Nobel Lecture

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The Activity of the Nerve Fibres

The sense organs respond to certain changes in their environment by sending messages or signals to the central nervous system. The signals travel rapidly over the long threads of protoplasm which form the sensory nerve fibres, and fresh signals are sent out by the motor fibres to arouse contraction in the appropriate muscles. What kind of signals are these, and how are they elaborated in the same organs and nerve cells? The first part of this question would have been answered correctly by most physiologists many years ago, but now it can be answered in much greater detail. It can be answered because of a recent improvement in electrical technique. The nerves do their work economically, without visible change and with the smallest expenditure of energy. The signals which they transmit can only be detected as changes of electrical potential, and these changes are very small and of very brief duration. It is little wonder therefore that progress in this branch of physiology has always been governed by the progress of physical technique and that the advent of the triode valve amplifier has opened up new lines in this, as in so many other fields of research.

I shall deal mainly with some of the results which have followed from this new technique, but the present state of our knowledge will be made clearer by a brief survey of the position as it was twenty years ago when I was a student in the Cambridge laboratories.

In the closing years of the last century the improvement of the capillary electrometer had marked a new phase. It was already known that some kind of rapid wave, called the nerve impulse, could be set up in the nerve by an electric stimulus, and there was good reason to suppose that the signals normally transmitted were made up of similar impulses. The disturbance due to an electric stimulus travelled at much the same rate as the natural signals, and it would produce similar effects on the muscles or on the central nervous system. It could be detected in the nerve by the change of potential which accompanied it; in fact Bernstein had already elaborated the "membrane hypothesis"which regards the impulse as a wave of surface disintegration spreading by reason of the electric disturbance which it creates. With the development of the capillary electrometer it became possible to make direct and accurate records of this electric disturbance. Before long the work of Gotch and Burch, Garten, Samojloff, and finally of Keith Lucas had given a detailed knowledge of its time relations and of its connection with the impulse. It was made clear that the wave of activity is invariably accompanied by a change of potential, that the activity at any point lasts only for a few thousandths of a second, and that it is followed by a refractory state which must pass away before another wave of activity can occur. The existence of a refractory period in the heart muscle had been recognized long before and its discovery in the nerve was of fundamental importance. It showed that the nerve fibre, when stimulated electrically, could only work in a succession of jerks separated by periods of enforced rest, and this was true both for the waves of potential change and for the underlying impulse which produced them.

In the same period came Gotch's observation that the potential wave in a nerve had an equal duration whether it was set up by a strong or a weak stimulus. As it seemed unlikely that a feeble and an intense disturbance would last for the same time, Gotch suggested that in each nerve fibre the disturbance was always of the same intensity, and that a strong stimulus set up a larger potential wave merely because it brought more fibres into activity. This agreed with the fact that the rate of conduction and the length of the refractory period were also uninfluenced by the strength of the stimulus. It seemed, therefore, that each pulse of activity in a nerve fibre must be of constant intensity, involving the entire resources of the fibre whatever the strength of the stimulus which set it in motion. The fibre was a unit giving always its maximal response, behaving like the heart muscle in this respect as well as in that of its refractory state. Conclusive proof was lacking, but Gotch's work made it likely that the same all-or-nothing behaviour might be found in skeletal muscle fibres. Keith Lucas recorded the contraction of a band of muscle containing only a few fibres and found that with an increasing stimulus the contraction increased in sudden steps. The number of steps was never greater than the number of fibres in the preparation. It was clear, then, that skeletal muscle fibres followed the all-or-nothing rule.

I have mentioned this work of Keith Lucas (confirmed later by Pratt) because it was the first direct evidence of the ungraded character of the wave of activity in excitable tissues other than the heart. It was also the first successful attempt to record the behaviour of the units in muscle and nerve instead of inferring the behaviour of the units from that of the whole aggregate. A few years later I had the great good fortune to work with him, to appreciate his technical skill and his penetrating thought. I cannot let this occasion pass by without recording how much I owe to his inspiration. In my own work I have tried to follow the lines which Keith Lucas would have developed if he had lived, and I am happy to think that in honouring me with the Nobel Prize you have honoured the master as well as the pupil.

After Keith Lucas's work on muscle, attempts were made to secure more evidence as to the all-or-nothing reaction of the nerve fibre. Verworn and his school showed that the strength of the stimulus made no difference to the ability of the impulse to pass through a narcotized area, and Lucas and I made use of the same method. Its value seemed to lie in its offering a means of measuring the impulse in terms of its ability to travel, but Kato has since pointed out the fallacies which arose from supposing that the impulse became progressively smaller as it passed through the affected region.

More direct evidence was lacking, but at the end of this period we had good reason to believe that the nerve impulse was a brief wave of activity depending in no way on the intensity of the stimulus which set it up. We did not know for certain that the nervous signalling in the intact animal was carried out by means of such impulses, but it seemed highly probable - so much that we could elaborate hypotheses to explain the working of the central nervous system in terms of the interference and reinforcement of trains of impulses.

It was at this point that the need arose for a more sensitive electrical technique. When a nerve trunk is stimulated by an electric shock every fibre is thrown into action simultaneously and the total potential change in the whole nerve is large enough to be recorded directly. But in more normal circumstances the nerve fibres work as independent conducting units, and simultaneous activity in many fibres is a rare event. Potential changes could be detected when there was reason to believe that signals were passing, but to analyse these changes was a far more difficult problem. Granting that they were caused by the passage of impulses of the familiar type, there was little or nothing to show how the impulses were spaced. Records of the electric changes in contracting muscle seemed to one school to imply a very high frequency of discharge in each nerve fibre. Others believed that the frequency was lower, but neither side could find convincing evidence. To show clearly what kind of signals passed from the sense organs to the brain and from the brain to the muscles it would have been necessary to record the electrical events in the individual nerve fibres. The potentials to be dealt with are of the order of a few microvolts lasting for a few thousandths of a second. They were quite beyond the reach of the instruments available at the time, and other lines of evidence had to be followed. These were indirect and, in fact, most of them led nowhere.

The revolution in technique has come about not from any increase in the sensitivity of galvanometers and electrometers but from the use of the thermionic valve to amplify potential changes. The recording instruments used nowadays are actually far less sensitive than their predecessors. Since the energy available is almost unlimited, any system can be chosen which will react rapidly enough and the limiting factor has become not the period of the instrument but that of the amplifying circuits. There is a lower limit to the sensitivity of a valve, but fortunately a change as small as one or two microvolts is within the range of useful amplification. Many workers have contributed to the introduction of this technique into physiology, notably Forbes of Harvard, Gasser of St. Louis, who was the first to use very high amplification, and Matthews of Cambridge who devised the convenient moving-iron oscillograph which is now in common use; to all these my own work is deeply indebted.

Seven years ago it became clear to me that a combination of the capillary electrometer with an amplifier would permit the recording of far smaller potential changes than had been dealt with previously, and might enable us to work on the units of the nerve trunk instead of on the aggregate. A preliminary survey confirmed this, for it showed that the normal activity of sensory and motor fibres was always accompanied by potential changes of the familiar type. The problem was then to limit the activity to only one or two nerve fibres. In this I was happy to have the cooperation of Dr. Zotterman of the Caroline Institute. We found that the Sterno-cutaneous muscle of the frog could be divided progressively until it contained only one sense organ; this could be stimulated by stretching the muscle, and we could record the succession of impulses which passed up the single sensory nerve fibre.

A variety of methods now exists for studying in this way the activity of individual sensory and motor nerve fibres. Many records have been made of the signals which they transmit in the normal working of the organism and in every case the signals are found to be extremely simple. They consist of nerve impulses repeated more or less rapidly, impulses which differ in no way from those already studied by the classical methods of electro-physiology. This may have seemed no more than a proof of what was already obvious, but our records showed another point which was more illuminating. To illustrate this we may take the discharge produced by stretching a muscle spindle. A record of the potential changes in the nerve shows a succession of brief diphasic waves, each due to the passage of a single impulse along the nerve fibre. The waves are of constant size and duration, but they begin at a frequency of about 10 a second, and as the extension increases, their frequency rises to 50 a second or more. The frequency depends on the extent and on the rapidity of the stretch; it depends, that is to say, on the intensity of excitation in the sense organ, and in this way the impulse message can signal far more than the mere fact that excitation has occurred.

In all the sense organs which give a prolonged discharge under constant stimulation the message in the nerve fibre is composed of a rhythmic series of impulses of varying frequency. Hartline, for instance, has shown that the discharge from one of the light-sensitive receptor organs in the eye of Limulus is a fairly close copy of that from a frog's muscle spindle. With some kinds of sense organ there is a rapid adaptation to the stimulus, and the nervous discharge is too brief to show a definite rhythm, though it consists as before of repeated impulses of unvarying size.

The nerve fibre is clearly a signalling mechanism of limited scope. It can only transmit a succession of brief explosive waves, and the message can only be varied by changes in the frequency and in the total number of these waves. Moreover, the frequency depends on the rate of development of the stimulus, as well as on its intensity; also the briefer the discharge the less opportunity will there be for signalling by change of frequency. But this limitation is really a small matter, for in the body the nervous units do not act in isolation as they do in our experiments. A sensory stimulus will usually affect a number of receptor organs, and its result will depend on the composite message in many nerve fibres. A good example of this is to be found in the discharge which passes up the nerve from the carotid sinus at each heart beat. Bronk and Stella have shown that as the blood pressure rises, the impulses in each nerve fibre increase in frequency and more and more fibres come into action. Since rapid potential changes can be made audible as sound waves, a gramophone record will illustrate this, and you will be able to hear the two kinds of gradation, the changes in frequency in each unit and in the number of units in action.

The sense organs which are most easily investigated in this way are those which react to mechanical deformation-tactile endings, muscle spindles and the like. They are supplied by the larger nerve fibres in which the potential change can be readily detected. But there are many sensory nerve fibres which are exceedingly small. The recent work of Erlanger and Gasser and of Ranson has made it highly probable that some of these fibres are concerned with pain, and this alone makes it essential to learn more about their normal activities. For such problems our present methods are still scarcely adequate, for in the smallest fibres the potential changes are probably too small to appear above the random fluctuations due to the operation of the thermionic valve. But we may hope that this failure will be remedied before long.

There is another field of sensory physiology which seemed at first to offer special difficulties but is now more promising. This is the field of the special sense organs. With Mrs. Matthews I investigated the activity of the vertebrate optic nerve, but although the usual impulse messages could-be recorded they gave very little information about the working of the receptor organs in the retina. The reason is that the retina is a complex nervous structure. The messages in the optic nerve fibres have been elaborated by the interaction of many nerve cells, even though the stimulus is restricted so as to fall on a very small number of rods and cones. We learnt something of the processes which take place in groups of nerve cells with synaptic connections, but little about the action of light as a sensory stimulus. Fortunately this difficulty has been overcome by Hartline, who finds that in the eye of Limulus there is no evidence of such interaction and no reason to expect it on grounds of structure. And since his work is showing what takes place in the receptors themselves, the complexities of the vertebrate retina become less formidable.

The messages in the vertebrate optic nerve have come not from receptor organs but from nerve cells. They are comparable, therefore,- with the messages which are sent from the motor nerve cells to the muscles. The grading and coordination of muscular activity is a subject which has been so greatly illuminated by my friend Sir Charles Sherrington that I mention my own work as a very small supplement to his. It has dealt as before with the signals which are sent by the individual nerve fibres, and its results emphasize the close correspondence between the sensory and motor activities of the nervous system. The messages which pass down the motor fibres to the muscles have, of course, the same limitations as the sensory messages, and again we find that the effect is graded by changes in the frequency of the impulse discharge and in 'the number of units in action. In a contraction of gradually increasing force the nerve fibres transmit a succession of impulses beginning at a very low frequency (5 to 10 a second) and rising to 40 or 50 a second at the height of the contraction; and as the frequency rises in one nerve fibre, another will start at a low frequency and then more and more, until it becomes impossible to distinguish the individual rhythms. The force of contraction varies with the impulse frequency, because in a muscle fibre each impulse produces a mechanical effect of relatively long duration and the successive effects of a series of impulses can be summed to give a greater contraction. Thus the result of the intermittent message in each nerve fibre is a much less intermittent contraction in a group of muscle fibres, and in the whole muscle there are so many of these fibre groups working independently that the contraction rises and subsides smoothly.

On the whole it appears that the frequency of the impulses varies over a more restricted range in the motor than in the sensory discharge, but the two are so closely alike that the mechanism of the sense organ and of the motor nerve cell must have much in common. They have, of course, the common factor of a nerve fibre which can only respond in one way, but the likeness goes beyond this. Also the particular frequencies which commonly occur are lower than they would be if determined solely by the characteristics of the nerve fibre. In quiet breathing, for instance, at each expansion of the lungs the sense organs of the vagus send up a train of impulses rising to a frequency of about 20 a second at the height of inspiration, and simultaneously the movement of expansion is being produced by trains of motor impulses rising to much the same frequency and almost indistinguishable from the discharge in the sensory fibres. In fact the motor nerve cells seem to be acting just like a collection of sense organs responding to a rhythmic stretch.

Resemblances of this kind show that there is an underlying unity of response in the various parts of the neurone in spite of their differentiation into axon, dendrites or terminal arborizations. They show, too, that a knowledge of the mechanism of the sensory end organ might lead us very far in our search for the mechanisms of the central nervous system. Here we must enter a more speculative region, but there are certain pointers to guide us. In the nerve fibre, for instance, a rhythmic discharge of impulses may arise from an injured region. Electrically such a region behaves as though it were permanently instead of momentarily active. It is at a negative potential to the rest of the fibre owing to the destruction of the polarized surface membrane, and we have fair grounds for supposing that the rhythmic discharge is a consequence of this depolarization. A closer parallel with the sense organ is afforded by a muscle fibre bathed in a solution of NaCl instead of its usual Ringer's fluid. Sooner or later such a fibre becomes spontaneously active, the activity consisting of a serial discharge of impulses from some point. At an earlier stage, however, the activity can be started, as with a sense organ, by mechanical deformation, and it ceases when the deformation is over. Thus a muscle fibre may discharge impulses in response to stretch or touch almost as though it had been transformed into a muscle spindle or a touch receptor, though naturally it is a far less perfect instrument for translating mechanical stress into an impulse message. Here again there is reason to suppose that discharge of impulses is due to a breakdown in the polarized surface, a breakdown which is repaired as soon as the mechanical stress is removed.

Analogies of this kind suggest that sense organs and nerve cells send out impulses because some part of their surface has become depolarized. There are certain difficulties to be faced before this can be treated as more than a crude working hypothesis, but it is one which has important consequences. If the regions from which the discharge originates remain partly or wholly depolarized as long as they are excited, it should be possible to detect potential changes of relatively long duration in sense organs and in the motor nerve centres. Such changes are well known to occur in the eye, and they have been found in the vertebrate brain stem and in the nerve ganglia of insects. Unfortunately the structures in which they occur are so complex that it is difficult to be sure of their interpretation, but at least they suggest the possibility of obtaining direct records of the activities of the grey matter. To extract much information from such records is likely to be a far harder task than it has been in the case of peripheral nerve. In the latter our chief concern is to find out what is happening in the units, and this turns out to be a fairly simple series of events. Within the central nervous system the events in each unit are not so important. We are more concerned with the inter-actions of large numbers, and our problem is to find the way in which such interactions can take place*.

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*The lecture was illustrated by lantern slides and gramophone records.

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