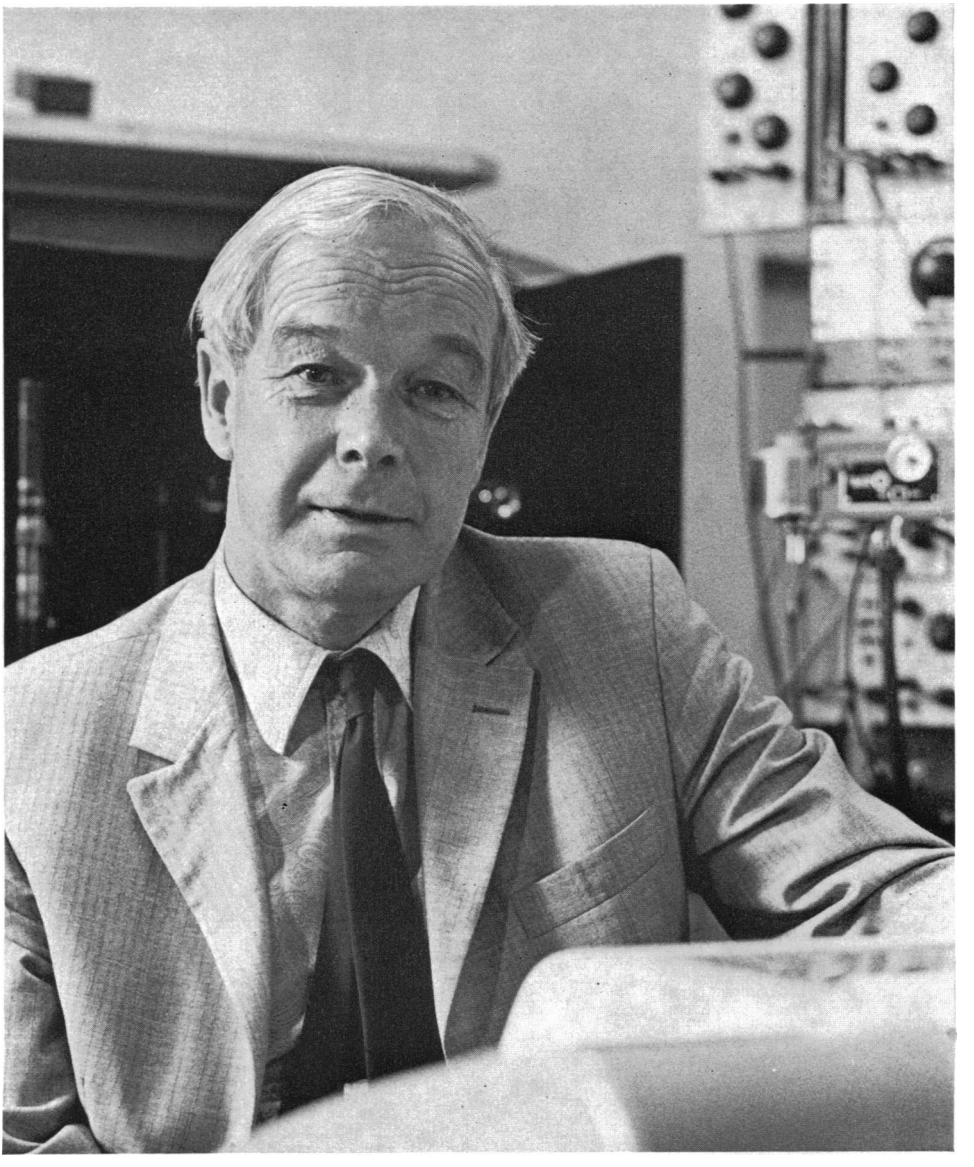

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J. Physiol. (1976), **263**, *pp.* 1–21
With 7 text-figures
Printed in Great Britain

CHANCE AND DESIGN IN ELECTROPHYSIOLOGY: AN INFORMAL ACCOUNT OF CERTAIN EXPERIMENTS ON NERVE CARRIED OUT BETWEEN 1934 AND 1952

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My aim in this lecture is to give you some idea of the informal background to the series of papers on nerve conduction which my colleagues and I wrote between the years 1937 and 1952. The sort of questions which I wish to consider are these: when was the work started? And why? How much was done by accident and how much by careful planning? Was the equipment found to be satisfactory in its original form or did it evolve gradually? What books, papers or people determined the choice of that particular piece of research? And so on. Such recollections are likely to be somewhat personal and may not be fair to others. Yet I think it necessary to give such an account, because I believe that the record of published papers conveys an impression of directness and planning which does not at all coincide with the actual sequence of events. The stated object of a piece of research often agrees more closely with the reason for continuing or finishing the work than it does with the idea which led to the original experiments. In writing papers, authors are encouraged to be logical, and, even if they wished to admit that some experiment which turned out in a logical way was done for a perfectly dotty reason, they would not be encouraged to 'clutter-up' the literature with irrelevant personal reminiscences. But over a long period I have developed a feeling of guilt about suppressing the part which chance and good fortune played in what now seems to be a rather logical development.

I can illustrate some of these points by considering the 'history' (if that is not too grand a word) of my first two papers, which were published in the *Journal of Physiology* in 1937 under the title 'Evidence for electrical transmission in nerve'. The aim of the papers is stated in the first two sentences: the method is straightforward; fire an impulse at a local block and see what happens beyond – and the result now seems so obvious that one wonders whether the work was worth doing at all. I suspect that this was one of the papers which caused a very distinguished biologist to say, 'The trouble with you Cambridge electrophysiologists is that you never discover anything; you think hard, decide what is right and then work

away until you prove it'. In defending myself and my colleagues against this accusation I must come clean and dispel any impression of tidy planning which our papers may have created.

I first started the block experiments in the summer of 1934. I was then a second-year undergraduate, undecided whether to read Physiology or Zoology in Part II. My inclination was towards the former but I was advised that there were no prospects for physiologists without medical degrees. Curiously enough the thing that finally converted me to Physiology was a rather unfair remark made by my director of studies, Jack Roughton, who said, 'All experimental zoologists do is apply to many animals the conclusions which physiologists have reached by working on one particular animal; if you want to find out anything really new you must join us in Physiology'. As the Physiological Laboratory in Cambridge then contained J. Barcroft, E. D. Adrian, B. H. C. Matthews, Grey Walter, F. J. W. Roughton, G. S. Adair, E. N. Willmer, F. R. Winton and several other distinguished physiologists, there was something to be said on Roughton's side. At all events I was converted by the remark although it cannot be defended against the examples of J. Gray, D. Keilin, H. W. Lissmann, P. B. Medawar, C. F. A. Pantin, J. W. S. Pringle, V. B. Wigglesworth and J. Z. Young, to name only a few of the very distinguished British scientists who have approached biology from the zoological side.

During my first two years at Cambridge I had become interested in membranes, mainly through reading James Gray's (1931) *Experimental Cytology* and A. V. Hill's (1932) *Chemical Wave Transmission in Nerve*, both of which were then relatively new. I had also read the excellent review by Osterhout (1931) on 'Physiological studies of large plant cells' and was impressed with the evidence obtained by Blinks (1930) for an increase of membrane conductivity during the action potential of *Nitella*. It seemed to me that this crucial piece of evidence was lacking in nerve and I tried to test it by the method illustrated in Fig. 1*A*. Using class apparatus, some of which had been designed by Keith Lucas* twenty years earlier, I arranged to block a nerve locally by freezing it, and applied two pairs of shocks to it in the position shown. I argued that if the permeability and conductivity of the membrane increased during activity, then arrival of an impulse at the block should increase the fraction of current which penetrated the nerve and hence lower the electrical threshold at the distal pair of electrodes. I set up the equipment, using a silver rod and a tin of ice and salt to cool the nerve, a Keith Lucas spring contact-breaker to time the

* I was much influenced by Keith Lucas's collected papers which I read all through as a student, partly at least because I knew his widow and sons. My father and Lucas were close friends; both died in the first world war; Lucas in an aeroplane accident in 1917 and my father of dysentery in Baghdad in 1918.

two shocks and a smoked drum to measure the size of muscular contraction. The experiment consisted of establishing a block, and then alternating between shock 2 by itself, and shock 2 preceded by shock 1 with an interval of a few milliseconds between them. If there was any facilitating effect then the muscle twitch evoked by the two shocks was greater than that produced by one alone. I first tried the experiment in July 1934. I got a negative result, but on trying again in October the experiment worked and I was very pleased indeed. Later that year I made a note to the effect that

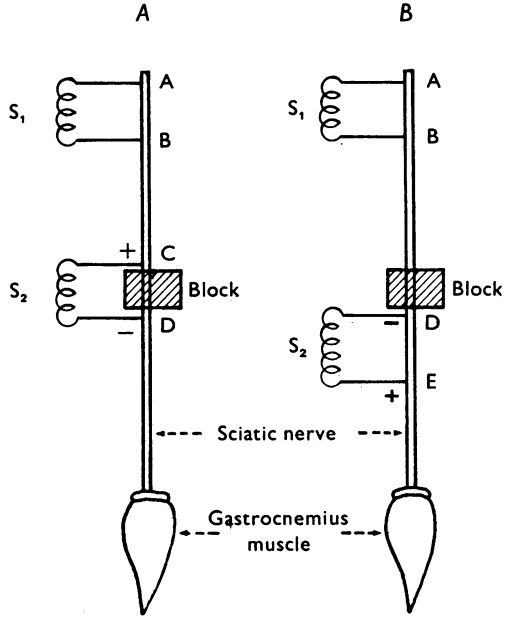

Fig. 1. Diagram of method of testing the effect on excitability of a blocked nerve impulse, using sciatic gastrocnemius preparation.

'Freezing must be light and reversible. In long vac term [i.e. July] non-reversible freezing or ligaturing used and no effect could be detected'. The threshold near the block was very variable and it was difficult to obtain quantitative results. However, a number of controls established the genuine nature of the effect, for example it was abolished by crushing between B and C, was unaffected by reversing A and B, and developed with a shock separation consistent with the time taken for the impulse to travel from B to C.

Then I had a horrid surprise. I switched the anode from just above the block to a position beyond it, i.e. from C to E, as in Fig. 1 *B*, and found that the effect still persisted. It therefore had nothing to do with an increase in membrane conductivity and was most simply explained by

assuming that local circuits were spreading through the block and raising excitability beyond it, as shown in Fig. 2. More generally, one might attribute the effect to whatever agent was responsible for conduction. The existence of the effect did not provide any evidence for electrical transmission, but it offered a nice way of testing the theory. At the time I was disappointed that I had not obtained any evidence for an increase in membrane conductivity and I gave up the experiments for the undergraduate Part II work that I should have been doing all along. I specialized

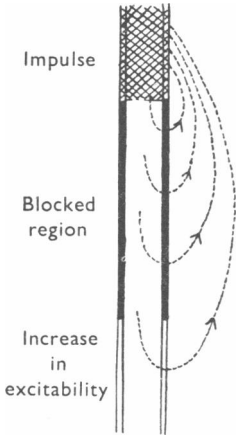

Fig. 2. Diagram illustrating local electric circuits spreading through block and increasing excitability beyond it (from Hodgkin, 1936, 1937*a*, *b*).

on nerve conduction and was annoyed that we didn't have any questions on nerve in the final exam. One of the examiners told me later that this was deliberate, which seemed rather mean – I still have an occasional nightmare about taking exams.

During my Part II year I read all the papers of the St Louis School, J. Erlanger, H. S. Gasser, G. H. Bishop, H. T. Graham, R. Lorente de Nó and F. O. Schmitt. This made it clear to me that the leading axonologists were thoroughly sceptical both of the membrane theory in general and of the local circuit theory in particular. I came to the conclusions that it would be well worth while to see whether the transient increase of excitability beyond a localized block was an electrical effect, and decided that I would take up this as a research project.

In those days laboratory life was rather informal, at any rate in Cambridge. I never worked for a Ph.D. and didn't have a research supervisor. You might easily start in a bare room and have to build most of your equipment yourself, apart from a few standard bits like smoked drums, Palmer stands and kymographs. This sounds depressing but it actually

wasn't. Nowadays, scientists are apt to become neurotic and give up work if they know their equipment is markedly inferior to other people's. Indeed it is regarded as somewhat unscientific to carry out experiments with anything but the best equipment. This certainly wasn't my feeling when I started research and, to begin with, all that mattered was that one should have enough equipment to do something new. I may have been rather extreme in this respect but the general attitude to equipment was certainly very different from that existing today. In his comments on the pre-war Cavendish Laboratory in Cambridge, the distinguished physicist J. A. Ratcliffe (1975) explains that in the 1920s and '30s an elegant piece of apparatus or an elegant experiment meant one that could be built or carried out very cheaply. He says,

> There was, I think, a feeling that the best science was that done in the simplest way. In experimental work, as in mathematics, there was 'style' and a result obtained with simple equipment was more elegant than one obtained with complicated apparatus, just as a mathematical proof derived neatly was better than one involving laborious calculations. Rutherford's first disintegration experiment, and Chadwick's discovery of the neutron had a 'style' that is different from that of experiments made with giant accelerators.

Ratcliffe illustrates his point with this anecdote:

> ...as a young research student I wished to try out a radiocircuit, in the way that was then common, by screwing some components to a wooden 'bread board'. When I went to get a piece of wood for the purpose Lincoln [the head of the workshop] pointed to a pile of scrap wood in the corner and invited me to take a piece, but as I was leaving the room he ran after me and said 'Here, Mr. Ratcliffe, do you really need mahogany?'

I was lucky because I inherited a Matthews oscilloscope and other electrical equipment from Grey Walter. In those days it wasn't considered proper to use an amplifier built by someone else. So I constructed a condenser-coupled triode amplifier in a series of biscuit tins which I painted bright blue. At that time there were no electric soldering irons, no resin-cored solder and the valves, which were usually microphonic, needed anti-vibration mountings, so building an amplifier took longer than it would today. But I was helped in this and other things by Martin Wright who already showed signs of the mechanical ingenuity and inventiveness for which he is now well known. I also received much help from Charles Morley Fletcher who worked next door to me on *Mytilus* muscle.

In the autumn of 1935 I managed to record the electrotonic potential produced by local electric circuits spreading through the blocked region. However, the Matthews oscilloscope wasn't really fast enough – although admirable for recording the presence of impulses – and the whole set-up was terribly cumbersome, with an arc lamp, rotating mirrors, moving film and a cylindrical paper screen all arranged to give the same effect as a

modern cathode ray oscilloscope. So I bought a cathode ray tube and accessories from Cossor, and a second-hand film camera from Wardour Street in London. I also got our workshop mechanic, Mr Hall, to build a rotary contact breaker for starting the sweep and timing two shocks. This did what I wanted but made an incredible din as a series of huge cams smacked into three magneto contact-breakers ten times a second. As I had to pay for this equipment myself I bought the cheapest kind of cathode ray tube; this was a 'soft' tube in which electrons are kept in a column by positively charged gas molecules, rather than by focusing electrodes. Bryan Matthews was away in the Andes that year, but I received much help and advice from A. F. Rawdon-Smith who had a first-class knowledge of electronics and worked next door in Psychology. In the end all the equipment worked well though I had terrible and quite unnecessary trouble with it. At that time there was a sort of mystical idea that the noisiness of an amplifier varied inversely with the skill of the man who built it, and amplifier noise was regarded as a sort of moral penalty for bad workmanship. As I have always been rotten at making things I naturally attributed my noisy base line to poor workmanship. In fact, as I eventually discovered, the base line in my set-up was relatively noisy because the frequency response of my cathode ray tube was very much higher than that of the Matthews oscilloscope used in the basement. Then the whole business of shock-artifacts was shrouded in mystery and I didn't learn to think rationally on this subject until I went to the Rockefeller Institute in 1937. There I met Dr Toennies who looked after the electronics in Gasser's group; he told me to forget about radiation fields and other irrelevant ideas that I had been struggling with, and to think only in terms of electrical leaks, stray capacities and actual spread of current in the tissue.

By mid July 1936 I had been through the main experiments and wrote up the results in a Fellowship thesis for Trinity College, where I had lived happily for four years. I was surprised and very pleased to be successful but also a little alarmed to be joining a society which included people like J. J. Thomson (the Master), Rutherford, Aston, Eddington, Gowland Hopkins, Adrian, Wittgenstein, Hardy and Littlewood. After getting a fellowship I spent several months repeating and tidying up experiments; eventually two papers were published in the *Journal of Physiology* (1937) almost exactly three years after the beginning of the experiments. The conclusions were more or less all right except that for a myelinated nerve one would nowadays redraw Fig. 2 to show the current concentrated at the nodes. I think I was lucky not to be completely messed up by the electrical polarizability of the nerve sheath (perineurium) and I have wondered since whether this may not have been made leaky by the ice crystals which formed in the cooled region of nerve.

Chance and good fortune were equally important in my next piece of research. I had grown interested in cable theory and had come to the conclusion that it was necessary to excite a finite length of nerve in order to start an action potential. The argument, which was developed independently and much further by Rushton (1937), led to the idea of a subthreshold response which might explain the unexpected results obtained by Katz (1937) and Rushton (1932) in their studies of excitability. But I didn't make any deliberate attempt to test these ideas and instead followed a suggestion of Professor Adrian that I should work on crab nerve. I am now not sure what I intended to do, but I think I hoped to test the idea that accommodation might be due to the polarization of some structure in series with the nerve fibres. I found it very easy to split crab nerve into fine strands and one of the strands I picked up turned out to be a single axon – to judge from its enormous all-or-nothing action potential. This really was a great piece of luck as I had no dissecting microscope and the chances of picking up one of the half-dozen or so 30 μm fibres in a nerve trunk a millimetre thick are not very high. The next day I borrowed a dissecting microscope and from that time to this I have never worked on a multifibre preparation again. (What, never? Well, hardly ever.)

Soon after I got the preparation going I noticed that a shock which was just below threshold produced something like a small graded action potential, which grew rapidly in size as the stimulus approached threshold. This clearly was exactly what was needed to explain Bernard Katz's results and I was very pleased to be getting evidence of something as unorthodox as a graded response in a single nerve fibre. My electrical technique wasn't really up to recording from single axons as you can see if you look at the illustration in the preliminary note describing the Cambridge experiments (Hodgkin, 1937*c*). However, help was at hand because Herbert Gasser, who was then Director of the Rockefeller Institute in New York had invited me to spend a year working in his group, and I had been awarded a travelling fellowship by the Rockefeller Foundation. Soon after I arrived, Dr Toennies, the electronics expert in Gasser's group, pointed out that it was essential to use a cathode follower if one wished to make accurate recordings of rapid changes from a high resistance preparation like a single crab axon. He provided the necessary equipment and I learnt a great deal about electronics and electrical recording from Gasser and his group which included Lorente de Nó, Grundfest, Toennies and Hursch.

At that time the Rockefeller Institute was a very distinguished laboratory – as indeed it still is. At lunch time the great men led their flocks to separate tables and one would see little processions headed by Landsteiner, Carrel, Avery, P. A. Levene, van Slyke and so on. It was a pretty formal place and I missed the free and easy casualness of the Cambridge

laboratories. But it was a valuable experience to work in a big well-organized laboratory and helped to turn me from an amateur into a professional scientist. Apart from Gasser's own group the people who influenced me most were Osterhout (large plant cells), Michaelis (membranes) and MacInnes and Shedlovsky (electrochemistry), not to mention Peyton Rous and his family on the personal side.

But the contact which had the greatest immediate effect on my scientific life was with Cole and Curtis at Columbia. I was still anxious to know whether the membrane conductance increased during activity and had obtained some evidence that it did, by showing that a shock applied at the crest of the spike produced less than half the normal polarization (Hodgkin, 1938, p. 107). I had also obtained a positive effect in preliminary experiments with alternating currents but the results were untidy because the out-of-balance signal in the bridge was mixed up with a diphasic action potential. I abandoned these rather amateur attempts after I had visited Columbia University and seen the beautiful experiments which Cole and Curtis had already done on *Nitella* and were planning on squid axons (having studied the passive transverse impedance in the previous year). Cole asked me to visit him at Woods Hole in June, and at some point during the spring of 1937 we agreed that I should bring up equipment for measuring the membrane resistance of squid axons by a modification of the resistance-length method used by Rushton (1934) (see Cole & Hodgkin, 1939).

Meanwhile I visited St Louis, on the way to a 3 weeks holiday in Mexico, which was then a wild and remote country, and also an incredibly inexpensive one where you could live for less than a dollar a day. In St Louis I stayed with Joseph Erlanger who was exceedingly nice to me, but expressed total disbelief in subthreshold activity in myelinated axons and was also very sceptical about the local circuit theory. I had tried hard but without any success to isolate single myelinated axons from cat spinal roots so I knew I could not win on that front. But there was more hope on the other and I got a good idea from a conversation with Erlanger in which he said that he might be convinced if I could alter conduction velocity by changing the electrical resistance outside a nerve fibre. Somewhere on that holiday, which included a four-day train trip from Mexico City to New York, I saw that it would be very easy to alter the electrical resistance outside a crab fibre from a high value in oil to a low one in a large volume of sea water. I did the experiment as soon as I got back to New York and obtained a large effect on conduction velocity (Fig. 3). This was one of the few occasions on which everything went according to plan and this time no hidden snags emerged. I showed Harry Grundfest the records next day and remember that he shook me by the hand like a character in a novel by

C. P. Snow. When I got to Woods Hole in June, Cole and Curtis very kindly let me use their amplifier and I was able to repeat the experiments on squid axons as well as making some other tests of the local circuit theory.

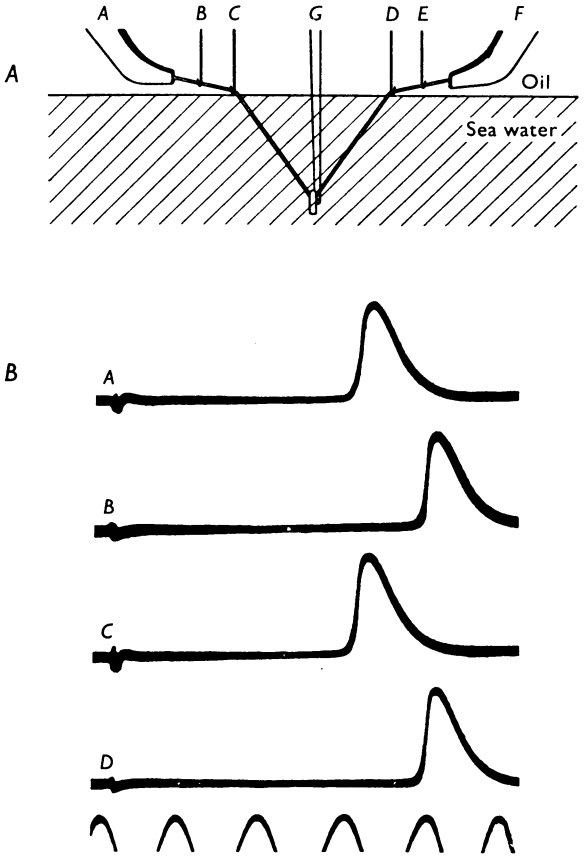

Fig. 3. *A*, arrangement for comparing the conduction velocity of a single nerve fibre in sea water and oil. As shown, the conduction stretch is in a large volume of sea water; on raising the electrode assembly, the volume of conducting fluid is reduced to the thin film of sea water which clings to the fibre in oil.

B, effect of external resistance on conduction velocity. *A* and *C*, action potential recorded with sea water covering 95 % of intermediate conduction distance; *B* and *D*, fibre completely immersed in oil. Conduction distance 13 mm. Time, msec (from Hodgkin, 1939).

This was a very exciting time to be at Woods Hole. I remember arriving in Cole and Curtis's laboratory and seeing the increase in membrane conductance during the action potential displayed in a striking way on the cathode ray tube (Fig. 4). After learning to clean squid axons and repeating

the velocity experiments I settled down with Cole to measure resistance length curves. Towards the end of this work Cole noticed that there appeared to be something like an inductance which showed up in the longitudinal impedance at low frequencies; this was a puzzling observation which did not receive a satisfactory explanation till about ten years later

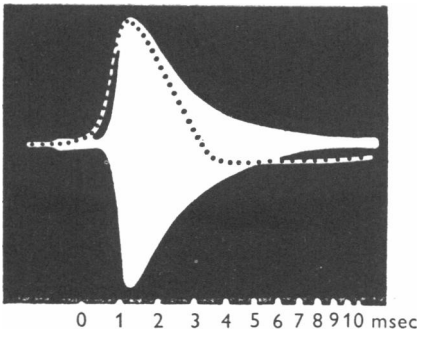

Fig. 4. Action potential (dotted curve) and increase in conductance (white band) in squid axon at about 6° C (from Cole & Curtis, 1939; see also Cole & Curtis, 1938, and Curtis & Cole, 1938).

(the inductance is mainly due to the delayed increase in potassium conductance which can make membrane current lag behind voltage provided the internal potential is positive to the potassium equilibrium potential (Cole, 1941, 1947; Hodgkin & Huxley, 1952*d*)). Curtis and I also did a few long-shot experiments trying to push electrodes up the cut end of a giant axon. I think we both came away with the idea that it might not be too difficult to record action potentials with an internal electrode; at all events, we both carried out the experiment with different partners in the following year.

Before leaving New York in July 1938 I went to say goodbye to Dr R. A. Lambert at the Rockefeller Foundation who had looked after me with great kindness during the preceding year. Someone, probably Herbert Gasser, had suggested that the Foundation might provide me with an equipment grant and Toennies had helped to prepare a list of some of the things I might need. I mentioned this to Lambert and was electrified to learn later that I might expect a sum of £300, an unheard of amount for a young scientist in those days.

When I got back to Cambridge in the autumn I decided to set up the kind of equipment used in the Rockefeller, with racks, electronic timing, d.c. amplifiers and so on. I joined forces with A. F. Rawdon-Smith, K. J. W. Craik and R. S. Sturdy in Psychology, and between us we built three or four sets of equipment some of which were still in use twenty-five years later. I did a bit of wiring but the three psychologists did nearly all the

work. Rawdon-Smith designed the d.c. amplifier and most of the rest of the equipment, but I had help from Toennies over cathode followers, Otto Schmitt over multivibrators, and Matthews over the camera and many other details. I also remember consulting Britton Chance who was then working in the Physiological Laboratory in the Roughton–Millikan suite.

In the late thirties we were becoming 'professionals' and the objective in designing electronic equipment was not to make some neat miniaturized unit but to build up as massive and imposing an array of racks and panels as you could get – possibly with the idea of cowing your scientific opponents or dissuading your rivals from following in your footsteps. These large units were a nuisance if you wished to move to Plymouth or Woods Hole, but they did have the great advantage of being difficult to borrow when you were on holiday or writing-up results.

It took three or four months to get all the equipment built and to be ready for experiments again. I had worked very hard for the previous six years and as there was obviously going to be a European war I thought it best to choose a straightforward problem which would leave time for non-scientific activities. So I decided to use my new d.c. amplifier to check how close the action potential came to the resting potential. Andrew Huxley, who was doing the Part II Physiology course, joined me in some of the experiments. We measured external electrical changes in *Carcinus* axons immersed in oil and took the resting potential as the steady p.d. between an intact region and one depolarized by injury or isotonic potassium chloride. We found that the action potential was much larger than the resting potential, for example 73 mV for the former as against 37 mV for the latter. Although I wasn't aware of it till much later, Schaefer (1936) had previously reported a similar discrepancy in the sciatic and gastrocnemius muscles of the frog. I got the same result with lobster axons, a preparation which Rushton and I studied later that year in order to calculate passive electrical constants, using the cable-equations which he and others had developed (Hodgkin & Rushton, 1946). These results required much analysis and were put on one side until 1945 when the war was nearly over and my part in it was finished.

The results with external electrodes did not give the absolute value of the action potential and resting potential, because of the short circuiting effect of the external fluid. But there was no reason why this should affect one potential more than the other, and the difference seemed much too large to be explained by some minor difference in the way the two potentials were recorded.

I decided to continue the experiments at Plymouth where I had worked several times since my first visit there as a schoolboy in 1931. I bought a trailer which I attached to my ancient car and with some difficulty

managed to drag the bulk of my equipment from Cambridge to Plymouth in July 1939. After a few weeks, Andrew Huxley joined me and started to measure the viscosity of axoplasm by seeing how fast a mercury droplet would fall down the axis cylinder. He set up this experiment very quickly using a horizontal microscope and an axon hanging vertically from a cannula. Within a day or two he came up with the unexpected answer that axoplasm is normally solid and that the mercury droplet does not fall at all, unless it is in axoplasm which has become liquefied as a result of damage or

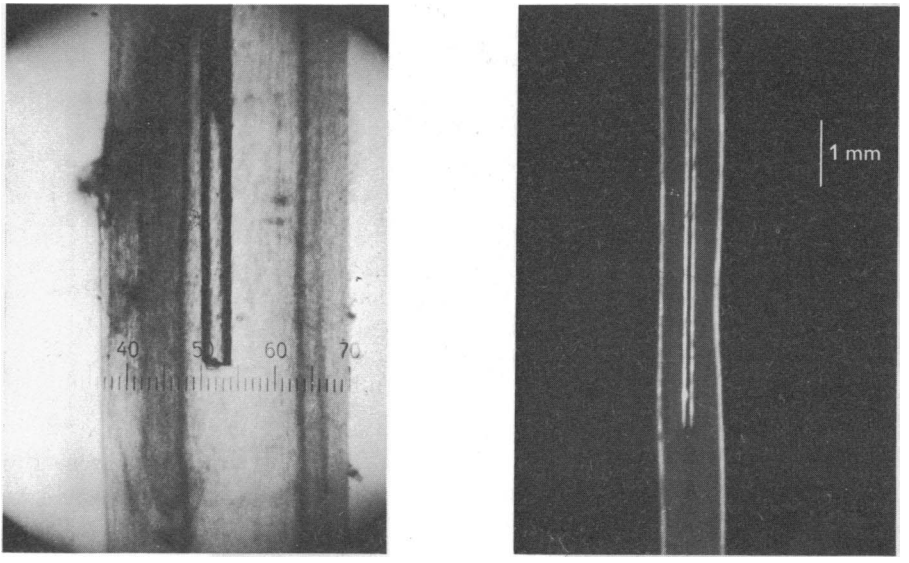

Fig. 5. *A*, left, photomicrograph of a recording electrode inside a giant axon, which shows as a clear space with small nerve fibres on either side; one division = 33 μm (from Hodgkin & Huxley, 1939). *B*, right, cleaned giant axon of *Loligo forbesi* with glass tube 0·1 mm in diameter inside it; dark ground illumination (from Hodgkin & Keynes, 1956).

proximity to a cut region. However, this negative experiment, which is responsible for the vertical set-up used on and off for thirty years at Plymouth, was to have an interesting sequel. Huxley said he thought it would be fairly easy to stick a capillary down the axon and record potential differences across the surface membrane. This worked at once, but we found the experiment often failed because the capillary scraped against the surface; Huxley rectified this by introducing two mirrors which allowed us to steer the capillary down the middle of the axon. Fig. 5 shows the technique. The result, illustrated in Fig. 6, was that the action potential of nearly 100 mV was about twice the resting potential of about 50 mV.

We were tremendously excited with this finding as well as with the

potentialities of the technique and started other tests like the effect of potassium ions on resting potential and action potential, an experiment later done very elegantly by Curtis & Cole (1942). However, within three weeks of our first successful impalement, Hitler marched into Poland, war was declared and I had to leave the technique for eight years until it was possible to return to Plymouth in 1947.

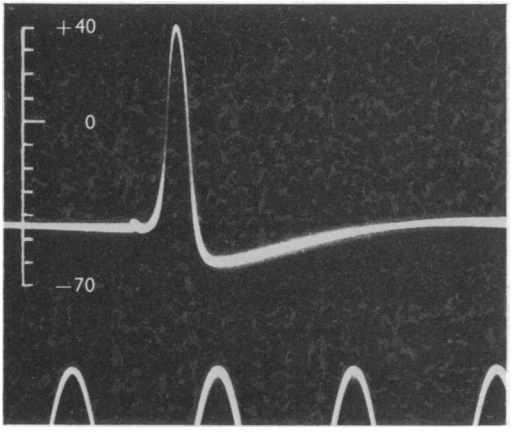

Fig. 6. Action potential and resting potential recorded between inside and outside of axon with capillary filled with sea water. Time marker 500 Hz. The vertical scale indicates the potential of the internal electrode in millivolts, the sea water outside being taken as at zero potential (from Hodgkin & Huxley, 1939; see also Hodgkin & Huxley, 1945; Curtis & Cole, 1940).

Huxley and I wrote a cautious note to *Nature* about our results and for the first few months of the war I tried to work on a full paper. But this didn't get very far as it had to be done in the evenings after a long day at the Royal Aircraft Establishment, Farnborough, where I was working on aviation medicine with Bryan Matthews. After I had switched to radar, there were other things to study in the evenings and by June 1940 the war had gone so disastrously, and the need for centimetric radar was so pressing, that I lost all interest in neurophysiology and did not even bother to keep my copies of the *Journal of Physiology*.

By 1944 the position of the Allies had improved, radar was less demanding and I had married Peyton Rous's daughter, Marion, whom I first met in New York in 1937. There seemed to be a reasonable chance of getting back to Physiology and I was feeling happy enough to start thinking again about nerve. Cole had sent me reprints of the work which he and his group had done up to 1942 and reading these got me going again. Andrew Huxley was working on Naval gunnery and his visits to Malvern (where I worked on

radar) enabled us to finish the paper about the action potential and resting potential which we had started in 1939 (Hodgkin & Huxley, 1945). Later on both of us came to regret the discussion in that paper and I have often been asked why we did not mention the sodium hypothesis, or whether we had thought of it at that time. In the absence of documentary evidence it is dangerous to answer such questions from memory and I shall not attempt to do so here. However, I do know that things looked rather black for the sodium theory, both then and several years later. In the first place there was a report which later proved to be wrong that the action potential of *Loligo pealii* might exceed the resting potential by as much as 110 mV (Curtis & Cole, 1942); on the sodium hypothesis this required an internal sodium concentration of less than 6 mM which compared unfavourably with the value of 270 or 162 mM obtained by subtracting potassium from total base in the early analyses of Bear & Schmitt (1939) or Webb & Young (1940) respectively. There was also a preliminary report, which again proved to be wrong, to the effect that the action potential and resting potential of a squid axon were unaffected by removing all ions and circulating isosmotic dextrose (Curtis & Cole, 1942). This seemed to fit with the well-known observation that frog nerve would survive for many hours in salt-free isotonic sugar solutions, a result now known to be due to an impermeable layer in the perineurium.

I have often been asked how much working for nearly six years on radar affected the rest of my scientific life. I would like to be able to say that it made a profound difference, and I expect it did, indirectly. But the fact remains that when I returned to Cambridge in August 1945 I continued working on crustacean nerve using almost exactly the same equipment as before the war. The first big changes in technique coincided with the arrival of Richard Keynes (another ex-radar scientist) who started working on radioactive tracers after completing Physiology Part II in the summer of 1946. At the same time David Hill was developing optical methods of studying nerve and muscle and we made a push towards chemistry by bringing in Peter Lewis from the Hinshelwood school of chemistry at Oxford. All these developments, as well as scientific hospitality to a very distinguished series of visitors, were made possible by a generous grant of £3000 per annum from the Rockefeller Foundation to Professor Adrian.

But to go back to the immediate post-war period. After a few months Andrew Huxley was released from the Admiralty and we were able to continue the very happy collaboration which we had started in 1939. Some work on an indirect method of measuring potassium leakage in activity*

* Hodgkin & Huxley (1947). For the results of direct measurements of Na and K movements see Keynes, 1948, 1949, 1951*a*, *b*; Keynes & Lewis, 1951; Rothenberg, 1950; Grundfest & Nachmansohn, 1950.

got us thinking quantitatively about ionic movements during the nerve impulse. Towards the end of 1946 and in the early part of 1947 we spent much time speculating about the kind of system which might give rise to an action potential.

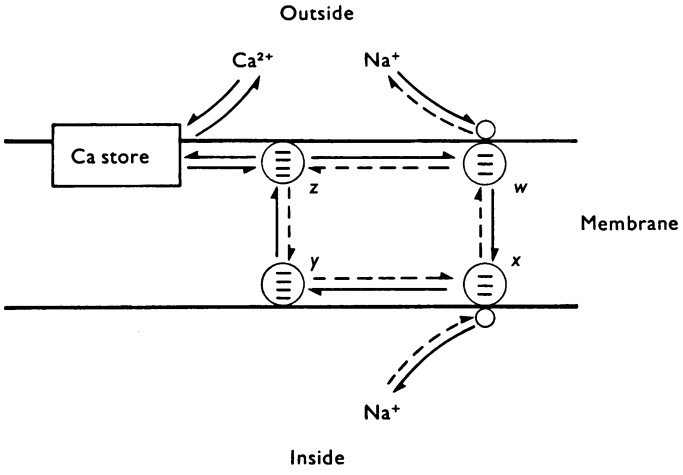

Fig. 7. Diagram illustrating theoretical carrier model considered by Hodgkin & Huxley (1948, unpublished). See also Hodgkin, Huxley & Katz (1949). With a high resting potential (inside negative), all the carrier molecules, both uncombined and combined, are pulled to the outside of the membrane and sodium movement is low; depolarization allows the carriers to move and increases the inward flow of sodium ions. The effect is increased and made asymmetric by external calcium ions which are assumed to combine with the carriers and form an immobile reservoir on the outside of the membrane.

The general idea underlying our initial hypothesis was that sodium ions were transferred across the membrane by negatively charged carrier molecules or dipoles. In the resting state these were held in one position by electrostatic forces and unable to ferry sodium ions. These carriers were subject to 'inactivation' by reacting slowly with some substances in the axoplasm. A propagated action potential calculated by Huxley in 1947 incorporated the main features that emerged two years later from the voltage-clamp experiments – i.e. a rapid rise in sodium permeability followed by a slower decay, and a slow rise of potassium permeability.

In all these theoretical action potentials the reversed potential difference at the crest of the spike depended on a selective increase in sodium permeability and a low internal concentration of sodium ions. Huxley felt all along that this was a likely mechanism but I was more doubtful, partly for the reasons given above, and partly because I hankered after a mechanism which would give a transient reversal, so accounting for repolarization,

inductance and the transient nature of the spike. We tried various ingenious schemes involving dipoles that I thought might operate in this way, but Huxley's numerical calculations shot them all down, leaving a rise in permeability to sodium ions, or perhaps to an internal anion, as the most likely cause of the overshoot.

Towards the end of 1946 Bernard Katz sent me a manuscript in which he showed, among other things, that crab axons became inexcitable in salt-free solutions.* As this agreed with my own experience† of squid axons I began to think the Woods Hole result was wrong and that there was hope for the sodium theory. In January 1947 I decided to test the theory by measuring the effect of sodium-deficient dextrose solutions on (1) the action potential recorded externally from single crab axons and, (2) the longitudinal resistance of external and internal fluids in parallel. The second measurement was needed because if sodium chloride is replaced with dextrose the external resistance rises; this reduces short-circuiting and partly counteracts any 'true' effect of sodium deficiency. However, if you divide the external action potential by the longitudinal resistance you get a quantity proportional to the p.d. across the membrane. By this method I found that lowering the external concentration of sodium reduced the action potential by about the right amount – for example lowering $[Na]_o$ to 1/5 reduced the action potential by 40 % – from 120 to 72 mV if one assumed equality of external and internal resistances. The reduction of 48 mV was not far from 58 log 5 = 41 mV and seemed reasonable.

These experiments were brought to an end by the first of our many energy crises, in this case precipitated by an exceptionally prolonged cold spell which lasted until the end of March 1947. It was soon found that national coal stocks were exhausted and the central heating was switched off in many buildings, including university laboratories We then had no cold room in our part of the laboratory and I remember that David Hill took the opportunity of carrying out a series of experiments at 4° C. But you can't dissect single fibres at such temperatures and I spent the time writing at home or talking with Andrew Huxley in Trinity where he could be seen cranking a Brunsviga calculating machine with mitten-covered fingers. I started experimenting again in April but by then the summer vacation was approaching and I had decided to do the sodium experiments properly at Plymouth using the squid axon and an internal electrode. I found it hard work to get going again. The Plymouth laboratory had been partly demolished in the great air raids of 1941 and was being rebuilt; squid were in short supply and I'd forgotten much of the technique. Worst of all I was short of a partner. Bernard Katz wasn't free till September and

* Katz, 1947.

† See small type paragraph on p. 303 of Webb & Young, 1940.

Andrew Huxley was just getting married. However, the basic experiments of determining the effect of sodium concentrations on overshoot and rate of rise are straightforward and by the time of the Oxford congress (21–25 July 1947) there was strong evidence for the sodium theory. I left the equipment at Plymouth and with the help of Bernard Katz made a thorough attack on the problem in September. We wrote up the results during the autumn but publication delays held up our paper for 15 months. Meanwhile there were interesting developments on several fronts and I shall have to depart from a strictly chronological account if I am to retain any logical order.

Since the end of the war I had corresponded fairly regularly with Kacy Cole and on 26 August 1947 I wrote to tell him about the sodium results and to discuss future joint research. We had made a tentative plan (which never came off) to join forces at Woods Hole in 1948, and were starting to discuss research possibilities. I was clearly in an optimistic mood because I wrote,

> I should rather like to have a shot at perfusing the inside of the axon with potassium or sodium salts and have some ideas about the best method of doing this. I am also interested in the possibility of stimulating the axon with a diffuse electrode in such a way that the axon is excited uniformly over a length of 1 or 2 centimetres. This might give useful information about the nature of the active process uncomplicated by propagation and local circuit action. What are your plans and views?

In his reply of 7 October 1947, Cole said,

> ...I am sure that you will be excited to hear that we spent the whole summer with an internal electrode 15 millimetres long and about 100 microns in diameter... The two principal ideas are first the use of the central outside region with a guard region on each side, and second the use of a feedback circuit to control either the current flow in the central region or the potential difference across the membrane in that region to the desired value....

In the end the plan to spend a summer at Woods Hole fell through but I did have an exceedingly helpful visit to America in the spring of 1948 when I spent a week or two in Chicago at Cole's invitation in order to exchange information and discuss future experiments.

Andrew Huxley and I were very anxious to test our carrier theory and when we heard about Cole and Marmont's experiments we felt that voltage control, with current applied through a long metal wire, might be a good way to prove or disprove the theory. But we were worried about electrode polarization and decided to use two fine silver wires, one for current and one for voltage. Before leaving for America in March 1948 I made a short double-spiral electrode out of two 20 μm wires wound round a 100 μm glass rod. On returning to Cambridge, Mr R. H. Cook built our first feedback amplifier along roughly the same lines as those used in the final model.

Our apparatus differed in several respects from that of Cole and Marmont but it owed a great deal to the experiments which they started in 1947 and to the information which they so generously provided in the spring of 1948.

As on previous occasions we approached the experiments more circuitously than might appear from the published record. Katz and I first spent several weeks in July 1948 trying to perfuse squid axons with virtually no success, except that we learnt that calcium ions would liquefy axoplasm. Having failed here we started to try to make and insert double spiral electrodes. This didn't work either until we realized that one should first pre-drill the axon with a smooth glass capillary. Then things started to move and by using short shocks and constant currents with different external solutions we obtained indirect information about the permeability changes to sodium and potassium. Andrew Huxley arrived in mid-August and settled down to make the feed-back amplifier work. We managed to do a few voltage-clamp experiments, which were published in 1949, but realized that we needed a proper system of guard electrodes and would do better to work at low temperatures. We didn't shoot down the carrier hypothesis until the next year and for some time had no clear evidence of sodium inactivation.

During the next year Huxley and I spent a fair amount of time improving the equipment and we returned to the attack at Plymouth in June 1949. At first squid were in poor supply and we took a few weeks to get going. But by mid July 1949 Katz had joined us, there was a fine supply of living squid and in the next month we obtained virtually all the voltage-clamp records that were used in the five papers published in 1952 (Hodgkin, Huxley & Katz, 1952; Hodgkin & Huxley, 1952*a*, *b*, *c*, *d*). I think we were able to do this so quickly and without leaving too many gaps because we had spent so long thinking and making calculations about the kind of system which might produce an action potential of the kind seen in squid nerve. We also knew what we had to measure in order to reconstruct an action potential.

We spent over two years analysing and writing up the results and I have often been asked why this took so long. The answer, as usual, is multiple. In the first place we continued with some experimental research and a mild amount of teaching. The second reason which must now seem surprising is that although we had obtained much new information the overall conclusion was basically a disappointment. We had started off to test a carrier hypothesis and believed that even if that hypothesis was not correct, we should nevertheless be able to deduce a mechanism from the massive amount of electrical data that we had collected. These hopes faded as the analysis progressed. We soon realized that the carrier model could not be made to fit certain results, for example the nearly linear instantaneous

current voltage relationship, and that it had to be replaced by some kind of voltage-dependent gate. As soon as we began to think about molecular mechanisms it became clear that the electrical data would by itself yield only very general information about the class of system likely to be involved. So we settled for the more pedestrian aim of finding a simple set of mathematical equations which might plausibly represent the movement of electrically charged gating particles. But even that was not easy, as the kinetics of the conductance changes were unlike anything we had come across before, particularly the S-shaped 'on' and exponential 'off' of the conductance curves. I think we both appreciated the need to involve several particles, but it was Andrew Huxley who eventually came up with the ideas which led to the m^3h and n^4 formulation.

Finally there was the difficulty of computing the action potentials from the equations which we had developed. We had settled all the equations and constants by March 1951 and hoped to get these solved on the Cambridge University Computer. However, before anything could be done we learnt that the computer would be off the air for 6 months or so while it underwent a major modification. Andrew Huxley got us out of that difficulty by solving the differential equations numerically using a hand-operated Brunsviga. The propagated action potential took about three weeks to complete and must have been an enormous labour for Andrew. But it was exciting to see it come out with the right shape and velocity and we began to feel that we had not wasted the many months that we had spent in analysing records.

In trying to give a connected account of the development which led to the voltage-clamp experiments I am conscious that I have followed only one of several interconnected strands and that I have left out a number of very important lines of research. Thus I have said nothing about the direct measurement of ionic movements with radioactive tracers and nothing about saltatory conduction or the developments which followed the introduction by Ling and Gerard of their type of micro-electrode. These omissions should not be taken to imply that these developments are of less importance. My reason for concentrating on one line is that I felt you might be more interested in informal detail than in a broader, less personal review which you can in any case obtain for yourself from the literature.

This Review Lecture was delivered at the Centenary Meeting of the Physiological Society in Cambridge in July 1976.

The photograph of A. L. Hodgkin was taken by Dr. P. Gaskell.

REFERENCES

BEAR, R. S. & SCHMITT, F. O. (1939). Electrolytes in the axoplasm of the giant nerve fibres of the squid. *J. cell. comp. Physiol.* **14**, 205–215.

BLINKS, L. R. (1930). The direct current resistance of *Nitella*. *J. gen. Physiol.* **13**, 495–508. See also Blinks (1936).

BLINKS, L. R. (1936). The effect of current flow on bioelectric potential. III. *Nitella*. *J. gen. Physiol.* **20**, 229–265.

COLE, K. S. (1941). Rectification and inductance in the squid giant axon. *J. gen. Physiol.* **25**, 29–51.

COLE, K. S. (1947). *Four Lectures on Biophysics, Rio de Janeiro*. Publication of the Institute of Biophysics, University of Brazil: Rio de Janeiro.

COLE, K. S. & CURTIS, H. J. (1938). Electric impedance of *Nitella* during activity. *J. gen. Physiol.* **22**, 37–64.

COLE, K. S. & CURTIS, H. J. (1939). Electric impedance of the squid giant axon during activity. *J. gen. Physiol.* **22**, 649–670.

COLE, K. S. & HODGKIN, A. L. (1939). Membrane and protoplasm resistance in the squid giant axon. *J. gen. Physiol.* **22**, 671–687.

CURTIS, H. J. & COLE, K. S. (1938). Transverse electric impedance of the squid giant axon. *J. gen. Physiol.* **21**, 757–765.

CURTIS, H. J. & COLE, K. S. (1940). Membrane action potentials from the squid giant axon. *J. cell. comp. Physiol.* **15**, 147–157.

CURTIS, H. J. & COLE, K. S. (1942). Membrane resting and action potentials from the squid giant axon. *J. cell. comp. Physiol.* **19**, 135–144.

GRAY, J. (1931). *A Text-book of Experimental Cytology*. Cambridge: Cambridge University Press.

GRUNDFEST, H. & NACHMANSOHN, D. (1950). Increased sodium entry into squid giant axons at high frequencies and during reversible inactivation of cholinesterase. *Fedn Proc.* **9**, 53.

HILL, A. V. (1932). *Chemical Wave Transmission in Nerve*. Cambridge: Cambridge University Press.

HODGKIN, A. L. (1936). The electrical basis of nervous conduction. Fellowship dissertation. Library of Trinity College, Cambridge.

HODGKIN, A. L. (1937*a*). Evidence for electrical transmission in nerve. I. *J. Physiol.* **90**, 183–210.

HODGKIN, A. L. (1937*b*). Evidence for electrical transmission in nerve. II. *J. Physiol.* **90**, 211–232.

HODGKIN, A. L. (1937*c*). A local electric response in crustacean nerve. *J. Physiol.* **91**, 5–6*P*.

HODGKIN, A. L. (1938). The subthreshold potentials in a crustacean nerve fibre. *Proc. R. Soc.* B **126**, 87–121.

HODGKIN, A. L. (1939). The relation between conduction velocity and the electrical resistance outside a nerve fibre. *J. Physiol.* **94**, 560–570.

HODGKIN, A. L. & HUXLEY, A. F. (1939). Action potentials recorded from inside a nerve fibre. *Nature, Lond.* **144**, 710–711.

HODGKIN, A. L. & HUXLEY, A. F. (1945). Resting and action potentials in single nerve fibres. *J. Physiol.* **104**, 176–195.

HODGKIN, A. L. & HUXLEY, A. F. (1947). Potassium leakage from an active nerve fibre. *J. Physiol.* **106**, 341–367.

HODGKIN, A. L. & HUXLEY, A. F. (1948). A theoretical model of nervous transmission. Unpublished manuscript.

HODGKIN, A. L. & HUXLEY, A. F. (1952*a*). Currents carried by sodium and potassium ions through the membrane of the giant axon of *Loligo*. *J. Physiol.* **116**, 449–472.

HODGKIN, A. L. & HUXLEY, A. F. (1952*b*). The components of membrane conductance in the giant axon of *Loligo*. *J. Physiol.* **116**, 473–496.

HODGKIN, A. L. & HUXLEY, A. F. (1952*c*). The dual effect of membrane potential on sodium conductance in the giant axon of *Loligo*. *J. Physiol.* **116**, 497–506.

HODGKIN, A. L. & HUXLEY, A. F. (1952*d*). A quantitative description of membrane current and its application to conduction and excitation in nerve. *J. Physiol.* **117**, 500–544.

HODGKIN, A. L., HUXLEY, A. F. & KATZ, B. (1949). Ionic currents underlying activity in the giant axon of the squid. *Archs Sci. physiol.* **3**, 129–150.

HODGKIN, A. L., HUXLEY, A. F. & KATZ, B. (1952). Measurement of current-voltage relations in the membrane of the giant axon of *Loligo*. *J. Physiol.* **116**, 424–448.

HODGKIN, A. L. & KEYNES, R. D. (1956). Experiments on the injections of substances into the squid giant axons by means of a microsyringe. *J. Physiol.* **131**, 592-616.

HODGKIN, A. L. & RUSHTON, W. A. H. (1946). The electrical constants of a crustacean nerve fibre. *Proc. R. Soc.* B **133**, 444–479.

KATZ, B. (1937). Experimental evidence for a non-conducted response of nerve to subthreshold stimulation. *Proc. R. Soc.* B **124**, 244–276.

KATZ, B. (1947). The effect of electrolyte deficiency on the rate of conduction in a single nerve fibre. *J. Physiol.* **106**, 411–417.

KEYNES, R. D. (1948). The leakage of radioactive potassium from stimulated nerve. *J. Physiol.* **107**, 35*P*.

KEYNES, R. D. (1949). The movements of radioactive sodium during nervous activity. *J. Physiol.* **109**, 13*P*.

KEYNES, R. D. (1951*a*). The leakage of radioactive potassium from stimulated nerve. *J. Physiol.* **113**, 99–114.

KEYNES, R. D. (1951*b*). The ionic movements during nervous activity. *J. Physiol.* **114**, 119–150.

KEYNES, R. D. & LEWIS, P. R. (1951). The sodium and potassium content of cephalopod nerve fibres. *J. Physiol.* **114**, 151–182.

OSTERHOUT, W. J. V. (1931). Physiological studies of large plant cells. *Biol. Rev.* **6**, 369–411.

RATCLIFFE, J. A. (1975). Physics in a university laboratory before and after World War II. *Proc. R. Soc.* A **342**, 457–464, from a discussion on the effects of two world wars on the organization and development of science in the United Kingdom, organized by R. V. Jones.

ROTHENBERG, M. A. (1950). Studies on permeability in relation to nerve function. II. Ionic movements across axonal membranes. *Biochim. biophys. Acta* **4**, 96–114.

RUSHTON, W. A. H. (1932). A new observation on the excitation of nerve and muscle. *J. Physiol.* **75**, 16–17*P*.

RUSHTON, W. A. H. (1934). A physical analysis of the relation between threshold and interpolar length in the electric excitation of medullated nerve. *J. Physiol.* **82**, 332–352.

RUSHTON, W. A. H. (1937). Initiation of the propagated disturbance. *Proc. R. Soc.* B **124**, 201–243.

SCHAEFER, H. (1936). Untersuchungen über den Muskelaktionsstrom. *Pflügers Arch. ges. Physiol.* **237**, 329–355.

WEBB, D. A. & YOUNG, J. Z. (1940). Electrolyte content and action potential of the giant nerve fibres of *Loligo*. *J. Physiol.* **98**, 299–313.