CHEMICAL WAVE TRANSMISSION IN NERVE

THE PROBLEM

I AM glad indeed to have this opportunity of presenting to an audience of chemists (and I hope there may be physicists and engineers among them) a problem in physiology which is one of the most fundamental of its kind and seems likely to need all the resources of science for its solution: and I am very grateful to the Master and Fellows of Christ's College for their invitation to give the Liversidge Lecture which provides the opportunity. I have borne in mind that my duty is to speak to chemists: if there be physiologists present they come at their own risk, the risk, namely, of hearing much that they know already. The opportunity I welcome is to discuss one of the essential problems of biology, stripped for once, so far as may be, of its biological clothing, exposed in its full chemical and physical nakedness.

The title chosen assumes that the "something" which is transmitted in nerve, when an impulse runs along it, has some of the properties of a wave, and that these properties can best be described in chemical, or strictly speaking in physico-chemical, terms. It does not imply that chemistry is able now, or will be able some day, to explain all the behaviour of the nervous system: no such hypothesis is necessary, as Laplace said of another matter: indeed, for all I know, the boot may prove to be on the other leg: it may some day be necessary to invoke the properties of the human nervous system to explain the theories which chemists, or at any rate physicists, invent to account for the phenomena they observe! It may be that the discontinuous nature of sensation and, so far as we are aware, of all nervous action, including probably thought itself, the fact that these depend on the transmission not of continuous states but of discrete and separable wave-like impulses, allow only certain types of phenomena and relations to be perceived and appreciated: so that atomic and quantum hypotheses may ultimately be found to depend upon the nervous apparatus through which the phenomena, on which they rest, have filtered. I say this, not as an expression of faith, not even to discipline my physical friends, but to show that I am not too confident a mechanist, that I am perfectly well aware that stripping a problem of its biological clothing may be like depriving a man not of his shirt but of his skin!

All our sensations, all our movements, probably most of the activities of our nervous systems, depend upon the properties of a certain transmitted disturbance which we call the nervous impulse: this to neurology is what the atom is to chemistry, the electron and the quantum to physics. Such transmitted disturbances, as a matter of fact, are not peculiar to nerve: they occur rather generally in the protoplasm of cells, not only of animals but of plants. A rapid reaction to events occurring at a distant point may be necessary for efficient working or for safety. Most living cells, however, are small, so that the distances involved are usually a few thousandths, or at most a few hundredths, of a millimetre: and over such small distances the velocity of transmission being of no great concern, a highly differentiated process is unnecessary. As soon, however, as larger complex animals were evolved, the problem of reaction to events occurring at a distance became more acute, and special cells were developed to deal with it. These cells are still small in all dimensions but one: a fine thread, however, the axon or nerve fibre, runs out from them, which is only 3–25 μ (0·003–0·025 mm.) in diameter, but in the largest animals may be many metres in length. Along these threads messages—not material substances—are sent. We are concerned with the nature of these messages.

THE VELOCITY OF NERVE IMPULSES

Medullated nerve, mammal,[1] 37° C., about 100 m./sec.
Medullated nerve, dogfish,[2] 20° C., about 35 m./sec.
Medullated nerve, frog,[1] 20° C., about 30 m./sec.
Non-medullated nerve, crab,[5] 22° C., 5 and 1·5 m./sec.
Non-medullated nerve, mammal,[3] 37° C., about 1 m./sec.
Non-medullated nerve, olfactory of pike,[4] 20° C., 0·2 m./sec.
Non-medullated nerve, in fishing filament of *Physalia*,[3] 26° C., average 0·12 m./sec.
Non-medullated nerve, in Anadon,[1] 0·05 m./sec.
Comparate the velocity of sound in air at 0° C., 331 m./sec.

[1] See Broemser (1929).
[2] See Monnier and Monnier (1930, p. 14).
[3] See Parker (1932 *a*).
[4] See Nicolai (1901).
[5] See Monnier and Dubuisson (1931).

THE NERVOUS SYSTEM

Each nerve fibre depends, for its continued existence, on an intact connection with its cell—it is part of the cell (see fig. 1). Cut it at any point in its course and the peripheral portion (that remote from the cell) loses its function and dies. The "degeneration" takes a few days and travels progressively down the fibres. It is not the absence of normal activity which causes loss of function,

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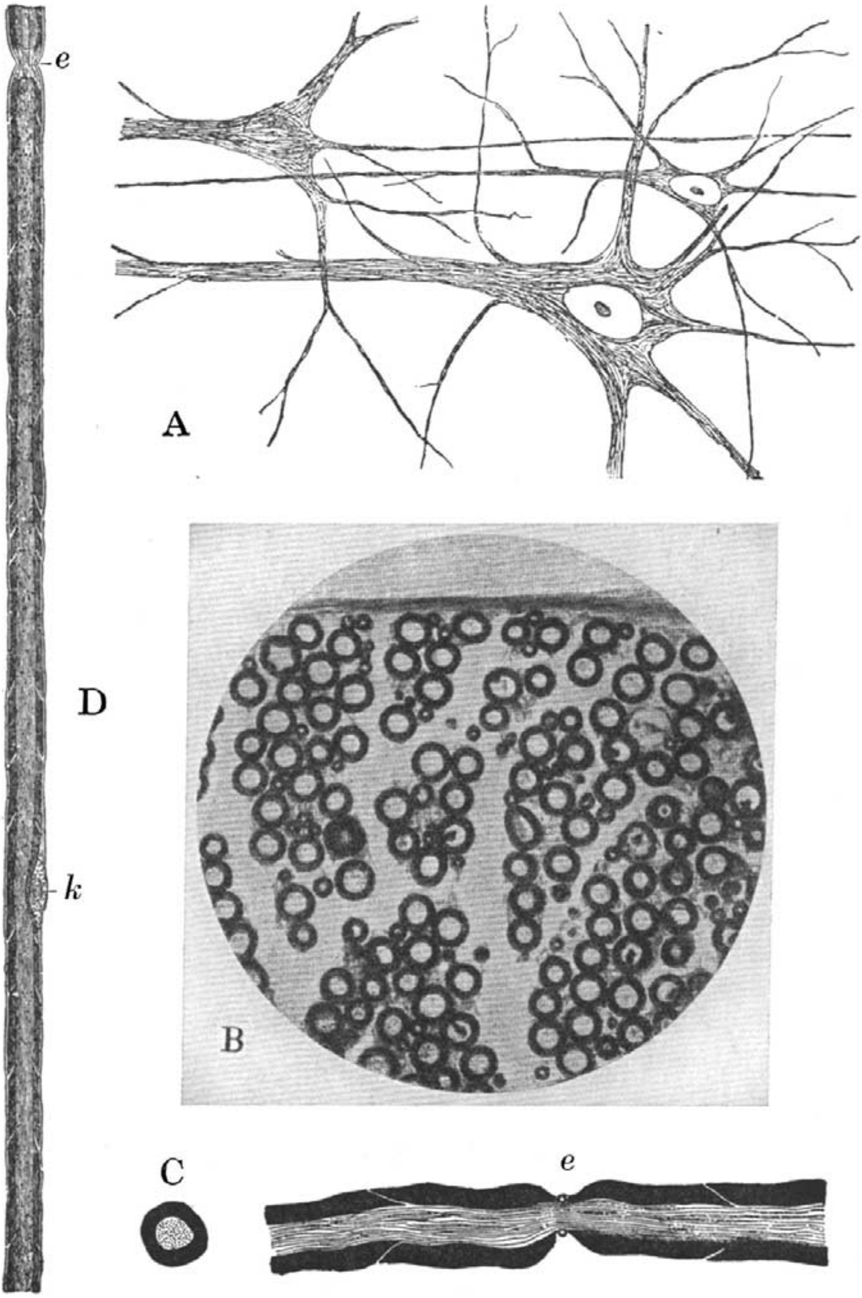

Fig. 1. *A*. Three nerve cells with "processes". The nerve fibres shown in *B*, *C* and *D* arise as processes from such cells: other processes maintain functional connection between the cells. *B*. Section of the sciatic nerve of a cat, showing the variation in size of its constituent fibres. The black rings are the sheaths, the white areas inside are the axis cylinders. *C*. Diagram of medullated nerve fibre on larger scale, transverse and longitudinal sections. *e*, node of Ranvier. *D*. Medullated nerve fibre. *e*, node of Ranvier; *k*, nucleus. In *A* the preparation was treated with Ramón y Cajal's silver nitrate "photographic" method: in *B*, *C* and *D* with osmic acid, which stains the lipins black.

for in a sensory nerve such normal activity starts from the peripheral end where it can still start after the lesion. It must be the absence of a connection with the nerve cell which makes the axon degenerate. The latter will grow down again from above if the cut ends are kept in juxtaposition, but that is a slow matter.

At first it might have seemed that the cell is supplying something material which is passed along the intact fibre. The distances involved, however, may be so great that some very special method of passage would be required: as Sir W. B. Hardy once said, it would require geological time for diffusion to work between the spinal cord and the tail of a whale! (see also Hardy, 1927). Moreover, with a surface so relatively large, 2000 sq. cm. or so per gram, and a wall so thin, there could scarcely fail to be loss on the way. I doubt therefore whether any material substance travels far along the fibre, although Parker (1932*b*) thinks that some hormone-like controlling substance percolates down the nerve from the nucleus of the cell. I am more inclined to believe that its state is maintained by an influence of some sort, by the field of one molecule on the next. If so, here is another type of transmitted effect, one which physical chemistry may help to make intelligible; it is altogether different, however, from the rapid wave-like impulses which make up nervous activity, and we will return to these.

In a telephone system it is impossible to arrange that each subscriber shall be connected with every other by a separate line: exchanges and groups of exchanges are required. Similarly in animals where it is necessary that any part shall be able, on occasion, to call for reaction in any other part, ganglia and groups of ganglia are needed: a central nervous system comes into being, based in its highest forms largely upon the distance receptors, particularly on those which are sensitive to light. Into this central organ most of the cells themselves (*A*, fig. 1), as distinguished from the fibres in which the messages go (*B*, *C*, *D*), are collected. This is not the occasion to discuss the central organ itself: those who wish to know more about it and the way in which messages are sorted and co-ordinated there, are referred to a recent work, *Reflex Activity of the Spinal Cord*, by Sir Charles Sherrington and four of his collaborators (Creed, Denny-Brown, Eccles, Liddell and Sherrington, 1932).

MESSAGES—EVENTS, NOT MATTER OR ENERGY

I have spoken of messages, not material substances. It is inconceivable indeed that discrete packets of any actual substance could travel 100 m. per second and 500 times per second in either direction along a jelly-like thread only 0·01 mm. in diameter and containing 80 p.c. of water: and yet apparently not accumulate at the end, or leak over into similar threads lying within a few thousandths of a millimetre. There are no tubes in nerves through which "vital spirits", or Descartes' subtle vapour, or Borelli's "succus nerveus" might be squirted (see Borelli, 1710, Part II, p. 37): and there is no conceivable mechanism by which separate material projectiles, with the properties which I will describe, could be fired along such an unpromising channel.

Nor, on the other hand, is there any evidence that the nerve impulse is a special form of energy. We hear the expression "nervous energy", and some psychologists speak as though this peculiar entity could be "drained" along tracks in the nervous system. The expression and the mental picture which it calls up have no more scientific basis than the "iron nerves", or the "steel sinews", or the "icy stare", of common speech. They may be justified when we speak in parables, but they have no place in scientific discussion. Energy, as we shall see, is liberated during nervous activity as in all natural processes, but there is no reason to think that this energy has any peculiar properties: it is derived from chemical reaction. It is safer to avoid expressions which can be, and often are, misunderstood.

THE NERVE FIBRE

The nerve impulse then is an event, not a substance or a form of energy, and it is transmitted along a tiny thread of protoplasm which in some cases, but not all, consists of two separate parts, an axis cylinder and a sheath (see fig. 1). It then looks like an electric cable with conducting core and insulating cover. The sheath contains a large proportion of fatty substance, as is shown by its staining properties: and it has little breaks at intervals, the nodes of Ranvier, to which no definite function has yet been allotted. Its material is of high specific resistance (Appendix 1). The axis cylinder, or core, is a soft transparent thread of protoplasm, a jelly-like substance much the same as is found inside other living cells: its specific resistance is low. In non-medullated fibres, which occur in the peripheral parts of the involuntary nervous systems of vertebrates and in the finer connections of their central nervous systems, and are the only type to be found in most lower animals, nothing but the jelly-like core can be seen: the sheath is so thin that it amounts to no more than a film, probably only a few molecules thick, such as exists at the surface of many living cells. The structure, alas, particularly after fixing and staining, tells us little about the function: we have to employ other methods than those of the microscope.

The osmotic pressure of the core of a nerve is the same as that of blood and other organs: in frogs it is that of a 0·7 p.c. NaCl solution, in mammals 0·95 p.c., in sea crustaceans (crabs, etc.) more than 3 p.c. This is made up almost entirely by common ions, $Na^{\cdot}$, $K^{\cdot}$, Cl', phosphate. In blood, of the cations $Na^{\cdot}$ is in great excess: in nerve, as in muscle, there is a large preponderance of $K^{\cdot}$. The potassium is of great importance, as we shall see, in relation to the electrical potential difference normally existing across the boundary.

THE ELECTRIC “ACTION CURRENT” OF NERVE

One naturally asks—how can the presence of an impulse in a nerve, or its arrival at the other end, be detected? Firstly, of course, by the physiological effect—sensation or response as the case may be. That, however, requires an intact animal, or at least that the nerve should be connected to some organ, e.g. a muscle, to effect the response. It is fortunate, therefore, that isolated nerves work well for hours, indeed for days, after separation from their original owner, and that another method is available for detecting the presence of an impulse in a nerve—the method of recording the electric change which goes with it. This electric change seems to be a universal accompaniment of the impulse, it can be used as a sign of its presence, as a measure of its size.

No difference of electrical potential can be detected in an uninjured resting nerve: without injury or stimulation we can examine only the uniform outside surface. If, however, a nerve be injured, as by cutting it, a potential difference is found, of the order of a few hundredths of a volt, between the injured and the uninjured points, in the sense that positive current runs in an external circuit towards the injured part. The source of this potential difference is probably a polarized state (fig. 2) in the surface membrane of the nerve fibre, the electrode at the injured point making contact, more or less effectively, with the inside of the fibre, the inner surface of the membrane. The injury *does not produce* the potential difference, it merely allows it to be manifested. In certain very large plant cells direct contact can be made with the inside of the cell by a capillary electrode and analogous electrical phenomena can be shown (see Osterhout, 1931, p. 381, etc.).

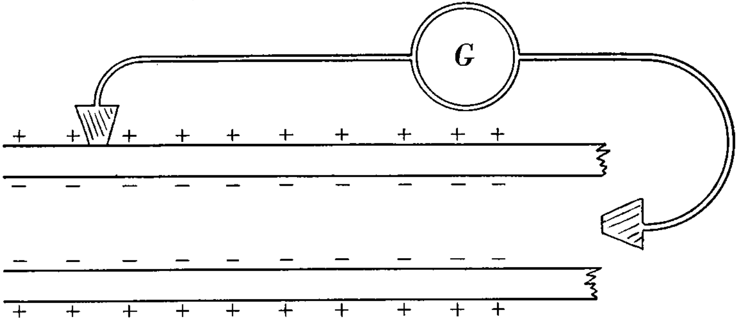

Fig. 2. The polarized state at the surface of a nerve fibre, shown by means of an injury at one end and two electrodes placed, one at the injured and the other at an uninjured point. By using a potentiometer, instead of the galvanometer *G* shown, the potential difference may be measured. Allowing for the degree to which it is short-circuited by the conducting fluids around the fibre it is probably of the order of 50 mv. In crab's nerve, with a strong salt solution between the fibres, it is regularly measured as 30 mv.

If two electrodes be placed upon a nerve and the nerve be stimulated, e.g. with a single rapid condenser discharge or a single induction shock, a momentary change travels along it which can be recorded with the cathode ray oscillograph, or some other suitable instrument. At any given instant a certain length of the nerve, of the order of a few centimetres, is found to be the site of a wave of negative potential, that is to say a positive current will run, in an external circuit, from a resting to an active point. The amplitude of this wave is a few hundredths of a volt: it moves at a speed depending on the nerve and the temperature—anything from 0·05 to 100 m. per second. We are probably right in thinking that the impulse itself, whatever it is, occupies the same region, and moves at the same speed, as its electrical accompaniment (see figs. 3, 4, 5, 6).

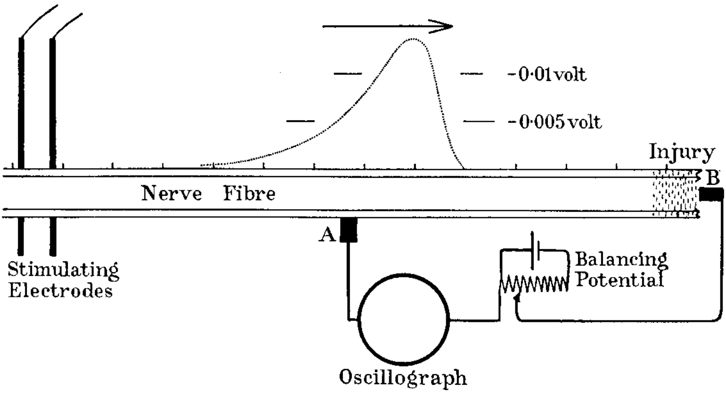

Fig. 3. The action current in a medullated nerve fibre at about 6° C. Distances marked in cm. A shock is given at the electrodes shown on the left, and the impulse travels to the right at about 10 m. per second. The action current ("monophasic") is picked up by electrodes at an uninjured point *A* and an injured point *B*, so as to avoid the complication of a diphasic record, which occurs if the wave passes both electrodes. The "injury" or resting potential between *A* and *B* is balanced and the potential difference caused by the passage of the wave is recorded on the oscillograph. It follows the course represented by the dotted line, occupying at any given instant a few centimetres length of the nerve.