

*John Nicholls
with best wishes
from Bernard Katz*

*Different Forms of
Signalling employed by
the Nervous System*

By BERNHARD KATZ

An Inaugural Lecture delivered at
UNIVERSITY COLLEGE LONDON

DIFFERENT FORMS OF SIGNALLING
EMPLOYED BY THE NERVOUS SYSTEM

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DIFFERENT FORMS OF SIGNALLING EMPLOYED BY THE NERVOUS SYSTEM

WHEN PREPARING THIS LECTURE, MY FIRST THOUGHT was that I should be more or less obliged to take as my subject the recent emergence of Biophysics as an independent branch of Science. It seemed that something on this theme might be expected from me, having been appointed to an almost newly-founded chair.

However, second thoughts deterred me. After all, our Biophysics Department is only new in name, for Biophysics has long been a tradition here, a tradition linked for all time with the name and work of A. V. Hill. I greatly regret having unwittingly chosen a time for this lecture when A.V. could not be present; but his absence gives me at least the opportunity, without embarrassing him, of expressing my gratitude to him for all I have learnt, not only as a pupil of a great master of experimental research, but by having served my apprenticeship with a man who never, under any circumstances, allows the deceptive counsels of human vanity to enter into your argument—with a man whose one inflexible purpose has always been the pursuit and the acknowledgement of truth.

As the place of Biophysics here in the College has been firmly established by A. V. Hill, I felt that it would ill become a person of my own dubious qualifications to introduce himself to you by trying to tell you what Biophysics is, or ought to be. I am therefore discouraged, at the outset, from pursuing this line, but another consideration impresses me as an even more powerful deterrent. During recent years quite a formidable literature has developed, not altogether free from controversy, in which many different attempts were made to define the word 'Biophysics'. The definitions range from the very simple one, namely that Biophysics is what Biophysicists do, to quite elaborate discourses. If I may express at least one of my estimates in a proper quantitative fashion, I should say that the ratio between the number of existing definitions of the word 'Biophysics' and the number of persons professing to be Biophysicists must come close to, if indeed it does not exceed, unity. I

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have alluded to the somewhat contradictory nature of these discourses, but the more serious ones had one peculiar feature in common, namely that they were concerned not only, and perhaps not so much, with the positive definition of what the new branch of science was to comprise, but with what was to be left of the already mutilated torso of its parent, Physiology. I had the impression that in these discussions the authors were engaged in the performance of a severe surgical amputation on a close friend without first obtaining, or even asking for, his consent. That shocked me a little, because having once been trained as a doctor, the impropriety of this conduct happens to be one of the very few items of indoctrination which have been retained by my memory.

But to conclude this preamble on a somewhat more serious note: I have had, of course, to consider carefully—not so much the *general* purpose of Biophysics, which presents itself in different ways to those engaged in it—but the way in which I might discharge my own obligations here. My academic background is very limited, my training—the truth has been let out—was an ordinary medical course, and that must have some effect on my attitude. I think that one of the most practical things which we can do here is first of all to serve Physiology. There are certain branches of Physiology which require a continuous, rather intimate, acquaintance with the mental and technical equipment of physics and physical chemistry. It is these branches of Physiology which suffer most from the inevitable process of specialization, with the result that they may easily become starved, deprived of devoted students, and would tend to disintegrate unless special efforts are made to save and foster them. Now if you can create a few institutions here and there, where such borderline work is maintained, and if you can promote an active turnover and frequent exchange of the junior staff with that of other—and I should think mainly of Physiology—departments, then it should be possible and not difficult to maintain a fresh vivid interest in these precarious parts of physiological science and re-inject such interest continually into the general circulation of the parent body.

But now I really must leave this business of pretentious definitions and policy statements and the like, and come to the point of

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my lecture, the point being one of those special subjects in which biophysicists have for long been interested, namely the modes of signalling which exist in our nervous system.

I have chosen as my subject: 'The different forms of signalling employed by the nervous system.' This will by itself convey little to most of us here, but those who have had some acquaintance with our physiology teaching course may regard it as a little provocative. For have they not been taught by my colleagues, and probably by myself, that there is only one exclusive form of signalling employed by the nervous system, a very simple form which in some ways resembles the elementary Morse code. And it can be said to be even simpler than the Morse code in that it is made up entirely of dots, and has no use whatever for dashes. If they will bear with me, I think I had better try and explain this a little. Our nervous system is often compared with a vast telephone exchange, which contains a very elaborate central switching system and an enormous number of private trunk lines, which are also known as nerve fibres. During the normal signals traffic, brief electrical pulses keep travelling along these fibres at about the speed of a good racing car or even a little faster. The individual signal which sweeps along the optic nerve when a flash of light falls on our eye, or which causes a muscle to twitch, can be described as an electrical pulse which travels along the surface of the fibre. What actually happens is that the cylindrical surface membrane of the fibre, which is normally kept charged to about a tenth of a volt and positive on the outside, momentarily reverses its electrical charge, and becomes negative on the surface, and this change passes on automatically and rapidly from point to point. It is a transient event, all over within one or two thousandths of a second, and it leaves the fibre in a state of enforced silence for about the same length of time before the fibre becomes ready to conduct another, identical impulse.

Modern methods enable us to obtain faithful records of this electrical change from nerve bundles, or better from single fibres, and perhaps the most outstanding feature of this phenomenon is its relative constancy, constancy in amplitude, which amounts to a little more than one-tenth volt, and in duration—which is one or a few thousandths of a second; and this general rule applies to many different conditions, to many sorts of nerves and many kinds of

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animals. What does vary from one type of fibre to another are certain quantitative details of this signal, mainly the speed of its propagation. Now it is this stereotype standard form of nerve impulse which physiologists meet wherever they record nerve activity, and which one may fairly compare with the dot, or flash, of a single-element communication code. All information conveyed along nerve fibres is carried by these signals, and as they are individually of standard form and of practically fixed amplitude, nerve messages may be likened to a cypher, the sole key to which is provided by the timing of successive signals, their intervals, and the pattern of groups of such intervals. You will presumably have heard of the classical investigations of Dr Adrian, which have shown us the truly universal role of this type of coding in all kinds of nerve tissues. I expect you will also have heard of the so-called 'all or nothing' law by which the rigid and almost invariable form of the nerve impulse has often been described. And perhaps it was really unnecessary to go here into all these rather elementary details, because I should think that at least one or two of my most distinguished friends have already explained all this to you *via* the B.B.C. They will have told you quite plainly that all the business of the nervous system is transacted by these stereotype brief nerve impulses whose intensity and duration have been fixed once and for all, and which cannot be modulated in the normal process of signals traffic.

But the purpose of this lecture is to suggest—and this is of course well known to the experts—that what I have just said is not the whole truth, and that the nerve impulse is only one of the forms of signalling which we employ; it is a technique of transmission which nature has invented to establish connection between distant points, and to ensure that messages can travel over the long trunk lines in our body without fading or being lost in transit. I shall endeavour to point out that this rigid type of coding, based on a fixed impulse, and very necessary as it is for our long-distance lines, is certainly not the only method which we use; it is discarded at many points for a more flexible form of activity. I am thinking of the innumerable junction points or, as it were, the switch points and sorting-out stations of our nervous signals exchange, the places at which messages from different sources converge and interact. At

these junctions, sets of impulses of different origin must be combined and integrated into new signals, and for this transformation a different and much more flexible form of activity is needed. This is evidently so because the nerve impulse in its normal form does not lend itself to any integration at all; it is an 'all or none' event which can precede or follow, but which cannot summate with other signals. What we require, at our nervous junction points, is a pliable form of signal, one that can be modulated and will allow converging messages to summate. With this aspect I should like to deal a little more in the rest of my lecture.

It is perhaps desirable first to explain in simple terms the meaning of the 'all or nothing' law, and the reason why the operation of our long-distance lines inevitably depends on it. I have already made use of the telephone analogy, and I should think that ever since the telephone and other electrical communication apparatus have been invented, it has been customary to compare them with our nervous system. These analogies are often quite interesting, and it is also quite instructive to discuss their most obvious failings. I think the most obvious and essential differences between model and reality are to be found first, in the entirely different spatial scales which are being employed and, secondly, in the fact that our nervous system, like the rest of our body, is made of much cheaper, much more consumable, material. I do not think that even the most adventurous engineer would come forward and make a tender for the construction of a communication equipment if all the materials he could use were water and a small quantity of the commonest chemical elements that you can find in the sea, and the air around us, but no copper wire, and no good insulating materials. And yet, many physiologists have considered it worth their time to study and appraise the properties of nerve fibres, regarded simply and only as transmission lines, as cables, and there is no doubt that the structure of a nerve fibre resembles in a way that of a submarine cable, even if this resemblance holds good only on a miniature scale.

To understand why nerve fibres have, even remotely, the properties of cables, I must say a few words about their physical construction. They are long cylindrical tubes filled with a material which is relatively speaking, that is as biological materials go, a

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good electric conductor. It is a jelly-like substance which contains mainly water and dissolved in it some salt of the same concentration as in the surrounding body fluid. But while the osmotic and electrical properties of the interior of the fibre are much the same as those of the surroundings, its chemical composition differs greatly. We know, for instance, that instead of sodium ions which are the most abundant cations in the tissue fluid, we have mostly potassium ions inside the cell. Now the important point to remember is that at the surface of our tube, separating the two aqueous solutions, there is a delicate layer of material which acts almost like an insulator. It presents a very formidable barrier to ions and, judging from all its known properties, is best described as a layer of non-conducting lipoid material. We call it the surface membrane. It has been possible to measure its electrical properties; we know for instance that the nerve membrane has an extraordinarily high resistance, several thousand ohms across one square centimetre, and a high capacity, about one or a few microfarads per square centimetre. We also know that it is electrically charged, the interior of the fibre being nearly 100 mV negative with respect to the outside. But while we can make these measurements quite accurately, we cannot claim ever to have seen our membrane under the microscope. And this has placed us into a slightly embarrassing position, especially when we are confronted with those of our colleagues who disbelieve any evidence that has not been obtained by optical methods. Fortunately some of our electrical measurements allow us to make a deduction about the thickness of this insulating surface layer, and although these estimates are far from certain, we have grounds for believing that our membrane is an extremely thin structure, probably only a few molecules across. This has provided us so far with an excuse, or I think one can say with a good reason, for refusing to identify our nerve membrane with any of the interesting microscopic structures whose tempting pictures we are occasionally shown by our friends the anatomists. Admittedly such persistent refusal to commit ourselves leads occasionally to an acrimonious scientific dialogue, but I think it remains quite true to say that anything which is coarse enough to appear as a visible structure under the microscope is not the membrane which we are after but, more probably, a skeleton sheath, perhaps serving to

support and to protect mechanically the more delicate material whose properties we have been measuring.

Let me summarize once more. The electrical structure of our nerve fibre can be described as a long narrow cylindrical tube filled with conducting material and surrounded by conducting fluid, but separated from it by a highly resistant, almost insulating membrane. This is, at long last, the explanation of the cable properties of the nerve fibre; for a cable, like a nerve fibre, is a flexible, cylindrical transmission line consisting of two coaxial conductors separated by a cylindrical insulating sheath. But this is only a qualitative picturesque analogy, and when we come to consider quantities, the picture is not nearly so attractive. We find that the conductivity of our nerve fibre is about a million times less, and the leakage of its insulating membrane about a million times greater, than what we demand of a good commercial cable, and that is of course an important point where our whole telephone analogy breaks down. It follows that the dimensions and the quality of the nerve materials are quite unsuitable if our physiological trunk lines were to act simply as cables and to carry messages whose energy had been supplied solely at their point of origin.

Of course, the events that take place in a nerve fibre when an electric signal is applied to it differ very substantially from what happens in a simple electric transmission line. The events in our nerve depend critically upon the strength of the applied signal; and there is one level of signal strength at which a dividing line between two kinds of behaviour can be drawn. If the intensity of the electrical signal, say of a brief pulse of current which flows through one segment of our nerve, is less than this critical so-called threshold level, then nothing at all is registered at a distant point. But it can be shown that in a region, extending a few millimetres around the place of origin of the signal, the nerve cell behaves indeed as a simple, though very badly made, cable. The weak, subthreshold signal is transmitted over a very short distance, and because of the deficient quality of our nerve materials, it completely fades away while it travels over a length of a few millimetres.

This subthreshold, cable-like behaviour of the nerve cell has sometimes been regarded as of little or no physiological significance; it is evidently a mechanism which, taken by itself, is of little

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use for long-distance communication and quite inadequate when we require to convey information along the whole length of a limb. But we must remember that at many points of the nervous system the message does not require to be immediately conveyed over long distances, but rather to be held, balanced against, added to, or subtracted from, other messages of different origin which arrive at the same sorting point. It is at these places of mixing, sorting, and balancing that the subliminal spread of signals becomes very important, for this is a process which allows each signal to be presented in a form in which its amplitude and duration can be modified, and in which it can be modulated, for instance, by the addition of other electric signals at nearby points of the same cell, or even at regions which are a few hundred microns away.

The subthreshold cable-spread which I have just described differs greatly from the much more dramatic process which I have mentioned initially, namely the firing of a brief impulse of all-or-nothing character. This event occurs when the electric signal at any point of the nerve exceeds a critical threshold intensity. At this firing level a powerful reaction occurs in the surface of the nerve cell. Thanks to the work of Professor Hodgkin and his colleagues at Cambridge we now know a good many of the steps, electrical and chemical, by which this reaction proceeds and by which it is subsequently cut off, but for our present purpose we are only concerned with the immediate result of the reaction. The result is invariably a large electrical pulse amounting to some tenfold amplification of the originally applied threshold signal, and this amplification is achieved at the expense of energy resources within the nerve cell itself. In other words, quite unlike an ordinary telegraph wire, the nerve fibre can be stimulated to release energy which had been stored in it, to amplify electric signals, boost them up to a saturation level, and to enable them so to be passed on from point to point along the whole trunk line without the otherwise inevitable loss of signal strength. Although the elementary constituents of our nervous apparatus would seem to be cheap and poor by comparison with the metals and insulators preferred by electrical engineers, these deficiencies have been compensated by nature, and supplanted with an elaborate organization of energy-

giving and energy-releasing reactions. In the particular case of the nerve impulse, the immediate reaction to the stimulus is of a self-amplifying, or explosive, type, in which the resultant electric change reinforces its initial cause.

Let us be a little more explicit about this. I mentioned earlier that the resting nerve membrane is subjected to an electric field. There is a potential difference of about one-tenth volt, the inside of the fibre being negative, the outside positive. Now our membrane must be presumed to be extremely thin, perhaps only one-millionth of a centimetre across, and one-tenth volt across such a thin dielectric is equivalent to a field strength of 100,000 volts/cm. Such a strong field is likely to have a profound effect on the physico-chemical properties of the membrane material, and there is indeed some interesting evidence, due largely to Hodgkin and Huxley, that the electric field across the membrane, and variations of this field, control in some subtle manner the membrane permeability or, if you like, the specific resistance which the membrane material offers to different species of ions. We know that under normal resting conditions, with one-tenth volt across it, the membrane is *relatively* much more permeable to potassium than to sodium. However, if you suddenly reduce the electric field, for instance, by passing a current in the outward direction, the immediate effect is a large, specific increase of sodium permeability. This has interesting consequences. Sodium ions rapidly enter the fibre, flowing down their concentration gradient: some of the residual negative charge inside the fibre is neutralized by the entering cations, and, as a result, the electric field across the membrane is further reduced, and consequently the sodium permeability again increases and more sodium enters. Here we have a snowball phenomenon, an action which increases its own momentum and proceeds automatically until a saturation level is reached. This is attained when the charge of the interior of the fibre is sufficiently positive to repel electrostatically any further influx of sodium ions. But before this happens, a second reaction usually occurs, which cuts the whole process off and reverses it. We know, again from Hodgkin and Huxley's experiments, that the second reaction is accompanied by a vastly accelerated outflux of potassium ions, and that the original electric field across the membrane is restored by the outward

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movement of potassium ions. Thus the brief electrical impulse which constitutes our nerve signal is associated with an exchange of cations across the fibre surface, in which some $2 - 4 \times 10^{-12}$ mols. of sodium move in across one square centimetre of fibre surface, and an equivalent amount of potassium moves out. This exchange involves only a minute fraction of the ion content of the fibre, but it means that some of its potential energy store has been expended, and sooner or later the loss must be made up by extruding the excess of sodium and re-accumulating potassium to the original concentration level. But do not let me stray too far from my argument. The important thing to remember is that the influx of sodium across the membrane is controlled by the electric field, and that the influx of sodium in turn alters the electric field in a regenerative or automatically self-reinforcing manner. And this is why electric excitation of a nerve fibre is a self-amplifying reaction, a reaction which manifests itself in an explosive event of all-or-nothing character. Once fired off, it proceeds towards saturation point; which is really what 'all or nothing' reaction means. In other words, the impulse, once released and on its way, is a self-supporting event, quite independent of the original initiating stimulus. It is a process which runs through its own cycle, depending upon the provision of energy by the cell and no longer in any way dependent upon the form and quantity of energy which the originator of the signal supplied.

The implications of the 'all or none' reaction are so well known and have been presented in so many popular talks that I can pass them over quite quickly. As I have already pointed out, it imposes a rigid coding system upon our communication equipment whose key is provided entirely by the time sequence of its standard dots. The main advantage of this system is that the transmission of the signal is ensured along the whole length of the line with a good safety margin. But this advantage has been achieved at a considerable cost. The price is loss of flexibility, the only medium by which information can be conveyed being a rigid, almost invariable, standard pulse, which cannot be modulated in any way. It does not allow other signals to pass it, in opposite direction; and in any one nerve fibre there must be throughout its normal life a strict one-way traffic. We can see why it is necessary for our nerves to rely

upon this rigidly simple method of coding, but it makes it necessary for us to have ready, for simultaneous use, an enormous number of separate private communication channels. This is necessary so that a large volume of messages can flow simultaneously at an adequate rate and in both directions, and that we may be able to pass all the required signals, informatory as well as executive, between centre and periphery without risk of a traffic jam. To illustrate the multiplication of nerve channels which we need, there are about one million nerve fibres, that is to say one million private lines, emerging from each eye into the optic nerve.

Now it has always been clear that the all-or-none type of signal is subject to great limitations and cannot possibly serve more than the limited function of providing a rapid through-connection between two fixed points. As I have already pointed out, it could not be used in unchanged form at any of the nervous junction points where a message is to be held and balanced against, or added to, other signals. It is here that other, less rigid forms of signal service must be employed, and during the last fifteen years some light has begun to be shed on the physical and chemical properties of these junctional processes.

It was suggested by Keith Lucas some forty years ago that the nervous junction points, the so-called synapses, may be regarded as microscopic regions in which the nerve impulse undergoes what he termed a 'decrement'. We should now say that the impulse loses its explosive, through-conducting force at these points, and is, at any rate temporarily, reduced to a subliminal signal which tends to fade out, but is capable of being modulated by other signals. It took some twenty years or more since Lucas' first pronouncement to find good experimental evidence of such subthreshold junctional effects, and I am thinking here in particular of the work of Barron and Matthews in 1936. But since then, the evidence has been extended to every junction which it has been found possible to investigate by modern means.

The original findings of Barron and Matthews were so important that I should like to describe them in some detail. If you pull a frog's leg, or perhaps I should say if you pinch its foot, the result of this stimulation is a reflex discharge of motor nerve impulses which emerge from the spinal cord and cause the animal to withdraw its

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leg. We call this automatic attempt at removing or neutralizing the effect of a stimulus, a reflex. It had been well known long before their work that such a reflex involves the passage of impulses in sensory nerve fibres up to the spinal cord, and a burst of impulses in motor nerve fibres coming out of the cord and activating a suitable set of muscles. Barron and Matthews were able to record the local electrical events which occur at the relay station of the spinal cord, at the point where the incoming sensory messages are transcribed into executive signals to the motor nerve. They showed quite unequivocally that the first signal impressed on the motor nerve cell was not an impulse, but a local subthreshold potential change which varied in strength and duration with the intensity and duration of the original leg-pull. It remained localized, fading out within a few millimetres of the motor nerve root, unless its intensity exceeded the threshold of the cell, in which event motor impulses were fired, proceeding in the usual non-stop manner down to the muscle. The local electrical change appeared to be an essential link in the transmission of the reflex discharge, and Barron and Matthews made the pertinent observation that it resembled in every respect the local cable-spread of a subthreshold potential in a nerve fibre around the region where a weak electric signal has been applied. Here then we have the form of local activity which can do precisely what is required and can account for the summation of converging impulses. The question arises whether reflex inhibition can be explained by some form of local activity by which a subthreshold signal is reduced in size or cancelled by signals of opposite sign. No final answer to this has yet been given. Some investigators still believe—though this is a rather old-fashioned view—that inhibition may be due to excessive strength of local signal activity, to a process of exhaustion rather than cancellation; and it may well be that a number of different mechanisms exist by which nerve signals can be suppressed at the central filter stations. But whatever the nature of the inhibitory influence it can only act by modulating and, in general, it acts by reducing, the strength of the local electric signal detected by Barron and Matthews. Subsequent investigators have found similar evidence of local, adjustable electric activity at many other nervous junction points. If I may generalize, I think one may say that the explosive type of signal, our long-distance

impulse of the all-or-none type, is transformed at every junction, at least temporarily, into a subthreshold form which, at the expense of a little extra time, adds flexibility to the communication system, the possibility of adjustment, of modulation of the signal and of its integration with other signals.

It is almost a commonplace to state that the process of signal transmission at the nervous relay junctions differs in important aspects from the process of signal transmission along continuous trunk lines. We know, notably from the work of Sir Henry Dale and his associates, that such special processes occur at the endings of one nerve relay, as well as at the beginning of the next unit. The story of the nerve endings, which is in itself a most fascinating chapter of physiology and full of mysteries, does not directly come into my present argument. Suffice it to say that many nerve endings are capable of releasing chemical stimulants. These are special highly potent molecules or ions having a specific chemical affinity to other receptor molecules, so called, in the contact surface of the next unit, and by this chemoreceptor action start a local electrical change in the surface of the adjoining cell. I believe this chemoreceptor mechanism at nerve junction points contains the key to what is the most probable mechanism of nervous inhibition. At least I feel inclined to agree with those who explain the antagonism between excitatory and inhibitory nerve impulses by the release of two different chemical substances at adjacent nerve endings; that is to say, the release of substances which either produce signals of opposite electric sign, or which compete for a hold on a common receptor molecule, just as curare and acetylcholine compete for the chemoreceptor molecules in the muscle fibre.

But we are not so much concerned at the moment with what happens at nerve endings. The relevant point is that the immediate electrical change which is produced at the beginning of a nerve cell is a local, graded signal capable of modulation, which may, or not, work up above threshold to a new explosive long-distance impulse. In many cases it does so only by coalescing and summing with other subliminal signals of a similar kind, impinging on the same cell at nearby points and at about the same time.

You may ask how it comes about that a powerful nerve impulse should be transformed at many junctions into a relatively weak

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subthreshold signal. Here again, the mechanism of chemical mediation provides a plausible answer. The intensity of the local signal set up in the next relay unit depends upon the quantity of chemical transmitter substance released by the nerve endings of the preceding unit, and not directly upon the size of its impulse. The matter is actually more complicated than this. Often extremely fine nerve endings make contact with the surface of a very much larger cell, and even if protoplasmic continuity between them existed, the impulse travelling along the fine endings would hardly be powerful enough to travel past the junction, for the simple reason that the two transmission lines are very badly mismatched. The electric current which a fine terminal branch can generate would, in general, be too weak to make much impression on the enormously expanded surface of the next unit. A special local amplifier would probably be needed here in order to produce even a modest subliminal signal on the far side of the junction. This important point is not always realized by those who argue that special chemical mediators at nerve junctions are redundant innovations of nature. On the contrary, they are probably needed to make a significant local impression on the surface of the next nerve cell.

During recent years the electrical signs of our local graded signals have been observed in an ever-increasing number of instances. Many investigators have recently been able to place their recording instruments close to a point in the nervous system where a signal is being started in a nerve cell, and the electrical signal at these points was invariably found to differ from the trunk-line impulse and to show the characteristics of the more pliable subliminal change. Electrical records of these local, non-explosive signals have been obtained at sensory nerve terminals, in the ear, eye, and muscle spindle, at the synaptic contacts of autonomic ganglia, and at the motor neurones in the spinal cord, especially in the most recent experiments of Professor Eccles and his colleagues, and even at such simple and usually straight through-conducting synapses as the vertebrate nerve-muscle junction. This last example, though not quite comparable to the relay contacts of our central apparatus, has the advantage of having received the most thorough experimental battering to date, and it has yielded results which are of

general interest. Even here, it has been found that the electrical reaction of the motor end-plate represents a non-explosive type of change which, at least potentially, is capable of summing with other signals to a higher level, and of being reduced in size and suppressed by an inhibitory agent. At the vertebrate nerve-muscle junction, there is no need for integration, the final balancing and sorting has already occurred higher up in the junctions of the spinal cord, and therefore the signal is only very slightly delayed—it may be held up for a fraction of a millisecond—at this junction. But I think that the distinctive features of the end-plate potential will be found to resemble fairly closely the characteristic properties of many synaptic—or perhaps I should say for the connoisseurs, post-synaptic—events in our central nervous system.

One final point. You may well ask: Have these local non-explosive signals, with all their capacity for interaction and modulation, any significance other than leading to another explosive non-stop event, another impulse in the next section of the system? And if so, why all this fuss? Isn't their role quite subordinate? Aren't they of very second-rate importance compared with the nerve impulse? Well, this question reminds me a little of the ancient and, I think, still debatable priority claim of chicken versus egg. As Dr Adrian once pointed out, at the beginning and at the end of the signals chain leading from a sensory stimulus to its eventual perception, there are not impulses, but phenomena continuously graded in strength and duration. There is very little that I should care to say about the properties of our conscious sensations, but one thing at least seems clear; namely that what we feel about a sensory stimulus is a more faithful image of the stimulus itself than of the nerve impulses which helped to report it. Certainly, nothing in our conscious perception has not previously passed through the medium of nerve impulses, but equally certainly nothing in our consciousness bears any resemblance to nerve impulses, and to their discontinuous staccato nature. Nerve impulses are only carriers in the signals traffic, elements of a code, into which the message has been transcribed at the place of origin and from which it must be decoded at the other, receiving, end. Thus, we know that at sensory nerve endings the stimulus produces a graded electrical change, of the flexible character which I have been

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describing. This is then transcribed into a set of nerve impulses, and at their final station in the brain, this set or any corresponding set of impulses must be deciphered into a graded continuous change. We do not know what the physical basis of the decoding process is, and you need not fear that I shall now perform some final acrobatics by boldly jumping from matter to mind and back again. I am afraid I have such a pedestrian mind that it is difficult for me not to shut my eyes (and ears) when others of more nimble mind are about to essay this jump. All I think one may suggest is that the first step in the central decoding of a sensory message is one in which impulses are again transformed into the local continuous type of signal found at so many other junction points—a form of signalling which does not travel further, but has the capacity of integration and of restoring to a sensory message the graded and continuous character of which it had been deprived in transit. Now this is only a minute and almost irrelevant initial step in a most mysterious process of transformation, and my only purpose in putting this speculation before you is to show that, as regards their relative importance, there is probably little to choose between the two types of signalling activity with which I have been concerned.

My time is up and very glad I am, because I have been leading myself right up to a domain on which I should not dare to trespass, not even in an Inaugural Lecture. This domain contains the awkward problems of mind and matter about which so much has been talked and so little can be said, and having told you of my pedestrian predisposition, I hope you will give me leave to stop at this point and not to hazard any further guesses.