to absorb the food, some are mainly concerned with oxidizing it and obtaining muscular energy; others are concerned with fabricating particular substances needed by the organism.

Unicellular organisms, such as free-living cells which float about in a pond, and bacteria, have to get along by performing all the necessary processes themselves. They have to absorb food, transforming it into the compounds they need and building it into their substance. This involves a multitude of chemical actions which are carried out with

a speed, smoothness, and efficiency the laboratory chemist cannot approach. Chemists work laboriously. They transform compounds one step at a time, using powerful chemicals, heat, and sometimes electric action, to bring about the changes they desire. It may take months, in a complicated sequence of reactions, to build up a compound, which a single cell can make in a matter of minutes or hours. For example, certain streptococcal bacteria can make a quantity of lactic acid equal to their own weight in half an hour, and this is only one of many reactions they carry out.

How are these manifold changes brought about? We will take a simple living thing — the yeast cell — a unicellular organism which causes fermentation of sugar. It is a jelly-like bag, containing a viscous sticky fluid. It is in this fluid that the chemical changes take place. Yeast will grow in a liquid containing a few simple compounds like sugar, nitrogen compounds, phosphate, and a few other essential nutrients. These enter the cell through its skin or membrane, and when inside are transformed. The nitrogen compounds are built up into the proteins required for growth and reproduction, the sugars are partly elaborated into more complex carbohydrates and partly burnt to provide the energy required for the other transformations, yielding either carbon dioxide or alcohol, according to the circumstances.

This property of yeast was discovered in the early stages of pastoral civilization. The carbon dioxide was used to leaven the dough in the baking of bread; and the production of alcohol has been used for the manufacture of alcoholic drinks from time immemorial.

If you were to ask a chemist to take sugar and turn it into alcohol, he could do it, but only with great difficulty and through a long and complex series of changes. In fact most of the alcohol of commerce is manufactured by the fermentation of sugars by the humble yeast cell. How

does it bring about this change with such surprising ease? At one time it was thought that only the living cells could bring about such changes, which were connected with the essential vital activity of the cell. Then a German chemist, Büchner, showed that it was possible to squeeze the juice out of the living cells, and this juice, freed of cell fragments, was capable of fermenting sugar. It contained substances, which he called *enzymes*, which bring about these changes.

Before this, substances which assist chemical change had been discovered and called *catalysts;* for example, platinum, which makes hydrogen and oxygen combine. Enzymes were vital catalysts or *bio-catalysts;* but for many years, indeed until quite recently, their nature has been quite unknown. Many chemists tried unsuccessfully to purify and isolate them. They were found to be both varied and ubiquitous.

Before we examine their nature, let me give a few examples of enzymes. When food passes through the digestive tract of animals, it encounters enzymes throughout its passage which break it down and make it suitable for absorption. In the stomach there is pepsin, which begins the break-down of proteins. Into the intestine, the pancreas pours other enzymes, which continue the digestion of protein, break down starch into sugars, digest the fats and so on. A very large number of enzymes, which facilitate a multitude of chemical changes, have been distinguished in every kind of living organism and no doubt there are many others to be discovered. All living things contain them, not only in their digestive organs, but also in every tissue. The sap of the growing plant contains a host of them. Even in the seed there are enzymes packed away, which will act on the starch when germination begins and produce the sugar which feeds the plant until it has roots and leaves (see Plate I, lower pictures).

I have already mentioned the enzymes of yeast and other

unicellular organisms. These cells do not wait for food, such as soluble sugars which can penetrate the cell membranes, to come to them. They liberate enzymes into the medium in which they are growing in order to solubilize substances and break them down into a state in which they can be absorbed. They use the liquid around them as a sort of auxiliary stomach. Some thirty or forty different enzymes have been distinguished in the liquid in which some fungi grow!

What are the substances which have these remarkable properties? In 1926, Professor J. B. Sumner of Ithaca obtained from jack beans a crystalline substance, which had the property of breaking down urea. It appeared to be the enzyme called *urease*, and further investigation has confirmed this. It was the first enzyme to be prepared in a crystalline condition as a pure substance so that its nature could be determined. It was found to be a *protein*. Since then a considerable number of enzymes have been isolated. Pepsin, the protein-splitting enzyme of the stomach, was crystallized by Dr. J. H. Northrop at Princeton in 1929. More recently the animal pancreas has been found to be a rich mine of proteins, and Drs. Northrop and Kunitz and their collaborators have isolated a succession of crystalline digestive enzymes from it. Enzymes have also been isolated from varied materials such as yeast, malt, potatoes, and fruit juices (see Plates II and III).

All these substances are very powerful bio-catalysts, *i.e.* they bring about rapid chemical changes when present in very small amounts, without being changed themselves. A solution containing a ten millionth of an ounce of pepsin has a powerful effect on clotting of milk; rennin, another enzyme present in calves' stomachs and used for making junkets and cheese, can clot ten million times its weight of milk in 10 minutes. Urease crystals produce a hundred times their weight of ammonia from urea in 5 minutes; it is said that one molecule of catalase can decompose

over two million molecules of hydrogen peroxide every minute.

Enzymes have all turned out to be proteins. Besides their other uses, Nature makes use of proteins to perform the special functions of bio-catalysts. These functions are in fact very highly specialized. There is usually a separate enzyme for each distinct chemical process. Sometimes an enzyme will bring about the change in a single substance only; sometimes it will react with a number of closely related substances.

Scientists still know very little about how enzymes bring about these chemical actions. In some cases it has been shown that the first step is the combination of the enzyme with the substance undergoing change. This combination is very specific. The enzyme will combine with one, or perhaps a few similar, molecules, but with no others. There must thus be a close fit between the enzyme and the molecule or molecules it acts on. The molecules must fit exactly into some part of the surface of the enzyme molecule.

What happens then is largely a matter of conjecture, but it is not difficult to see that if the enzyme unites firmly to the two halves of a molecule, the bond joining them may be broken and the molecule may be thus divided into two parts. In the same way a body of soldiers can be made to divide if it is attacked in two distinct places. The fact that the men around these places give their attention to repelling the attacks, necessarily lessens the cohesion of the force as a whole and if the attacks are sufficiently energetic, more and more men become involved until the whole force is divided into two parts. This is a possible way in which an enzyme can facilitate the rupture of a molecule into two parts. Readers who are interested will see the idea worked out in more detail in Fig. 4.

The synthesis of a molecule from its parts can also occur if they fit closely into adjacent parts of the enzyme surface,

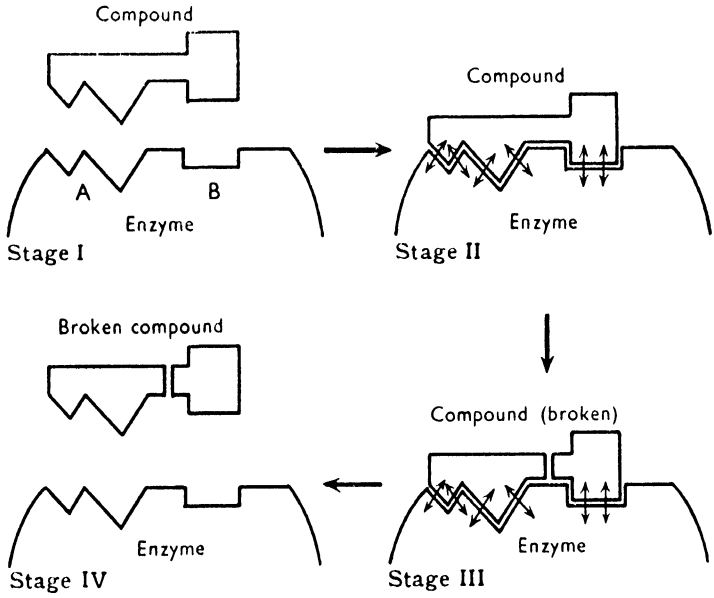


FIG. 4.—How an enzyme breaks a compound

The enzyme has two parts, A and B, of its surface, which fit and combine with the two halves of the compound. The compound is firmly held to these parts of the enzyme by strong binding forces, which are indicated by the double ended arrows (Stage II). This weakens the union between the two parts and the compound is thus broken into two (Stage III). The two parts then become detached from the enzyme surface (Stage IV)

so that they are brought into juxtaposition under conditions in which they will then unite. The enzyme provides a kind of "jig" which holds the bits together while a bond between them is formed.

In either case the important thing is that the enzyme must provide a structure which is exactly adapted to the work it has to do.

Thus we can see that life is a matter of enzymes. All organisms contain large numbers of them — all working together and bringing about the extraordinary changes which life produces in its environment. Not only has every organism a considerable number of enzymes, but also it

appears that an enzyme of one species is not exactly the same as an enzyme with similar functions in another. The enzymes are thus not only highly adapted to the chemical change they have to bring about; they are also stamped in some way with the individuality of the species they belong to. We do not know how this is achieved. In the amino-acid chains of proteins, which were described in Chapter II, we have seen that there exists the possibility of almost innumerable different patterns. Nature has apparently taken advantage of this to produce the specialized patterns of enzymes, but at present we are ignorant as to what they are.

It is an extraordinary fact — and an unexpected one — that the simplest organisms seem to be provided with enzymes which are very similar to those of the higher organisms. Life, in the simplest forms which have survived to this day, has practically all the types of enzymes which we find in the higher animals. It is possible that new types may be discovered associated with nervous systems, but so far we have not very much evidence that this is the case. If life has evolved from simple unicellular organisms to complex ones, there does not seem to have been any great improvement in the enzymes. There has merely been an increase in specialization and in the possibilities of co-operation and of division of labour between cells.

In fact, as we have seen, the simpler organisms, in order to live, have to carry out a greater range of chemical actions, so they are very rich in enzymes.

Let us take a look at a specimen of this kind — a single cell of a small bacterium, of which the solid parts weigh 10^{-13} of a gram, *i.e.* about 300 million million will make up one ounce. In this tiny volume it can be calculated that there will be about 200,000 protein molecules altogether. A moderate estimate suggests that the bacterium must have several hundred distinct enzymes at least for all its activities,

or perhaps a thousand or more. Obviously there cannot be very many molecules of each enzyme — an average of two hundred or so of each, some possibly considerably less.

Our picture of the smallest, though perhaps not the simplest, of all living cells, is thus already one of a complexity which the mind finds difficult to grasp — a veritable microcosm. How all these separate and complex molecules are packed away in a tiny fragment of protoplasm, how they work in harmony with each other, producing that result which we recognize as the life of the organism; we hardly know. How they are made out of the food which the organism lives on, we shall discuss in a later chapter.

IV

HELPERS AND HINDERERS OF VITAL PROCESSES

> Were this globe's area of land
> Wholly cover'd from sight, pack'd close to the watery margins
> With mere empty vessels, I could myself put in each one
> Some different substance, and write its formula thereon.
> Thus would speak the Chemist . . .
>
> ROBERT BRIDGES

IT would be wrong to give the impression that living things contain only proteins. An enormous number of smaller molecules have been found, usually in rather small quantities, in living tissues. They are the intermediates, the partly completed structures which will eventually enter into the larger aggregates, the messengers which go to and fro, carrying energy or otherwise facilitating the working of the principal agents which they serve. Like money in human society, they help along the transactions of the important members of the community.

The organisms make many of these substances themselves, but different organisms differ enormously in their ability to synthesize compounds. Some, like plants, can create all they need from very simple nutrients — a few inorganic salts, ammonia or nitrate, phosphate and carbon dioxide from the air. Generally speaking, the higher an organism is in scale of complexity, the less is its ability to synthesize. Micro-organisms usually have much greater power of synthesis than animals, but they are found to differ greatly in their nutritional requirements. Some are perhaps

even less exacting than the plants; for example, the nitrogen-fixing bacteria which exist in nodules of leguminous plants and have the ability to use the nitrogen directly from the air.

The basic food requirements of the higher animals are certain inorganic materials like salt, phosphate, calcium, iron (the *mineral* elements of diet), proteins or their constituent parts, with which to build new protein, carbohydrates, and perhaps some fat as a source of energy. It was found in many laboratories engaged in nutritional studies that animals fed with what appeared to be completely satisfactory diets, containing all these constituents in a purified form but nothing else, failed to grow and often developed severe symptoms of disease.

In one of the earliest experiments of this kind, made in 1912, Sir Frederick Gowland Hopkins found that young rats would not grow properly on a diet made from the purified constituents of milk, but even small quantities of whole natural milk restored the rate of growth. Much earlier than this, diseases in both humans and animals were suspected to be due to deficiencies of diet. Beri-beri, a disease of the Orient, which was prevalent in the Japanese navy up to 1882, was almost eliminated by a change of diet involving a reduction of the amount of rice consumed. Eijkman in 1897 found that hens and pigeons fed on white polished rice developed a type of paralysis, which disappeared when the rice polishings were added to the diet. The inference was that the polishings contained something necessary for health. Such auxiliary substances were named *vitamins* by Funk, a scientist who tried to separate the essential factor from the rice polishings.

Following the observation of Hopkins, experiments were made to try to distinguish the factor which was present in raw milk, which was not present in the purified milk constituents. It was found in fact that there were two factors,

and the lack of either produced growth disorders. The first, which was present in the fat, was called vitamin A, and the second, present in the watery part of the milk, vitamin B. This was the beginning of the discovery of the vitamins, and up to the present time at least twenty-seven such substances which are necessary, in small quantities, for the growth of various animals have been distinguished.

Many of them have been isolated in the pure form and their chemical structures have been determined, and in many cases this has been followed by their synthesis by chemists. The first to be identified and reconstructed in the laboratory was vitamin C. It had been known for many years that people who live for a considerable time on a diet which contains no fresh vegetables or fruit juices develop scurvy. Vitamin C was identified with a substance called ascorbic acid, and it was then built up by Sir Norman Haworth and his co-workers.

Another somewhat similar deficiency disease was pellagra, which was common in the southern part of the United States among the poorer people whose diet was mainly corn meal, sugar, molasses, and sometimes pork. Elvehjem discovered in 1937 that pellagra could be cured in a few days by a substance called nicotinic acid or niacin.

Hopkins suggested, as long ago as 1906, that rickets was a deficiency disease, and it was found that cod-liver oil had an excellent effect. The active substance, which was called vitamin D, has been shown to consist of a group of rather similar complex molecules called *sterols*. Sterols exist in many foods, as well as in skin, in an inactive form, and it has been found that if this is exposed to a source of ultra-violet light, such as bright sunlight, out of doors, the active vitamin is formed. This is one of the reasons why sunshine is health-giving.

Vitamin B has been found to contain quite a number of different substances, many of which have been identified and

some synthesized. Vitamin B_1, now called aneurin or thiamine, is the substance of which a deficiency causes beri-beri. B_2 was identified by Kuhn and Karrer with riboflavin, a substance present in milk, eggs, or liver, the lack of which produces dermatitis, facial sores, etc. B_3 is possibly a substance called pantothenic acid, which was first found to be required by yeasts and later recognized as a food requirement of animals and insects. B_6 was identified with pyridoxine in 1938, and in 1944 a more active form of the vitamin was discovered in the compound pyridoxal.

Other substances which are essential to the life and growth of many organisms are choline, a simple substance required by rats and birds and possibly by human beings; biotin, originally recognized as a food requirement of yeasts, but since known to be required by the higher animals; inositol, a particular type of sugar, and folic acid, a substance abundantly present in green leaves.

Having discovered all these substances, which must be present in our food in minute quantities, to keep us healthy, working organisms, scientists naturally began to wonder what their action is. If the lack of them produces such serious effects, they must perform a very vital function.

The clue to this came from quite a different direction. It will be remembered that the juice squeezed out of living yeast cells contains enzymes which can by themselves ferment sugars. It was discovered by Harden and Young in 1906 that if this juice was divided into two parts, one containing the big (protein) molecules and the other small molecules, neither part separately could bring about the fermentation, but when they were again mixed the fermentation went on as in the original juice. Hence both the big molecules and the smaller molecules were necessary to bring about the fermentation. The big molecules, as we have seen, are proteins and some of them enzymes. The smaller molecules include some which are also needed for enzyme

action, and these were called *co-enzymes.*

In the course of time a number of co-enzymes have been separated and distinguished. It has been found that frequently one co-enzyme is shared by several different enzymes. This appears to be a device of Nature to economize materials which are rather scarce. The yeast juice can be likened to a machine-shop containing many large and complicated machines. The tools used by these machines are, however, in short supply, so the management, instead of firmly attaching each tool to a machine, arranges to have them shared, so that each machine can have the use of the tools when needed.

Enzymes are so active that only small quantities of them are required, and it is not surprising that minute quantities of the co-enzymes are also sufficient. Dr. H. McIlwain has found that some bacteria only have a few molecules of some of them in each cell.

The co-enzymes are small molecules, and some of them have been purified and their chemical structures ascertained (see Fig. 5). It has been found that the *vitamins* are either the co-enzymes themselves or important constituents of them. This has been proved in at least eight cases so far, in which the enzyme system with which the vitamin works has been identified. For example, nicotinic acid is a constituent of the co-enzymes of yeast juice; aneurin (vitamin B_1) is required by an enzyme called *carboxylase;* riboflavin (vitamin B_2) is the co-enzyme of several coloured enzymes which bring about oxidations in the cell.

The vitamins are required by animals, first because animals cannot make them themselves, and secondly because they are unable to perform many of the vital processes of life without them. If the vitamin is not present, the corresponding enzyme system is paralysed, and the animal organisms function only imperfectly or not at all.

Micro-organisms such as bacteria and fungi also need

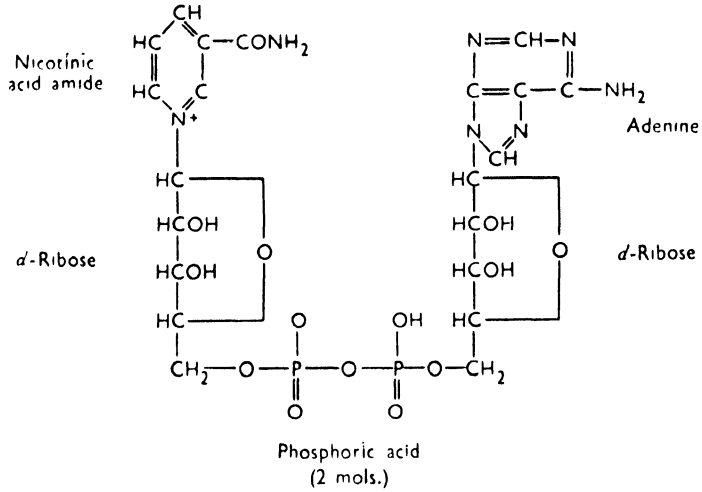


FIG. 5.—Structural formula of co-enzyme I — a detachable bit of an enzyme

vitamins — the same vitamins which are required by animals. Eight essential substances have been distinguished as essential to the life of micro-organisms — and they all serve as vitamins for the higher animals. They are aneurin (vitamin B_1), riboflavin (vitamin B_2), pyridoxin (vitamin B_6), biotin (vitamin H), pantothenic acid, folic acid, co-enzyme I or its components, and choline. The curious can see their architecture in Fig. 6.

On these substances, together with the twenty-odd amino-acids out of which proteins are constructed, and perhaps a few others, the phenomenon of life seems to be based. The ability to synthesize these substances is very haphazardly distributed among micro-organisms. Some, like yeasts, have a considerable ability of making vitamins and are in fact rich sources of some of them. The wild mould *Neurospora crassa* needs only glucose, ammonia, and biotin in order to live; all other necessary substances it can

make for itself. Other micro-organisms can only grow if they are provided with certain of these substances; they are unable to make them for themselves, and they must have them if they are to grow. It was found that some animals seemed to get along quite well on diets which lacked some of the B vitamins. There was no evidence that the animal itself was capable of synthesizing them. The mystery was solved when it was discovered that the microflora of the animal's digestive tract were manufacturing vitamins and so contributing to the nutrition of their host.

The wide occurrence of vitamins in all kinds of living things is another proof of the essential unity of life. From micro-organisms to man, they are all built on much the same plan. They all have extremely similar enzyme systems which require the same auxiliary substances. But some

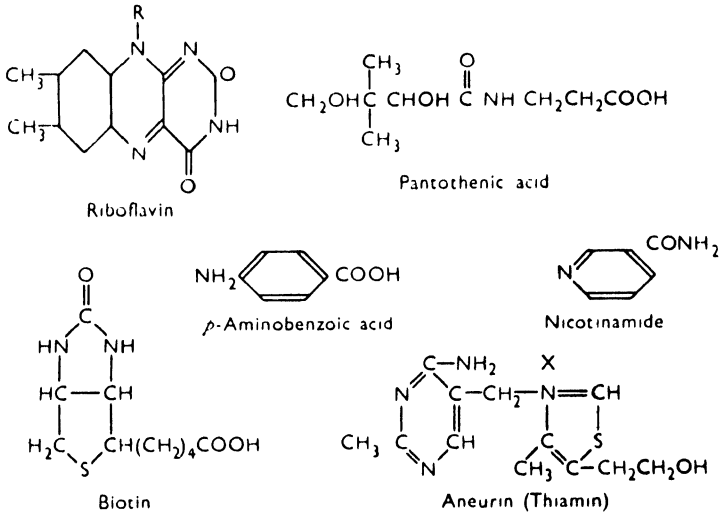


FIG. 6.—Some of the vitamins — substances essential to life in large and small organisms

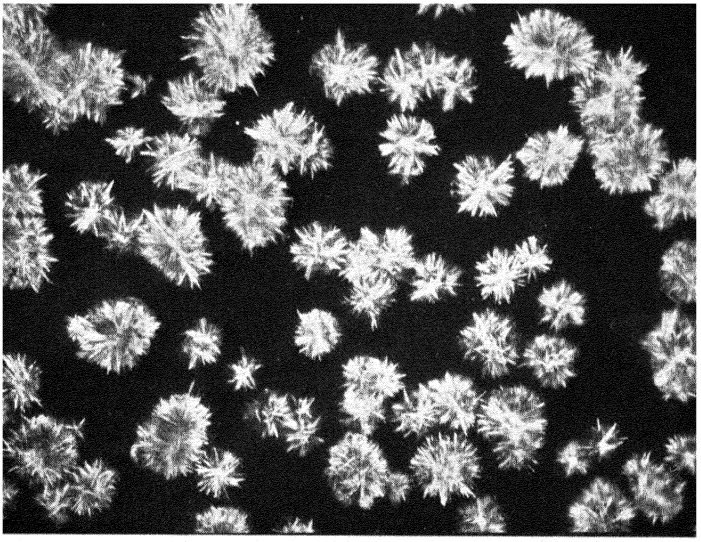
(In these formulae there is understood to be a carbon atom at each corner of the hexagons, when nothing else is shown)

organisms are dependent on others for some of these vital substances, as they have lost the power of making their own. Broadly speaking, the higher the organism is in the scale of living things the less is its synthetic ability, and its dependence on other forms of life for the compounds it needs is greater.

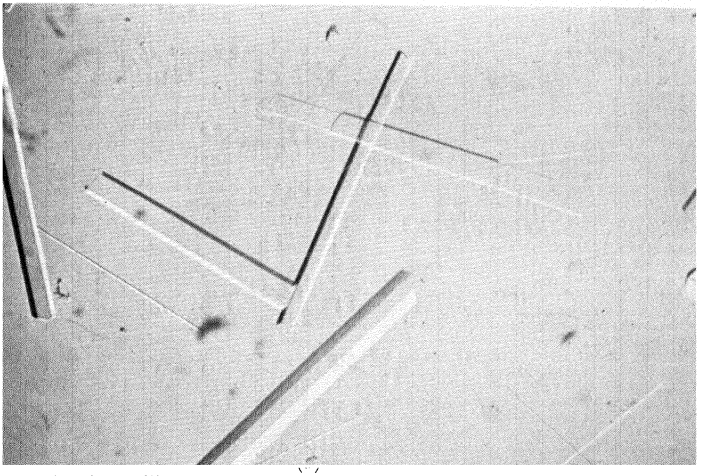
As I have said before, many of the vitamins can be constructed in the laboratory. Chemists can do more than this. Not only can they construct the actual vitamin, the molecule which has been selected in Nature to do a particular job; they can also make a variety of similar molecules, which may differ from the vitamin in a slightly different arrangement of atoms or in the slight additions here and there, which do not spoil the general plan of the molecule. What happens when an organism is presented with these *pseudo* vitamins? Does it reject them or can it make use of them? Actually it tries to make use of them, but often unsuccessfully. The " unnatural " vitamin combines with its enzyme. The protein part of the enzyme does not notice that the vitamin is not quite right. It accepts it as a co-enzyme but, alas, the combination does not function properly. As we have seen, enzymes act by achieving a very exact fit with the substances they act on — like the fit of a lock and key. If a part of the enzyme, the co-enzyme for example, is changed slightly, the key will not go into the lock. Moreover, even if the natural vitamin is also present, it may be partly prevented from doing its work, for the unnatural vitamin competes for the available enzyme molecules and puts a proportion of them, at least, out of action.

So the result is that " unnatural " vitamin molecules act as antagonists to the real vitamins. They often prevent the proper functioning of the real vitamin and produce the same symptoms as a severe vitamin deficiency.

This seems to provide a wonderful way of preventing the growth of harmful organisms, like bacteria. All you need do is to introduce a suitable antagonist which will put out



(*a*)



(*a*) Crystalline ribonuclease, a digestive enzyme (Kunitz)
With a molecular weight of 17,000, its molecules are the smallest yet found among the enzymes

(*b*) Crystalline hexokinase (Kunitz and McDonald)
An enzyme which changes glucose into glucose phosphate — the first step in the breakdown of sugars. This sample was prepared from brewer's yeast, but the enzyme is also found in muscles, where it takes part in the complicated changes by which muscular energy is obtained

of action a vital enzyme in the bacteria, which will then be unable to grow.

Unfortunately, living things — the hosts and the parasites — are very much alike and possess very similar enzymes, and it is usually found that they require the same vitamins and respond similarly to their antagonists. A large number of vitamin antagonists have been made, which do in fact interfere with the growth of bacteria; but in most cases they are nearly as harmful to animals as to the bacteria.

There is, however, one case in which successful use is made of an antagonist, and this is the basis of the well known "sulphur" drugs (sulphanilamides). These were discovered by trial and error. Until recent years there was very little to guide chemists in the search for valuable drugs. Enormous numbers of compounds have been made and tested; some had curative properties, but no one knew why. This group of drugs was discovered after long research to be extremely effective in some kinds of infections. The reason for this was not clear at once. Then it was discovered that a somewhat similar substance, *p-amino-benzoic acid* (PAB for short), interfered with the bactericidal action of the drug. If PAB is administered with the drug, much larger doses have to be used to produce the same effect. This suggested to Fildes and Woods that the "sulphur" drugs were really antagonists of PAB. At this time PAB had not

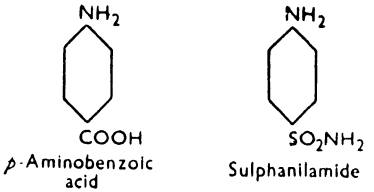


FIG. 7.—A vitamin (PAB = *p*-amino-benzoic acid) — which is essential to the growth of some micro-organisms, and sulphanilamide, an antagonist to it

been recognized as a vitamin, but its presence in many micro-organisms has since been confirmed. It is now known to be a component of folic acid, a substance which occurs abundantly in green leaves and has a stimulating effect on the growth of some bacteria. Folic acid seems to be concerned in the formation of the highly specialized substances required in the nuclei of cells. The higher animals as well as many of the lower organisms require PAB; but it is not known definitely why certain bacteria are more sensitive to PAB antagonists than are the hosts. More recently it has been found that another compound of the same kind (PAS = *p-amino-salicylic acid*) is very effective in arresting some types of tuberculosis.

If it were possible to find enzymes in the disease-producing organisms which were more sensitive to antagonists than those of the animals, the problem of finding drugs to kill the bacteria would be very simple; but unfortunately this is not usually possible. Drugs which harm the parasite usually injure the host as well.

The problem of producing substances which will harm bacteria more than their hosts is one which has been solved more effectively by many organisms than by the conscious efforts of scientists. Many living things must have encountered the problem of how to repel the attacks of bacteria and other parasitic forms, and it is perhaps not surprising that those which have survived are provided with chemical protection. The best known of these substances is *penicillin*, which is produced by a fungus, *Penicillium notatum*, the greenish mould which grows on damp bread. The story of the discovery of penicillin by Sir Alexander Fleming in 1929 has often been told. He noticed that there was a clear patch around a growth of the fungus on a plate on which colonies of bacteria were growing. He recognized that the fungus was producing a substance which prevented the growth of the bacteria. The isolation and identification of this sub-

stance, as the result first of the efforts of a group of workers headed by Sir Howard Florey in Oxford and the co-operative effort of scientists on both sides of the Atlantic during the 1939–45 War, and its large-scale production and use in medicine have been one of the greatest triumphs of intensive research. Penicillin is unique in having an extremely powerful effect on some types of bacteria and in doing no harm to animals, and is the most powerful means of combating many kinds of bacteria which is available at the present time. The nature of its action is not clearly understood.

But many other " antibiotics ", as they are called, have also been discovered in recent years. Many of them are too harmful to human beings to find use in medicine. Others, like gramicidin, and streptomycin, both prepared from soil bacteria, are still being tested.

Streptomycin, which is produced by a micro-organism first isolated from the soil of a field near Caracas in Venezuela, seems to be effective in some cases of tuberculosis. This family of micro-organisms (*Streptomyces*) — in this case a type isolated from a compost heap in Illinois — has also yielded *chloromycetin*, which has been found to be a most successful curative agent for typhus — a louse-carried fever which is common in overcrowded conditions in the tropics. It almost completely fulfils the two requirements of an effective drug — it is deadly against the agent of the disease, and harmless to the human body. Although it is also effective against some bacteria, it is of great interest because typhus is a virus disease and this is the first drug to be discovered which is effective in such cases. Virus diseases have hitherto been very refractory to treatment by chemical agents, so that this discovery opens up great possibilities of new treatments. Chloromycetin has been found to be a comparatively simple compound and has been synthesized. Another useful agent of the same type is known as *aureomycin* or *duomycin*, which is very effective in Rocky Mountain fever

and other virus diseases of the same type.

All these substances may be similar to fragments of proteins — probably warped fragments, which will not fit into the normal protein molecule.

Competition in the world of micro-organisms, which multiply at a very rapid rate, must be very intense, and any species which can produce something which kills, or merely prevents the multiplication of, organisms in its neighbourhood, secures for itself the chance to multiply. Such substances, which may have been produced originally by the faulty working of a single cell, would immediately be of value to the organism, and would ensure its survival. It is not surprising that in the innumerable generations through which they must have passed in the course of ages, the micro-organisms have found effective chemical weapons for self-preservation. At one time or another almost every possible substance must have been made in individuals which show a variation from their parents, or are faulty in some way. It is not surprising that the results of such a long spread-out period of trial and error should have disclosed effective compounds and that the compounds tried by chemists at present are less effective than some of the natural substances.

Life Uses Metals — and Some Consequences

For the want of a nail . . . the kingdom was lost
Nursery Rhyme

Vitamins are not the only materials, besides the basic amino-acids, which are required in constructing the large molecules of living cells. Life seems to have explored every possibility and has made use somewhere or other of nearly every material available on the surface of the earth. The common metals sodium, potassium, and calcium are ubiquitous. There are a fair number of proteins which contain

other metals. Iron, for example, is an important constituent of haemoglobin, the red protein of the blood of mammals. The iron, present in a particular combination, enables the haemoglobin to pick up oxygen in the lungs and to carry it into the tissues, where it is released. Lobsters and other crustaceans offer a variation on the same theme. Their respiratory protein contains copper instead of iron, and as a result their blood is literally blue.

Even more extraordinary is the fact that *Ascidia* (star fish) have green, blue, and orange corpuscles in their blood, as well as colourless ones. The coloured ones contain appreciable quantities of vanadium, although its concentration in the sea water in which they live is so small it cannot be detected by any known test. Other types of animal, the beautiful annelid worms called *sabellids* and *serpulids*, have green blood, the colour of which is due to a haemoglobin-like protein called *chlorocruorin.*

Plant life uses the same kind of compound in chlorophyll — the all-important pigment of green leaves — but the metal is now magnesium. It might be thought that the difference represents the great division between animal and plant life, the animals being based taking haemoglobin or similar oxygen-carrying proteins and the plants using chlorophyll: but as a matter of fact haemoglobin-like proteins have been detected in the nitrogen-fixing nodules of leguminous plants. So it would appear that both chlorophyll proteins and haemoglobins were present before the division into plant and animal life took place, but plants have relied increasingly on chlorophyll and many of them have lost ability to make haemoglobin-like proteins.

Enzymes have also been isolated which contain copper, zinc, manganese, iron, and vanadium. The amount of the metal in the enzyme is usually quite small, less than 1 per cent, and as only small quantities of the enzymes are present in the tissues, the amounts of the metals used in this way are

very small — mere traces are sufficient to satisfy the needs of organisms. Living things usually get what they need without any difficulty, but sometimes the supply falls below the level required.

It has been found in experiments with plants growing in carefully purified solutions, that iron, manganese, boron, copper, and zinc are essential for plant growth, at concentrations of less than one part in a million. No more than this is necessary, and much larger quantities may be harmful. If the soil is seriously deficient in any of the metals, plant growth suffers, but it can be improved by making good the deficiency. Thus, the application of manganese and zinc compounds to marshland fields in Kent increased the yield of potatoes from seven to eleven tons per acre. In south-east Australia there is an extensive coastal strip in which a copper deficiency limits vegetation. Oats, wheat, and lucern all failed without added copper, but grew luxuriantly when a copper salt was added to the soil. Further inland, zinc is also needed, but extra copper was also required before the clover would set seed. It has been found that plants often grow quite well without much copper up to blossoming time, but seed formation is interfered with. The effect of copper on clover growth is greater if the copper salt is applied a season in advance, due apparently to its effect on nitrification bacteria. Fruit trees, which will not fruit, have been made to do so by inserting capsules of a manganese salt into holes bored into the trunks.

Even when plants can grow well, they do not always satisfy the mineral requirements of the animals feeding on them. Diseases due to cobalt- and copper-deficiencies in sheep and cattle are well known in various regions. In Scotland and Australia sheep " pining " occurs on soils with less than 5 parts per million of cobalt. It has been found that this condition is remedied if cobalt, together with copper, in the form of salts, of course, is added to the food.

Apparently only ruminants suffer from this deficiency; horses, kangaroos, and rabbits do quite well under the same conditions.

Copper is utilized, rather oddly, in putting the " crimp " into sheep's wool. If the herbage is deficient in copper, the wool grows straight. The reason, apparently, is that the molecules of the wool protein are first formed in a straight parallel form. The " crimp " is produced when the long protein chains are joined by -S-S- bonds, an operation performed by an enzyme containing copper. It has also been found that black sheep are unable to grow black wool on a copper-deficient diet, a copper enzyme being the agent of the formation of the black pigment.

Until recently, it was not known in what substances the animals made use of cobalt, but in 1948 two teams of workers, one headed by Dr. Lester Smith in England and the other by Dr. Rickes in New Jersey isolated a cobalt-containing substance (sometimes known as vitamin B_{12}) from the liver; this substance cures pernicious anaemia. If the animal is unable to make enough of this substance, red blood cells are not manufactured in the marrow. But injecting sheep with either a cobalt salt or this pernicious anaemia factor, did not cure the deficiency condition. Cobalt taken by the mouth is effective, but not if injected directly into the blood. It was therefore thought that even in cobalt-deficient pastures, sheep get enough cobalt to make the anti-anaemic factor; but insufficient to satisfy the micro-organisms which play so large a part in the digestive apparatus of ruminants.

How the micro-organisms use the cobalt is not known at present; but it may be that they synthesize for their own purposes compounds similar to the pernicious anaemia factor. In fact this substance has been isolated from a mould, *Streptomyces griseus* — the same one which yielded streptomycin. What an astonishing thing! After years of

great effort, scientists succeed in isolating, from liver, the substance which is necessary for the formation of red blood corpuscles in the bone marrow. No sooner is it isolated than it is also discovered as the product of a mould.

If all this is correct, the emaciation and eventual death of the animals on cobalt-deficient pastures is due to the lack of a milligram or so of cobalt daily, which is apparently required in the enzyme systems of certain micro-organisms, which possibly synthesize vitamins or other substances required by the animal in small amounts. The whole situation rather reminds one of the disastrous consequences of the loss of a nail in the nursery rhyme — but in this case the nail is a cobalt one, and it possibly holds an enzyme together.

V

HOW PROTEINS ARE MADE

All flesh is grass, is not only metaphorically, but literally, true; for all those creatures we behold are but the herbs of the field, digested into flesh in them, or more remotely carnified in ourselves.—T. BROWNE in *Religio Medici.*

The cell is an organized factory conducting manifold chemical processes. It hydrolyses, it pulls to pieces, it excretes. Further, it constructs. From bacterium to tree, from animalcule to man, proteins broadly taken, are the stones of which the house of life is built. The cell makes its own proteins. It remakes them for itself from others supplied to it. "Life" is a maker of proteins.—C. S. SHERRINGTON in *Man on his Nature.*

WE have tried to discover what living things are made of, and we have found in them very complex mixtures of many kinds of proteins, together with a number of simpler molecules, which act as auxiliaries in various ways. The proteins have a variety of functions — as structural elements of the cells, as enzymes, hormones, carriers of oxygen, and so on. They are the jack of all trades of the living cell. Even if we knew their structures (which is at best a very distant goal) we would only be at the beginning of our quest. We should still have to ask: How do living cells make and renew their complement of proteins? Are there enzymes which construct proteins out of the amino-acids, which are absorbed from food?

There may be protein-forming enzymes, but they have not been detected. An enzyme is a substance which will act even when removed from the cell. It will do its work,

when the appropriate substances are present, even in a test-tube. No one has ever extracted from cells any enzyme which will turn a mixture of amino-acids into proteins. This does not, however, conclusively prove that none exists.

There is, however, one good reason why proteins cannot be constructed in a very simple way. Enzymes, being " catalysts ", accelerate changes which can occur of their own accord. They merely hasten spontaneously occurring changes. The protein molecule is like a house, a rather fragile house. It will tumble down of its own accord, but no one has ever seen a heap of bricks and timber erect themselves into a house. The enzymes hasten changes which can occur of their own accord, but they cannot do the reverse. Building a house requires the expenditure of energy, as well as organizing ability, such as the architect with his plans provides. Building a protein, like a house, requires energy, and the enzymes, by themselves, cannot provide it. How then can a protein be made?

In factories the raw materials are often transported to the top and gradually move downwards on moving belts, under their own weight, being assembled together and fabricated on the way down. This is probably what happens in the manufacture of proteins.

The amino-acids are first turned into " high-energy " compounds, from which proteins can be formed spontaneously. What these high-energy compounds are, we do not know. They probably involve phosphates, because it has been found in experiments with radioactive phosphorus that the rate of " phosphorus turnover " is high — that is, phosphorus enters into chemical change at an enhanced rate when proteins are being synthesized.

There is another reason why it is difficult to accept an enzyme mechanism of protein synthesis. As we have seen, there are an enormous number of different proteins, with highly specific properties in each cell. We should have to

have at least one distinct enzyme for each protein which is to be made; and it would be just as hard to explain the origin of these enzymes. In other words, we need to explain what does the organizing. What provides the plan, and how is it executed?

There are a few clues which may lead to some knowledge of these things. They are more like hints which may suggest to scientists directions in which to work, than certain knowledge; but we may as well describe them.

We might ask, to begin with, whether there is a kind of basic protein from which the more highly specific proteins are made by undergoing superficial changes. Just as ready-made tailoring shops keep a number of standard suits, which they alter here and there to suit their individual customers, so there might be a few standard types of protein from which the others are made by chopping off a few groups here and there, or adding others.

There is nothing impossible in this idea. The transformations which proteins undergo are quite extraordinary. A cow eats grass, in which protein has been synthesized from nitrogen compounds in the soil and carbon dioxide in the air, under the action of sunshine. The protein is broken down into its constituent amino-acids in the cow's stomach so that it can be absorbed into the blood. Somewhere in the cow it gets fabricated into the blood proteins, and in that form it passes into the glands in the udder, where the cells which make milk are located. The constituent of blood from which the milk protein is formed is known to be the *globulin*. We do not know what happens to the globulin in the udder, whether it is broken down and built up afresh as the casein of milk; or if it is just changed in some superficial way. Whatever the mechanism is, these cells manufacture casein in relatively enormous quantities. Here is a description by Professor H. D. Kay of how they work:

"The day's work of one of these cubical cells entails the

following cycle of operations. It begins as a rather short squat cell with the nucleus in the middle. Granules or globules, some of which stain with fat-soluble dyes, then begin to appear in the part of the cell nearest the ulveolar space. The cell begins to increase in length and size, the nucleus remaining fairly close to the basement membrane. The secretory products soon fill the whole of one end of the tall distended cell. These products, and possibly a small part of the cytoplasm, of the cell itself, are now extruded into the lumen as milk, following which discharge the cell returns to its original squat shape. This whole process is repeated several times. . . . During the 24 hours in an actively lactating cow there may be up to four or five, or even more cycles in operation."

To get some clues as to how proteins are made we have to look in other directions. There is a curious phenomenon known as the adaptation of enzymes to the food, which is exhibited by some micro-organisms. The nature of the enzymes of organisms, such as bacteria, yeasts, and fungi, appears to depend on the compounds provided as food. It will respond to a change in the nature of the food available, so as to be more suitable to deal with it. The enzymes become *adapted* to a new kind of food.

For example, many types of yeast will grow in media containing glucose as the source of energy. If they are transferred to a new medium, which contains a different kind of sugar, such as one of the less common sugars like galactose or melibiose, they are at first unable to utilize it and do not grow. After an interval the yeast sometimes acquires the ability to grow in the new sugar. Some strains of yeast have this ability and some have not, and the ability is an inherited character. It has been found that in these cases a new enzyme has been formed which can deal with the unfamiliar sugar — in other words, the new foodstuff induces the organism to make an enzyme which deals with it.

This is a very important observation, because it means that the formation of enzymes has some connection with the substances they have to act on. It appears that the final structure of the enzyme is determined by what particular compound is presented to the organism. This can only mean that this compound actually modifies in some way the final stages, at least, of the enzyme fabrication. Perhaps the enzyme is actually built around examples of the molecules it has to act on, so as to ensure a good fit. It is not a ready-made article, which has to do its best to deal with whatever variants of the compound it may meet; it is " made to measure " for the actual compound on which it has to act to ensure a perfect fit.

Further evidence of the same kind comes from the production of *antibodies*, substances which appear in the blood of animals to protect them against foreign proteins which may be accidentally introduced or produced by the bacteria of disease. When a foreign protein or certain other substances are present, the animal produces an antibody which will combine with it, neutralize its action, and often precipitate it and so remove it from the blood. Bacteria often produce harmful toxins, to which the characteristic symptoms of the disease are often due. The body responds by making an anti-toxin, and if the anti-toxin production is sufficiently vigorous the patient recovers. The antibodies may be either produced by the toxins of the invading organism or by the substance of the organism itself. Viruses also cause the production of antibodies. The immunity produced by one attack of diseases like measles and whooping-cough is due to antibodies, which may remain in the blood of the recovered person for a long time, or for life. The body can also be stimulated to produce antibodies by introducing toxins which have been chemically changed so as to be incapable of producing the symptoms of the disease (toxoids), yet still able to elicit the formation of antibodies. Killed bacteria

(vaccines) may act in the same way.

Artificial immunity to diseases is produced in medicine in all these ways. Antibodies can also be prepared in an animal, such as a horse, which may have the disease in a mild form.

There is a period after the onset of the disease and before the defence mechanism can come into play when the body is vulnerable, and it is often a valuable treatment to inject antibodies which have been so prepared, or which have been taken from the blood of immune persons. Everyone who has had measles has in his blood some measles antibody, and the " banks " of dried blood collected for transfusion purposes contain a valuable store of this antibody, which can be separated and safely used for immunizing children.

Antibodies are extremely specific. They will react with the protein which caused their formation and with no other. It has been shown by Heidelberger and others that if proteins are modified by attaching to their various chemical groups the antibodies which they give rise to are similarly modified and will only combine with the modified protein. A comparatively small group attached to a protein can produce the complementary change in the antibody; so it is obvious that antibodies make a very close " fit " with their protein.

It is difficult to avoid the conclusion that the protein is present when its antibody is being made. The antibody is in fact " tailor-made " to an exact fit.

VI

LIFE GOES ON

> From seed and shell, from fish and feather, the self-same lesson may be learned. Bristle and horn, lichen and leather, all repeat it. The frenzied dance of matter, from cottage to cosmos, has been potent for all time to create, with careless prodigality, sprightly, slothful, intricate, infinitesimal and monstrous manifestations of life.—LLEWELLYN POWYS in *Swiss Essays*.

So far we have not told the full story of how proteins are made. We have only obtained a few glimpses of the synthesis of proteins in the working of living cells. There is more to life than growth — important as that is; it must always renew itself. Cells are not immortal and must be replaced by new ones by some kind of reproduction. Every species has its own complement of distinct and highly specific proteins and we have to ask how the ability to make exact copies of the proteins of the parents is passed to their offspring. To put the question in its ultimate form, we shall have to ask how the qualities of a human being — not only its functions, the ability to fashion the body of a living man with all its organs, but also quite subtle characteristics of shape and constitution, and even of character — are transmitted from the parent to offspring in a single microscopic cell.

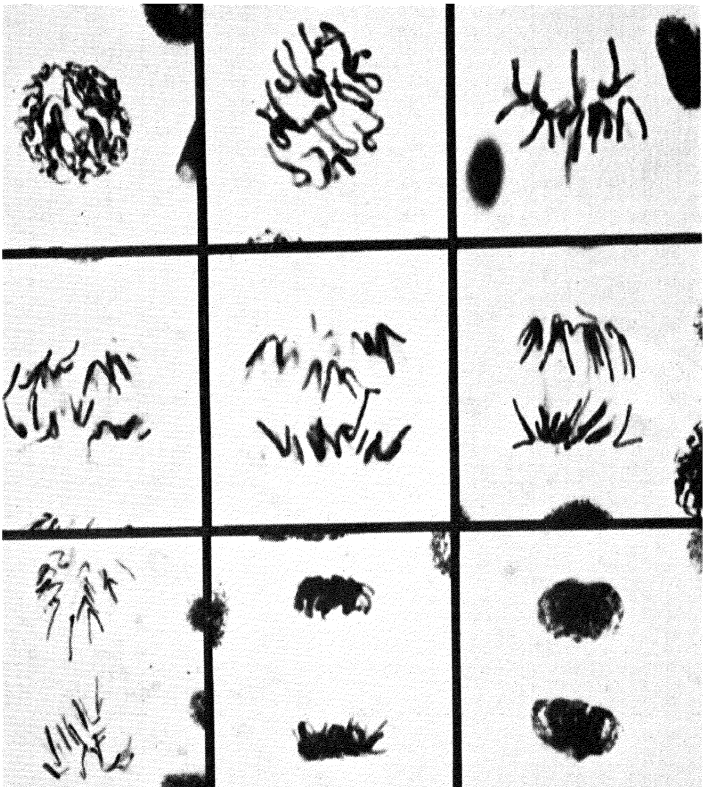
But before we can even approach that problem we must come back to the unicellular organisms and ask how they have solved the problem of transmitting their characteristics to their offspring. Reproduction often occurs by simple

cell division, and we might think that the problem is then quite simple. The cell would just grow to a sufficient size, manufacturing its proteins in ways such as we outlined in the last chapter, and then divide into two; with half the proteins in each portion. This would seem to be a perfectly feasible method of multiplication; but in most of the unicellular organisms which have been studied the actual process is more complicated. This is because life has found it necessary to concentrate the reproductive apparatus in a specialized part of the cell, the *nucleus*. Nearly all cells have distinguishable nuclei and when these are stained with certain dyes they can be shown to contain curious coils or thread-like particles, known as the *chromosomes*, their shape and size and, in fact, their visibility, depending on the stage in the reproductive cycle in which the cell is studied (see Plate IV).

This process of staining kills the cell and it is not possible in that way to study the actual changes in the chromosomes during the life-cycle. These can, of course, be inferred from observation of a large number of cells in different stages, but recent optical techniques have made it possible to watch the whole process in the living cell. There is no doubt that these happenings in the nucleus control the whole process of reproduction, in fact the whole life of the cell.

Just before the cell is ready to divide, the contents of the nucleus can be seen, vaguely, as a tangle of fine threads. They become thicker and resolve themselves into a number of separate chromosomes, which finally split longitudinally. While this is going on, a small portion of the nucleus, the *attraction sphere*, divides into two parts, which move to opposite sides of the cell, drawing with them a spindle of fine fibres. Then one of each pair of chromosomes seems to be drawn by the fibres to each pole.

In this way the full complement of the divided chromosomes is collected around each pole, forming the nuclei of



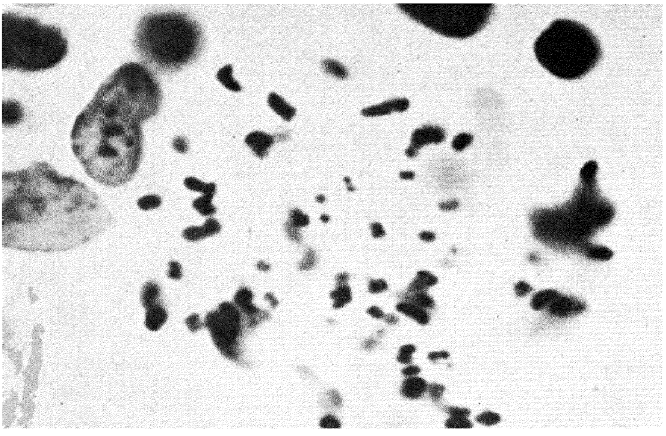
Preparations and photographs by S. H. Revell, The Chester Beatty Research Institute, Royal Cancer Hospital, London; reproduced with his permission

Chromosomes in the nucleus of cells from the growing tip of the onion root at various stages of the process of cell division

First row: (*left to right*)
(1) The chromosomes are emerging from the resting-stage. They have already thickened and are visible as long coiled threads which occupy most of the nucleus
(2) The separate chromosomes (16 in number) are becoming visible
(3) The chromosomes are ready to separate longitudinally into two halves

Second row: Division has taken place and the two sets of daughter chromosomes are being pulled away towards the poles of the new cells

Third row:
(1) The separation of the two sets of chromosomes is almost complete
(2) Cell division is almost complete, and the chromosomes form the two new resting-stage nuclei
(3) The two new nuclei. The individual chromosomes can no longer be distinguished



Photograph by Dr. P. C. Koller of the Chester Beatty Research Institute, Royal Cancer Hospital, London

The effect of a chemical substance (a nitrogen mustard) on the chromosomes of a tumour cell

Photograph by Dr. A. F. Hughes, Strangeways Laboratory, Cambridge

Photograph of a living cell

The large oval body in the right half of the picture is the nucleus, and the darker smears within it, the nucleolus. The dark particles to the left of the nucleus are mostly fat particles while the woolly streaks are made up of mitochondria. The colourless circles are vacuoles — bubbles of gas

the two new cells when division occurs. The process is known as *mitosis*.

Cytologists have seen in this the essential process of all nuclear reproduction, and regard the chromosomes as the essential carriers of the hereditary qualities or *genes*. They have found that the genes are arrayed in a linear order along the chromosomal threads and it has been possible, by a study of what characters go together, to locate particular genes in the chromosomes.

Sexual reproduction is more complicated. The organism sets aside special cells; the sperm from the male, and the ovum from the female. In these there is only one of each kind of chromosome, instead of the normal pair of each. They are formed by a special process of reduction whereby the number of chromosomes is halved. When they unite in the fertilized ovum, or egg cell, from which the new individual develops, the number of chromosomes is consequently restored; but one of each pair now comes from the male and the other from the female parent.

This device, which permits two parents to contribute to the heredity of a single individual, seems to have been a crucial one for the development of the higher organisms. In simple cell division, all lines of descent are distinct; any change occurring in a cell which improves its chance of survival, can only affect its own lineal descendants. In sexual reproduction, every individual has many ancestors. It may seem a very small change to have two parents instead of one; but the effect over a number of generations is overwhelming. If one individual receives contributions from two parents, four grandparents, and eight great grandparents, it is easy to see that the number of ancestors only twenty or thirty generations back may be enormous.

Ancestral trees which show the "descendants" of an individual are extremely misleading. They leave out a great many of the collateral ancestors of succeeding genera-

tions. They would be much more informative if written backwards, so that a man or woman could see who are his four grandparents, his eight great grandparents, and so on, up to 1,048,576 ancestors of the twentieth generation. Even allowing for a considerable amount of duplication, as for example the likelihood that not all these lines of descent are distinct, it is obvious that most of us are descended from practically the whole population of our country twenty generations back, or a mere five or six hundred years ago.

It is not difficult to see that sexual reproduction is in the long run a very effective device for spreading and uniting all the useful and desirable characteristics in a population. The fact that all the higher forms of life use sexual reproduction, shows that it has made them possible by increasing the tempo of evolution.

The essence of sexual reproduction is the contribution of chromosomes by both parents to the fertilized egg cell. The two chromosomes of each pair come, one from the male and one from the female parent.

The new individual, formed by the subdivisions of this fertilized cell, thus contains characters derived from both parents. Some of the cells formed are set aside to be the germ cells of the next generation, and these undergo the reduction division already described, which halves their number of chromosomes. It might be thought that when this occurs either the maternal or the paternal chromosome will be lost, so that the new germinal cell will contain either the one or other chromosome. At this point one of the most effective provisions of the sexual process comes into operation. Before the reduction process occurs, the two chromosomes which have been derived from the father and mother, become aligned with each other and exchange parts with each other. By this process, known as *crossing over*, the chromosomal thread which is formed in the germinal cell contains elements from both the previous parts. The

crossing over may occur at different places and in different ways, so that each germinal cell gets a different selection of the paternal and maternal genes. This wonderful provision ensures that every possible permutation and combination of the genes is produced, so that specially favourable combinations of characters have the opportunity of appearing in the individual progeny and of proving their worth.

In the chromosomal filaments we come very near the core of the mysterious processes of life. Strung along them are the genes and since these must have a material basis, we must picture them as molecular patterns which have the power both of maintaining themselves through succeeding generations and of impressing the characters they represent on the organism. It has been suggested that they are the templates or moulds in which protein molecules are built, with the pattern impressed. Since it would be difficult in some cases for a single gene to make all the molecules of one kind which are needed, it is suspected that there may be an intermediate stage. The gene impresses its pattern on a second particle in which the protein molecules are actually laid down. The gene will then be a model of the protein it produces. Round it is fashioned a mould in which exact copies are produced.

We have seen that special enzymes may be produced in response to a change in the food-molecules supplied, and it was concluded from this that the food-molecule was present when the enzyme was being fashioned, so that an exact fit of the enzyme with the substance it acts on was achieved. How shall we fit this fact into the picture we are making? We have only to suppose that the molecule, of which a fit is required, becomes attached to or incorporated in the mould, so when a copy is made it will exactly fit this substance (Fig. 8).

The chromosomal material must have two properties. It must be capable of a great variety of pattern and it must

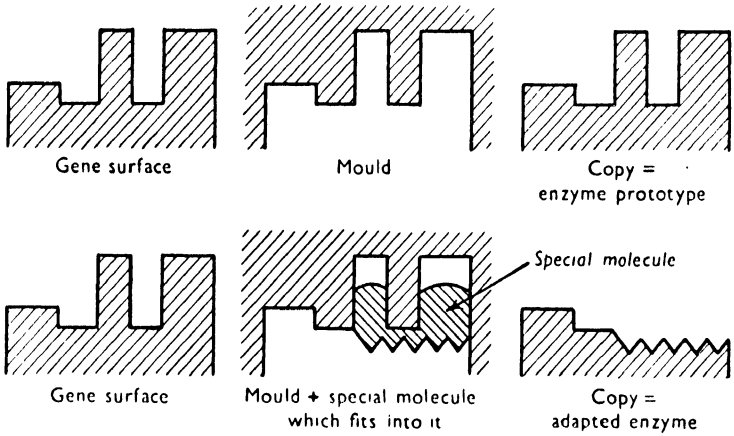


FIG. 8.—How an enzyme might be made from its gene and how the enzyme might become changed so that it will fit a particular molecule

In the lower row of drawings the mould has a new molecule attached to it and the copy will then closely fit the outline of this molecule

have great permanence. We know that the same patterns have been transmitted through countless generations. We know from a study of fossils that some organisms have persisted essentially unchanged from geological times down to the present day. For example, there is the fossil tree *Metasequoia*, which flourished during the Cretaceous period, 60,000,000 years ago. In 1945 a Chinese botanist discovered a living species on the borders of Hupeh and Szechuan. This species may have acquired some special characters in the interval; but the fact that it can be identified with the fossil species shows that many of the genes have come down to this day unchanged. They exhibit an extraordinary permanence, which is outside our experience in a world in which change is the more conspicuous feature. At the same time changes in species do occur, for, if there were no such changes, there would be no evolution.

What is the substance which provides the basis of these

properties? It was discovered by Miescher in 1871 that the nuclei of cells contain a substance which he called nucleic acid. It is not protein in nature. It consists of a particular and unusual type of sugar, ribose, combined on the one hand with certain basic molecules and on the other with phosphoric acid (Fig. 9). The exact mode of combination of these substances is still unknown, but it is known that they form long chain-like molecules having a molecular weight of many thousands. Two forms of the substance are known; the first is more prevalent in plants and was isolated from yeast (yeast nucleic acid) and the second was first found in animals (from which it was isolated from calf's thymus gland, whence the older name, thymo-nucleic acid, comes). But it is known now that both forms of the substance occur in plants and animals. It has been found that the thymo-nucleic acid is particularly associated with the chromosomes and particularly with their thickening and duplicating in the phenomenon of mitosis, while the yeast nucleic acid is concerned with the synthesis of proteins in the cytoplasm. Their distinctive rôles have not, however, been clearly established, but there is no doubt that they perform vital functions in the nucleus. They have a very strong affinity for enzymes and other kinds of proteins. The virus par-

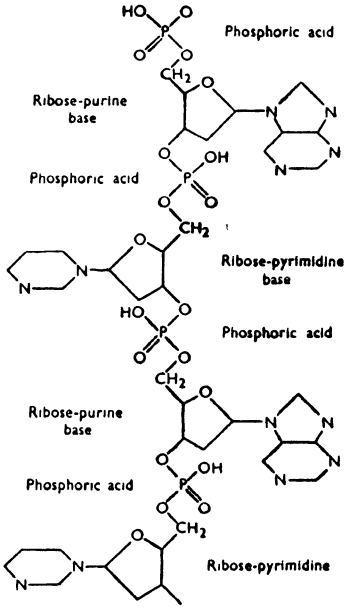


FIG. 9.—A nucleic acid—a characteristic constituent of the chromosomes which is concerned in the process of reproduction

ticles have been shown to consist of *nucleoproteins* — that is, a combination of nucleic acid and protein — and the chromosomes are similarly constituted. It is possible that the nucleic acids provide a kind of skeleton or framework which holds the proteins together, in a particular order. It has been suggested that nucleic acid forms, or is an important part of, the templates or moulds required for protein building; but this suggestion has still to be proved, since it is not known if the nucleic acids are capable of the great variety of shape and structural form which this hypothesis would require.

Whatever the chemical structure of the gene substance may turn out to be, there is no doubt that it must combine the ability of producing an almost infinite variety of configurations with great permanence. Even the size of the single gene is unknown, but it has been estimated that the upper reasonable limit is that of a largish protein molecule. We do not know how many genes are required to transmit the hereditary qualities of a large and complex organism such as a man. The least possible number is many thousands. Yet all these are carried in the chromosomes of a single sperm (or ovum).

The gene not only combines the permanence which enables the same character to be transmitted through numberless generations; it also has within it the potentialities of change without which evolution would not have been possible. It has been found in the study of heredity that when a large number of individuals of a species are observed, we occasionally see a new character, which suddenly appears and is called a *mutation.* A mutation, when once it has happened, is transmitted to the progeny in accordance with the laws of heredity. It therefore is due to an alteration in the gene.

The frequency with which certain mutations occur has been worked out in some cases. For example, the genetics

of the fruit fly (*Drosophila*) has been very thoroughly studied. Since 1911, Morgan, Müller, and Bridges at Columbia University in New York have bred a large number of these flies through many generations. They are very suitable for investigations on heredity. A new generation appears every week and they are simple to keep and to feed. Morgan and his colleagues made a very careful investigation of the chromosomes of these flies and succeeded in locating the positions of a large number of genes in the chromosomes. However, this is not the aspect I want to emphasize here. In the course of the work no less than eight hundred distinct mutations were observed. These all bred true to type and undoubtedly were due to changes in the genes.

In the fruit fly it has been estimated that an individual gene has an average chance of less than one in a million of undergoing a mutation in a given cell cycle. This means that a single gene will make no mistake in producing its daughter genes in something of the order of million copyings — which will occupy between a thousand and ten thousand years. Even when a gene mutation does occur, it will usually be disadvantageous and eventually cause the non-survival of the organism. Professor J. B. S. Haldane has estimated that with the human genes the likelihood of a mutation occurring may be only of the order of once in a million years.

It was discovered by H. J. Müller that gene mutations are stimulated by X-rays and similar agencies. X-rays have a very violent effect on the cell nucleus. Massive doses produce breakage of the chromosomes and a general disruption of the reproductive mechanism. It is for this reason that X-rays are used in the treatment of cancer in order to kill malignant cells and so prevent their reproduction. With moderate doses of X-rays, only an occasional gene may be modified or destroyed without causing the death of the organism. Müller has calculated that a half-hour's applica-

tion of 5000 r. units of X-rays to the spermatozoa of the fruit fly increases the mutation frequency 50,000 times.

Many experiments of this kind have been also carried out on simple organisms — especially fungi. Beadle and Tatum in California have exposed the fungus *Neurospora* to X-rays. Many of the spores are killed by this treatment, but among the ones which survive, a proportion are found which have lost the power to perform one or more of the chemical reactions which they could originally bring about. The original " wild " *Neurospora* is an organism with remarkable synthetic ability. All it requires to live and grow, besides water and some inorganic substances, are glucose, as a source of carbon, ammonia to provide nitrogen, and one vitamin, *biotin*. The others it requires, it can make for itself. It makes aneurin, riboflavin, pyridoxin, pantothenic acid, folic acid, choline, inositol, twenty amino-acids, and a variety of purines and pyrimidines! Out of these, the basic substances of nearly all living things, the fungus constructs the proteins, the nucleoproteins, and its whole organization.

The mutants produced by X-rays often lack the ability to make one or other of these compounds, and growth will not take place unless the missing substance is supplied. Fig. 10 shows how the nutritional requirements of the mutants are tested. A large number of these different mutant strains of the organism have been made, each of which appears to lack one enzyme, and from this it is inferred that one gene has been damaged by X-rays. Of course strains are also encountered where two or more substances must be added to the basal diet, but it can be proved by suitable cross-breeding experiments that in such cases the genes are distinct. In fact, a missing gene can often be replaced by cross-breeding with a strain which possesses it. This is the clearest evidence we have at present of the close and unitary connection between genes and enzymes.

It has also been possible in some instances to track down

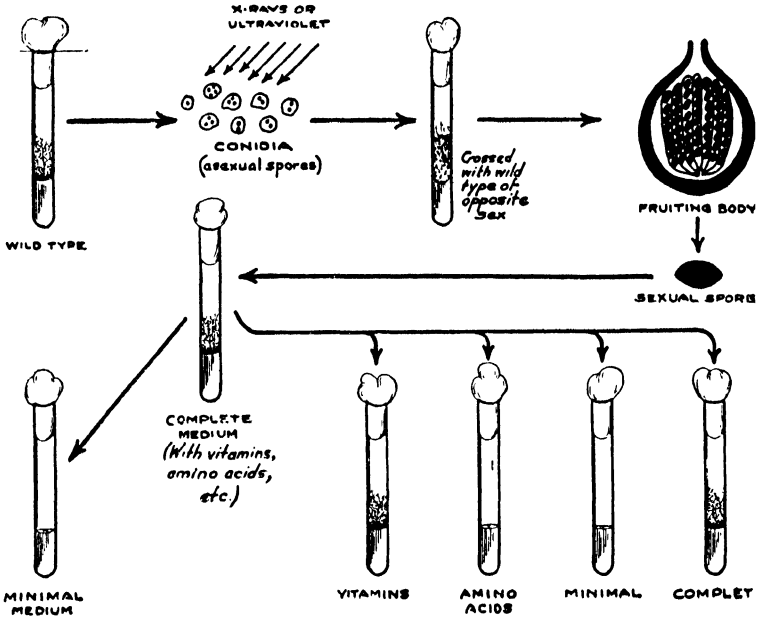


FIG. 10.—How mutants of the fungus *Neurospora* are made and tested for their nutritional requirements

Asexual spores of the wild type of fungus are exposed to X-rays or ultra-violet light. They are then crossed with spores of the original wild type and the progeny is examined. (This ensures that the changes observed are real alterations of the genes.) In the first place the spores which will grow in a complete medium, *i.e.* one containing added vitamins, amino-acids, etc., but not in the minimal medium which supports the wild type, are distinguished. Separate experiments are then made to discover which compounds these spores require for growth which are not provided in the minimal medium. (Diagram reproduced from *Frontiers of Science*, Series V, by permission of Prof. G. W. Beadle and the Yale University Press, and of Prof. G. A. Baitsell and Oxford University Press)

the chain of reactions by which these substances are formed, and it is found that there is a gene which controls each stage of the process. If this gene is destroyed by X-rays, the progeny of this individual is unable to perform the corresponding step in the chain of synthesis and no growth can take place unless the missing substance is made good in some way. Also if the chain of synthesis is broken at one point,

the substance formed just before the break in the chain cannot be used up in the normal way and is liberated into the medium. It is by studies such as this that the complex reaction processes in simple organisms are being unravelled.

The mutations produced by radiations, such as X-rays and the high-speed particles emitted by radioactive substances, all result in the loss of genes. The hereditary material loses some of its capabilities. Something is destroyed, but no case has been recorded in which a new quality has been gained. This is perhaps not surprising considering the violently disruptive nature of the means applied. This has serious complications in a world in which powerful sources of radiation are becoming common, for the effect of radiations is cumulative. A small dose continued for a long period is as effective as a large dose acting for a few minutes. The chance of the rays damaging the chromosomes is simply proportional to the amount of radiation to which they have been exposed. There are thus serious possibilities of damage to the germ cells of persons who spend considerable periods in the vicinity of X-ray machines or of radioactive materials, unless great care is taken. If the gene represents a character which is recessive the injuries may only be apparent in the second generation, or later. It is only fair to add that those in charge of installations are well aware of the dangers; but it is a factor which will seriously hinder the widespread use of atomic energy.

It has been found recently, by Miss C. Auerbach and Drs. Robson and Carr, that mutations can also be produced by certain chemicals — in particular by mustard gas and related substances, which were developed as chemical warfare agents of considerable potency. These substances have a profound effect on organisms. When they penetrate to the nucleus of cells, they cause disruption and breakage of the chromosomes. For example, the disruption of the chromosomes of a "Walker tumour" cell which has been

exposed to a chemical substance is shown in Plate V (upper picture). Very few cells survive when so treated; but it was found that in organisms which do survive, mutations similar to those produced by X-rays occasionally occur.

It used to be thought, in fact it was almost held as an axiom, that the germ plasm could not be influenced through the cytoplasm. The nuclei of the germ cells passed on from one generation to the next uninfluenced by what happened to the individual. The mutations on which evolution depended were rare spontaneous events.

This view now has to be modified to some extent. We see that the genes, although well screened from outside influences, can be reached by powerful radiations, as well as by some powerful chemical agents. These kill many of the cells exposed to them, but a few survive, in which some genes have been injured or destroyed, although the cell is still able to live.

The substances which bring about such effects are not very likely to be found in Nature — in fact they are so reactive that they do not remain unchanged in the presence of water for more than a short time. But the possibility exists that cells not functioning properly may produce such substances, which may then cause mutations in normal cells; indeed it has been suggested that cancer may be caused in this way, by a mutation produced in a cell or a group of cells. Nearly all the substances which are known to damage the chromosomes, in sufficient doses, have been also found to initiate cancer under conditions less severe than those likely to cause the death of the cell.

VII

INSIDE THE CELL

Wonder is the feeling of a philosopher, and philosophy begins in wonder.
SOCRATES

BECAUSE the extraordinary behaviour of the chromosomes can be studied easily under the microscope, the nucleus has had most of the attention of recent generations of cytologists. The rest of the cell, which shows no such dramatic happenings, has been rather neglected until recently. Its contents — the cytoplasm — were thought to serve mainly to nourish the nucleus and perhaps do the ordinary work of providing the cell with food and energy.

Much is now being learnt about the cytoplasm by the application of new methods. The traditional technique of the microscopist was to cut thin sections of the material and to stain them with dyes so as to make visible one or more of the cell structures. These staining processes were often quite drastic and destroyed many of the cell constituents, so that the cells were not merely dead but profoundly altered as well.

In recent years several new techniques of studying the interior of living cells have been worked out. New types of microscopes have been devised which depend not on the absorption of light by the specimen, as in the ordinary microscope, but on refractive differences of different parts of the object. For example, one of these, the phase contrast microscope, which was invented by Zernike, makes it possible to see and photograph transparent objects, if they

differ in optical " density " from other parts of the field. Structures inside living cells can thus be made visible without damaging the cell or interfering with its life.

Dr. A. Hughes of the Strangeways Laboratory, Cambridge, has obtained in this way many beautiful pictures of living cells " in action ". He has also made a motion picture of cells undergoing division. As it is not possible to show this in a book, we have to be content with a still photograph as an example (Plate V, lower picture). The film shows cells not as static things but as an arena of constant motion and change. Besides the nucleus and its contents, we see many particles of different sizes. Besides granules of fat and empty spaces (vacuoles), there are many filaments of material, which under some circumstances appear as separate particles called mitochondria.

Methods of separating these constituents of cells have been devised by Dr. A. Claude. By gentle rubbing of soft tissues, the cell walls are broken and their contents released. The particles can now be separated according to their size and density by careful centrifuging at different speeds. The first particles to come down are the nuclei, if the treatment has not been so rough as to break the nuclear membrane and release the chromatin material of which the chromosomes are made. Next come the large granules (mainly mitochondria), and at a still higher speed we get small particles known as microsomes, which are invisible in the microscope, but are still much larger than separate protein molecules. When these are removed some dispersed molecules still remain in the cell sap, but not very many. Most of the contents of the cytoplasm are present in granular form. We learn from these experiments that the constituents of the protoplasm are not all mixed up together, they are carefully done up into little bundles. Fig. 11 gives a diagrammatical representation of the contents of a cell according to these findings.

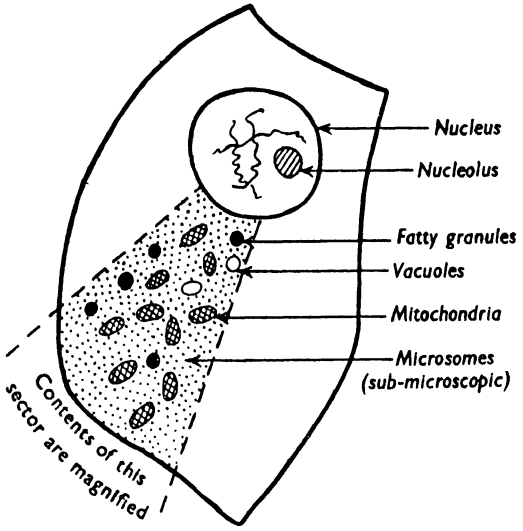


FIG. 11.—Diagram of the contents of a cell (after Lazarow)

This is the beginning of an analysis of what used to be called "protoplasm", the mysterious viscous fluid which fills the cells. Very little has been done so far to explore the nature of the particles. It is not difficult to separate them, but little is known so far of their composition. It has been found, however, that the oxidizing enzymes of the cell are concentrated in the mitochondria. These particles seem to contain the power plant of the cell. A typical mitochondrion is a particle 2μ long and about $\frac{1}{2}\mu$ wide and contains perhaps a million protein molecules. Even if there were 500 different enzymes in each particle, as there well may be, there is room for a good many molecules of each. A single mitochondrion may thus be able to bring about a long chain of reactions. Besides protein, the particles contain nucleic acid and fatty substances, probably held in combination with protein.

How all these constituents are arranged will be a

tremendous problem for the structural chemist. So far the door has only been opened a little and we do not know what secrets remain to be revealed in these minute bodies. We do not know for example how they are formed, whether they are all the same or of many kinds. Dr. Claude thinks that all the particles in the cell are self-reproducing; but the mechanism of how this occurs is completely unknown.

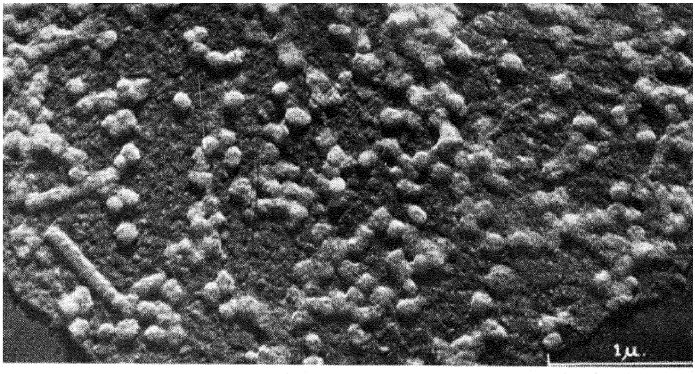
If these particles reproduce themselves, as they may well do, without the intervention of chromosomes, we should be obliged to conclude that some part of the inheritance of the cell is carried by the cytoplasm — by the " plasmagenes " as they have been called. The existence of such independently hereditary agents, though suspected, has not been clearly proved so far. All we can say is that cellular reproduction is more complicated than was thought and that the cytoplasm is more important and more highly organized than was suspected.

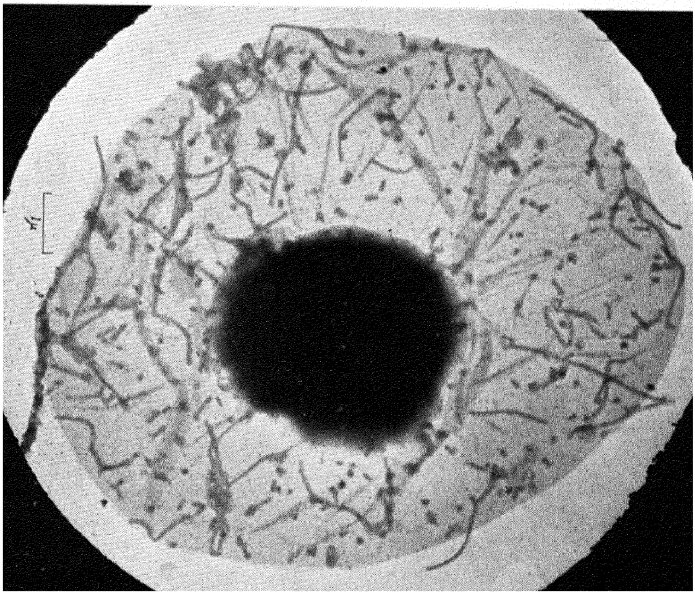
It was discovered a good many years ago that some agents of disease are of an essentially smaller magnitude than bacteria since they will pass through filters that retain bacteria. This was observed by Iwanowski as long ago as 1892, when he discovered that the sap of tobacco plants infected with the tobacco mosaic disease, after being passed through a fine porcelain filter candle, still had the power of infecting healthy plants, when rubbed on their leaves. In 1898 Loeffler and Frosch showed that the infective agent of foot and mouth disease could also pass through such filters. The importance of these observations was not understood at first, but gradually a distinction was drawn between bacteria, which were usually visible in microscope and were stopped by fine filters, and filter-passing agents, usually invisible in the microscope, which were called viruses. The list of virus diseases, even of man, is now very long and includes measles, mumps, influenza, poliomyelitis, chicken-pox, rabies, and yellow fever.

For many years, viruses belonged to the realm of the invisible. Estimates of their sizes were made by various means. Dr. W. J. Elford, for example, made collodion membranes having pores of different sizes, by means of which an estimate of the size of the particles of the infecting agent could be obtained. Methods of concentrating the viruses were also worked out. Dr. W. M. Stanley in 1935 applied to infected tobacco plant juice the same methods of salt precipitation which had been successfully applied to the isolation of enzymes. He obtained a protein of high molecular weight, in a form which had some of the properties of a crystal and was highly infective. Here was a pure, or comparatively pure, chemical substance which had the property of infecting healthy plants. An extremely small quantity of this substance, when introduced into the plant, increases so that after a time a much larger quantity can be obtained from the juice. It therefore appears to have the property of self-reproduction, or at least of multiplication in the living plant.

A considerable number of viruses have now been isolated in what appears to be a pure condition, and some of them form excellent crystals. This is not necessarily a sign of the non-living. It merely means that they have a well-defined shape, and pack together in a regular lattice arrangement and so give rise to a crystalline solid with a regular geometrical shape. In recent years the virus particles have been made visible in the electron microscope, and the shapes and sizes, which conform with the estimates which were previously made of them, are well known (see Fig. 12). They vary greatly in size and shape. In composition, they are a kind of nucleoprotein, akin to that of chromosomes but containing the kind of nucleic acid which is found in the cytoplasm rather than that of the nucleus. Little is known of the nature of the proteins they are made of.

Unlike bacteria, they have not been successfully culti-



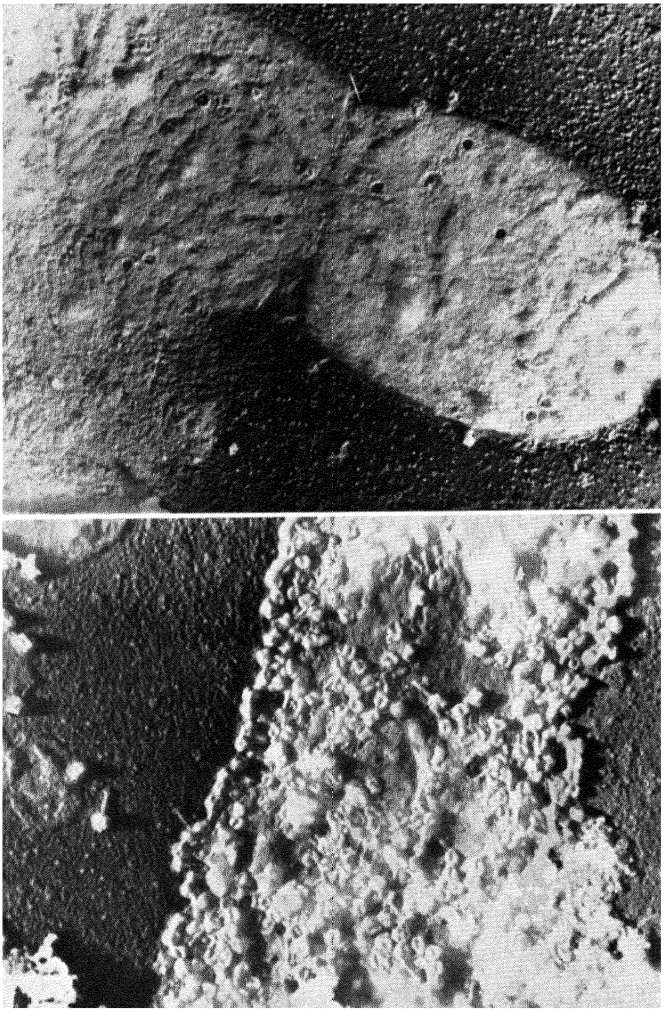


Electron micrographs, shadowcast with palladium, reproduced by courtesy of Drs. Chu, Dawson and Elford from their paper in the "Lancet", April 9, 1949

Electron micrographs of Influenza A virus adhering to a red fowl cell

The upper picture shows the round form of the virus particles and the lower picture, at a lower magnification, the long filaments which it sometimes forms

PLATE VII



Two pictures of bacteriophage attacking a bacterium (*B. coli*), taken with the electron microscope by Dr. Ralph W. G. Wyckoff

The first picture shows two cells, on one of which the attack of bacteriophage has only just begun, while in the other the cell is disrupted and the contents are escaping. The second picture shows a cell which is full of bacteriophage particles into which its contents have been transformed

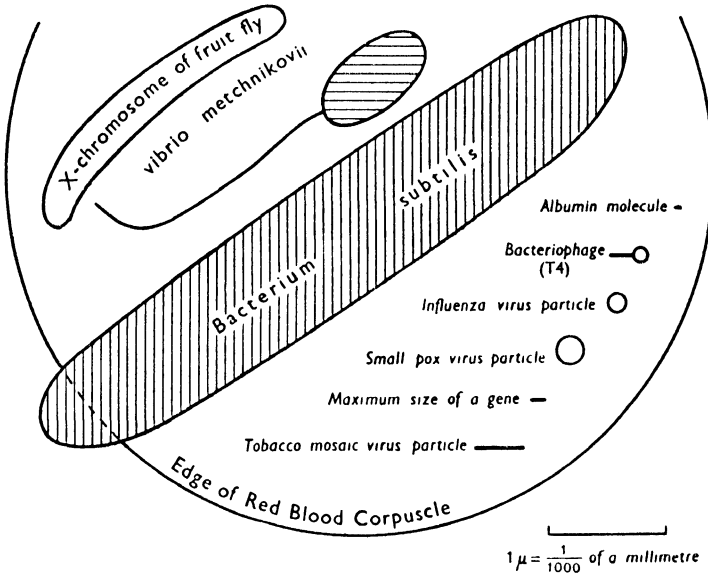


FIG. 12.—Relative sizes of virus particles and bacteria. Compare with Fig. 2

vated in artificial media. When introduced into the living cells or in the presence of a few living cells they multiply, but either their nutritional requirements are so extremely exacting that it has not been possible to meet them, or they require and make use of some part of the metabolism of a living cell. They do not seem to be able to provide for themselves completely in a non-living environment.

What is the nature of these protein-like substances? The size and crystallizability of their molecules bring them almost in touch with the inanimate world, yet they have the basic ability of living things — the power of reproduction. Should we class them with the non-living or with the living? They seem to be on the dividing line between the two. Perhaps it is too much to expect to find a definite point at which we can say, here life begins. Let me quote Dr. Stanley's view

on this. He says, " As we go from the admittedly non-living to the admittedly living, I think there must be a transition stage while there are entities that may possess some properties of the non-living and of living things. What could fill this place more simply and logically than the high molecular weight virus proteins that are intermediate in complexity between the protein enzymes and hormones, the wonderful properties of which we already recognize, and the system of proteins that we call protoplasm and which constitutes life? There is evidence that even within the virus group there is a gradual increase of complexity of structure from the small nucleo-proteins to the more ' elementary-body ' type of virus.[1] There is, however, no sharp break. . . ."

It seems that a certain degree of the complexity is needed before an organism can maintain itself as an independent living thing with the ability to live on its environment and to grow and reproduce itself. Possibly the virus particle, although endowed with some of the properties of life, is just below that level. Perhaps it is a parasite of healthy cells which, dispensing with cytoplasm of its own, makes use of their cytoplasm — a kind of cuckoo in the nest.

Viruses are very specific and usually attack only a limited range of organisms or often only one species. The tobacco mosaic virus will not multiply except in the tobacco plant. In fact it often happens that a virus will only injure certain strains of a species and not others. Some varieties of potato, such as the King Edward, are resistant to the potato mosaic virus which injures other varieties. Virus resistant strains of raspberries and strawberries are well known to growers.

The relation between a virus and its host is therefore a very intimate one. It has been suggested that the virus particles have arisen as a mutation of some normal self-reproducing constituent of the cells in which they grow.

[1] Large round virus particles, about 175 mμ across.

Suppose that a self-reproducing particle in a cell makes an error of reproduction and produces particles which, although they can " live " and multiply in the cell, do not function correctly. These particles will behave as the viruses do. They will be " rogue " particles which interfere to a greater or lesser degree with the normal working of the cells. If they are introduced into healthy cells, they will continue to reproduce themselves there. But if they go on multiplying, they may eventually cause such disturbances of the normal working that the death of the organism results.

It might be objected to this that the virus particles are very unlike the normal cell constituents. The tobacco mosaic virus consists of long narrow rods, which are unlike any normal cell particles. But there is evidence that the rods are made up of a number of smaller particles joined end on end. Electron micrographs have been taken which appear to indicate that the virus particle grows length-wise by the joining up of smaller units. These smaller units may not be so different from normal cell particles. The influenza virus (Plate VI) also occurs in both a filamentous and a round compact form.

The common viruses must have gone through innumerable generations since they first originated. Even in short periods of observation new strains are often found. The viruses of disease may thus easily have originated in a self-reduplicating particle of a normal cell, which underwent mutations and reached its present state after a long sequence of changes, in which it may have diverged considerably from the original particle, while still retaining the essential property of being able to live and multiply in the host.

There are other cases in which the virus is not strongly differentiated from the normal cell particles. Peyton Rous in 1911 observed a certain type of fowl tumour which could be transmitted from one bird to another by a filterable virus. This is shown by mincing the tumour and passing

the mince through a filter which removes the whole cells and large fragments. If the cell juice so obtained is injected into another bird, a tumour is formed round the site of injection. It was therefore recognized that the filter-passing fluid contained a virus which is able to cause the growth of a tumour in a healthy bird. The particles of this virus are not clearly distinguishable from the smaller particles which are normally present in the cytoplasm and cannot at present be separated from them. It is possible that this virus consists of normal cell particles which have only been slightly modified. Instead of producing a lethal injury, it stimulates the cells to abnormal growth.

This observation naturally gave rise to the suspicion that all cancerous growths were caused by a virus which upsets the normal controls and stimulates the cells in some way to unchecked growth. But although much effort has been devoted to attempts to isolate a virus which will transmit cancer, it is only in a few tumours of a very special kind that such a virus has been found. The cause of cancer still remains a mystery, but now that the means of isolating and examining the particles of cells are at hand, we may hope to discover much more about the internal economy of cells and in time, perhaps, the cause of abnormal growths.

Bacterial cells also have their virus enemies. It was noticed by Twort in 1915 that bacterial cultures sometimes cleared suddenly and the bacteria appeared to break up and dissolve. A few drops from this liquid added to another culture caused it to behave in the same way. Two years later d'Herelle made similar observations. The agent which destroyed the bacteria could not only be transferred from one culture to another, but its activity increased with each transfer. This phenomenon is now recognized as being due to bacterial viruses, which are known as bacteriophages. Their form has been definitely demonstrated by electron micrographs of the particles. A number of different types

have been found which differ considerably in size and shape. Plate VII shows some of the beautiful pictures of Dr. R. W. G. Wyckoff of successive stages of the attack of coli bacteria. The 'phage particles are easily recognized by their tadpole-like shapes, with short rod-shaped tails. The attack begins when one or two of these particles attach themselves to a bacterium. They then pass through the wall and multiply within the cell until, finally, the whole of the interior appears to be filled with the particles which escape through the disrupted cell membrane.

The bacteriophages offer a very favourable opportunity for the study of the elementary processes of life and reproduction. M. Delbrück and W. T. Bailey have made the startling discovery that bacteriophage particles are made up of still smaller units. They found that two different related strains of bacteriophage can be crossed with each other so as to produce a kind of hybrid. For example, one strain of virus known as T_2 produces a small colony and can destroy a strain of the bacterium called A; while another strain known as T_4r produces a large colony and can destroy a mutant strain called C. When both types are added together to a culture, not only are both of these original types released when the bacteria burst, but also two intermediate types, in which the characteristics are combined in a different way. One produces a large colony and destroys bacterium A. The other produces a small colony and destroys bacterium C. It appears that the characteristics of T_2 and T_4r have got mixed up in the new types, each of which has features drawn from both of the two parent types. The inference to be drawn from this is that bacteriophages break up in the cell into smaller particles which multiply independently and reassemble so as to give rise to all their possible combinations in the new individuals. Thus we find a kind of sexual reproduction even below the level of cells.

Another discovery by S. E. Luria of Indiana University also

indicates the composite nature of bacteriophages. Viruses can be " killed " by exposure to ultra-violet light. When infected by a single " killed " bacteriophage particle the bacterium usually dies, but no multiplication of the virus takes place; but if two or more of the " killed " virus particles enter the bacterium, it was found that they often multiplied as well as the undamaged virus. It looks as if the two damaged particles can share their parts and make up one complete individual between them. Luria has estimated from his results that the 'phage particle has about twenty independent units. When only one of these is damaged by ultra-violet light, the particle is incapable of multiplication, but the damaged unit can be made good from other particles.

These are wonderful discoveries. They mean that chemistry and physics can at last come to grips with living matter. Nearly everything described in these pages has been discovered in the last fifteen or twenty years. Before that time, the physical sciences were content to study simple inanimate materials and hardly dared to hope that the time would come when their methods would reach up to the complexities of life. But the coalescence of physics and chemistry with biology is now an established fact and the sciences of life have become neither physics nor chemistry nor biology, but an inextricable mixture of all three. It does not require much foresight to see in all this the beginning of a new era in science, a new start similar to that provided by Lavoisier's theory of chemical changes a hundred and fifty years ago and Kekulé's discovery of the plan of construction of " organic " compounds, ninety years ago.

Will it lead to an explanation of the nature of life in terms of atoms and molecules? That it will produce a great increase in our knowledge — at present superficial — of what goes on in living cells, there can be no doubt. But a caution is necessary. The road ahead will be a very long

one. I have already described the great chemical complexity — still largely unexplored — of even the simple proteins. The much larger cell particles, which have been found, may be giant molecules of a different order of magnitude — containing many millions of atoms in an integrated structure. Even when we have analysed these parts, we may find that we are still remote from knowing the secret of life, and that the whole of the living organism is greater than its parts.

It is not unusual to find properties emerging in the whole which would not be suspected in the parts. We have examples of this at every level of experience. No one, knowing carbon, hydrogen, oxygen, sulphur, and nitrogen, could have suspected that a few atoms of each, put together in a not very complicated arrangement, would produce the beautiful blue of indigo. It is true that, looking back, we can sometimes account for the colour in terms of the properties which we ascribe to the atoms; but we should hardly have expected it from what we know of simpler compounds. The colour is the property of the " whole " — a particular group of atoms, which has a peculiar power of resonance. If new properties emerge in such comparatively simple structures, how much more likely is it that we should find new and unsuspected properties, of which the smaller molecules give us no hint, in the vast conglomeration of atoms of which even the simplest cell particles must be composed? It is not necessarily true that because living things are made up of atoms, all the phenomena which occur in them are similar to those met with in the simple molecules. There may be types of behaviour, for example, self-reproduction, and extraordinary phenomena which occur in nerves, which only emerge in larger assemblies.

This is perhaps a pessimistic note on which to finish a review of the great advances of the last two decades. But the scientist, like all explorers, is happier in travelling than

in arriving. At the present moment of time he is fortunate in living at one of the climacteric phases of science. A whole new world has just been disclosed, offering unlimited opportunities of discovery. The landscape which has come into view, seen at present in only a flickering and uncertain light, is an exotic one; quite unlike the bare sharp outlines of nineteenth-century science.

VIII

CHEMICAL CONTROLLERS OF THE BODY

> The sperm enters the egg, the cell divides and divides, to become at last this man, that rat or horse. A cow's pituitary will make frogs breed out of season. Urine of a pregnant woman brings the mouse on heat. Sheep's thyroid transforms the axolotl from a gilled larva into an air-breathing salamander, the cretinous dwarf into a well-grown and intelligent human being. Between one form of animal life and another, patterns are interchangeable. Interchangeable also between animal and plant and the inanimate world.—ALDOUS HUXLEY in *Eyeless in Gaza.*

> It may be said, indeed, that without bones and muscles and the other parts of the body, I could not do what I would: but to say that I act as I do because of them, and that this is the way in which my mind acts, and not from choice of the best, why, that is a very careless and idle mode of speaking. —SOCRATES in *Phaedo.*

OUR organism is a society of cells, a highly organized society in which each kind of cell has a trade of its own. There are cells which manufacture special enzymes, cells which accumulate starch or fat, cells engaged in the process of breaking down and excreting unwanted products, cells which transport oxygen, those which burn sugars and perform mechanical work. All these activities must be regulated and controlled. They must be performed at the right time and to the right extent. At the sight or smell of food the salivary glands start to secrete the saliva which begins the digestive process. When the food enters the stomach, the lining liberates hydrochloric acid to acidify it and pepsin to digest proteins. The pancreas discharges other digestive enzymes

into the intestine. When we run, the heartbeat increases so as to give a greater supply of blood to the muscles; we breathe more deeply and as we get hot we begin to sweat. These and many other phenomena show what a complex system of controls the body has.

It seems that the primitive methods of regulation and control are chemical ones, since they appear in very simple organisms which have no nervous system. Even plants have such chemical regulators. How is it that the growing tip of a plant turns towards the light? Kögl showed that plants produce certain growth-stimulating substances called auxins, and these stimulate growth more on the side of the tip which is away from the light and so it is caused to bend towards the light.

In the higher organisms this method of control has been supplemented by a much quicker method — the use of nerves to send signals from one part of the body to another, but the older chemical controls, as we shall see, still underlie the whole nervous system.

It has been known for many years that there are in the animal organism a variety of glands — called the ductless or endocrine glands because they produce secretions which pass directly into the blood-stream. Towards the end of the nineteenth century it became known that these glands are intimately connected with the maintenance of bodily health and function. If they are removed or diseased, profound changes occur in the working of the body, and it was found that these changes could often be relieved by feeding extracts of glands obtained from animals.

Since then an enormous amount of research has been done on these extracts, and from them a large number of very potent substances — called hormones, *i.e.* " chemical messengers ", though the term is not very appropriate to some of them — have been isolated. These substances vary enormously in complexity. Some are comparatively simple

compounds, others are proteins. Because of the striking bodily effects they produce, the isolation and study of these compounds has been one of the most successful and dramatic chapters in biochemistry. Many of them are now used therapeutically, either as obtained from animals, or, in the case of the simpler ones, the synthetic equivalent. I shall not attempt a long description of these substances such as may be found in elementary text-books of biochemistry and physiology, but it will not be out of place to tell the story of some of the best known.

As long ago as 1884 it was recognized by Horsley that the removal or atrophy of the thyroid glands, a pair of small glands in the neck, produced cretinism, a kind of atrophy of the body and also of the mental faculties. It was found by Murray in 1891, that this condition could be relieved by feeding sheep's thyroid. The active substance in the thyroid extracts was isolated by E. C. Kendall in 1916, and in the course of time its structure was established, and it was finally synthesized in 1927 by Barger and Harington. It is a comparatively simple substance, a compound of iodine and a common amino-acid, tyrosine (Fig. 13). Because of this, the thyroid gland is the reservoir of most of the iodine in the body. If the water supply is deficient in iodine, as happens in some limestone districts, the thyroid is unable to make enough thyroxine and it seems to swell up in an effort to make up the deficiency. This produces goitre, once a common disease in mountain areas.

Thyroxine is concerned with the oxidation of fats and proteins. When it is absent, the body does not develop properly, giving rise to cretinism. Over-activity of the thyroid causes protuberant eyes and a kind of feverish activity. It is necessary for the metamorphosis of the lower animals. With the thyroid gland removed, tadpoles cannot metamorphose into frogs. On the other hand, when small quantities of thyroxine are added to the water, tadpoles will

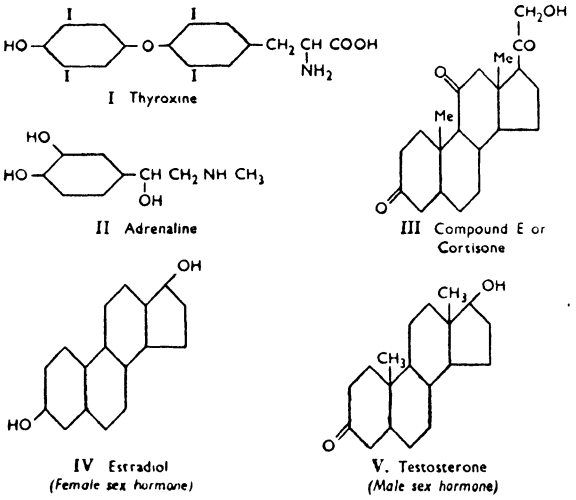


FIG. 13.—Some of the hormones

change prematurely into miniature frogs. It is intimately connected with the secretion of milk. Injection of thyroxine into cows markedly increases both their milk and their fat production — at least temporarily; and it has been found that feeding iodinated proteins, which probably help the cow to make thyroxine, has a similar effect.

Another gland, not strictly a ductless one, which produces substances necessary for health, as well as the digestive enzymes it pours into the intestine, is the pancreas. If it is damaged or removed, serious bodily changes occur, especially an inability to oxidize sugar, which then accumulates in the blood. This is what happens in the disease diabetes, which is due to an impaired action of the pancreas. It was found that this condition was relieved by extracts of pancreas from animals, and in 1921 Banting and Best in Toronto isolated from the pancreas a protein called insulin. Actually it is present in separate parts of the pancreas, distinct from the enzyme-producing parts, known as the islets of Langerhans.

Only a fraction of a milligram of insulin is required each day by a healthy person, and diabetics can be kept going indefinitely by injections of ox or swine insulin.

One of the first to benefit from insulin was Dr. R. D. Lawrence, who has since become one of the foremost authorities on diabetes. In 1922 during an operation, a bone splinter flew into and injured his right eye. The wound turned septic and he became very ill. His illness was eventually diagnosed as diabetes, and he was considered a hopeless case. He went to Florence to spend what time he had left and while there, in the spring of 1923, he heard of the discovery of insulin and at once went to obtain the treatment. He soon recovered and has been able to lead a normal and productive life during the last 26 years.

As we have seen (Fig. 3), insulin is a very complex substance and there is little hope of its being synthesized in the near future, so that diabetics are likely to remain dependent on the supplies of insulin which can be obtained from animals.

Above the kidneys are two small glands, known as the suprarenals. Each suprarenal consists of two distinct glands, as their inner parts have quite a different function from the outer cortex. It was found in 1895 by Oliver and Schäfer that extracts of the inner part produced very marked physiological actions, and some years afterwards an active substance called adrenaline was isolated from it. In due course the structure of adrenaline has been found and it has been synthesized, and the synthetic product has exactly the same action as the natural substance. It is also quite a simple substance (Fig. 13). Introduced into the blood-stream it causes an increase in the blood-pressure, a steadying of the heart-beat, and an increase of blood-sugar. It tones up the body and makes it ready to meet unusual stresses. The gland is stimulated by the sympathetic nervous system. Strong mental stresses, such as fear, anger, and strong emo-

tion, all cause it to secrete adrenaline into the blood-stream. The result is to prepare the body to meet unusual demands upon it. The gland thus acts as a kind of relay station — an intermediary between the brain and the chemical regulating mechanisms. The tiny nervous impulses from the brain enter the gland and cause it to release the hormone, which is carried by the blood to all parts of the body. This is naturally a relatively slow process, and when adrenaline has been released its effects only wear off slowly, so that when you have had a fright your heart continues to palpitate for some time after the cause has disappeared.

The suprarenal cortex produces quite different substances. It was not until 1931 that Swingle and Pfiffner succeeded in preparing stable extracts of the cortical hormones which would maintain life in an animal deprived of the gland. Soon after that, crystalline substances were obtained in several laboratories and their chemical nature was worked out. They belong to a group of substances called steroids which have the same rather unusual hydrocarbon nucleus, which is the central structural feature of a number of apparently unrelated compounds (see Fig. 13, III, IV, V). It turns up in the bile-acids, in vitamin D, and in the sex hormones which are mentioned below.

At least six of these compounds have been isolated from the suprarenal cortex. Some of them seem to be concerned with the breakdown of carbohydrates and proteins. When given in excess they have an anti-insulin effect and cause a rise of blood sugar which amounts to temporary diabetes. Others are concerned in maintaining the balance of inorganic salts in the body — the preponderance of sodium and chloride in the fluids of the body and of potassium and phosphate in the cells.

The astonishing discovery has been made recently (1949), by Dr. Philip S. Hench of the Mayo Clinic, that one of the first group of substances, namely, cortisone or compound E

(Fig. 13, III), originally isolated by E. C. Kendall, has a spectacular curative effect on some types of rheumatoid arthritis. This discovery offers a method of relief to the great numbers of people who are crippled by this condition. Unfortunately the supply of cortisone from suprarenal glands is very small and the expense of treating only a few patients with gland extracts is enormous. The substance can be obtained synthetically from a bile-acid, after a long series of difficult chemical transformations, but the yield at present is extremely poor. It will require an enormous expenditure of effort to discover effective synthetic processes which will yield cortisone in quantities sufficient to supply the requirements. The development of a method of manufacture may be shortened by the discovery that an African vine, *Strophanthus sarmentosus*, yields a related substance which can be converted into cortisone in fewer steps than the bile-acid previously used as the starting-point.

We come now to the hormones secreted by the male and female sexual organs. They govern the sexual cycles and all the processes of reproduction. They also determine the secondary sexual characters. A hundred years ago Berthoud showed that the sex glands of a cock transplanted into a hen caused her to develop a cock's comb. The capon develops only a rudimentary comb, but the male sex hormone from any species, even in minute amounts, causes its full development. Males have been known to turn into females, and *vice versa*, when their sex glands are atrophied and injured. Maleness and femaleness is the result of a hormonal balance which is easily disturbed.

Similarly, extracts from the ovaries have a powerful effect in causing females to come on heat. A number of substances (oestrogens) have been isolated which produce this effect to a greater or lesser degree. They are, in general, very similar to each other — in fact the differences between the characteristic male and female hormones are minor ones (Fig. 13, IV, V).

Finding out how these compounds are related to each other is like solving a complicated jig-saw puzzle in which many of the pieces are missing. Quite a number of synthetic compounds which are not present in the living organism also act as oestrogens. Some are surprisingly simple — for example, the simple compound stilboestrol, which was discovered by Lawson and Dodds to be more active than the natural hormone. What common characteristics these molecules have has not been discovered.

The last source of hormones I shall mention is the pituitary gland — a complex gland situated in a bony hollow at the base of the skull. Its effects are so extensive that it has been called by Sir Walter Langdon-Brown "the conductor of the whole endocrine orchestra". It stimulates, and indeed is necessary for, the action of most of the other glands. If the anterior part of the gland is removed, the thyroid, the suprarenal cortex, the islets of Langerhans, and the glands of the ovaries and testes all atrophy. It controls growth, in that an excess of pituitary action causes gigantism, while a deficiency is dwarfing. A number of different hormones have been isolated having distinct actions in stimulating the various hormone-producing glands.

There is a hormone which stimulates the sex glands; another which stimulates milk production, and still others which control various phases of the sexual cycle and control growth. One of them stimulates the adrenal cortex to yield cortisone and this alleviates rheumatism. This pituitary substance is much too rare and costly for general use in relieving rheumatism — 400,000 pigs being required to yield 1 lb. of the hormone! Unlike most of the other hormones, these are proteins, but Prof. C. H. Li has found that in some of them the protein molecule is made up of smaller parts which possess the activity.

The chemical control of the body thus presents a very complicated picture and much remains to be learnt about it.

The ductless glands produce a wide variety of substances and their actions are far from simple. A single hormone may be concerned in a great variety of different processes, and the glands also interact with each other; the pituitary, as we have seen, acts as a stimulator of the others; in other cases the proper working of the body depends on a delicate balance of the working of the various glands.

Since they are often quite simple compounds, and are also, generally speaking, indifferent to species, the hormones seem to be relics of a primitive system of control. The thyroxine of the frog is the same as that of cows and human beings. The sex hormones of the fowl are much the same as those of the horse. Very little is known about how they work and what constituents of the body they act on. The only clue in this direction so far is the observations by Prof. and Mrs. Cori in St. Louis, that insulin and the secretion of the pituitary gland both affect the action of an enzyme, hexokinase, which is concerned with oxidizing sugar. They act on it in opposite directions, so that the functioning of hexokinase depends on a correct balance between the two. This is the first glimpse we have of a complex interplay of enzymes and hormones through which the bodily functions are regulated and controlled.

The discovery of these substances in animal glands had wide repercussions on the social behaviour of the time. It fitted in with the mood of the nineteen-twenties and -thirties, which were marked by a strong anti-intellectual movement, a reaction from the excessive rationalization of the Victorian age. The discovery that mere chemical substances produced such striking effects on human and other life, that diseases of the endocrine glands, causing disturbances in the production of these substances, might bring about great changes of personality, led to the widely held theory that a man was what he was because of his glands.

This idea was taken up by many writers who wanted to

discredit the intellect, seeing human beings as creatures forced on by inward necessities outside their conscious control. Aldous Huxley, for example, has pictured men and women as slaves of their bodily urges, an unfortunate degradation of the spirit to the body which he painted with contempt and derision. Perhaps the most influential of those who urged that men should follow the necessities of their nature, the promptings of the body, was D. H. Lawrence. Here is a passage in which he explains his attitude: "The body feels real hunger, real thirst, real joy in the sun or the snow, real pleasure in the smell of roses or the look of a lilac bush, real tenderness, real warmth, real passion, real hate, real grief. All the emotions belong to the body and are only recognized by the mind. We may hear of a sorrowful piece of news and only feel a mental excitement. Then, hours afterwards, perhaps in sleep, the awareness may reach the bodily centres and true grief wrings the heart."

This was not meant, of course, to be a scientific statement and should not be judged as one; but it represents in an extreme form a view that underlay much of the outlook of the time, which was really based on and fostered by the scientific discoveries which I have described.

The inference to be drawn was that the mind is unimportant, only the impact of the emotions on the body matters. But the correct conclusion from the facts is surely the opposite. No one will deny that the emotions have a strong influence on bodily health, but this surely means that the mind acts on and through the glands. After all, emotion is a mental affair. We hate a person because of our knowledge of him, and even if the hatred is based on fear, it is a consequence of mental concepts. Hatred, sorrow, joy are all mental reactions, and if our emotions upset our appetites or give us stomach ulcers or send up our blood-pressures, we should conclude that the mind, acting through the brain,

affects the various glands, setting up a train of events which influences the performance of the other parts of the body. It is probably true that the nature of a man's personality depends to some extent on his glandular balance. It is also true that diseases of the glands may cause great changes of personality. The workings of the body certainly affect the mind — as everyone who has had toothache knows. It does not follow from this that the body is supreme. The rider of a motor bicycle may have trouble in getting his machine up a hill — but we do not, on that account, think that it has a will of its own which controls the rider.

A truer picture is perhaps one which sees body and mind as dependent on each other. I shall discuss in later chapters the kind of control which the brain exerts on the body. Perhaps I might anticipate this discussion and say that it provides a solid basis for thinking of the brain as the dominant partner in determining behaviour. But although we may conclude that the brain is the master of the body, we must nevertheless not forget that it is a dependent mastership — dependent on the correct working of the delicate chemical machine through which it acts. This machine may have its own idiosyncrasies; it may go more easily some ways than others, and it easily gets out of adjustment.

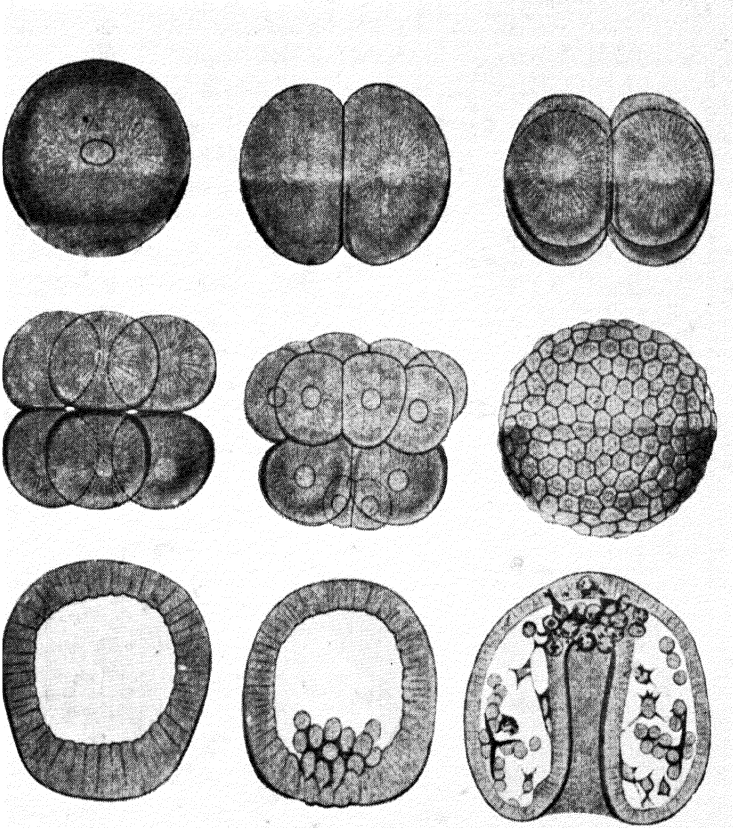
IX

DEVELOPMENT AND GROWTH

> Everyone has been impressed by the miraculous transformation of the sticky white and yellow mass of the hen's egg into a fully dressed, befeathered, respectable chick, all in 21 days. The original egg cell must have travelled at a dizzy pace to build up so complex a mechanism — probably exceeding in complexity the astronomical wonders with their galaxies and supergalaxies.—S. BRODY, *Bio-energetics and Growth.*

WE have been journeying through territory in which at least some of the more conspicuous landmarks have been discovered. Like in the early maps of the New World, there is a mountain here and there; one or two rivers leading into the interior; a rough outline of the extent of the region. There is much to be filled in; it is even possible that many of the really important features are still unknown, but at least we know in what direction to set sail in our future voyages of exploration.

The countries we are approaching are indeed *terra incognita.* They only exist as faint and distant smudges on the horizon. We can infer that they do exist. Just as Columbus concluded, from the knowledge that the world was round, that land could be reached by sailing to the West, so we must infer from the fact that plants and animals with high complex forms exist, the necessity of processes which control the development and growth of special organs; from the existence of the brain we must suppose that something goes on in its millions of cells when we look or think; but our knowledge of the nature of these events is almost negligible.



Reproduced from "Allgemeine Biologie: Eine Einfuhrung in die Lehre vom Leben", by Dr. Max Hartmann. Verlag Gustav Fischer, Jena, 1947

The miracle of growth. Early stages of the development of a sea-urchin from a single fertilized egg cell (from Boveri)

The first two rows show the successive subdivisions, which end up a round ball of cells called the blastula. The cells at the bottom then grow inwards and give rise to the inner parts of the animal. This is shown in cross-section in the last three pictures. In more complex animals like the frog the internal organs are all derived from a similar turning inwards of part of the original ball of cells

All the higher organisms go back to the single cell — the fertilized egg cell — at one stage of their life-cycle, and the complex individual arises from its subdivisions. About fifty successive divisions of the fertilized human ovum make a human being, with all the tissues of the human body, muscle, gut, liver, bone, and brain; all precisely fashioned and exactly knit together to make a functionary organism.

It is obvious that when cells in the growing embryo divide, they do not always give rise to two identical cells. There must be points at which *differentiation* occurs; the two cells formed from one cell will have different destinies; one will give rise to muscle; the other perhaps to nerve.

Embryologists are agreed that differentiation begins at the very earliest stages of the development of the fertilized egg cell. These stages can be seen under the microscope, and are well known. With an animal like the frog or sea-urchin, the fertilized ovum is darker at one end, and the first division occurs in such a way as to divide the pigmented parts equally between the two cells. The same thing happens in the next division into four cells, but these four cells then divide horizontally into eight, of which the lower four have most of the pigment and upper four little of it (Plate VIII).

Later the pigmented cells divide more rapidly than the unpigmented ones, and the result is a little ball of cells of which the upper part consists of larger unpigmented cells (yolk cells) and the lower part of small pigmented cells. The smaller cells continue to grow until they almost surround the larger yolk cells, which are now only visible at one point — the *yolk plug*.

The formation of the organs now begins. A small cavity at the edge of the yolk plug extends inwards and enlarges itself and eventually becomes the alimentary canal of the tadpole. A groove appears on the surface of the lip of the yolk plug, which develops into a tube and this is to become the spinal cord and brain. A belt of tissue is formed between

the yolk cells and the pigmented cells, which will form the muscular tissues, while another band under the roof of the embryo will be the basis of the skeleton.

These processes, the early stages of the development of a complex animal from a fertilized cell, can only excite our wonder and amazement, for we know very little about how this differentiation occurs and what controls it.

We can see how it might have begun. The first organism may have been a mass of cells, all of one kind, which perhaps found in proximity a certain amount of protection and the possibility of sharing some vital constituent. The next stage might well be a certain amount of differentiation — the outer cells perhaps developing a tough skin to provide a protecting wall for the colony. At a later stage there might be a certain amount of chemical differentiation; for example, some cells would have the specialized function of producing a particular enzyme — and later a primitive digestive tract might arise.

But a rough differentiation of this kind is only the beginning. The higher animals and plants are not just masses of cells of a number of kinds. They have form and structure of the most complex kind. They are in fact fantastically complex mechanisms, in which all the parts must work together with great precision.

How are we to explain the change of a tiny ball of cells into such a miracle? What makes the cells grow just so much in one region and no more? In a word, what is it that controls this extraordinary change of a few cells into a complex, intertwined, perfectly functioning structure? Can it be explained in terms of physics and chemistry?

We must admit our nearly complete ignorance, but there are a few pointers; gleams of light which can hardly be said to illuminate the landscape, but only to reveal one or two vague shadowy forms. It is known, for example, that in animals growth is in general controlled by substances

secreted by the pituitary gland, a small gland situated below the base of the brain. If this gland is removed, or does not function, the young animal is stunted. He can be made to grow by administering extracts from the gland of other animals; an excess produces gigantism.

But this only shows that the gland provides a substance which is necessary for the growth process; it does not explain differentiation, or the exact control of growth so that all the living parts grow equally.

Professor A. Haddow and his collaborators in the Chester Beatty Research Institute of the Royal Cancer Hospital have found that a substance called xanthopterin, which had previously been discovered in the pigment of butterflies' wings, has the curious property of causing the kidneys of rats and mice to become enlarged. When it is withheld, the kidney returns to its normal size. Since xanthopterin is a normal constituent of the kidney, it is possible that it is there as a growth regulator. This is the first example of a chemical substance which controls the growth of one organ. No doubt an intensive search will be made for others.

It has been suspected for some time that one of the vitamins, folic acid, is concerned in some way with growth processes. We saw in Chapter IV that a substance similar to a vitamin often has an antagonistic effect to it — because it simulates the behaviour of the vitamin up to a point, without being able to take its place completely. Following this line of thought, scientists in the Sloan-Kettering Institute for Cancer Research, in New York, prepared a series of compounds similar to folic acid, but with small differences. If folic acid were a growth vitamin, they thought that these might act as *anti-vitamins* and have an adverse effect on growth. It has been stated that they do have an adverse effect on the growth of tumours, but a final conclusion is still awaited.

It will be apparent that a small beginning has been made on the study of the chemical processes which regulate

growth, and no doubt these clues will be vigorously pursued by biochemists in the future. Out of such studies may eventually come methods of treating cancer. For in cancer the normal controls, which prevent the undue growth of parts of the organism, have broken down. Some tissues of the body begin to grow in a chaotic, undifferentiated fashion. If we can discover what are the controls in healthy tissue, which keep each organ in its proper size and shape, we should probably be able to deal with cancerous growths and thus control this scourge of humanity.

Some slight information on the factors controlling growth may also be yielded by the study of the phenomenon of regeneration; a power which is more widely possessed the lower one goes in the scale of life. The higher animals, like man, only possess it to a limited degree. If you cut your finger, the cells on either side of the cut begin to multiply and spread over the wound, reproducing the main superficial features in doing so. Animals lower in the scale of life have much more extensive powers. If a lizard loses its tail, it grows a new one; so can a fish. A starfish will reproduce a "ray" which is broken off; a worm will grow a new individual from a small segment. Plants can often grow a complete new individual from a small part of the plant tissues. It seems that the pattern of the whole individual is inherent in the parts; and if the pattern is broken it is reformed.

These are very difficult facts to account for. Why are the cells of a mutilated starfish stimulated to growth, and why does growth cease when it has just replaced the missing ray? It is only when the pattern is complete that growth ceases. We must ask in what way the pattern is carried by the organism. How do the cells of the growing "ray" know that growth is incomplete until a certain size and shape is reached?

Even more difficult to account for are the transforma-

tions of insects, etc., which pass through more than one form in their life-history. The larva which hatches out of the egg may be an entirely different creature from the finished insect — different in form, in habits, and in construction. Take a butterfly. It comes out of the egg as a gaily coloured caterpillar, which several times sheds its hard skin as it grows, and replaces it by a new one. When fully grown, the caterpillar winds itself into a cocoon and goes into a dormant state, in which its tissues melt away and are refashioned; and it ultimately emerges an entirely different creature, the finished butterfly.

The moulting stages and the final metamorphosis into the adult insect have been carefully studied by Dr. V. B. Wigglesworth in a blood-sucking bug, *Rhodnius prolixus*. This goes through five stages as a larva, with a moult between each, and then metamorphosis into the complete adult occurs. Between each moult it needs a single large meal of blood, and this starts off the train of events leading to the moulting, which takes place 12-15 days later. It has been shown that the moulting process is caused by a hormone, which is secreted into the blood by a gland situated in the brain.

It has also been found that the premature change into the adult is *prevented* by another hormone (the *juvenile* hormone) which is produced by the corpus allatum, a gland just behind the brain. If these glands are removed by chopping off the head of the larva at an appropriate interval after feeding, metamorphosis into the adult form takes place. On the other hand, if the head of a *young* larva is implanted into the 5th stage larva, which is on the point of turning into the adult insect, the metamorphosis is suppressed and a giant 6th stage larva is formed instead of an adult.

The ability of tissue to produce cells of differentiated types is greatest in the early stages and is gradually lost as the completed organism takes shape. In the early embryo

the future destiny of the cells seems to be largely undetermined. H. Spemann studied the early stages of the growth of newts before the stage known as gastrulation was reached. When they were cut in two, a whole embryo developed from each half. This possibility disappears very quickly, however, and it soon appears that each part possesses potentialities which not only cannot be altered, but will impress themselves on any other tissue implanted in them. " Transplant a young and indifferentiated cell group into the region of the head and it will form eye or brain; transplant it to the anterior trunk and it will form limb; or further back, kidney; and transplant it to the rear and it will form tail — the same cells forming different structures depending on their location. We may say: organizing factors take hold of the cells and direct them to appropriate functions." [1]

What are these " organizing factors " ? We hardly know anything about them. Indeed it is not surprising that many biologists see in the organism more than a mere collection of cells. The cells all fit in with each other. " Each cell develops in conformity with the character of its surroundings. . . . It becomes a cone or rod when in the retina, a cartilage cell when in the centre of the limb bud, a neurone when in the brain. Intrinsically capable of a variety of performances, the cell receives some definite cue from the locality indicating which trend it is to follow. These cues are decidedly of supra-cellular origin."

It is not surprising that some scientists have suggested a sort of continuous structure between the cells and uniting them. Some go further. Baitsell says: " The cell is essentially a protoplasmic crystal in which an almost infinite number of protein molecules, beginning with the genes in the chromosomes, are associated in a definite ultra-microscopic pattern characteristic of the particular type of cell. In such a condition . . . individual protein molecules are

[1] P. Weiss, *American Naturalist*, **24**, 43, 1946.

not present, but all are united to form the perfect unit, the complete crystalline pattern of a specific type of protoplasm, the terms molecule, crystal and cell becoming synonymous."

Dr. V. B. Wigglesworth is evidently thinking on similar lines when he writes: "What is the nature of this continuity that the cells are at such pains to restore? May we not regard it as a chemical organism? . . . On this view the difference in organization of unicellular and multicellular animals disappear. The latter, presumably for reasons of size, are subdivided into cellular units. . . . We may therefore picture the organism as a chemical continuum; a prodigious molecule, if the contradiction in terms may be allowed, with active centres requiring specific hormones to enable them to exert their activity. . . .

"The cells do not 'co-operate to mould the body form' they merely carry and care for a small segment of the continuum which is the organism and of which they are the servants." [1]

These are rather speculative ideas, and time and much labour will be needed before it is known how far they are justified. I quote them in order to indicate the kind of explanation to which biologists who have thought much about the difficult problems of form and growth are feeling their way. But I hope I have at least made it clear that very little is really known about what determines growth and differentiation, and on what principles the many cells of a large organism are united into a single whole. We must pass on to other topics; how life arose and how the necessity of co-ordinating muscles gave rise to brains and minds.

[1] *Essays on Growth and Form.*

X

HOW DID IT ALL BEGIN?

> Like some sublime fermenting-vat
> Heaving throughout its vast content
> With strenuously transmutive bent
> Though of its aim unsentient.
>
> THOMAS HARDY in *The Dynasts*

AT this point I must ask readers to look back for a moment, if they can, to the beginning of the story. We have travelled a long way from the simple chemical compounds of the chemist. Even the proteins, the first stepping-stones to life, have receded into the distance. Beyond them we have encountered larger aggregates like the nucleoproteins, represented by the virus particles and the hereditary material of chromosomes. At the higher levels of organization, in complete cells containing many proteins and in complex organisms with many cells, we scarcely did more than obtain a few glimpses of a fantastic degree of organization, the basis of which is for the most part still unknown.

All this must have originated and been elaborated on the earth. There must have been a time when the earth was too hot to harbour life of any kind. The igneous rocks, which underlie the present superficial strata, were all molten, and until they cooled no living thing and possibly no organic compounds, except the simplest, could exist. The stratified rocks which overlie them bear witness to the long history of life on the earth. Many of them, the chalks, corals, limestones, are themselves the actual products and remains of former life. There is no doubt that the geological record

shows a gradual increase in the complexity of living things. But the whole of the early part of the record is missing. Until life had developed parts enduring enough to last, or hard enough at least to leave some impressions in the mud, it left no sign. Three-fourths of the real journey towards a complex organism, probably all the crucial chemical elaborations which make complex organisms possible, had been travelled before we find any recognizable traces.

Scientists see in the ever-increasing complexity of organisms, as we follow up the course of evolution, a process which seems to be contrary to the tendencies which occur in inanimate Nature. The inanimate universe is, in fact, running down. We find everywhere in it a dissipation of energy. If we put a hot body and a cold body together, heat flows from the one to the other until they arrive at a common uniform temperature. In this process energy becomes less available for use; less free. Inequalities are continually being levelled down. The sun is pouring out its energy in heat and light, which except for the tiny fraction which falls on other astronomical bodies, is dissipated in the depths of space. The final result of all inanimate processes, so far as we can see, is a gradual decay to a dead level in which everything is at a uniform temperature, all inequalities are levelled out and nothing can happen any more. This tendency in Nature was recognised by Kelvin and formulated as the law of dissipation of energy. It is one of the foundation stones of nineteenth-century physics, and has been stated in many ways. As energy is always becoming less available or free, all natural processes result in a loss of free energy. Now free energy involves order or organization of one kind or another. The tendency of the world is from order to disorder. The energy of the universe was originally highly concentrated in a comparatively few bodies (like the sun). This is a state of high organization or order. Just as we have seen that heat always flows from

hotter to colder bodies, so the tendency is for energy in general to flow from the regions in which it is concentrated; to become dissipated or to lose its original highly organized condition. Mathematicians tell us that in such a process disorder, or mixed-up-ness, as it is sometimes called, is increased and they have invented a term which indicates the dissipation of energy, or the amount of mixed-up-ness in a system. It is called the *entropy*, and the general rule is that entropy is always increasing in the natural processes, which occur of their own accord in Nature.

The growth of an organism seems to be a direct contradiction of this law. It involves the elaboration of very complex structures; an increase in the complexity of matter involving a decrease in its entropy. The whole progress of life on this planet, leading to the evolution of ever more and more complex forms of life in the progress of time, seems in fact to be directly contrary to the laws of inanimate Nature.

Life seems to have found some way of evading the otherwise universal tendency to dissipation and decay. Are living things, as J. N. Lewis of Berkeley thought, " cheats in the game of entropy "? Have they found a way of circumventing the laws of inanimate nature? Kelvin, when he formulated the law of dissipation of energy, made a possible exception in favour of the operations of living things. But present-day scientific opinion, on the whole, favours the view that such an exception is unnecessary. The entropy law only requires that *on the whole* energy is dissipated and entropy increased. There can be a local decrease of entropy and increase in organization, if it is balanced by a greater amount of dissipation elsewhere.

If we look at the question more carefully, we see that life is not independent of the great processes and tendencies of Nature. All life depends directly on the great outflowing of energy from the sun, and if the sun's rays were cut off life could not maintain itself for long on this planet.

All life depends on the photosynthetic processes of green plants; that is, the elaboration of complex organic compounds under the influence of sunlight. Organisms which have no photosynthetic ability must feed on the products of those which have. In this photosynthetic process complex compounds with a high free energy are made, but there is no reason whatever for thinking that the free energy of the compounds formed in the green leaf is greater than the free energy absorbed from the sunshine; so there is no real contradiction to the law that energy is always becoming less free.

Animals must eat the compounds rich in free energy elaborated in plants, like the starches and sugars. These are really stores of energy. They are high-energy compounds, which the chemist finds difficult to produce. In fact, ordinary cane sugar has only been produced in the laboratory in the most minute quantities, if at all. If it were not for the fact that plants produce it in great profusion, so that it is an article of commerce which is bought and sold by the ton, it would be a great rarity, and perhaps unknown.

So we conclude that animals live on the store of free energy in such compounds, and we have no reason for thinking that the free energy of the complex animal organism is greater than that it receives in its food.

Living things thus seem to be able to divert, either directly or indirectly, some of the vast outflowing of free energy of the sun for their own use, and make use of it to build up their extraordinarily complex living structures. But when we enquire how these complex arrangements for making use of the flow of free energy came into existence, we encounter a much more difficult problem.

In fact, we do not know how these complex structures came to exist on the earth. We find it difficult to conceive of any natural process by which any structure even as comparatively simple as a protein molecule could be formed.

We cannot imagine the atoms of a protein molecule spontaneously coming together in the right order to form a protein. Calculations have been made of the probability or chance of this happening fortuitously. The result is a " chance " which is so small as to have no real meaning.[1]

Not only is this so, but even the simple organic compounds do not seem to be formed spontaneously on the earth at the present time in any circumstances of which we know. Wherever we find organic compounds, we discover when we investigate their origin that they are the products of present or past life.

In the face of these facts, some scientists have concluded that the almost inconceivably remote chance, in fact, came off once. The chance of an event happening may be extremely small, but that does not prohibit it entirely, nor does it decree when it shall happen. Life, they think, is the result of a very improbable coming together of atoms, which happened once and gave rise to the first self-perpetuating molecule, from which all life has developed by gradual modification.

Other scientists, like Arrhenius, have despaired of finding a reasonable origin of life in the time available on this earth and have suggested that the primordial speck of living matter arrived through space as a spore from another world, where perhaps a more ample time had prevailed. But this does not solve the problem of the origin of life; it merely translates it elsewhere. Fairly convincing evidence has been given by astronomers that the age of the whole visible universe is not so very different from that of our own solar system. There appear to be no regions in sight where a

[1] According to G. E. Guye, the *chance* of a protein being formed from atoms of carbon, hydrogen, nitrogen, oxygen, and sulphur spontaneously coming together is 100^{160}, and this would only be likely to happen once in 10^{243} years! (See Mottram, *Listener*, April 22, 1948.) The meaning and definition of these figures are very obscure, but at least they indicate that the spontaneous formation of proteins is extremely improbable.

more ample time, an earlier epoch, can be found. So there is no escape from the problem in this way. We must try to find the origin of life in the early days of our own earth.

There is, however, a possible way out of this dilemma. The conditions on the earth were not always what they are now. It is likely that the early times after the cooling of the earth's crust provided an environment much more favourable to the formation of complex organic compounds than that which exists now. This view has been cogently stated by the Russian scientist A. I. Oparin in a book on the *Origin of Life*, of which an English translation was published in 1938.[1] Oparin argues that in the early stages of the earth's history, the surface rocks contained considerable quantities of metallic carbides, which reacting with the water formed first methane and then more complex hydrocarbons. This would provide an *organic* environment, which would be much more favourable to the formation of complex compounds than that now available. There is evidence that hydrocarbons like methane are present in the atmospheres of other planets. Methane and ammonia have been detected in the atmosphere of Jupiter, and methane alone in the atmospheres of the colder planets, Uranus and Neptune.

Consider what may happen in such an environment exposed to the intense solar radiation. It is well known that when exposed to ultra-violet rays and to the action of the high-speed particles shot out by the sun, which may have been much more intense in the past, hydrocarbon molecules are broken into reactive fragments called radicals. These radicals are reactive not only because they are incomplete molecules, but also because they may have been *activated* by the action of the radiations into a state having a high energy. Under these conditions they can not only build up long-chain and branched-chain hydrocarbon molecules, but can also form compounds which need energy to make them. In

[1] The Macmillan Co., New York.

the presence of ammonia and some oxygen, a very great variety of organic compounds could arise in this way. Such conditions might have produced a very complex organic environment in which some self-perpetuating molecules were eventually formed.

The ways in which large molecules are formed are being studied in connection with synthetic plastics. These are large molecules in which one or more small units are made to combine repeatedly so that they give rise to long chains. The unit *A* is made to combine with itself to form the repeated unit, $A—A—A—A—$. To be able to do this the molecule *A* must be unsaturated, *i.e.*, it must have combining abilities which are unsatisfied, but not so markedly so that the simple molecule cannot exist by itself. The molecule *A* is a fairly stable structure, but when it is " softened " or " loosened up ", its unsaturated character becomes apparent and it joins up with others into the long chains. An example of this kind is the common compound $CH_2 : CH_2$ (ethylene) which can be made to combine into the long-chain rubbery *polyethylene* — $CH_2 — CH_2 — CH_2 — CH_2$. The " loosening up " of the parent molecule is brought about by ultra-violet light, intense radiations, active metal atoms and so on.

All these agencies may have been present in the original atmosphere of the earth, and if ethylene existed in it in large quantities, we should expect the formation of long chains to take place. This kind of " polymerization " may also occur with the amino-acids, and it is in fact easy to obtain the long amino-acid chains which, as we have seen, are the basis of the structural patterns of the proteins. When such a chain is formed from the amino-acids, water is eliminated at each junction where the acidic group combines with the basic group, and to bring this about, energy has to be supplied. If, however, the water is removed from the amino-acid in the first place, as can be done, the residues which are left (amino-acid anhydrides) can combine spontaneously

with each other and build up long chains such as occur in the proteins. Large artificial molecules have been made in this way recently by Woodward and Schramm. It is a long way from this to the exact and beautifully organized structures of the natural proteins, and we do not know how this tremendous gap could be bridged. If it is a reasonable theory that a surface layer rich in organic compounds was present in an early stage of the history of the earth, we must admit the possibility of very complex compounds being formed; and out of the myriad possible combinations, we may suppose that there occurred eventually simple self-reproducing systems; that is, those in which one molecule brings about the formation of more molecules like itself. We have no idea what this primitive self-reproducing system may have been like, or of the ways in which more complicated systems developed. Life itself seems to have destroyed entirely all the primitive environment in which it arose — unless perhaps some of the petroleum deposits are residues from this primitive stage.

There is one difficulty about the theory of the primitive complex organic environment. The most stable forms of carbon and hydrogen are the completely oxidized forms, in which all the carbon is oxidized to carbon dioxide and all the hydrogen to water. There is plenty of oxygen in the atmosphere of the present world to burn all the organic compounds completely. In fact, all the organic materials which now exist at the surface of the earth, except perhaps some petrol, are products of life and sunshine. It is difficult to see how a complex organic environment could arise in the presence of the enormous amount of oxygen which now exists in the atmosphere. It is not easy to find a way out of this difficulty, unless there was originally much more hydrogen, which has been lost because the gravitational pull of the earth was insufficient to hold it.

The only conclusion we can draw is that if the laboratory

in which life was originally fashioned was on the earth, as we must suppose, it was a very different earth from the present one. To find anything akin to it now, we should perhaps have to travel to the larger planets, which may be more like the primitive earth, or possibly make the much longer journey to the planets of distant stars. The scientist contemplating these facts is painfully aware of his limitations in time and in space.

XI

MUSCLE AND BRAIN

> Can material things, oxygen, hydrogen, carbon, water, lead, stone, electrons or protons, or any combinations of such things become conscious of themselves? Can the stream rise above its source or the result outsoar its cause? Can carbon recognize itself as carbon, or say 'Ah, here is hydrogen'? — W. McNeile Dixon in *The Human Situation.*

No account of life would be complete without attempting to assess the place in it of nerves and brain, but before we come to them, it is necessary briefly to consider muscles. Nerves and brains seem to have appeared originally as appendages of muscle. Indeed, plants and trees, the stationary forms of life, which have no muscles, have not developed nerves or brains at all.

In muscular tissue, animals have developed a type of protein which is capable of undergoing contractions, and in doing so, of exerting a considerable "pull".

How this happens is still far from clear, notwithstanding the efforts of numerous biochemists and physiologists, over a long period. It has been suggested by some that the muscle proteins exist in two forms; the first, a long, extended form in which the amino-acids of the proteins are arranged in long straight chains, and the second, one in which they are bent into a shorter zigzag or spring-like shape. Whatever the details may be, there is no doubt that something like this must happen when a muscle contracts. It is like a lazy tongs which can be extended or contracted; but whereas lazy tongs have to be worked by an outside source

of power, the muscles contain their motive force within themselves. They are, in fact, not only engines for performing work, but they contain their own power station, in which fuel is taken from the blood and burnt.

It is known that they contain enzymes and other substances by means of which sugar is burnt by a very complex series of reactions. There can be no doubt that the energy which is obtained from the burning of the sugar provides the motive power of the muscle, but exactly how the energy-providing reactions are coupled to the mechanical process, is not known. Whatever the arrangement is, it is a very efficient one, as about 40 per cent of the available energy of the fuel may be converted into muscular work. Perhaps in the early stages of life, the muscular proteins were only capable of producing simple contractions of the cell walls which gave a limited power of movement. But the larger animals have, in their muscles, arrangements both for producing movements of the internal organs, such as propel food through the alimentary canal or force blood through the blood-vessels, and also for moving parts of the body in relation to each other. It is obvious that, in order to produce a coherent result, the muscles have to be under a strict control, and their existence requires a controlling mechanism.

In the higher animals this requirement has been met by the development of nerves. Some of the cells in the organism develop long thread-like filaments, which are used to transmit messages from one part of the organism to another.

The messages usually originate in the senses, for an animal needs senses to give it information about its surroundings. The simplest arrangement is a nerve cell, or neurone, which has one or more extensions leading to a muscle and others leading to the sensory area. Messages originating in the latter can then be transmitted direct to the muscle. More commonly some nerve cells have nerves leading to muscles and others have nerves going to sense organs, and

the nerve cells are connected with each other either directly or through others, by short nerve-like extensions which meet at what are called synapses.

We shall see later that many animals have developed a complicated mass of neurones — a brain — to co-ordinate and sift the many and diverse messages they get from their senses, and to ensure that the muscular action resulting from them is reasonably coherent and directed to a single purpose. Before we begin to consider what goes on in a brain and how this result is achieved, we must think for a moment about what happens in simple nerves.

It has been found that what passes down a nerve is an electrical impulse. This is true both of the sensory nerves, which carry the messages originating in the sense organ, and of the nerves which stimulate the muscles. This has been shown by delicate electrical instruments which can pick up these impulses. Neurologists can insert tiny probes into a bundle of nerves, like an electrician testing electrical circuits, and detect the passage of these electrical impulses. They can also stimulate nerves by electric discharges. In a nerve leading to a muscle, electric stimulation causes the muscle to contract; in a nerve leading from a sense organ, stimulation produces a sense impression; for example, stimulating an optic nerve produces the impression of a flash of light.

We do not know exactly how this electrical message stimulates the muscle to contract. It was found by Sir Henry Dale that when the electrical impulses arrive at the nerve endings, adjacent to the muscles, a substance called *acetylcholine* is liberated, and it appears to be this substance which sets the muscle machinery in action. Acetylcholine is an almost ubiquitous substance in living things. Enzymes able to synthesize it, and to destroy it, were in existence long before nerves or even muscles were developed. Some bacteria, even, are effective synthesizers of acetylcholine, and it is also present in the primitive unicellular organisms like

protozoa. Hence animals, in developing the nervous control of muscles, did not have to elaborate entirely new substances. They have made use of substances which were already present and produced by cells — another example of the unity of life and the adaptability of the chemical systems developed in its primitive form.

When a doctor strikes your knee, he judges from the vigorous kick of your leg that your " reflexes " are in order. When a bright light shines into your eye, the iris immediately and involuntarily contracts. If I push a needle into your hand, you automatically pull it away. These are examples of the simplest types of nervous action — reflex action. The messages from the senses produce immediate muscular action ; the impulses from the sensory nerves pass straight into the " motor " nerves which control the muscles.

But highly organized animals could not live like this. For one thing, the sense impressions they receive are many and varied. Some will suggest one type of response, some another. In order to produce a coherent pattern of behaviour, they must be sifted and sorted, and for this purpose many animals, as I said before, have a very complex organ, the brain, into which come all the messages from the sensory nerves and are there sorted out and rearranged, and a consistent set of stimuli is dispatched to the muscles.

Before we can understand the kind of work done in the brain, we must get an impression of the complexity of the messages which it receives from the senses. Sensitiveness to the environment is probably a fundamental property of living protoplasm. The most primitive kinds of life respond in some degree to heat, cold, light, and to chemical substances. Out of these primitive responses, living things have developed during the ages the most astonishing sense organs. In a world in which the competition for food was severe, the possession of even slightly more effective senses must have had great survival value, and it is not surprising that

the struggle for existence has produced an almost continuous improvement until the beautiful arrangements possessed by the higher animals at the present time were elaborated.

The human eye, for example, is a most fantastic example of fitness and efficiency. It is incredibly complicated. The retina of each eye contains about 120 million sensitive elements in the form of rods and about 6 million cones. About a million nerve fibres take their responses to the brain. It is obvious that many of the sensitive elements must share a single nerve fibre.

The purpose of this arrangement is to provide both night and day vision. The rods are extremely sensitive and provide for night vision. A large number of rods share a single nerve fibre. The nerve fibre thus has a large number of sensitive terminations spread out on the retina to catch every trace of light. On the other hand, some of the cones have an optic nerve to themselves and others share an optic nerve in groups of two or three. They provide an extremely discriminating kind of vision; the image transmitted by the nerves, if the eye is focused properly, is extremely sharp. They also respond differently to colours.

Thus we see that the optic nerves are extensions of brain cells, which are provided with endings sensitive to various kinds and intensities of light. When light falls upon them, they are stimulated and give rise to electrical impulses which begin to pass along the optic nerves to the brain. When the eye is steadily illuminated, a continuous series of electrical impulses pass along the fibre, each impulse taking about a thousandth of a second to pass one point.

A nerve fibre is unable to modify the amount of its response, but it can respond more frequently. All the separate impulses which pass down the fibre are the same, but if the nerve ending is stimulated to a greater degree, they follow each other more rapidly. Thus a steady light of a certain intensity produces 8 impulses every second; while a

tenfold greater illumination produces 25 impulses in every second. The nerve impulses travel at quite moderate speeds, ranging from a fraction of a metre per second in small fibres, to 120 metres per second in large ones.

I have described the mechanism of a single sense or organ, the human eye — perhaps the most complex and delicate of all — in order to show what kind of information the brain gets from its senses. The brain has to construct its picture from electrical impulses arriving along the million optic nerves. These impulses are nothing like the light which stimulated them — they are merely electrical disturbances which follow each other along the nerves, sometimes slowly, sometimes in rapid succession.

These messages arrive along millions of separate nerve fibres. It is the duty of the brain to co-ordinate them all, to reduce them to order, to attend to those which are important and ignore the rest, to see that the outcome is at least a self-consistent action.

Our knowledge of what goes on in the brain is extremely meagre. We have, in human beings, a great mass of nerve cells — some ten thousand millions of them — with a great many extensions connecting one to another. There are no doubt innumerable pathways by which impulses may pass between the nerve cells. There is certainly a great deal of electrical activity going on. When electrodes are placed on the skull, sensitive electrical instruments can detect the electrical oscillations going on within (Fig. 14). We can detect a surge of electric waves, going on almost ceaselessly, making, in normal objects, a rather irregular pattern in its ebb and flow. We hardly know anything about how this is connected with the mental activity of the brain. We are like strangers outside a great power station. We hear faintly the hum of the activity going on inside, but we do not know what it means. We do know that the hum is louder when we are awake and giving attention, and it falls

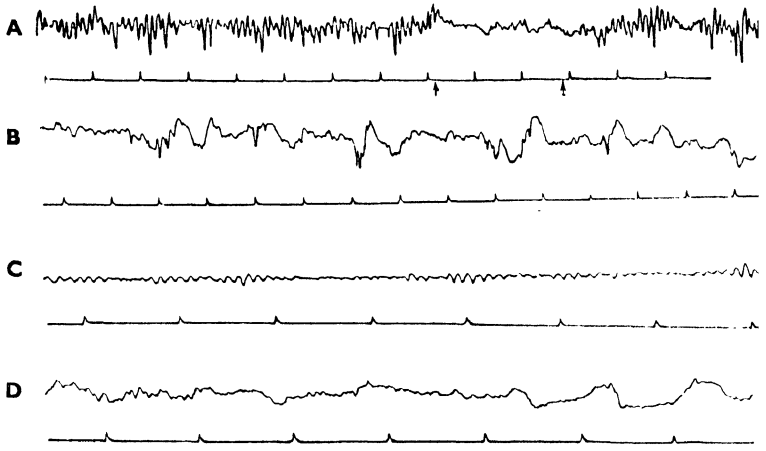


FIG. 14.—Electrical oscillations in the brain, recorded through the skulls of human beings (the regular marks below the tracings are time signals at 1 second intervals)

A. A normal subject. The eyes were closed between the two arrows on the time line
B. A subject who has had a brain injury. The sharp downward spikes are very characteristic of certain brain injuries
C. A normal subject. (The oscillations are less magnified vertically than in A)
D. The same subject as C, in sleep induced by a drug
(Reproduced by courtesy of Mr. W. F. Floyd of the Middlesex Hospital Medical School)

away to a long, slow rhythm when we sleep. By careful exploration inside and outside the skulls, especially of animals, we can find out what parts of the brain receive the messages of the different senses. We find, for example, when we track the picture seen by the eye into the brain, that the messages from the image on the retina are spread out over a great area of the brain. The picture is enormously magnified and it seems that millions of brain cells may be concerned with the vision of one moment.

We cannot say what goes on in these cells, what is the equivalent in the brain of the sensations we are aware of; but there are some features of the functioning of the brain to which we may call attention. The brain of human beings at least, and probably of the higher animals also, is primarily

an instrument for co-ordinating a large number of separate impressions. The *pattern* of the impressions means much more than the separate elements from which it is constructed.

When we look at a half-tone picture in a newspaper, we no doubt see the separate dots, but we are only interested in the pattern of light and shade which they make. The brain has pre-eminently a remarkable power of finding the pattern in millions of diverse sense impressions and there must be something basic and inherent in its structure which permits it to do this. If it is more concerned with the pattern of the diverse sense impressions than with the details of the individual impressions, it must follow that the inter-relations between the brain cells which receive the impressions are more important than the actual impression made on each one.

If we look at a square, it is the fact that it is a particular kind of geometrical figure that we seize upon. We are indifferent to its size. The actual size of the image on our retina depends on our distance from the object. The projection of the square in our brain thus depends on our distance from it — yet we have no difficulty in recognizing it as the same square. It is clear that in interpreting very simple experiences, the brain has to make very complicated adjustments.

It must do more, however, than co-ordinate the sense impressions of the moment. It must provide for recognition. It is useless to look at a tree unless you recognize it as a tree. An animal must find his way back home by recognizing the familiar landmarks. Recognition implies memory of things seen previously and a comparison of present and past experiences. Without memory few of the higher animals, at any rate, could live their lives.

The brain, therefore, not only co-ordinates a multitude of sense impressions; it makes a permanent record of many of them. It is perhaps a fundamental and primitive characteristic of living matter, that it is changed irreversibly by

whatever happens to it, so that all living things probably carry in them some sort of a record of everything which has happened to them — a consequence of their extremely sensitive state of equilibrium.

The brain record is perhaps a highly efficient adaptation of this primitive responsiveness. The impressions received from the senses leave in some way a permanent mark. We know little about the physical nature of this mark, but since we have this large specialized organ we are justified in thinking that some physical basis of memory exists among its millions of cells — and that among the million or so molecules in each of these cells, some are permanently altered when a message from the senses is received.

But the memory record, if it is to be of any use, must have one characteristic. It must be available for inspection. It is no use having a gramophone record unless we can play it. So our memory impressions are useless unless they can at least be used for recognition. Exactly how recognition occurs is not at all clear. Perhaps our sense impressions circulate among the cells until they find something, with which they correspond — holes into which they just fit, or resonating patterns which they match.

We do know that our more vivid experiences can be remembered — the memory record perhaps gives off fainter signals, resembling the original messages from the senses — a kind of emanation or echo. As everyone knows, even when we cannot recall from our memory a place which we once visited, yet if we go there again, we remember it perfectly. The record is still in our minds, but the signals it gives out have become too faint to rise to the level of conscious memory unless they are renewed.

This brings us to another and important feature of the ability of our brains. The memory record is not a static thing. It is not even like a picture which we are painting and gradually filling in with fresh details. It is more like a

message on a long tape, on which fresh signals are arriving all the time. But it has also this vital difference from an ordinary record. The messages as they arrive are co-ordinated with previous parts of the record. We recognize this or that. In other words, we compare our immediate sense impressions with our past ones. Our awareness at this moment must include not only the messages which are momentarily reaching us from the senses, but also the echoes of our previous experiences arising from the memory.

It is this combination of sense impressions with memories of the past, the fact that our immediate experience is a combination of the sense images of the moment with the emanations of the memory record, which gives our mental life its peculiar property of regression. The picture of the world which I make at the moment includes to some extent all the previous pictures and contains myself as well as other things. A new I is always emerging which includes in some degree all the previous I's.

The cumulative character of experience — the combination of immediate sense impressions with the records of past experiences — seems to be a fundamental ability of the brain of men and perhaps to a slighter extent of the higher animals. The relative importance of the contribution of the senses and that coming from the memory may vary greatly. But something of this kind seems a necessity where behaviour is to be determined both by present and past experiences. If the animal is to deal with his complex environment successfully, he must make a picture of it and the picture must include elements of both the immediately present sensations and the past experience. Only thus could it assemble the multifarious sense impressions into a manageable form — a form which can embody past experience and have a consistent outcome in action.

We therefore see that the brain must not only receive and, to some extent, record the sense impressions. It must

produce from them a consistent picture — representing not only the environment but the animal's own relation to it — a picture on which action can be based. Such a picture necessarily involves distinguishing and abstracting the important elements from the whole mass of sense data. The animal's survival will often depend on the accuracy with which it does this.

If this account of how the brain deals with the sense impressions is on right lines, it must determine our views on how actions originate, which will be discussed in the next chapter. I need only preface it here by saying that it is important not to simplify the problem too much, by isolating very simple mental phenomena.

Philosophers have often done this. They try to describe what happens when we see, for example, a table. " When I am said to see ' a table ',' says Bertrand Russell, " what really happens is that I have a complex sensation, which is, in certain respects, similar in structure to the physical table. The physical table, consisting of electrons, positrons and neutrons, is inferred and so is the space in which it is located." [1]

This is quite true and I do not wish to suggest that it is not a useful exercise to look at a table philosophically and consider what is implied, but it is not representative of the common and usual operations of the brain. We do not *merely* look at a table; our experience is always much more complex and it includes the setting of the table and its history. The table takes its place in our mental picture of the room, so that we can walk round it without bumping into it. Our picture of the table may also contain its past history and associations. It will mean quite different things to a stranger and to a man who has sat at it for years and perhaps has known it all his life.

The brain is an organ which has to deal with the great

[1] Bertrand Russell, *Human Knowledge*, p. 237.

complexity of matters which affect animal life. It is in essence complex. Scientists can only approach the problem of how it works little by little. Experiments may give a bit of information here and another bit there, and perhaps after many years it will be possible to build these bits of knowledge into a coherent whole. At present we have very little knowledge of what goes on in the millions of brain cells, what is the physical basis of memory, how sense impressions are co-ordinated.

XII

ACTION AND FREE WILL

> The quivering electricity of attraction and repulsion quickening the wanton atoms into images of thought and feeling, is ignorant of what it is at. In the making of crystal and snow-flake, of mouse and man, it works by rote, by fixed inexplicable laws in the charmed circle of an amphisbaena.— LLEWELLYN POWYS in *Swiss Essays*.

THE full story of the brain is still far from told, even in this superficial account of what it does. The animal has senses which tell it something of the outside world. In the last chapter we tried to formulate some of the problems it encounters in dealing with this information, but we have still to consider how it makes use of it; how its actions are determined. Is the action completely determined by the data brought by the senses, or has it freedom of choice between alternative actions — any free will? We must ask these questions because, without them we leave out, what are, to us, the most vital aspects of life, even if the answers which can be given are fragmentary and unsatisfying.

The information obtained from the senses is, as we have seen, so complex that in many situations its outcome in action could not be determined in any simple way. There are, however, some actions of the brain which are comparatively simple, such as the simple reflex actions already mentioned, in which a stimulus produces an immediate automatic response. Again, those which control automatic muscular rhythms, like the beating of the heart, are not subject to conscious control and are not linked directly with

the senses. Others, like breathing, are semi-automatic. They normally look after themselves, but we can interfere with them if we want to. Some actions, such as walking, usually require very little attention from us, but are under general conscious control, when it becomes necessary.

There must obviously be several types or degrees of control of muscular action, extending from the automatic controls which function below the level of consciousness, to the fully conscious behaviour of an individual performing a difficult task.

Something is known of the ways by which the automatic actions are controlled. The muscles themselves are provided with sensory nerves which send out messages indicating their state of contraction. This was discovered by Sir Charles Bell, as long ago as 1826. In his famous paper to the Royal Society, he said:

"We are sensible of the most minute changes of muscular exertion, by which we know the position of the body and limbs, when there is no other means of knowledge open to us. If a rope-dancer measures her steps by the eye, yet on the other hand a blind man can balance his body. In standing, walking and running, every effort of the voluntary power, which gives motion to the body, is directed by a sense of the condition of the muscles and without this sense they could not regulate their actions."

He showed that for this purpose muscles are provided with sensory nerves, which send out messages indicating their state of contraction. These nerves also go to nerve cells in the brain so that: "between the brain and the muscles there is a circle of nerves; one nerve conveys the influence from the brain to the muscle, another gives the sense of the condition of the muscle to the brain".

This method of control is quite common in machines, which often have governors or controllers, arranged so that the state of the machine controls its action. A good example

is the governor on a steam engine, which opens a valve and releases the pressure when the speed reaches a critical point. The flow of water through a pipe can be kept constant by letting the outflowing water work a valve in such a way that, if the outflow is greater than the amount it is set for, the valve is closed a little.

The sensory nerves of the muscles control the " motor " impulses in the same way. Both nerves may meet in a single nerve cell, where the impulses arriving along the sensory nerve control the impulses going into the motor nerve and so decide if the muscle shall be more or less stimulated. If the sensory nerve is cut, the muscle is as completely paralysed as if the motor nerve were cut. It is easy to see how on this plan a muscle is kept in a constant state of tension or going through a rhythmic cycle of tension and release. The general principle is that known in machines as " feed-back ", *i.e.* some of the output is used to control the input.

The nerve cells which control the automatic actions of the brain are in the spinal cord or in the lower brain or cerebrum, while conscious control involves the higher brain, a great mass of cortical tissue in which, in man, the cerebrum is embodied. This is a great membrane, extensively folded and convoluted about a hundred nerve cells or *neurones* deep and containing in all perhaps 10,000,000,000 of them. Here are established the connections between the sense impressions and memory images on the one hand, and the muscular actions which emerge from them.

It is obvious that these connections are frequently of a most complicated kind. Sense impressions frequently do not emerge into immediate action. A cat sees a mouse. He does not pounce immediately. He watches and waits. His past experiences tell him to be cautious, to wait, to look around and not to expose himself. His eventual action is determined by the merging of his past experience with his present sensations. When the action does take place, an

enormous burst of muscular energy is released. Hundreds of muscles come into simultaneous action, all in precise and beautiful co-ordination, in the sudden and effective " pounce ". In bringing this about the brain has been exercising its primary function and we must ask how it is done.

If the cat's decision to act is guided by his previous experiences, by what he remembers about similar situations and their results, his action is determined by what he has *learnt* to do with his muscles. He has, in fact, *learnt* to use and co-ordinate his muscles by playing with objects as a kitten. At first the movements are aimless, and uncoordinated. The kitten, like the baby, discovers that some movements produce satisfying results and he tries to repeat them. Only after many trials and experiments is he able to perform the highly complex and co-ordinated movements, which a difficult situation requires.

We see, therefore, that muscular co-ordination is something which has to be learnt. Actions are determined not only by the data of the senses, combined with recollections of previous situations, but also by what actions have been learnt. We and the higher animals learn, often slowly and with difficulty, how to perform the complex actions which produce satisfactory results. When performed a number of times, an action, or a complicated series of actions, becomes much easier and may, in time, become almost automatic.

The process of learning has been much studied in animals, and it would take too much space to describe what has been found out except in the broadest terms. Pavlov discovered what he called the " conditioned reflex ". If a hungry dog is shown food, its mouth begins to water. This is a simple reflex action, the sight of food producing an involuntary response. If a bell is rung when the food is shown, the animal will associate the sound of the bell with food; and the sound of the bell alone will, for a time, cause his mouth to water. That is a conditioned reflex. Paths of action have

been established in the brain between the neurones receiving the messages from the ear and the normal responses to the sight of food. The animal will learn to follow up such stimuli with appropriate actions.

An individual may have established in his brain a great many of such conditioned responses — patterns in the brain which represent acts which he can perform and which an appropriate stimulus tends to bring out. Dr. J. B. Watson and the behaviourist school of psychology see in all behaviour the responses to environmental influences. The responses may be direct, like the knee jerk, or modified by recollections of previous situations (delayed responses) or " conditioned " by circumstances only indirectly connected with them. Behaviourists see all actions as responses, direct or indirect, to the action of the environment.

Before we discuss this any further, there is one other faculty of the brain, which is possessed by human beings as well as, at any rate, the higher animals, which we must consider, namely, its power of making predictions of the outcome of its actions. If an action is to be successful, it must be based on some sort of an estimate or forecast of its results. A man who is throwing a cricket ball has a clear idea of the result of his action, and his ability as a bowler is dependent on the success of his predictions. His muscular actions are based on an unconscious calculation of their results. In the cat pouncing on a mouse, the whole complex matrix of muscular action which is brought into play, is planned as a coherent whole, with reference to the result.

A way in which this is brought about in the brain has been suggested by Craik. He thought that the brain organizes muscular actions by making models of external things. These models are, of course, nothing like the objects they represent — they are reproductions of the outside world in terms of the electrical vibrations and impulses which constitute our sense impressions. Having made such

models, the brain can " try out " the results of possible actions and select the one which, by past experience, seems likely to yield the best results. He says: " If the organism carries a ' small scale ' model of external reality and of its own possible actions within its head, it is able to try out various alternatives, conclude which is the best of them, react to future situations before they arise, utilize the knowledge of past events in dealing with the present and future and in every way react in a much fuller, safer and more competent manner to the emergencies which face it ".[1]

It does not follow, however, that all behaviour is necessarily directed to a definite purpose. It must be recognized that there is also something spontaneous and undirected in the animal's approach to its environment. There is an element of caprice and chance, which may perhaps be a relic of the playfulness of the young animal. The kitten uses its muscles in a frankly experimental way. The movements are at first spontaneous and without purpose, and only gradually does it learn to co-ordinate them to produce purposive actions. There remains in the adult animal an element of play, or adventure — call it what you will — which is, in fact, necessary if the animal is to have any initiative.

This spontaneous element in behaviour is very deeply rooted in Nature. It existed before the development of brains and nerves. The amoeba pushes out its pseudopodia in an apparently aimless way; its protoplasm flows first one way then another without apparent rhyme or reason. The paramecium oscillates endlessly in the water in its search for food. Such movements are perhaps a consequence or reflection of the Brownian movements of small particles, as they are buffeted about by the ceaseless and chaotic thermal motions of matter.

It is a long way from this to even the most irregular

[1] K. J. W. Craik, *The Nature of Explanation*, Camb. Univ. Press.

movements of an animal; but it seems a reasonable inference that undirected movements come first and have to be gradually reduced to order. The animal does not so much have to *initiate* movement as to impose control and order, on the aimless movements of its limbs. This control may be as much negative as positive. On the one hand it must eliminate or inhibit movements which lead to danger. On the other, it must co-ordinate many incoherent movements into purposeful actions. Craik's suggestion gives us a possible method of how this is done. It is a method of finding solutions, by trial and error, to the problems set by the senses. In solving such problems the brain acts as a kind of super-calculating machine. This kind of control *narrows* the movements to those which satisfy, or seem to satisfy, the needs of the situation. The more successful the degree of control which is achieved, the less is the margin within which chance, randomness and initiative can operate. An animal which can perform actions which are perfectly adapted to a certain end may be unable to cope with the changed conditions. Thus, the animals which have survived the changes produced by human life are those which were adaptable enough to live and prosper under changed conditions. The sparrow survives, but the fen buzzard is as good as lost.

We see then that although the animal must have the ability to solve its problems by calculation, an element of spontaneity should be left to give it initiative. Without initiative is it likely that the swallows would build their nests under the eaves of houses? Even random impulses are often useful, but the balance between initiative and routine is a very delicate one. Too much initiative may be as destructive as too little. The animal is often poised on a razor-edge between the perils of deviating too much from its way of life and too little.

Here we reach the crucial questions about the nature of life. Does the animal have any free will or effective choice

in its actions? Are they completely determined by the various influences acting on it? Looking at living things from one point of view, we see mechanism, calculation, and determinism; from the other we see adventure, spontaneity, and free will. Is it possible to reconcile the one with the other? We can hardly doubt that mechanism and calculation of a most beautiful and effective kind exists. Does it leave any room for spontaneity and free will?

Even if our picture of how actions are initiated is inadequate and possibly in many ways inaccurate, it will be obvious that they are the outcome of very complex processes. There is often no simple connection between the sense impressions and the acts which follow them. But this does not dispose of the question of choice and free will. A machine is still a machine even if it acts through numerous cogs and circuits. What it turns out is determined by what is put in, no matter how complex the intermediate steps may be. Is there any reason for believing the brain to be any different — that its resulting actions are not really the product of the many influences acting on it, both immediate and delayed?

Our brains are made up of atoms and molecules. The sensations we receive become electrical disturbances among them; our memory records are impressions of a molecular nature which are stored away somewhere in the nerve cells, our " thoughts " must have some physical basis in electrical impulses passing through innumerable circuits of the brain. If we knew enough about these complicated patterns of molecular architecture in which these effects take place, could we account for everything that goes on in our brains in terms of the ordinary laws of physics?

Let us first examine the nature of these laws. In the older physics of the eighteenth and nineteenth centuries, every particle of matter moved according to the laws of motion, which were finally formulated by Newton. Knowing the position and velocity of a particle at any one time

and the forces acting on it, one could determine its velocity and position at any future time. The same is true of any collection of particles, provided one knows the nature of the forces between them. The mathematical difficulties might be insuperable, but a superhuman calculator, as Laplace pointed out, could determine from a known starting-point the state of the universe at any future time.

The chain of causation seemed to be complete. There seemed to be no place in it at which an individual could exercise will-power; at which purely mental events could influence the movements of particles of matter.

The work of twentieth-century scientists has shown that this rigid determinism must be modified in two ways.

In the first place it is recognized that rigid deterministic mechanics do not apply to atoms. Modern physics is content to describe the movements of particles in terms of probabilities. It cannot say exactly where every particle is at a given instant; its calculations only aim at predicting, with a high probability, that a certain proportion of the particles will be found within a certain region at a given time.

Secondly, it will be clear, I think, that we must take into account the great complexity of the events in the brain which precede any action. It might be argued that complexity does not essentially change the nature of the problem. But, in fact, what happens is not a chain of events set in motion by something in the environment and resulting in some movement of the body, but the action of the environment on a most complex organ, which is not in a static condition, but is already a scene of continual flux and change. The brain is at all times the laboratory of all the complicated chemistry of life; its component molecules are continually breaking down and being repaired, electrical disturbances are throbbing to and fro in it; many of the experiences of the past have left impressions which can evoke faint images of previous sensations. The new experience

enters the scene of all this activity and is absorbed and made to cohere with it. Out of the amalgam comes the decision — a particular action.

In these circumstances, has the animal really made a choice? Is not its action really pre-determined, even if modified by the experiences of the past? Is it not really an inevitable consequence of the influences, past and present, which are acting on it? The answer would seem to be that if an action is determined not only by the immediate sensations, by what the animal sees, hears, and feels, but also by its past experience and what it has learnt throughout its life, there may be an element of uncertainty. If the action is brought about by a process involving past experiences, which are combined in various ways by trial and error, we may expect that the action which emerges will not always be the same, *i.e.* will not be completely pre-determined.

We can therefore allow an animal some " choice " in its actions. The effectiveness of the choice will, in fact, depend on its ability in distinguishing the various possibilities and on the amount of past experience and what it has learnt from life. If the animal's experience and learning are very limited, its powers of choice will obviously be limited too. If its patterns of behaviour are largely inherited, as with insects, and not coupled with the sensations at every step, the amount of choice may be meagre. In other words, the action is determined not only by old experiences acting in a delayed way, but by *what has happened to them* in the animal's brain: what it has learnt from them, how far it has succeeded in combining them — in putting two and two together; in other words, by the manner in which it has co-ordinated its experiences — the general structure of its mind.

The simple cause and effect of the physical world are not very relevant to this complex world of the brain, where there is at all times ceaseless activity, where images of the past are continually rising and merging with present sensa-

tions, and out of the amalgam possible actions are continually being planned and their effects predicted. Some of these possibilities may rise almost spontaneously from the past, with very little reference to the immediate situation.

The brain, trying out possible actions, selects the one which seems to fit the situation best; or, to put it in another way, finds one which is not inhibited because of unfortunate consequences foreseen or because it conflicts with the principles of action which the animal has learnt; in a word, which conforms with his whole mental structure — his character. It may well be that at this level, where the past, present and forecasts of the future meet, all that happens in the making of a choice, in the initiation of action, is that that plan of action which has passed the various criteria which are applied to it — passes directly on into action. The model of the action, the paths through which the muscular stimuli must pass, already exist.

On this view it is clearly impossible to say exactly at what point an action originates. There is no clear-cut " decision ". The action emerges from the whole of the animal's experience, from what we have called its " mind ". What is the nature of this mind? It is clearly based on something which has occurred in the brain — a compound of sensation, memory, recollection, trial. As a manifestation we have the ceaseless ebb and flow of electric impulses which appear to accompany these phenomena. Is consciousness just this or something more? Is the objective mind, that is, the sum of animal's experiences, the same as the subjective mind which is *aware* of at least some of them? Perhaps the distinction is illusory. Mind and matter may indeed be, in Llewellyn Powys's phrase, an amphisbaena — a two-headed serpent — the two sides of one medallion. Mind may be something inherent in simple matter, but which only rises to effective action in these fantastically complicated knots of matter we call brains.

XIII

SPEECH AND THOUGHT

My words
Echo thus, in your mind.

T. S. ELIOT

Our reverence for the nobility of manhood will not be lessened by the knowledge that Man is, in substance and in structure, one with the brutes; for he alone possesses the marvellous endowment of intelligible and rational speech, whereby in the secular period of his existence, he has slowly accumulated and organized the experience which is almost wholly lost with the cessation of individual life in other animals; so that he now stands raised upon it as on a mountain top, far above the level of his humble fellows and transfigured from his grosser nature by reflecting here and there a ray from the infinite source of truth.—T. H. HUXLEY, *On the relations of man to the lower animals.*

NEARLY everything I have said so far will apply, though sometimes in a rather rudimentary fashion, to the higher animals. They have memory and recognize things; their acts are determined partly by their immediate sense impressions and partly by what they remember. They are capable of learning complicated actions; they appear to choose between possible actions and to base their choice to some extent on an estimate of the results which are likely to follow. Have we left out anything in this description which would distinguish man?

There would appear to be two faculties which separate mankind decisively from the other animals: the extensive use of tools and of language. They are both the result of greatly increased mental abilities, which permit human

beings to carry out with ease operations which animals can only perform to a limited degree; if at all. If we are to finish our survey of life with man and not at a lower level, we must consider briefly what these abilities imply.

Tools are external objects which human beings use as extensions of themselves, so as to improve the reach and performance of their own limbs. They are controlled by the brain, through the muscles, in much the same way as the limbs themselves. When a skilled violinist plays, the muscles which operate the instrument are controlled by means of data reaching the brain from the senses of touch and hearing. The nervous circle thus goes from the muscles to the instrument and re-enters the brain through the senses. The accurate use of tools depends on the ability of the brain to use the data brought by the senses for the exact control of muscular action. No new faculty is needed, only a more precise use of those which the higher animals possess.

The use of the larynx and tongue in making articulate sounds involves just the same kind of muscular control as when an exacting task is performed by the limbs, or with the help of a tool. We listen to the sound of the voice and modify it according to what we hear. The muscles which control the voice are thus coupled with the sense of hearing.

By making possible the communication of experiences, language was the basic discovery which created mankind. It enabled one person to become aware of what was in another's mind. What could be learnt in a lifetime was no longer confined to the experiences and abilities of one individual. Human society could be built on shared knowledge and experience enriched by discussion. Language is such a vital element in human life that we must consider what it implies.

How does it come about that speech, consisting of articulate sounds, can convey information and have meaning? It has been variously suggested that speech originated

in imitations of natural sounds, in an elaboration of gestures, or as a development from the inarticulate, but expressive, cries of infancy. Whatever its origin may have been, speech, in civilized languages at any rate, is now mainly symbolic. The sounds usually have no obvious similarity with what they represent. Words are sometimes used as the names of particular objects, but more frequently for classes of objects. Instead of giving a name to every separate object, we group similar objects together and use a word to denote the group, as when we call two similar, but not identical, objects "trees". To be able to do this we must be able to distinguish the essential likenesses of different objects and abstract from their whole appearance what they have in common. In the same way we group together similar actions, relations, and qualities, and give them names which are symbols of some abstracted features of experience. Thus, we see that human beings have in their minds not only their own picture of the world — that is, their actual memories of the people, places, and objects they know — but also, a set of word symbols which they can draw upon in order to describe their experiences. A word picture is obviously much more generalized than the actual picture of the world which an individual has, and because of that it permits communication between two individuals and enables them to compare their experiences. When I see a tree the mental picture which I have belongs to me alone. I can only communicate my experience to another person by using symbols like *tree*, *green*, *tall*, *elm*, which call up similar impressions from his own experience.

These words are obviously closely coupled both with an individual's actual memory of objects and acts, and with his speech mechanism; that is, the muscular movements by means of which he pronounces words. Learning a language involves learning how to make these connections, so that the word can be pronounced when required. An individual will

have not only a memory of his experiences but also a memory of the words he has used or heard. He may remember words without actually speaking them; he may put words together in his mind. So the use of symbolic language provides a medium for thinking. It permits of the deduction of general relations which do not involve actual objects. We see that in working out a means of communicating experiences with their fellows, men have also found a way of exploring the relations between their own experiences.

After spoken language came the discovery of writing. Words were represented by permanent marks on paper — sometimes like the objects represented, as in Chinese; sometimes in a sort of phonetic alphabet, as in European scripts. Communications thus acquired permanency and could also be sent from place to place.

These basic discoveries of mankind must have been possible because they utilized pre-existing abilities of the human brain. They involve the ability, first, to abstract essential qualities from a complex mass of data brought by the senses; secondly, to replace the abstractions by symbols; thirdly, to translate rapidly from the one to the other: from the actual experiences to the sound of the spoken word on the one hand and to the appearance of the written word on the other.

Our ability in doing these things is phenomenal. If it were not an everyday ability possessed by nearly everyone, we should regard the reading of a book, for example, as an achievement of the most extraordinary complication, like feats of calculating geniuses, such as Mr. Bidder, who, given the number 17,861, "would instantly remark it was 337 × 53". You look at the black marks on the paper; in an instant you recognize the words; in a mysterious effortless way, at the rate of perhaps a hundred words a minute, the words evoke echoes of the ideas or objects they stand for. They cohere to make a picture which excites your interest

and perhaps your feelings, or at least has some meaning for you. You hear the conversations in your mind and are moved to laughter, anger, or pity. In some way the black marks have interacted with your whole experience; with your background of memory and character and have become an integral part of yourself.

Words must owe this power to a close correspondence with the structure of the mind and to the way in which the mind deals with its data. They represent not so much things and actions as the way we respond to them.

Mankind has created a wonderful variety of effective languages, having, if one can judge only by the commoner ones, a profoundly logical structure. Languages could so easily have been degraded into a set of conventions; but living languages, as a whole, have resisted degradation and grow in power and variety as time goes on. The beauty and logic of the spoken word is a clue to the nature and the power of the minds which use it.

It is not surprising that in primitive societies the distinction between a word and the thing it represents was not very clear. A man's name seemed to be part of himself, like his eyes and teeth. Therefore names were precious and vulnerable. A man could be injured if his name was misused; hence, for example, among Australian aborigines, a person's real name was often kept secret. The names of kings and high priests were guarded with great care, lest their owners should come to harm. Even more sacred were the names of the gods. "The name of the guardian deity of Rome was kept a profound secret, lest the enemies of the Republic might lure him away." [1]

We thus recognize in language a primary token of the abilities which distinguish men from beasts. By replacing actual experiences and perceptions by a system of symbols

[1] For many more examples, from which these are cited, see Sir James Frazer's *Golden Bough*.

it gives them a permanence and continuity which the fleeting images of life do not have. It also provides a framework which helps the individual to interpret and understand his experience and also provides general concepts which are necessary to give coherence to a society.

As a means of conveying information, it makes possible accurate statements of the relations between things — statements which can be verified and can secure assent from large numbers of people. Out of such communicated knowledge came the primitive discoveries of mankind — fire, agriculture, building, the domestication of animals, the pastoral arts, and more recently the organized body of knowledge we call science.

We do not know how the translations from sensations to symbols are brought about. We may know what parts of the cortex are excited when the image of a tree falls on the retina, but we do not know how we pick out the essential characteristics which enable us to recognize it as a tree, and how the translation to and from the level of words takes place.

But it is perhaps not too fanciful to see in these processes an extension of the kinds of ability which already exist in animals. The problem of the animal in dealing with its sensations is already a difficult one. It takes an extremely complex pattern of sensation and has to deduce from it appropriate and effective actions. No simple scheme like the connection of one set of circuits with another set in a telephone exchange will do, because the animal has to connect two essentially unlike things with each other — the sensory pattern and the pattern of muscular action.

We can perhaps surmise that the connections are made at a level where the two situations are so simplified that they have something in common. This involves abstracting from the whole picture the features which are vital. The animal *must* seize upon the essentials of the situation. Its picture of

the world must emphasize features which are relevant to possible actions and ignore others. It will obviously help if similar situations are recognized as such and grouped together in the mind so that they can be recognized at a glance. It would therefore seem that animals' brains must both make abstractions and classify them according to their important likenesses.

The next step, which human beings have made, of associating groups of related abstractions with verbal symbols, is but a continuation in the same direction. In associating abstractions with words, the brain may only be making use, in an elaborated form, of previous modes of dealing with actions. From the planning of actions involving muscles we might easily pass to combinations of verbal symbols and thus to ideas and thoughts. Human speech and symbolism may thus have arisen gradually from brain processes which were developed in animals to enable them to act effectively.

XIV

IS THE BRAIN A CALCULATING MACHINE?

There is a great deal of unmapped country within us.
GEORGE ELIOT

HAVING completed our survey of what the brain does, we can return to the question of how it works. Its actions can be summarized under two headings. The first kind consists of those which maintain the individual within the limited range of conditions in which it can function. These include many of the automatic functions of the brain, and make use of the general principle of feed-back, *i.e.* when the performance diverges from that desired, the controls operate to bring it back. The second kind are those in which the animal uses the data brought by its senses in order to achieve some objective — such as access to food. As we have seen, these controls are sometimes fairly direct, as when a sensation produces a simple response and sometimes very indirect, involving such complex factors as recognition, memory, judgement, prediction.

Little is known about what goes on in the brain in the exercise of its higher functions. Something has been learnt with the electro-encephalograph (which detects minute electric vibrations through the skull) about the areas of the brain which are excited by different kinds of sensations. Brain surgery has also contributed something to the knowledge of brain function, and no doubt will do more. It is surprising how much damage can be done to the brain without apparent impairment of its functions. A hundred

years ago a quarryman in Vermont, Phineas Gage, had a crowbar driven through his skull, causing an ugly wound in both of the frontal lobes of the brain. By an extraordinary chance the wound healed and the man was able to return to his work. His intelligence and ability were not seriously impaired, and his memory was good; but it is said he was less balanced and more easily excited to anger.

An operation known as prefrontal lobotomy or leucotomy, in which many of the connections between the frontal lobes are severed, has been performed on a considerable number of persons with mental disease. It appears to have a genuine effect on the tendency of the patient to worry, but does not radically affect his memory. It appears, then, that a considerable number of connections in the brain can be broken without seriously affecting the memory, although the more general controls of judgement and character and the individual's ability to review his experiences may be impaired. Possibly the reason is that the number of possible connections between the nerve cells is so enormous that only a small proportion is actually used. When some paths are broken alternative ones can be found, so that simple memories may be restored and only the broader integrations involving many memories are lost. If even a simple memory involves large numbers of cells and the connections between them, one can hardly guess what judgements of broad issues imply.

Nevertheless, in the last few years new approaches have been suggested which may lead to an understanding of some brain processes. The brain, we have seen, consists of an enormous number of neurones, which are connected by thread-like connections, called *axons*, which connect them together in a most complex network (see Fig. 15). The connection between one neurone and another is, however, not a simple one. Between them there is always a junction, known as a *synapse*, which has certain peculiar properties.

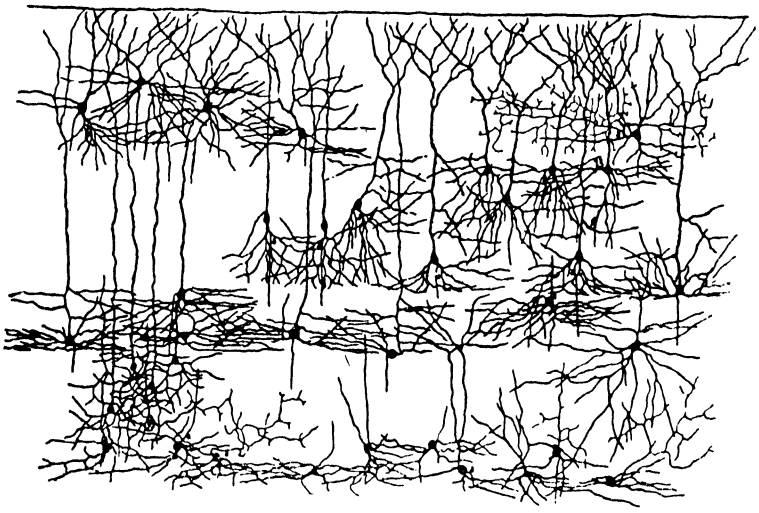


FIG. 15.—Typical neurones and their branching connections found in different layers of the cortex of an ape

Reproduced with permission from Dr. Lorenté de Nó's article in Fulton's *Physiology of the Nervous System* (Oxford University Press)

It gives an " all or none " response, which takes no account of graduations of the signal strength. If the signal is strong enough, it will pass; below a certain strength, nothing passes.

In order to excite a neurone a certain fixed number of signals must reach it through its synapses within a definite period. When it is excited, it fires a " volley ", *i.e.* a complete signal, which is independent of the nature of the stimulus, provided alone that it is sufficient. After firing, there is a refractory period which lasts for about one-thousandth of a second during which the neurone is incapable of being stimulated.

The neurone is thus essentially a relay which repeats a sufficiently strong signal. After firing it cannot be stimulated until the refractory period has passed. It can also be

inhibited, i.e. a signal from another neurone may bring it into a state in which it will not fire.

To what extent can the abilities of the brain be explained in terms of an enormous network of neurones having these properties? In the first place, can we find a basis for memory? A good many years ago Dr. Lorenté de Nó pointed out that a number of neurones arranged in a ring could act as a permanently reverberating circuit. A pattern of impulses fed into such a ring will continue to circulate indefinitely. It is only necessary that the neurones should be able to provide sufficient energy and that the ring be sufficiently long, so that the first neurone is in a receptive state when the message arrives back. Patterns of impulses could thus be stored in the brain in a permanent or semi-permanent form. Drs. McCulloch and Pitts, who investigated mathematically the properties of such networks of neurones, have pointed out that this provides a basis of memory, in that the patterns would continue to circulate long after the immediate occasion which produced them had passed.

They have also suggested ways in which networks of neurones could be built which would pick out the pattern from a complex sensation. How, for example, does the brain distinguish a tune, or a chord, independently of the absolute pitch? How does it distinguish a particular geometrical figure independently of the size? These abilities require a mechanism of translating from one pitch or size to another.

Drs. McCulloch and Pitts suggest that the sensory impulses are received in the brain, not on a single row of neurones, but on several layers of them which are, as it were, tuned to different keys, or scales of magnitude. Each of these is brought in turn into a receptive condition by a " scanning " mechanism. The signals sent on to the reverberating circuits are thus a sum or average of those produced

by the pattern, as measured in all the different scales. In this way the essential character of the pattern is abstracted, irrespective of its actual size or pitch.

They have found, in the architecture of the cortex, patterns of neurones which appear to be organised in this way. They also suggest that the α-rhythm, which is the electrical oscillation of 9 to 11 cycles per second observed in normal subjects when electrodes are placed on the skull, is due to the oscillations of this scanning process as it moves repeatedly over the layers of neurones, activating each in turn. The interval between one oscillation and the next is about sufficient to enable an impulse to pass successively through one hundred successive neurones, which constitute a vertical section of the cortex. The time taken by one cycle of the scanning process — about a tenth of a second — would be the least time in which we can distinguish objects clearly.

In these ideas it appears that a beginning, at least, has been made in the understanding of the higher abilities of the brain. It will be evident from the previous chapters that there are many other problems which require elucidation and that an enormous elaboration would be necessary before we could be said to understand what goes on in the brain. Indeed the real problem is the capacity of the brain to cope with such enormous numbers of sensations, continuing for many years, and reduce them to manageable order.

The principles on which these neurone networks operate are very similar to those employed in calculating machines, particularly the modern electrical machines, which make use of electrical circuits and relays in the form of radio valves, which will either pass a signal or refuse it. The analogy between these machines and brains has been stressed by Drs. Wiener, Rosenblueth, and Bigelow, who have given to their comparative study the name *Cybernetics*.

No doubt the types of machines which have so far been constructed are rather rudimentary, but they do carry on in some form or another, operations which we have noted as among the abilities of brains. For example, they can be provided with *sense organs*, which detect and respond to sounds, light, or other kinds of physical factors; with *memory*, in that the data put in can be stored away for future use; with the power of *recognition*, in that the data supplied can be compared with that already in the machine, and of *prediction*, as when a gun predictor follows an aeroplane and causes the gun to deliver a shell, not where the aeroplane was, but where it will be when the shell arrives. Machines can also be capable of *logic*, *i.e.* they deduce the consequences to be drawn from a set of facts. They do this, for example, when they are used for mathematical computations.

There is no obstacle, except time and expense, to the construction of much more elaborate and efficient machines, which could perform very complicated operations involving all these abilities. Could such a machine be compared with a brain? Are brains complicated machines of this kind?

In attempting to answer these questions, we may observe in the first place that calculating machines are tools. They are, in fact, extensions of the brains and muscles of human beings. They are set by human beings to carry out pre-arranged tasks. They do not have their own objectives, or change them by themselves from time to time. Indeed they work with symbols which have already filtered through the brains of human beings. The gun predictor may make use of a raw sensation to guide the shell, but the objective — the destruction of an aeroplane — has obviously been determined by human symbolism.

We must conclude that calculating machines imitate certain isolated functions of the brain. Even if they were enormously improved they would still be a reflection, or imitation, of brains. You might make a machine which

would recognize a mouse and pounce upon it. But you have not thereby constructed the brain of a cat. A cat is also an animal which plays, runs up trees for fun, and walks abroad by night. If a man has lost a leg, you might give him a substitute, a mechanical leg. For some purposes it might even be better than his own leg; but you have not thereby reconstructed a human leg, or even discovered how it works.

Let us see what sort of a calculating machine we should have to construct to imitate the human brain. Suppose we replace every neurone by a radio valve. If each valve with its connections occupies 12 cubic inches (a modest figure) we should need a building a mile long, a hundred yards wide and six yards high to hold them. An enormous staff of people would be required to run and service such a machine. The problem of how to make it work would certainly tax *their* brains.

Even then it would only do what it was planned to do. It would not profit by its experience — although the operators might. It would not learn gradually to use its abilities, as living things do. It would lack the spontaneity of even simple creatures. It would neither grow by itself nor reproduce itself. The gap between machine and organism would still be immense.

XV

THE STATURE OF MAN

. . . darkened Man, that complex multiplicity
Of air and water, plant and animal,
Hard diamond, infinite sun.

EDITH SITWELL in *The Canticle of the Rose*

All bodies, the firmament, the stars, the earth and its kingdoms, are not equal to the lowest mind; for mind knows all these and itself; and these bodies nothing.—B. PASCAL, 1670.

But this much is evidently true, that of all substances which nature hath produced, man's body is the most extremely compounded.—FRANCIS BACON, *Of the Advancement of Learning*, XI.

WE have come to the end of the story and all that remains is the summing up. We return to the questions we started with. What is the importance of life? What is the stature of man? I think it will be clear that, under the microscope of science, man does not shrink into insignificance. The more we study, the more complex and bewildering is the vista unfolded.

We started with simple atoms and molecules — the building bricks of the complex patterns which have been discovered in living things. We have worked our way upwards, through proteins and enzymes — molecules already beyond the present powers of the synthetic chemist — to the larger aggregations, such as nucleoproteins, which occur in viruses and chromosomes. At a much higher level of complication we reached living cells — the simplest units which are able to cope with all the business of living in

a natural environment. Here we caught glimpses of the invisible world of microscopic life which exists in great profusion and variety. Readers can decide for themselves how far we are on the way to the test-tube reconstruction of microscopic life — let alone the manufacture of a synthetic man!

In the microscopic world, the smallest viable cell probably contains about a quarter of a million protein molecules of many kinds — and the larger ones many more. We find then in the smallest independently living units something like ten thousand million (10,000,000,000) atoms, united in many patterns of great complexity and these patterns organized into a single functioning whole. There are about as many (or rather more) cells in the human body as atoms in a single cell, so that the simple cell comes roughly midway in the scale of complexity between atoms and man. The body of a man is no negligible organization, even on the cosmic scale. What the simple cell is to the atoms, so is man to his component cells. But another step in size of the same magnitude would include much of the visible universe! Man is thus in a midway position between the minute atoms of which the universe is constructed and the almost unimaginable whole. It is probably this which gives him his powers of coming to terms with and of understanding both.

In a broad sense we have been tracing the great landmarks in the ascent of life. They are four in number; although no doubt there have been many intermediate gradations. The first stage, the complete elaboration of the basic chemistry of life, is already achieved in the simple free-living cells, and, very broadly speaking, it undergoes no further change.

The second stage, the organization of cells into large organisms, involves a further step, as great as that of the elaboration of the cells from the simple molecules. But the problems are different. They involve differentiation, special-

ization, growth; the uniting of vast numbers of cells into a single organism.

The third stage occurred when the organism became a mobile animal and acquired muscles, sense organs, and a brain. The function of the brain is to co-ordinate and use the information given by the sense organs in order to bring about effective muscular action. In this way the animal became aware, however dimly, of the world he lived in.

The fourth great stage in the ascent of life — which must be regarded as being still young — is the attainment by man of the ability to use symbols, and through symbols to acquire power over inanimate objects and to transform the world.

The first two stages of evolution were predominantly chemical, the last two essentially mental. I do not need to elaborate the chemical aspect, which has been discussed at length in the earlier chapters of the book. The mental aspect of animal life has not received as much emphasis in the study of life as a whole as it deserves. But it must have been of dominating importance — for it is useless to have a body unless you can use it and move it effectively. Which came first, the muscles or the brain, is a variation of the old question about the egg and the chicken. At least we can say that the organization of body demanded a simultaneous organization of brain. Efficient animals were those with not only efficient muscles but also brains to make them work. We might suspect that the dinosaurs disappeared because they had too much body for their brain. They were displaced by the more brainy mammals, in the same way as, in more recent times, the mammals are giving way to man.

In order to utilize his knowledge, however imperfect, of the outside world, an animal has to reduce the innumerable sense impressions it receives to a manageable picture. It must grasp, at its peril, the essentials of the situation.

It must *abstract* those which concern itself and ignore the rest.

The utilization of the picture involves prediction. Muscles are moved in order to bring about certain happenings. The momentary picture formed from the sense impressions is always feeling out into the future. In Craik's language, the brain makes models of experience and uses them in order to plan and to try out possible actions. It seems clear that the higher animals go at least as far as this.

The abilities of man seem to have arisen from these abilities of animals. From abstraction human beings have gone on to symbolism; from making models of possible actions, human beings have passed on to making and using symbols; from experimenting with muscular actions they have proceeded to experiments with symbols, to " adventures in ideas ".

We must recognize as a constantly occurring feature of human life the ability to think new thoughts and to try to do things which have never been done before. The whole achievement of mankind, much of it before the dawn of history, testifies to its essential creativeness, the common factor behind the discovery of both tools and speech. Before a man can make a spear, he must visualize it and its purpose. It must exist in the mind before it can be made. Early men saw flints and perhaps threw them, but one man saw how a flint could be attached to a spear. In the same way, all tools and machines must exist in human minds before they can be made.

The ability to think new thoughts, to make new and purposeful combinations of objects and to perceive new relations between things and symbols is thus seen to be an essential human ability, which has made human life what it is. This creativeness evidently springs from mental restlessness, from a continual urge to try things out and use to the utmost the powers of abstraction, combination, and

prediction which the human brain possesses.

Consider what human creativeness has produced in the last five thousand years — twenty or more separate civilizations, each with its own modes of thought and ways of life and distinctive institutions, culture, and arts; hundreds of languages and the vast accumulation of human knowledge, literature, and art.

Is not this evidence enough that human beings are inventive or, what comes to the same thing, imaginative creatures? They are always, it seems, " reaching for the stars ". As far back as records remain we find them, or at least some of them, pondering on the meaning of existence and the nature of the world. Out of their attempts to make sense of their experiences and out of their need to find in the meanings a rule of life, have come the many religions of the world. Whenever opportunities occurred, they have also added embroidery to the strict necessities of life. Every period and every civilization has produced arts, which go beyond mere utility and invest things and acts with heightened significance, give pleasure to the mind and provide food for eager imaginations. Even at the dawn of civilization, four thousand years ago, as Breasted has described, the ancient Egyptian found inspiration in nature to embellish his articles of everyday life. " The lotus blossomed on the handle of his spoon, and his wine sparkled in the deep-blue calix of the same flower; the muscular limb of the ox in carved ivory upheld the couch on which he slept; the ceiling overhead was a starry heaven resting on palm-trunk columns, each crowned with its graceful tuft of drooping foliage." [1]

When we consider what human beings have achieved in the brief period of human history, although it is obvious that much potential talent has come to nothing owing to lack of opportunity, we are obliged to conclude that creative gifts, which enable their possessors to see new relations or

[1] Quoted by James Harvey Robinson in *The Human Comedy*.

invent new objects, must have been fairly common. Indeed, some degree of inventiveness is necessary to *all* human beings if they are to solve the problems of their daily life. A valuable invention differs only in degree, and not in kind, from the devices we all think of to solve our everyday problems. It is impossible to make a sharp division between creative actions and thoughts and ordinary human acts and thoughts. This does not mean that every human being is a genius, but that the creative ability is a heightened form of a faculty or attitude of mind which is all but universal.

How do new ideas originate? As everyone knows words and ideas seem to come into the mind spontaneously. There are times when we cannot think of a name or a word. Later when one is thinking of something else, or the mind is relaxed, it suddenly appears in the consciousness. At times, though one wants to speak, one may be unable to find anything to say. At other times, words and phrases come rushing into the mind. " When my brain gets heated with thought," said Shelley, " it soon boils and throws off images and words faster than I can skim them off."

There is an overwhelming amount of evidence that the process by which new ideas, both artistic and scientific, arise is largely unconscious. The creator of new ideas may, and in fact must, strive with his material, but the solution of the problem, the synthesis he is seeking, appears suddenly, as if from nowhere, often when he is thinking of something else.

Many examples of this could be quoted from almost every field of creative endeavour. Gauss, the mathematician, describing his struggle with an arithmetical theorem, said, " Finally, two days ago, I succeeded, not on account of my painful efforts, but by the grace of God. Like a sudden flash of lightning, the riddle happened to be solved. I myself cannot say what was the conducting thread which connected what I previously knew with what made my success possible."

H. Poincaré, the French mathematician, describes how, having striven with a problem (fuchsian functions) for a fortnight, the solution finally came to him. "Just at this time, I left Caen, where I was living, to go on a geologic excursion under the auspices of the School of Mines. The incidents of the travel made me forget my mathematical work. Having reached Coutances, we entered an omnibus to go to some place or other. At the moment when I put my foot on the step, the idea came to me without anything in my former thoughts seeming to have paved way for it, that the transformations I had used . . . were identical with those of non-Euclidian geometry. I did not verify this idea; I should not have had time, as, upon taking my seat in the omnibus, I went on with a conversation already commenced, but I felt a perfect certainty. On my return to Caen, for conscience's sake, I verified the result at my leisure." [1]

It is recorded by his biographer that Alfred Russel Wallace, one of the originators of the theory of evolution, " would be disinclined to work for days or even for weeks. . . . He occupied himself with his seeds, by planning a new house or simply with a novel. Then, and suddenly whilst in one of his day-dreams . . . an explanation, a theory, a discovery, the plan of a new book, came to him like a flash of light." [2]

We get glimpses here of very strange powers of the human mind. Ideas seem to have a life and momentum of their own below the conscious level. They are in a state of continuous fermentation, of dissociation and re-combination; and out of this emerge at times combinations which the conscious mind recognizes as valuable. Does not this remind us of the processes, already discussed, by which actions and speech are planned?

[1] H. Poincaré: *The Foundations of Science* (1913).
[2] *Life of Alfred Russel Wallace*, by Marchant.

In trying out combinations of ideas, the brain may only be making use of these pre-existing modes of dealing with actions. The plans of the external world and the abstractions derived from them do not now necessarily lead to action, but the mind continues to explore their possibilities. Ideas may thus acquire a " life of their own ", entering into combinations of which we are unaware, until they rise, as they may occasionally do, to the level of consciousness.

Human creativeness is thus a development, made possible by the greater degree of abstraction achieved in the human brain, of the underlying spontaneity of action in animals. This, as we have seen, is very deeply rooted in Nature. It appears in the chaotic movements of primitive forms of life and has its origin in the underlying flux of the inorganic world.

As we have seen, human mental processes have become detached from immediate actions and from any actions. Because of this men have forfeited the comparative simplicity of animal life, obtaining in its place creative ability. They have eaten of the tree of knowledge and so lost the primitive Eden, the innocence of animal life. Creative ability has given mankind the possibility of rising to incredible heights of achievement and power, which may either make life rich and varied, or, as is shown by a most cursory reading of history, both ancient and modern, become the instrument of every kind of cruelty and devilry. Hence arises the basic dilemma of mankind, at present posed in its sharpest form — how to secure the benefits which may flow from knowledge and imagination and avoid their perversion.

Because of the restlessness of the mind of man, change has been the most characteristic feature of human life — at least during the historic period. Civilizations have not often stayed static. They rise and decay, and only continue so long as they can achieve a reasonable balance between stagnation and change, between Yen and Yang, the static and dynamic principles of life.

The individual, too, is confronted with the problem of ordering his creative urges. For most human beings most of the drama of life now goes on within themselves in the endless reverberation and clash of ideas within their brains. To tame this natural mental effervescence, we need to acquire strong guiding principles of thought and conduct. We have to learn not only how to use our muscles, but also general principles, with which to guide the use of our mental faculties; in other words, to establish character, as the educationists say. This is the argument of tradition and natural religion: the need of well-established channels and habits of thought within which we may succeed in harnessing the " bubbling-up " of ideas and making them harmonize with the legitimate aspirations of the individual and the needs of society. The problem of education is to establish such guiding principles, without hampering legitimate creativeness.

We have plenty of examples of what happens when " vaulting ambition . . . overleaps itself ". Great communities, like Hitler's Germany, can be carried to ruin by following the unbridled effervescence of one man's imagination. Most of us manage to keep the ebullition of thought within reasonable bounds. Many in fact have learnt to suppress their natural originality and conform in thought and action to the strict rules of their community. In some the effervescence gets beyond control and fancy no longer conforms with verifiable fact. A few rise to supreme heights of creative achievement, like the illustrious Newton, who, at the end of a long life, said: " I do not know how I may appear to the world; but to myself I seem to have been only like a boy, playing on the sea shore, and diverting myself in now and then finding a smoother pebble, or a prettier shell than ordinary, while the great ocean of truth lay all undiscovered before me ".

INDEX

Acetylcholine, 107
Action, 117
Adaptation of enzymes, 48
Adrenaline, 81
Amino-acids, 13, 102
Aneurin, 34
Antibodies, 49
Anti-vitamins, 36, 91
Aureomycin, 39
Auxins, 79
Axons, 136

Bacteria, chemical activities, 27, 69
Bacteriophage, 72
Behaviourism, 121
Biotin, 34
Brains, 8, 105

Calculating machines, 135
Cancer, 71, 91
Chlorocruorin, 41
Chloromycetin, 39
Chlorophyll, 41
Choline, 34
Chromosomes, 52, 57
Cobalt deficiency, 42
Co-enzymes, 33
Compound E, 82
Copper, use of, 43
Cortisone, 82
Creativeness, 145
Cybernetic, 139

Determinism, 124
Development, 88
Diabetes, 81
Differentiation, 89
Dissipation of energy, 97
Duomycin, 39

Emotion, effects of, 86
Endocrine glands, 85
Energy, dissipation of, 97
Entropy, 98
Enzymes, 23
Evolution, 96, 144
Experience, nature of, 113
Eye, human, 109

Feed-back, 119
Folic acid, 34
Free will, 117, 124

Galaxies, 1
Genes, 58
Globulins, 47

Haemoglobin, 41
Hormones, 78, 93

Immunity, 49
Insects, transformations of, 93
Insulin, 18, 80

Juvenile hormone, 93

Language, 130
Life, origin of, 101, 143
Life, place in universe, 1

Mechanical man, 8
Memory, 112, 138
Metals, use of, 40
Metamorphosis, 93
Microscope, revelations of, 3
Microsomes, 65
Milk production, 47
Mitochondria, 65
Models of outside world, 121
Muscle, 105
Mutations, 58

Nerves, 105
Nervous circle, 118
Neurones, 106, 119, 136

Nucleic acid, 57
Nucleus, 52

Oestrogens, 83
Organic compounds, 5
Oscillations in brain, 111, 138

PAB, 37
Pancreas, 80
Pantothenic acid, 34
PAS, 38
Penicillin, 38
Pepsin, 24
Peptide link, 13
Photosynthesis, 12, 99
Pituitary gland, 84
Planets, suitability for life, 2, 101
Plasmagenes, 67
Protein molecules, 17
Proteins, how made, 45, 102
Protoplasm, 12

Radiations, action of, 59
Reflex action, 108
Reflex, conditioned, 120
Reproduction, 51
Riboflavin, 34

Sex hormones, 83
Speech, 128
Spontaneity in life, 123
Steroids, 82
Sterols, 31
Streptomycin, 39, 43
Sulphanilamide, 37
Suprarenal glands, 81
Symbolism, 134, 145
Synapse, 136

Thermodynamics, laws of, 97
Thyroid gland, 79
Thyroxine, 79

Ultracentrifuge, 16
Universe, size of, 1, 143
Urease, 24

Virus, antibodies, 49
Virus, crystals, 68
Virus, size of molecules, 17, 69
Virus specificity, 70
Vision, 109
Vitamins, 30

Words, 132

Xanthopterin, 91
X-rays, action of, 59

THE END

PRINTED BY R. & R. CLARK, LTD., EDINBURGH