The Activity of Nerve Cells*

By PROF. E. D. ADRIAN, F.R.S.

SINCE the biologist seeks to understand life, he cannot be accused of lack of courage. But he can find out a great deal without approaching too near the central problem. He can find out how the living cell develops and how it behaves; he can follow many of the physical and chemical changes which take place in it, and could follow more if cells were not so inconveniently small. The immediate problems of the physiologist may be still further removed from the problem of life. They may deal, for example, with the mechanics of the vascular system or with the physical chemistry of blood pigments. But most physiologists aim at explaining the working of the body in terms of its constituent cells, and feel that this is a reasonable aim, even though we must take the cell for granted. Is it a reasonable aim when we are dealing with the working of the nervous system?

The nervous system is responsible for the behaviour of the organism as a whole: in fact, it makes the organism. A frog is killed when its brain and spinal cord are destroyed: its heart still beats and its muscles can still be made to contract, all the cells of its body but those of the brain and cord are as fully alive as they were before; but the frog is dead, and has become a bundle of living tissues with nothing to weld them into a living animal. This integrative action of the nervous system, to use Sherrington's classical phrase, we may be able to explain in terms of the reactions of the constituent nerve cells. We can at least discuss the point as physiologists. But the human organism includes a mind as well as a body. It may be best to follow Pawlow and to see how far we can go without bringing in the mind, but if the reactions of our nerve cells are to explain thought as well as action, we must face the prospect of becoming psychologists and metaphysicians as well. Fortunately, we need not yet go to such extremes.

The nervous system, the brain, spinal cord and peripheral nerves, is made up of a large number of living cells which grow, maintain themselves by the metabolism of food-stuffs, and carry out all the complex reactions of living protoplasm. In this there are enough problems for anyone; but we are concerned not with the general properties of living cells but with those special properties which enable the cells of the nervous system to perform their functions. Their function is to make the organism respond rapidly and effectively to changes in its environment, and to achieve this they have developed a specialised structure, and a complex arrangement in the body. They send out long threads of protoplasm which serve for the rapid transmission of signals,

and they are linked to one another by elaborate branching connexions in the brain and the spinal cord.

DEVELOPMENT OF THE NERVOUS SYSTEM

The mapping of this network of paths was begun many years ago, and was the first step in the analysis. No progress could have been made without it, and its results are of vital importance to neurology. We are now witnessing a fresh period of interest in the geography of the central nervous system, but the problem is not how the nerve cells and their fibres are arranged, but why they are arranged as they are. R. G. Harrison, in his recent Croonian lecture before the Royal Society, recalled the time when he first cultivated living nerve cells outside the body. That experiment, made twenty-three years ago, marks the new epoch better than any other, for, besides introducing the method of tissue culture, it settled a long and bitter controversy as to the origin of nerve fibres. Nowadays the most elaborate transplantation experiments are carried out by the embryologists on amphibian larvæ. Animals are produced with supernumerary limbs, eyes, noses, and even spinal cords. The growing nervous system is faced with these unusual bodily arrangements, and by studying the changes induced in it we can form some idea of the factors which determine its normal structure.

A review published this summer by Detweiler gives a vivid impression of the plasticity of the developing nervous system in the hands of the experimenter. As a rule it accepts the extra limb or sense organ, links it by nerve fibres to the rest of the organism and may develop more nerve cells to deal with it. The forces which mould the nervous system seem to come partly from within the central mass of nerve cells and partly from the body outside. These forces may be chemical or electrical gradients, and often the nerve fibres seem to grow in particular directions because they cling mechanically to structures already laid down, for example, to the main arteries of the limbs. It is unlikely that a simple formula will be found for such a complex arrangement, but the fact remains that the arrangement can be profoundly modified at the will of the experimenter. Its detail seems to depend not so much on the innate properties of particular cells as on the environment provided by the rest of the organism.

REACTIONS OF THE NEURONES

This new embryological work supports the older in showing that the nervous system is made up of 'neurones', cells with thread-like extensions, and that they are the only active elements in it. These elements are all cast in the same mould, but are shaped differently by the forces of development.

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To this we can now add the fact that all neurones seem to do their work in much the same way. The activity which they show is in some respects remarkably simple. It is essentially rhythmic: a series of rapid alternations between the resting and the active state, due probably to rapid breakdown and repair of the surface. This at least is a fair description of the way in which the nerve fibres carry out their function of conducting messages, and we can detect the same kind of pulsating activity in the nerve cells of the brain.

The evidence comes from the analysis of minute electric changes, for cell activity sets up electrical eddies in the surrounding fluid, and these can be measured with a minimum of interference. The clearest results are given by the peripheral nerve fibres which connect the central nervous system to the sense organs and the muscles. The nerve fibres are conveniently arranged in bundles to form the nerve trunks: each fibre is an independent conducting path and there may be a thousand such paths in a fair-sized nerve, but it is not a difficult matter to study what takes place in the single fibre when it conducts a message.

We may begin with an external stimulus acting on a sense organ, a structure which includes the sensitive ending of a nerve fibre as an essential part. The ending is excited by the stimulus, the delicate equilibrium of its surface is upset and the disturbance tends to spread along the fibre. The spreading is an active process: it takes place because the fibre has a store of energy ready to be liberated at a moment's notice, and because the changes which attend its liberation at one point upset the balance at the next point and cause the same activity there. The spread of a flame along a fuse is a well-worn analogy. But the nerve fibre is so constituted that a disturbance at any point is almost immediately cut short. The change spreads along it as a momentary wave—a brief impulse followed inevitably by a brief interval of rest and recovery. If the sense organ remains excited, a second impulse passes up the fibre, and then another and another so long as the stimulus is effective.

The impulses in a given nerve fibre are all alike in magnitude, rate of travel, etc., but the frequency at which they recur depends on the intensity of the stimulus, rising sometimes so high as 300 a second in each fibre, or falling so low as 10. All the nervous messages take this form.

The conducting threads or nerve fibres are exceedingly insensitive to changes in their environment: their endings in the sense organs are exceedingly sensitive. The sole function of the ending is to act as the trigger mechanism for firing off the impulses, and the sole function of the nerve fibre is to carry the message without distortion. Both are specialised parts of the neurone with specialised reactions, but it is important to note that these reactions are not peculiar to the nervous system. Muscle fibres, developed from the mesoderm and specialised for contraction, conduct

impulses which seem to differ merely in their time relations from those in nerve fibres, and they can also be made to behave like the sensory endings by treatment with various salt solutions. In sodium chloride, for example, a series of impulses will be set up in a muscle fibre when it is stretched, as they would be in one of the sense organs the sole duty of which is to act as 'stretch receptors'. The muscle fibre makes a poor copy of the nervous mechanism, for it reacts jerkily and is often damaged in the process, but the ground-plan of the mechanism is the same.

Thus in the activities concerned in the rapid conduction and in the setting up of rhythmic trains of impulses, it does not appear that the cells of the nervous system have properties not shared in some degree by other tissues.

So far we have only considered what happens in nerve fibres. We can tap the messages which pass along the wires between the front line and headquarters, but this does not tell us how they are elaborated there. A great deal has been found out already by the analysis of reflexes—that is, by sending in a known combination of signals and finding what signals come out to the muscles; indeed, the great part of Sherrington's work on the spinal reflexes and Pawlow's on the brain has been carried out in this way. The results are so well known, however, that I shall deal here with a recent line of attack of an entirely different kind.

This method relies on the fact that nervous activity, in the central grey matter as in the peripheral nerves, is accompanied by electric changes. They seem to be a reliable index of the underlying activity, and by recording them we come a step nearer to the main problem. The chief difficulty is to interpret the records. In the cerebral cortex, for example, very large electric oscillations are constantly occurring, except in the deepest anaesthesia, but they vary from moment to moment and from place to place, and it is only in the visual cortex that they are under a fair degree of experimental control. Here they can be produced by shining a light in the eye (Fischer, Kornmüller and Tönnies) or stimulating the optic nerve (Bartley and Bishop), and the prospects of analysis are more hopeful.

At the moment, however, the most significant feature of these records from the brain lies in the appearance of the waves. Whenever a group of nerve cells is in action, in the cerebral cortex, the brain stem or the retina, and whether the nerve cells in question belong to a vertebrate, or an insect, the waves are alike in general form. Instead of the abrupt spikes which appear in a record from a nerve fibre when a train of impulses passes down it, we have more gradual potential changes which form a series of waves of smooth contour. In the simpler structures where most of the neurones are acting in unison, the waves may have a regular rhythm (5–90 or more a second), which rises and falls when the stimulus changes in intensity. It is often possible to make out both

the abrupt nerve fibre impulses and the slower nerve cell waves, and to show that they occur together. In the cerebral cortex of an anaesthetised animal there is much more variety and less orderly repetition; the waves usually occur at irregular intervals; they vary in size and duration, and some of them may last for half a second or even longer.

Nerve cell waves may be the wrong name, for they are probably due to the branching dendrites and not to the cell body of the neurone; but there can be no doubt that they represent a characteristic activity of the structures which make up the grey matter. They show that the same kind of rhythmic breakdown and repair of the surface takes place in this part of the neurone as in the nerve fibre, with the important difference that the changes develop and subside much less abruptly. The surface is not specialised for rapid conduction; the forces which restore the resting equilibrium are less powerful and there is more tendency to spontaneous breakdown and to long periods of uninterrupted activity. We know that the activity of the grey matter is far more readily influenced by chemical changes than is that of the nerve fibre with its elaborate fatty sheath and wrappings of connective tissue, and it seems probable that both chemical and electric changes may be concerned in the spread of activity from one neurone to another. How this spread takes place is still uncertain, and it is admittedly the most important problem we have to face.

In spite of this, we can claim to have some of the main outlines of neurone activity. Our nervous system is built up of cells with a specialised structure and reactions, but the reactions are of a type to be found in many other cells. The rhythmic beat of the heart is probably due to surface reactions not far different from those in the group of nerve cells which produce the rhythmic movements of breathing; and the factors, nervous and chemical, which regulate the heart beat are probably much the same as the factors which control the discharge of the neurone. We have a store of energy, replenished constantly by cell metabolism and liberated periodically by surface breakdown. The electrical gradients at the active point cause a spread of the breakdown to other regions, but sooner or later restoring forces come into play, the membranes are healed and the cycle is ready to be repeated. It is a long step from the mechanical precision of an impulse discharge in a nerve fibre to the irregularities of a record from the cerebral cortex, but there are many intermediate cases which will bridge the gap.

THE NERVOUS SYSTEM AS A WHOLE

So far as the units are concerned, the prospect is encouraging. The difficulties begin when we come to the work of the nervous system as a whole. Many of its reactions are mechanical enough and can be explained in terms of the activity of groups of neurones, but there is much that resists this kind of treatment. It is perhaps encouraging

that the difficulties are greatest when the reactions depend on the cerebral cortex, when they involve learning and memory, or, if you prefer it, habit formation and conditioning. They have been clearly stated by Lashley, and most of them can be reduced in the end to a simple formula, the failure of anatomical models of the nervous system. The revolt from the anatomical model has been growing for many years, though it may be doubted whether its sponsors ever believed in it as much as their critics suppose. It gave us diagrams of nerve centres and pathways which were valuable enough when they referred to known anatomical structure, but not when they referred, as they often did, to hypothetical centres and to pathways canalised by use. These too may exist, but they are not the whole explanation of cortical activity.

Clinical neurology is partly to blame for the emphasis laid on exact localisation. The neurologist must locate brain tumours by analysing the disturbances they produce; consequently he welcomes the slightest evidence of localisation of function in the cortex, and finds the anatomical model valuable for correlating his observations. Undoubtedly there are well-defined nervous pathways, clear differences in cell structure and localised activity in different parts of the brain. As a modern addition to the evidence we have Foerster's recent work on the electrical stimulation of the human cortex, and his finding that stimulation of the temporal lobe may cause sounds and words to arise in consciousness, whilst stimulation of the occipital lobe gives lights or images. Bard has given another remarkable example of strict cortical localisation by his observations on certain postural reactions in the cat. These depend on a limited area in the frontal region, are not affected by damage to other parts of the brain, but are permanently lost if the frontal area is destroyed. The danger nowadays is that we may pay too little attention to such facts; but it is true, nevertheless, that the localisation is a matter of areas rather than of single neurones. This is shown by examination of habit formation, and by the remarkable way in which the nervous system adapts itself to injury.

It has often been pointed out that we learn to recognise shapes—the letters of the alphabet, for example—however they are presented to us. The pattern of black and white made on our retina by the letter A need not fall on a particular set of retinal endings connected with particular cortical neurones. We have learnt to recognise a relation of lines and angles, a pattern of activity in the cortex rather than an activity of specific points. This kind of reaction is not due to our superior intelligence. Lashley finds it in the rat, and psychologists of the *Gestalt* school have pointed out examples from all manner of animals. There is the same neglect of specific neurones in the formation of motor habits, for if we have once learnt to write the letter A with our right hand, we can make a fair attempt to write it with any group of muscles which can control a pencil.

The adaptations to injury present a different aspect of the same story. An insect which has lost a leg will at once change its style of walking to make up for the loss. This may involve a complete alteration of the normal method, limbs which were advanced alternately being now advanced simultaneously. The activities of the nervous system are directed to a definite end, the forward movement of the animal—it uses whatever means are at its disposal and is not limited to particular pathways.

When the central nervous system is injured, there is more evidence of localised function, but the localisation is no hard-and-fast affair. A rat uses its occipital cortex in the formation of certain visual habits. When this part of the cortex is destroyed the habit is lost, but it can be re-learned just as rapidly as before with what remains of the brain. A monkey's arm is paralysed if the corresponding motor area of the cortex is destroyed, but the paralysis soon passes away although there is no regeneration of the motor cortex. What is more remarkable is that the recovered functions are not associated with the development of a new visual region or motor region in the brain. Though they were originally localised, there is no longer any one part of the cortex which is essential.

In reactions where there is no evidence of localisation (for example, the learning of maze habits in the rat), Lashley finds that the important factor is the total mass of the cortex and not the presence of particular regions. The effect of an injury depends on its extent and not on its situation. It depends, too, on the amount of grey matter (nerve cells and dendrites) destroyed, and not on the cutting of connexions between the different parts of the cortex. Thus the ability of the brain to form new associations, and generally to control the behaviour of the animal, depends primarily on the total area covered by the nerve cells of the cortex and their interlacing dendrites. For certain reactions it depends to some extent on the arrangement of pathways, but this arrangement is not essential. There is more localisation of function in the large brain of man than in the very small brain of the rat, for different cortical regions may be completely equivalent when they are separated by 5 mm., but not when they are separated by 100 mm. But apart from this difference in scale, it is likely that the human cortex has the same mass effect and plasticity of function.

How do the individual neurones combine to produce a system which can recognise a triangle or direct the movements of the organism with such disregard of detailed structure? If particular neurones or pathways are not tuned to triangularity, how can the whole mass be tuned to it, and why should the tuning be more certain when the mass is greater? Our data may be at fault and the mass effect an illusion, but there is certainly enough evidence for it to be taken seriously. Though there is no solution at the moment, I cannot believe that one will not be found—a solution which need not go outside the conceptions

of physiology. It should be possible, for example, to find out how many neurones must be combined to give a system which reacts in this way and what kind of structure they must form. The nervous systems of insects may provide the clue, for these may contain a few thousand nerve cells in place of the ten thousand million in the human brain. It is possible also to study the reactions of isolated parts of the central nervous system, to see how far their behaviour can be explained in terms of the units which compose them. The retina is an interesting example of this kind, for it contains an elaborate structure of nerve cells and dendrite connexions, and has some of the reactions which we might expect from a mosaic of sensory endings, and some which depend on interaction between the different neurones.

Even now, however, we can form some idea of the way in which the grey matter can act as a whole. The electric oscillations in the cortex and in the grey matter generally are often due to a large number of units pulsating in unison. Sometimes there are several competing rhythms, and sometimes the collective action breaks down altogether, to reappear from time to time when some part of the system is stimulated to greater activity. When these collective rhythms appear, the neurones are already acting as though they formed one unit. There is no need to regard the dendrites as forming a continuous network—electric forces may well bridge the gaps between them—but they may form a system in which activity can be transmitted more or less freely in all directions. The patterns of activity in a system of this kind would be like the ripples on the surface of a pond, with the difference that some of the ripples may occur spontaneously, whilst others are due to incoming signals. Interference figures and nodes of vibration may then be all-important. They would at least give a basis for the recognition of relations such as those of triangularity or squareness without the need for an excitation of specific points, and they might be formed with less distortion in a large pond than in a small one.

This does not take us very far: in fact, the major problems of the central nervous system are left in greater obscurity than ever. But no one can observe these ceaseless electrical pulsations without realising that they provide a fresh set of data, and may give a fresh outlook on the working of the brain. The facts are still too uncertain to be worth treating in greater detail. But they accumulate rapidly, and several lines of evidence seem to lead in the same direction. For the present, it is enough to state our problem, that of the organisation of neurones into the nervous system. It is still a physiological problem, and I hope that a solution will be found on physiological lines. If it cannot be found, it will be extremely interesting to see where the breakdown occurs; and if it can, it will be even more interesting to see what light it throws on the relation of the nervous system to the mind.