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Sir Alan L. Hodgkin

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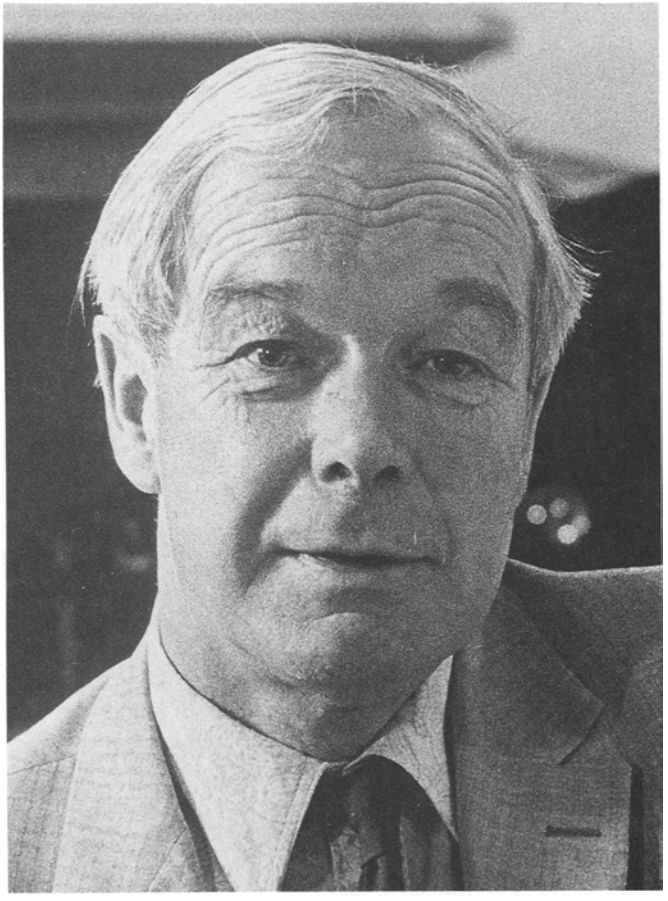

Sir Alan L. Hodgkin

BORN:

Banbury, Oxfordshire, England
February 5, 1914

EDUCATION:

University of Cambridge: Trinity College (1932), Sc.D. (1963)

APPOINTMENTS:

Fellow, Trinity College, Cambridge (1936 to date)
Foulerton Research Professor, Royal Society (1952)
Plummer Professor of Biophysics, University of Cambridge (1970)
Master of Trinity College, Cambridge (1978)

HONORS AND AWARDS:

Fellow, Royal Society of London (1948)
Royal Medal, Royal Society (1958)
Nobel Prize for Medicine or Physiology (1963)
Copley Medal, Royal Society (1965)
President, Royal Society (1970–1975)
Knight of the British Empire (1972)
Order of Merit (1973)
Foreign Associate, American Academy of Arts and Sciences (1974)
Foreign Associate, National Academy of Sciences USA (1974)

Sir Alan Hodgkin, together with Andrew Huxley, established the ionic basis of the resting potential in nerve cells and the ionic basis of nerve conduction. Later, he studied the biophysics of sensory transduction in the photoreceptors of vertebrates.

Sir Alan L. Hodgkin

I come from a long line of Quakers, some of whom were scientists and others historians. But until about 1870 the Universities of Oxford and Cambridge were not open to nonconformists, so scientists such as the meteorologist Luke Howard, my great-great grandfather, or the historian Thomas Hodgkin, my grandfather, relied on a profession—like banking—for financial support and pursued their academic interests in their spare time or, when they had made enough money, after early retirement. This may have had some indirect effect on my attempts to do scientific research because it encouraged me to try experiments at home with simple equipment. More generally it gave me the feeling that research was something one did for fun rather than part of a "9 to 5" profession.

It is customary to divide research into the pure and applied categories. Such a distinction is plainly unsatisfactory because pure research like that of Sir Alexander Fleming's may lead to results of great practical importance such as the discovery of penicillin, and applied plant breeding experiments may generate new ideas about genetic theories. I have no real quarrel with this classification, but think it incomplete because it says nothing about the actual motivation of scientists. If pure scientists were motivated by curiosity alone, they should be delighted when someone else solves the problem they are working on—but this is not the usual reaction. And of course the same is true of applied research: engineers or inventors are naturally upset if their designs are anticipated.

I mention these rather obvious points about motivation because they were strong influences on my own research. I certainly was curious about how a nerve conducts electrical impulses or an eye catches light quanta and am delighted that we have gone a long way toward solving both problems. But a good deal of my satisfaction comes from the fact that my colleagues and I helped to put theories for such problems on a firm footing and eventually came to see them taken for granted. Yet establishing a firm base for a scientific theory or discovering something new does seem to me a possible way of answering A.E. Housman's moving but melancholy question:

> Here, on the level sand,
> Between the sea and land,
> What shall I build or write
> Against the fall of night?

Tell me of runes to grave
That hold the bursting wave,
Or bastions to design
For longer date than mine.

Shall it be Troy or Rome
I fence against the foam,
Or my own name, to stay
When I depart for aye?

Nothing: too near at hand,
Planing the figured sand,
Effacing clean and fast
Cities not built to last
And charms devised in vain,
Pours the confounding main.

Family Background

As a Quaker and pacifist my father, George, took no direct part in military activities during World War I. Instead he joined two expeditions which attempted, with some success, to bring relief to Armenian refugees in the Middle East. On the second expedition he died of dysentery in Baghdad on June 24, 1918. This left my mother with three small boys—ages four, two, and one month—of whom I was the eldest.

One might have expected George's death to have made my mother, who then was only 26, unduly protective of her young family. But it seemed to have had the opposite effect, perhaps because she was buoyed up by some inner faith or because she recognized the danger of being overprotective. At any rate, when we were old enough she encouraged us to walk long distances on our own in the pleasant country round Banbury or Oxford, England, where we lived until I was 18. Or, after we had learned to use a map and compass, she allowed us to make all-day expeditions in the snow-covered hills in the Lake District, where we occasionally spent a winter holiday.

My mother also encouraged my interest in natural history, in which she was helped by my Aunt Katie—a talented but eccentric ornithologist with whom we stayed on the Northumbrian coast opposite Holy Island. Aunt Katie taught me to keep a bird diary and to hunt for the nests of rare birds. The nest most prized was that of the golden plover, of which there were one or two on some neighboring hills. We found our first nest in April 1928, having hunted without success in the same area in the two preceding years. The search followed a standard pattern not unlike scientific research. The strange creaking whistle of the plovers provided initial evidence of the likelihood of a nest in the vicinity, and one collected further

clues by watching the behavior of the birds. The resulting hypothesis as to the whereabouts of a nest was confirmed by finding the four beautifully marked but well-camouflaged eggs. But sometimes one had misread the evidence and there were no eggs because one had been watching the male, not the female, and it had been sitting on a "scrape" or dummy nest.

Starting a Scientific Career

At the end of 1931 I got a major scholarship at Trinity College, Cambridge. This came as a surprise to my school which had not thought I was was of that caliber. My main subjects at school were zoology, botany, and chemistry, in the first two of which I was helped greatly by my interest in natural history. I was to go to Cambridge in the autumn of 1932, and my mother had sensibly arranged for me to spend some time before then learning German in Frankfurt. I also was keen to have a shot at some research problem before going to Trinity.

Getting a scholarship encouraged me to visit one of my future teachers in Cambridge, Carl Pantin, a distinguished experimental zoologist who gave me some good advice which I had the sense to follow. He said that in my last term at school I should do no more biology but should concentrate on mathematics, physics, and German. He also told me that I must continue to learn mathematics—something that I have tried to do during the rest of my life, or at any rate until a few years ago. One of my bibles was Piaggio's *Differential Equations*, though I cannot claim to have done all the examples as I probably should have done.

As to a short-term research project, Pantin was doubtful about my attempting something at Plymouth Marine Biological Laboratory, which was my initial idea and where I had once been on a schoolboy course. He suggested that I work at the Freshwater Biological Station on Lake Windermere that had just been set up under the direction of two young zoologists, Philip Ullyott and R.S.A. Beauchamp. I jumped at the idea, not least because it provided an opportunity of spending May in one of the most beautiful parts of the Lake District. I lived in the tiny village of High Wray and many years later I found that my ancestors, Rachel and Isaac Wilson, had lived there two centuries earlier.

For my research project, Ullyott suggested that I study the effect of temperature on the freshwater planarian *Polycelis nigra* and in particular should see if they congregated in the cold end of a temperature gradient. I found that they did, and that this was only partly explained by their higher rate of movement in the warm end. Six months later I tried to continue the experiments in the spare bathroom at home, but nothing came of this apart from the disturbance to our guests.

I went up to Trinity in the autumn of 1932. During full term in Cambridge there was no time to attempt even the simplest kind of research.

An opportunity came during the much more leisurely, Long Vacation term, July to September, when a few optional courses are held. The first experiments I tried were aimed at comparing the effects of changes in external and internal pH on amoeboid motion. This research did not get anywhere but increased my interest in cell membranes, which I read about in James Gray's *Experimental Cytology* and A.V. Hill's *Chemical Wave Transmission in Nerve*. I had also read W.J.V. Osterhout's *Physiological Studies of Large Plant Cells* and was impressed by the evidence obtained by L.R. Blinks that an increase in membrane conductivity occurred when an electrical impulse traveled along one of the large cells of the water plant *Nitella*.

I felt that it would be nice to know whether the nerve impulse was accompanied and perhaps caused by a similar increase in membrane conductivity. It seemed to me that evidence for this crucial point was lacking and might be obtained by the experiment illustrated in Figure 1, which could be carried out with simple apparatus. I arranged to block a frog nerve locally by freezing a short length and applied two appropriately timed shocks on either side of the block. I argued that if the membrane conductivity increased during activity, then arrival of an appropriately timed impulse at the block should help the stimulating current to enter the nerve and so increase excitability—provided that the shock and impulse coincided.

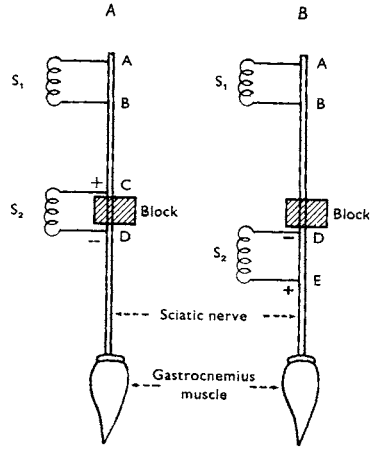

Figure 1. Diagram of method of testing the effect on excitability of a blocked nerve impulse, using sciatic gastrocnemius preparation [Source: Hodgkin (1976) *J Physiol* 263:1-21].

To begin with, I got a negative result but on trying again in October 1934 the experiment worked well, and I was pleased. However, after several weeks I got a horrid surprise. I switched the anode from just above the block to a position beyond it—from position C in Figure 1A to position E in Figure 1B—and found that the facilitating effect of the blocked impulse persisted.

The effect therefore had nothing to do with an increase in conductivity at position C and was simply explained by local electric currents spreading through the block and raising excitability beyond it, as shown in Figure 2.

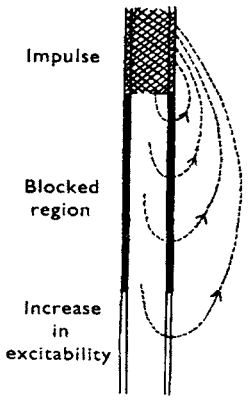

Figure 2. Diagram illustrating local electric circuits spreading through block and increasing excitability beyond it (from Hodgkin, 1936, 1937a,b) [Source: Hodgkin (1976) *J Physiol* 263.1-21].

More generally, the effect might be attributed to whatever agent is responsible for the conduction of the nerve impulse. The effect did not provide any evidence for electrical transmission, but it offered a neat way of testing the theory, and it was this subject that I chose when starting whole-time research in the following year, at the end of my undergraduate studies.

By mid-July 1936 I had been through the main experiments which strongly supported the idea that nerve impulses are propagated by electric currents spreading in a local circuit ahead of the active region. I wrote up these and other results in a thesis which brought me a fellowship at Trinity College in October 1936 and a Rockefeller Fellowship in New York for the following year. Both influenced my life in many ways, and for both I am deeply grateful.

During my last few months in Cambridge before going to America, I found that it was surprisingly easy to dissect single nerve fibers from the shore crab *Carcinus maenas*. I had also shown that there were transitional stages in the initiation of the nerve impulse as expected from the work of William Rushton and Bernard Katz. To begin with, H.S. Gasser and several other senior neurophysiologists were skeptical about this result, but Gasser did not mind my continuing on my own and provided me with a room and splendid equipment in the Rockefeller Institute in New York.

The Rockefeller Foundation encouraged travel and in the early summer of 1937 I worked with K.S. Cole and H.J. Curtis at the Woods Hole Marine Biological Laboratory in Massachusetts, where they introduced

me to work on the giant nerve fiber of the squid, which was to have a major effect on my scientific life.

In New York and on the personal side, far and away the most important contact that I made was with Marni Rous whom I first met in 1937 at a tea party given by her father, the distinguished and delightful scientist Peyton Rous, then working at the Rockefeller. Six months later I got to know her well while she was staying with her cousins in Connemara, Ireland, where I joined her on my return from America. I had fallen deeply in love and wanted to marry her, but she said no quite firmly and it was seven years before we met again and she changed her mind.

Someone, probably H.S. Gasser, suggested that the Rockefeller Foundation might help me buy or build a modern set of electronic equipment for my lab in the Physiological Laboratory, Cambridge. Dr. Toennies, the Institute's electronics man, suggested a list of things I might need, and before leaving New York in 1938 I learned that I would receive an equipment grant of £300, a large sum in those days.

When I got back to Cambridge and started work in the Physiological Laboratory, I joined forces with three psychologists, A.F. Rawdon-Smith, Rowan Sturdy, and Kenneth Craik, who were interested in building new electronic equipment. Among us we built three or four sets of equipment, some of which were still in use 25 years later. In addition to building equipment I gave a course of lectures in the laboratory and tutorials at Trinity College where I had the good fortune to teach some brilliant people, including Andrew Huxley in his fourth year and Richard Keynes in his first year.

I got my laboratory equipment going by January 1939 and started to measure the relative size of resting and action potentials in crustacean nerve, using external electrodes. This work led to my internal electrode experiments on squid nerve, carried out with Andrew Huxley at Plymouth, which showed that the action potential might exceed the resting potential by some 40 mV. In other words, the membrane potential at the peak of the nerve impulse reversed by 40 mV instead of falling to zero as assumed in the classical theory.

There obviously was much to be done with the exciting new technique, but it had to be abandoned when Hitler marched into Poland and war was declared on September 3, 1939. We left the equipment at Plymouth in the faint hope that the war would be short and that we could soon continue the experiments. However, the war lasted six years, Plymouth was badly bombed, and it was eight years before I could return. There also was a major disappointment on the personal side as Marni Rous, who had planned to be in Cambridge 1939 to 1940 on a Henry Fellowship, had to cancel her visit. We did not meet again until 1944 in New York when I was sent to the U.S. on a radar mission and we then lost little time in getting married.

I spent most of the war in Britain working extremely hard on 9-cm radar in night-fighters, Beaufighters and Mosquitoes, for the Royal Air Force. The most important and interesting job in which we collaborated with the (British) General Electric Company and several other firms, was to design an air interception set capable of bringing a night-fighter within about 500 feet of an enemy bomber in darkness, at which range the night-fighter's pilot should be able to see and shoot down the bomber.

Return to Cambridge

Toward the end of 1944 my work on radar grew less urgent, and I started working again on neurophysiology at home in the evenings and on weekends. I was released from military service soon after the end of the German war, and Marni and I, with our baby daughter, returned to Cambridge from Malvern on the Hereford/Worcestershire border at the end of July 1945. I was keen to start experimental research again but it was as difficult to get going in the Physiological Laboratory as it was to set up house. We had managed to buy a pleasant, smallish house, but there was a £10 limit on any unauthorized repairs. In six months the universities were to be flooded with war-surplus equipment, but to begin with there was nothing in the laboratory and little in the shops.

Some of the equipment that I had left at Plymouth was damaged in a major air raid, but I managed to salvage a good deal. Fortunately I had lent the main racks to Rawdon-Smith and Sturdy, and they had removed them before the main air raids began. Somehow I managed to collect everything and get the equipment going well enough to start experiments on *Carcinus* again.

E.D. Adrian, the professor of physiology at Cambridge University, had obtained my early release from military service on the grounds that he needed help with teaching. This was true, as we still had our full quota of medical students. One of my first jobs was to lecture on human physiology to student nurses. This job was good practice for me, but the nurses were under the charge of a fearsome-looking matron, and I could not get a flicker of interest out of them. I felt better when Adrian, who had given the lectures originally, said that he had had the same experience. Adrian let me off with a light teaching load, but I found it much harder to give tutorials than before the war. This difficulty was partly because I had forgotten a good deal and partly because I no longer believed in many of the principles that once seemed to hold physiology together. Thus the constancy of the internal environment was as important as ever, but the way in which it was achieved had grown more complicated. I suppose that after five years working as a physicist, I had little use for biological generalizations and preferred physicochemical approaches to physiology. This did not go down well with most medical students.

After a rocky start my experiments on crab nerve fibers began to go well. These experiments went even better after Andrew Huxley returned

to Cambridge from the Admiralty in 1945. Professor Adrian obtained a grant of £3,000 per annum from the Rockefeller Foundation, which helped to support a group working mainly on nerve and muscle. The original members of this group were D.K. Hill, Andrew Huxley, and myself. We were soon joined by distinguished visitors from abroad, among whom R. Stampfli and S. Weidmann were some of the first.

In 1948 I was encouraged greatly by my election to the Royal Society. This was welcome recognition, as the ionic hypothesis of nerve conduction then was not widely accepted outside Britain. Four years later the Society helped me in a more material way by appointing me to a Foulerton Research Professorship, which allowed me to concentrate on research with little teaching. More widespread recognition came with the award of the Nobel Prize in 1963 to Jack Eccles, Andrew Huxley, and myself.

Our work was influenced strongly by a number of new techniques, some of which had arisen during the war and others which we developed for ourselves. Huxley and I had obtained strong but indirect evidence that each nerve impulse was associated with a minute but rapid outflow of potassium ions. We also thought it likely, but had little evidence, that the potassium outflow was preceded by an entry of sodium ions.

It clearly was important to measure the sodium entry and potassium loss in a single nerve fiber. Richard Keynes was keen to have a go at this ambitious project, which he did successfully when he returned to Cambridge in 1945. In the end, he used several methods, including radioactive tracers, flame photometry, and activation analysis, but happily all three provided results that were in reasonable agreement. The quantity turned out to be exceedingly small, and a single nerve fiber loses only about one 100,000th of its potassium and gains a similar quantity of sodium in one impulse. However, this quantity is equivalent to several times the charge on the resting membrane, so sodium entry and potassium exit are a satisfactory basis for the nerve impulse.

For this scheme to work efficiently it is important that the sodium and potassium movements are separated in time. Ideally the sequence of events when the impulse passes a particular point on the nerve should be something like this: as the active region approaches, the membrane will be depolarized, i.e., grow less negative. This depolarization will raise the sodium permeability of the membrane, which in turn will cause sodium ions to enter the nerve and lead to further rapid depolarization. As a result of this regenerative process, the membrane potential will move from somewhere near the potassium equilibrium potential to a new value near the sodium equilibrium potential: say from –70 to +40 mV. In addition to changing the charge on the membrane capacity, the early entry of sodium to the nerve provides the inward current, which depolarizes the next section of the nerve and makes a wave of high sodium permeability spread along it.

If this were all that occurred, once the nerve were activated it would remain in a state of high sodium permeability indefinitely and so would be useless for further signaling. However, at the crest of the impulse slower processes begin to take effect. In the first place the sodium permeability does not remain at a high value but declines with a time constant of about 1 msec when the membrane is depolarized. This process is known as inactivation. Recovery of the original resting potential in the nerve is greatly accelerated by an increase in potassium permeability, which takes place with an S-shaped delay near the crest of the impulse. The mechanism responsible for the initial rise of sodium permeability is reversible. Hence any sodium conductance that has not been inactivated is cut off, and repolarization is accelerated.

After its resting potential has been restored, the membrane is ready to conduct another impulse, but it only does so with difficulty. In this condition, which is known as the relative refractory period and which lasts for a few milliseconds, a second impulse is harder to set up and is conducted more slowly. In the initial part of the refractory period, a second impulse cannot be set up at all and the nerve is said to be in the absolute refractory period.

In the years after the war my colleagues and I obtained much evidence for the essential correctness of the theory outlined above. So far as we could see, it applied to all nerves and to skeletal muscle, which also conducts something similar to a nerve action potential. However, it is necessary to make a reservation because in some cases—crab muscle is an example—the inward current that drives the action potential along the muscle is carried by calcium rather than by sodium ions.

One satisfactory point for us was that the evidence for the sodium theory of the nerve impulse was quantitative. Thus we found that the reversed membrane potential at the crest of the impulse varied as 58 mV $\log[Na]_o$, as it should if the membrane is selectively permeable to sodium ions.

In analyzing the behavior of nerve and other excitable tissues, much progress was made by using the voltage-clamp technique in which the membrane potential is displaced to a new value and held there by electronic feedback. The current, which flows through a definite area of membrane under the influence of the impressed voltage, is measured with a separate amplifier. The early work using this technique was done on squid axons, first by Cole and later by Huxley, Katz, and myself.

When an impulse propagates along a nerve fiber, the internal potential changes with time and distance, as does the membrane current. In the original voltage-clamp method, about a centimeter of the interior of the nerve was pierced by a long metal electrode and could be treated as an isolated patch of membrane.

A further advantage of the voltage-clamp method is that the experimenters control the voltage across the membrane and can make it do what they want. They can for example make the feedback apparatus suddenly reduce the membrane potential to zero, a procedure equivalent to suddenly

short-circuiting the membrane. If this is done the membrane capacity is discharged at once, and thereafter only ionic flow through the membrane contributes to the current. If the membrane is suddenly depolarized to some value between 20 and 110 mV below the resting potential, the ionic current consists of two phases. To begin with, sodium ions flowing down their concentration gradient give an inward current. This component is transient and after about 1 msec (at 10°C) is replaced by an outward potassium current. The two components of the current vary with the concentrations of sodium and potassium ions. By changing these concentrations the ionic current can be separated into its two components. From there it is a short step to calculate the sodium and potassium conductances and see how they change with time (Figure 3).

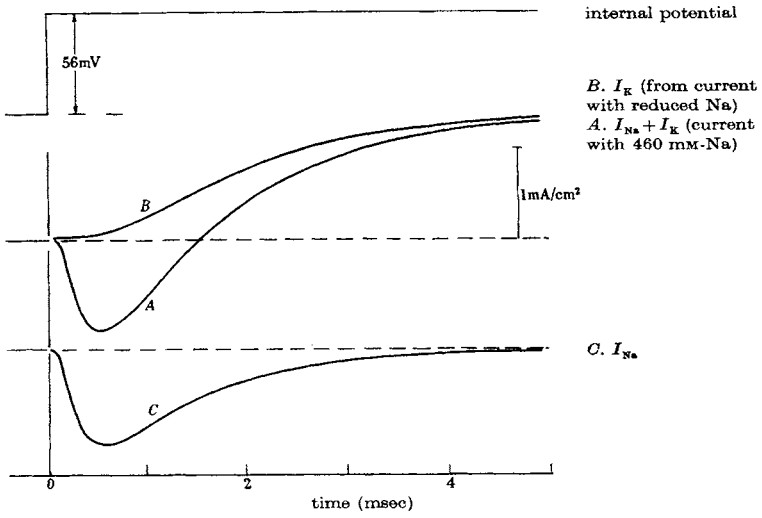

Figure 3. Separation of membrane current into components carried by Na and K; outward current upwards. *A*, Current with axon in sea water = $I_{Na} + I_K$. *B*, Current with most of external Na replaced by choline = I_K. *C*, Difference between A and B = I_{Na}. Temperature 8.5°C (from Hodgkin and Huxley, 1952a) [Source: Hodgkin, 1964a].

We made a few voltage-clamp experiments in the late summer of 1948, but nearly all the results on which we relied for our analysis were obtained a year later. After that it took a further two years to analyze and write up the results. I have sometimes been asked why this took so long. The reasons were multiple. In the first place we had other things to do, notably teaching and working with research students or visitors. Much of the analysis had to be done by hand, and we had no suitable computers to assist us. Fortunately for us, no one else was particularly interested in voltage-clamp analysis, and we were able to take our time.

Our conclusions could be summarized by saying that nerve conduction was brought about by changes in sodium- and potassium-selective chan-

nels. Both changes were graded and reversible in the sense that if the original resting potential of the nerve was restored, both channels reverted rapidly to their closed condition. For both channels the turn-on rate was increased and the turn-off rate decreased by depolarization. In addition the system controlling the sodium permeability was reduced more slowly by the inactivation mechanism, which was primarily responsible for the transient nature of the rise in sodium permeability.

At first it might be thought that the response of a nerve to different electrical stimuli is too complicated and varied to be explained by these relatively simple conclusions. Partly for this reason Huxley and I spent a long time developing what are sometimes known as the Hodgkin–Huxley equations, which are given in outline below. In using the equations it should be emphasized that there are no arbitrary constants, as the voltage-clamp results were used to supply the numerical data required.

The main features that had to be built into our theory are shown in Figure 4. A striking point that caused some initial difficulty was that both conductances were turned on with an S-shaped delay but were turned off sharply along an exponential curve. We dealt with this fact by assuming that each conductance was proportional to the third or fourth power of a variable which obeyed a first-order equation. A fourth power was used for potassium, and in this case, the rise of conductance was described by $[1-e^{-t}]^4$ and showed a marked inflection, whereas the fall was given by e^{-4t} and remained exponential with a faster rate constant.

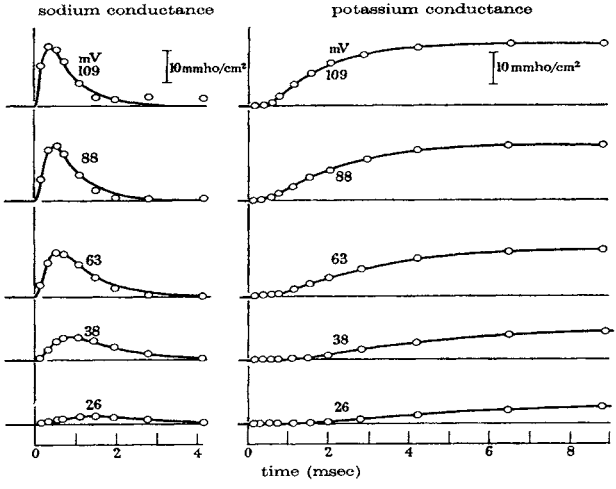

Figure 4. Time course of sodium and potassium conductance for different displacements at 6°C; the numbers give the depolarization used. The circles are experimental estimates and the smooth curves are solutions of equations (1) and (2) (from Hodgkin and Huxley 1952d) [Source: Hodgkin (1964a) or Hodgkin (1957) *Proc R Soc Lond B Biol Sci* 148,1-37].

A tentative picture of what might be going on, is that a path for potassium ions is formed when four charged particles have moved to the right place under the influence of the electric field. The probability of a single particle being correctly placed, denoted by n, obeys first-order kinetics, i.e.,

$$dn/dt = \alpha(1-n) - ßn \qquad (1)$$

where α increases and ß decreases as the inside of the nerve fiber becomes more positive. The potassium conductance is assumed proportional to the fourth power of n.

For the sodium channel, we assumed that three simultaneous events, each of probability m, opened the channel to sodium and that a single event of probability (1–h) blocked it. These events were not specified, but could be thought of as the movements of three activating particles and one blocking particle to a certain region of the membrane. The probability that there will be three activating particles and no blocking particle is then given by m^3h, and the sodium conductance is proportional to that quantity. Both m and h obey first-order equations similar to (1). However, both the rate constants and the way they are affected by membrane potential are different for the m and h variables. Thus the effect of making the inside of the nerve fiber more positive is to increase m by raising α and lowering ß; this effect on the h rate constant is the opposite, so that h decreases with V.

A striking feature of the nerve membrane is the extreme steepness of the relation between ionic conductance and membrane potential. Thus both sodium and potassium conductances may be increased e-fold by a change of only 4 to 5 mV in membrane potential. The corresponding figure for most physical devices at room temperature is 25 mV. Our model allows for the steep relation of the membrane by making the rate constants increase sharply with membrane potential and by involving several particles at each site.

The steepness of the conductance-voltage relation must be of value to the animal because it enables the nervous system to work at much lower voltages than those of our computers. On the other hand, although efficient in this respect, ionic gating systems are much slower than their electronic counterparts.

Although partly empirical, our equations did account satisfactorily for many aspects of a nerve's behavior. A simple case to deal with was the membrane action potential in which all parts of the membrane are activated simultaneously by applying a brief shock to a length of nerve. In the upper part of Figure 5 are theoretical curves for different initial displacements, and the lower curves are membrane action potentials recorded in an actual nerve. The agreement between real and model nerves is clearly satisfactory.

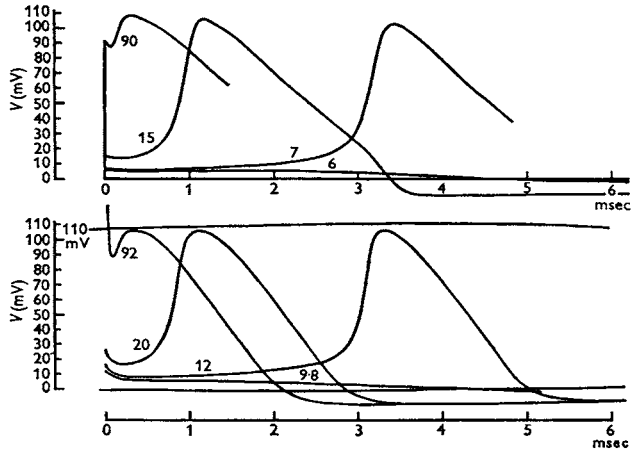

Figure 5. Upper curves, theoretical solution for different initial depolarizations of a uniform area of membrane. Lower curves, tracings of membrane action potential at 6°C obtained on same axon as that which gave Figure 4. The numbers attached to the curve give the strength of the shock in nanocoulomb/cm^2 (from Hodgkin and Huxley, 1952d) [Source: Hodgkin 1964a].

The form and velocity of the propagated action potential can be obtained by combining the equations for m, n, and h with the well-known relation between membrane current density (I) and membrane potential (V). For a wave propagating with velocity θ in an axon of radius a and resistivity R, this is:

$$I = a/2R\theta^2 \quad X \quad d^2V/dt^2 \qquad (2)$$

In the resulting second-order equation, the velocity is unknown at the beginning of the computation but can be found by guessing a value and running a trial solution. V then goes to $\pm\infty$ according to whether θ has been chosen too high or too low. The correct value that corresponds to the natural velocity brings the potential back to its resting value at the end of the run.

A solution of this kind was worked out by Huxley in 1950 and was found to agree with a real nerve in the following respects: the form, amplitude, and velocity of the action potential (Figures 6 and 7) and of the conductance changes, as do the total movements of sodium and potassium during the impulse. The equations also accounted satisfactorily for the refractory period and for a wide range of phenomena associated with the excitation of nerve under different conditions. A striking example was the oscillatory responses seen in response to a rectangular current in both model and real nerve.

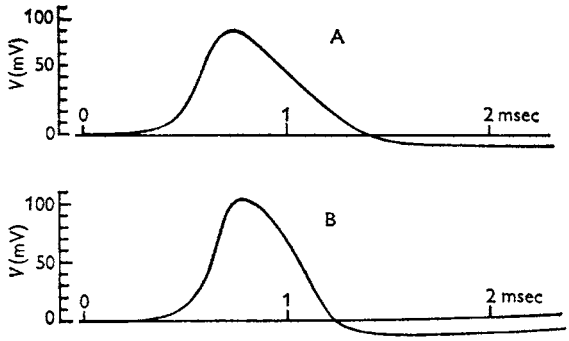

Figure 6. Propagated action potentials in *A*, theoretical model, and *B*, squid axon, at 18.5°C. The calculated velocity was 18.8 msec and the experimental velocity 21.2 msec (from Hodgkin and Huxley, 1952d) [Source: Hodgkin 1964a].

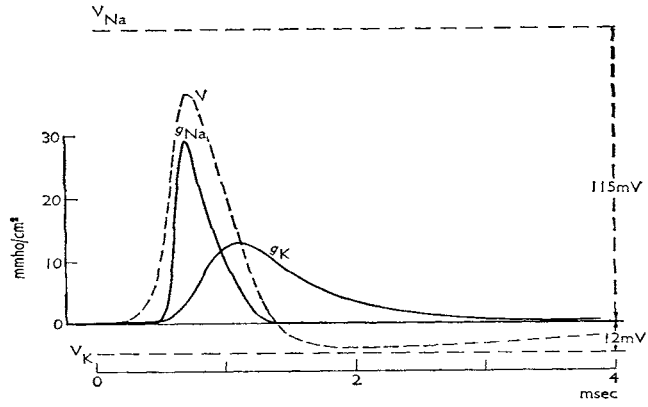

Figure 7. Theoretical solution for propagated action potential and conductances at 18.5°C (From Hodgkin and Huxley 1952d). Total entry of sodium= 4.33 pmole/cm^2; total exit of potassium= 4.26 pmole/cm^2 [Source: Hodgkin 1964a or 1957].

The immediate effect of carrying a train of impulses is that a nerve gains a small amount of sodium and loses a similar quantity of potassium ions. In large nerve fibers the changes in concentration of both ions resulting from a single impulse are extremely small, and a 500-μm diameter fiber might be able to conduct half-a-million impulses without recharging its batteries by metabolism. But whether large or small, nerve fibers would be of no value unless they could use metabolic energy to extrude sodium and reabsorb potassium after a train of impulses.

We guessed that nerve, like other tissues, would contain a sodium pump for extruding sodium and that it would be interesting to character-

ize the system using radioactive tracers. To begin with, Keynes and I, who worked together on this project, used cuttlefish axons. These were large enough to give us the necessary sensitivity and had the advantage that we could do the experiments in Cambridge. Later when we needed larger cells, we moved to Plymouth to do certain key experiments on squid axons.

This joint work with Keynes, which I enjoyed very much, lasted intermittently for more than 10 years. In the latter part of the work we were joined by P.F. Baker, T.I. Shaw, and P.C. Caldwell who contributed a great deal on both the theoretical and practical sides of the project. It has been a great sadness to me that all three of these brilliant and attractive people died relatively young: Caldwell and Baker from heart disease, and Shaw from an accident during a period of depression.

Although we were not able to give a full biochemical description of the sodium/potassium pump, we found out many interesting things about the way in which it works. In the first place it soon became clear that the downhill movements of sodium and potassium which take place during the impulse have completely different properties from the reverse, uphill movements that occur during recovery. For example, metabolic inhibitors which knock out the pump have no immediate effect on the action potential whereas tetrodotoxin, which blocks the action potential, has no effect on the pump. The systems also differ in their ionic selectivity. For example, lithium, which can replace sodium in the action potential, is not moved at all effectively by the pump. As might be expected, the downhill movements through sodium channels during the action potential are much faster than the uphill movements during recovery.

In the early 1950s it was clear that there had to be some kind of metabolic pump to drive out the sodium ions that leaked into the nerve or entered it during the impulse. However, the theory with regard to potassium was less clear, as these ions might be drawn in passively by the electrical negativity created by the sodium pump rather than by some chemical linkage between sodium and potassium movements. It also was not clear how the hydrolysis of ATP was involved with the pumping mechanism.

Our work at Plymouth clearly fitted well with the experiments of Skou (1957) in Denmark who showed that an essential component of the sodium pump was a membrane protein which catalyzed the hydrolysis of ATP into ADP and inorganic phosphate. This enzyme, which is widely distributed, is known as an Na,K,-ATPase. It is catalyzed by sodium inside and potassium outside the cell. We were able to obtain evidence for several of these points by restoring the sodium/potassium pump with injections of ATP or ATP generators. The quantity of sodium ions extruded was roughly proportional to the amount of ATP injected. The theory now generally accepted is that two potassium ions are absorbed and three sodium ions extruded for each ATP split.

I worked at Plymouth nearly every year between 1958 and 1970, usually in the late autumn when large squid were in good supply. I found, as

others have done, that it is easier to keep going with experiments when you are away from home and the laboratory has priority. My scientific partners during that period included P.F. Baker, T.I. Shaw, H. Meves, W.K. Chandler, M. Blaustein, and E.B. Ridgway. At first we worked mainly on perfused fibers, but later we studied calcium movements using radioactive calcium or the calcium-sensitive protein aequorin, extracted from certain jellyfish that emit light in the presence of calcium ions. Some of this work helped to advance the idea that internal calcium ions might be kept at a low level by a system in which several external sodium ions are exchanged for one internal calcium ion.

Move to Visual Research

The autumn of 1970 ended my experiments at Plymouth. After that I switched my interest to visual research which I could do in Cambridge with the help of colleagues or visitors. In the end I thoroughly enjoyed the change, but at the time I sometimes felt that in the middle of my scientific life "I found myself in a dark wood with no straight path before me." The main reason for the change was that in December I was to become president of the Royal Society in London with a tenure of five years. I thought that with the right colleague I could keep experiments going in Cambridge and combine a London life with a Cambridge one, but saw no way that I could add in Plymouth as well.

As a student in Cambridge I had been influenced by Adrian's work on the retina and by H.K. Hartline's work on the eyes of *Limulus*. Later, I was impressed by the work that Hartline and his colleagues were doing on generator potentials, which I heard about at the 1952 Cold Spring Harbor Conference.

In making the move to visual research I was helped by my friendship with M.G. Fuortes, an Italian physiologist whom I had met in Cambridge before his move to the United States in 1950. In 1961 we started to correspond about work that he was doing on the eye of *Limulus*. I was to lecture at Woods Hole in 1962, and Fuortes asked me to join him in experiments on *Limulus* eyes. We were interested in the long delay between a light flash and the electrical response, which we thought might arise from the time taken for a signal to pass through a cascade of intermediate chemical reactions, possibly stages of chemical amplification. We also wanted to know how the delay might change with light adaptation. It turned out that in the *Limulus* eye, as in most eyes, there is a trade-off between time resolution and sensitivity: the eye loses sensitivity but gains time resolution as it adapts to light. There was something in both these ideas, but looking back after 30 years, they seem absurdly amateur and oversimplified.

Fuortes, who was known as Mike (an abbreviation of Michelangelo), was one of the first people to get satisfactory readings from microelectrodes inserted into photoreceptors. Before that he had worked mainly on

motoneurons, a subject which he had studied with Bryan Matthews in Cambridge. I am not sure what caused Mike to switch to vision and have the temerity to work on *Limulus*, an animal generally regarded by workers at Rockefeller University as their property despite its great antiquity. But I can guess that one factor was the 1952 Cold Spring Harbor Conference, where we listened to an excellent paper by Hartline's team, illustrated by records of generator potentials in single ommatidia. This research showed that much could be done if microelectrodes could be inserted into photoreceptors without damaging them. By 1962 Mike had been doing this for several years, and I was familiar with his work as he sometimes sent his manuscripts to William Rushton and me for comments.

I found Mike a pleasant collaborator—patient, tolerant of other people's mistakes, and good at getting difficult experiments to work. I kept asking questions about generator potentials and he would reply, "Yes, I have done experiments on that but the films are back at NIH." When he came to Cambridge early in 1963 he brought a lot of films with him which we spent a long time analyzing. This work led to a paper published a year later. At Woods Hole we had also done experiments on the quantal bumps which Yeandle had discovered. These experiments never got published but they had a considerable influence on Mike's pupil, and my subsequent colleague, Denis Baylor.

The idea about a cascade of chemical reactions proved to be broadly correct, but the conjecture was too vague to be useful and it was some time before the nature of the intervening chemistry began to be understood. There also had to be a minor revolution in our understanding of the way in which vertebrate and invertebrate animals perceive light and dark.

Closure of Ionic Channels by Light in the Photoreceptors of Vertebrates

By 1965 a number of invertebrate photoreceptors had been studied, and the general pattern conformed to that in *Limulus*. In all cases, light was absorbed by rhodopsin and then, by a chain of events that was still unknown, the conductivity of the cell membrane was increased. The result was that the cell was depolarized—that is, the cell interior became less negative than in the resting condition. This result is what one would expect because the photoreceptor is electrically connected to the nerve fiber. A positive-going change (depolarization) is what is needed to activate the nerve, and one would expect light to set up a wave of this polarity in the cell.

Therefore many of us were surprised when A. Bortoff in Russia and T. Tomita in Japan and their colleagues showed that in the receptors of vertebrates light decreases membrane conductivity and makes the inside of the cell more negative. This finding breaks the general rule that sensory stimulation depolarizes cells and increases conductivity. One may find it unrea-

sonable to be disturbed by a simple change of polarity or to think that all animals should contain the same basic mechanism. But there is more in it than that. Electrical changes in the nervous system are usually conveyed from one cell to the next by a mechanism that involves the release of a chemical transmitter. Because transmitters are normally released by a positive-going change in the internal potential of the cell, it seems that vertebrate rods and cones must release transmitter continuously in the dark, and that light suppresses this release by making the inside of the cell negative.

There is nothing really surprising about this. Physiologists and psychologists often test the eye with flashing lights, but these are not the natural stimuli which an animal encounters in its everyday life. A dark object against a light background, which may be either predator or prey, may be a more important stimulus than a bright spot of light.

Figure 8 summarizes the position reached as a result of the work of several schools, notably those of Bortoff, Tomita, Fuortes, and W. Hagins.

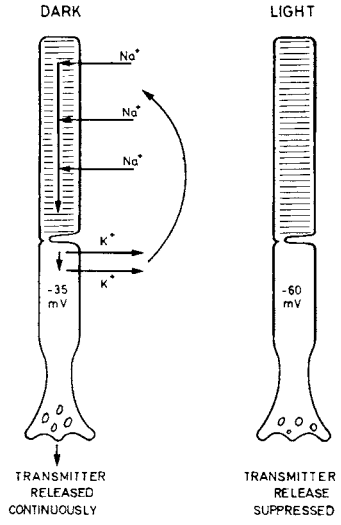

Figure 8. Effect of illumination in suppressing the dark current of retinal rods.

In the dark, the outer segment of a rod or cone is permeable to sodium ions and there is a steady circulating current with sodium ions entering the outer segment and potassium ions leaving the cell from the more concentrated internal solution. A steady state is maintained by a sodium/potassium pump located in the inner segment. The resting potential is about –35 mV, and the pedicle at the base of the cell is liberating a chemical transmitter (probably glutamate) at a high rate. All this is stopped by light. The sodium channels are closed; the resting potential rises to –60 mV and the release of transmitter is greatly reduced.

The electrical signal produced by a flash of light has a remarkable waveform which has repaid detailed study. Figure 9, which is from Baylor, Fuortes, and O'Bryan (1971), shows the signals produced by a turtle cone in response to 10 msec flashes varying in strength over a 1,000-fold range.

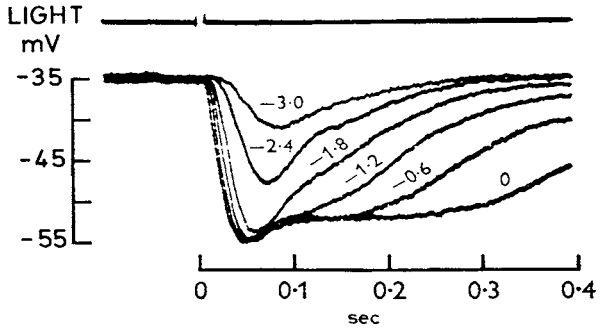

Figure 9. Response of turtle cone to flashes of light of different intensity; the numbers on each curve give the logarithm to base 10 of the light intensity relative to the unattenuated beam. The vertical scale gives the internal potential of the cone.

As can be seen, the response to a strong light saturates when the potential has increased from –35mV to –53 mV, but it continues to get longer as the brightness of the flash is increased so information about the strength of the flash is not lost. The upper level of –53 mV corresponds to the potential at which the variable sodium conductance is almost completely suppressed; the potential then becomes equal to that of the potassium battery.

A curious feature of the response, which is even more conspicuous in rods, is the initial hump before the plateau. It later became clear that this was a secondary event introduced by voltage-dependent changes in the inner segment of a rod or cone. When current was recorded from the outer segment, where the light quanta are caught, the effect was not seen. By saying that the effect is secondary, I mean that it happens later, not that it is unimportant. We now know that signals undergo several stages of processing as they are handed from one cell to the next in the retina. It is now clear that the first stage of processing happens when currents are transformed into voltage in the rod itself.

My first laboratory contact with the vertebrate retina was in the autumn of 1970 when Denis Baylor, who had worked for several years with Fuortes at the National Institutes of Health in Bethesda, Maryland, came for a two-year visit to Cambridge. This was the beginning of an alliance between Baylor's group in Stanford, California, and mine in Cambridge, which has led to several productive collaborations.

After some preliminary experiments and a long period assembling optical equipment (with much help from Andrew Huxley), Baylor and I settled down to study cones, and occasionally rods, in the retina of the tur-

tle *Pseudemys*, a preparation on which Baylor, Fuortes, and O'Bryan had already done important experiments.

As in other vertebrates with color vision, there are three main types of cone in the turtle eye, each with a different visual pigment and a different spectral sensitivity. We confirmed the division into red-, green-, and blue-sensitive cones and extended it by showing that the colored oil droplets, which are present in turtles and many other animals, sharpened the spectral sensitivity as well as helped to channel light into the outer segment of the cone.

Unlike most higher vertebrates, no placental mammal has oil droplets. One cannot help wondering whether turtles, birds, and other animals that do may not see the world in brighter, or at any rate different, colors than we do. But this raises doubts about the admissibility of such questions, and it is safer to stick to the experimental approach.

One useful result of our experiments was the demonstration that turtle cones obeyed a generalization enunciated by Rushton, sometimes known as the principal of univariance. This principle states that the output of a receptor depends only on the number of quanta absorbed and not on their wavelength. To put this in another way, a green-sensitive cone is poor at catching quanta in the red end of the spectrum, but when it does absorb a long-wave quantum it gives precisely the same signal as it would for a quantum of shorter wavelength. Figure 10 illustrates this result using the voltage response of a red-sensitive cone as a criterion and a small spot of different wavelength as a stimulus. One can see that all three colors give exactly the same shaped response and can be scaled onto a common curve.

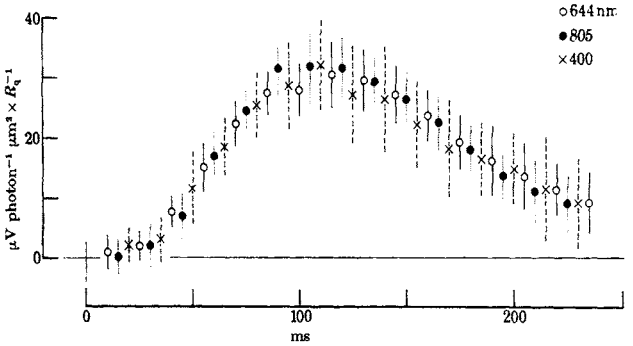

Figure 10. Linear response of a red-sensitive cone to 10 msec flashes of light of different wavelengths, scaled to give the same amplitude. The scaling factor Rq, the relative quantum sensitivity, was 1 for 644 nm, 8 ¥ 10^{-4} for 805 nm, and 0.24 for 400 nm. Vertical lines are ±1 SEM. Zero time corresponds to the midpoint of the flash. The recording was obtained from a microelectrode inserted into a cone in the isolated retina of the turtle Pseudemys scripta elegans. The diameter of the light spot on the retina was 150 μm (from Baylor and Hodgkin, 1973).

When the internal potential of the cone is used to measure the response, univariance holds only if a small spot is employed. This is because a large spot activates surrounding cones of different spectral sensitivity which affect the impaled cone through horizontal cells. A better method of measuring spectral sensitivity is to record the current produced by the outer segment. This has now been done by Baylor's group using the rods and cones of the Macaque monkey, which are known to be similar to those of humans.

About 50 years ago Hecht, Schlaer, and Pirenne concluded that a dark-adapted human can detect a flash in which something like 10 quanta fall on an area containing about 500 rods. This observation made it highly likely that a single quantum would have a detectable electrical effect on a rod. This observation was made satisfactorily when recording current from the outer segment with the suction electrode developed by Baylor, Lamb, and Yau (1979), who found quantal bumps of about 1 pA in amplitude and three seconds in duration. However, an apparent paradox appeared when an attempt was made to perform the same type of experiment with microelectrodes.

Figure 11 illustrates an experiment in which we introduced a microelectrode into a dark-adapted turtle rod and then applied a series of diffuse flashes of a strength such that on average each rod would absorb a quantum on about 70 percent of occasions. If rods were isolated one would expect such responses to be extremely variable. A simple calculation shows that one would expect to get nothing on 50 percent of occasions, 1 unit of 3 mV on 35 percent of occasions, 2 units of 6 mV on 12 percent of occasions, and so on.

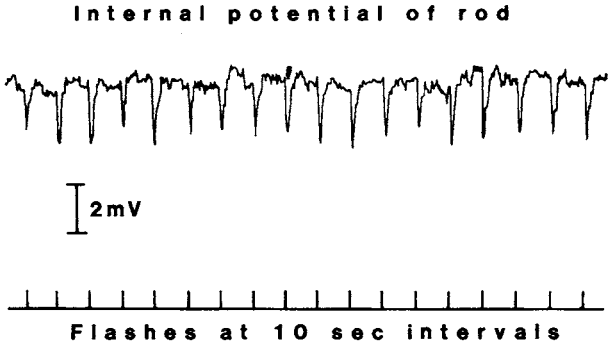

Figure 11. Voltage response of turtle rod to series of weak, diffuse, 500 nm flashes repeated at 10 sec intervals. On average each rod should have absorbed 1 quantum on about 70 percent of occasions. The trace shows the internal potential of a rod measured with a microelectrode inserted into the inner segment. The resting potential was –42 mV and the maximum response to a strong flash was 40 mV; flash duration 20 msec. Note that the variability of these voltage responses was small compared with the variability of the response when current was measured as in Figure 12 (from a record of Detwiler, Hodgkin, and McNaughton, 1980).

As can be seen from Figure 11 there is some variation, but nothing like this. In some way rods seem to have cheated the quantum theory. Physicists will know that this is impossible and may think that we and others who have observed the same discrepancy have got our calibrations wrong. But that is not the case. The answer is that rods are coupled so that the effects of one photon are averaged over about 100 rods. One does not get something for nothing because coupling reduces the acuity of the rods, and detail is seen less well than it would be if cells were isolated. In this connection I should mention experiments on dark-adapted turtle rods, which show that the effects of an absorbed photon spread out over a large area initially which then contracts down to a smaller one at long times (Detwiler, Hodgkin, and McNaughton, 1980). This must help to increase early awareness at short times while preserving some visual acuity for later.

Partly to get around the difficulty introduced by coupling, Baylor, Lamb, and Yau developed the suction method of recording, in which the outer segment of a single rod is sucked into a narrow, tightly fitting capillary (Figure 12). The potential difference across the tip of the capillary then gives the photocurrent.

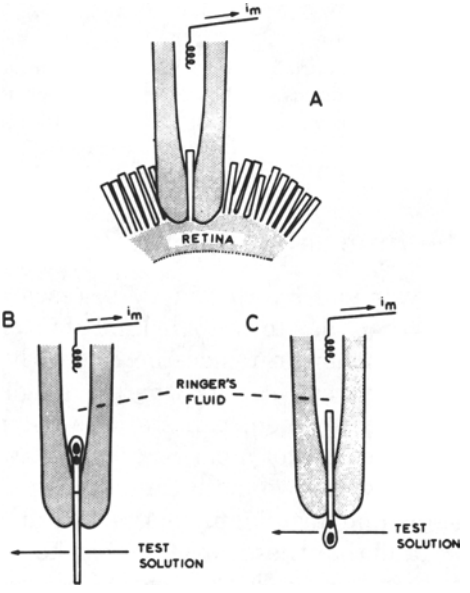

Figure 12. Arrangements for recording membrane current of rod outer segment. *A*, Original Stanford method of Baylor et al. *B* and *C*, Modifications introduced at Cambridge by McNaughton, Yau, Nunn, and the author to measure effect of ions on rod currents. In *B*, the inner segment of an isolated rod is sucked into a capillary and the outer segment is in flowing solution. *C* shows the reverse arrangement with the inner segment in flowing solution.

The method, or variants of it, showed that in a dark-adapted toad or salamander rod each absorbed quantum reduced the standing current in a single rod by 1 pA for about three seconds and that such events occurred in the expected random manner (Figure 13).

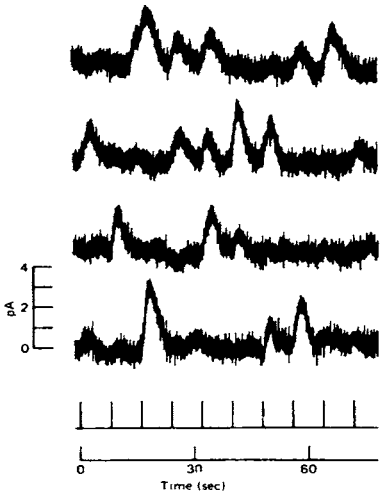

Figure 13. Current response of rod outer segment to 40 consecutive dim flashes repeated at eight second intervals; flashes of strength such that on average 1 quantum was successfully absorbed per flash on 53 percent of occasions. 20 msec flashes of wavelength 500 nm; flash timing monitored below [from Baylor, Lamb, and Yau (1979)].

The Nature of the Internal Transmitter

Since the work of Baylor and Fuortes in 1970, researchers have agreed that in rods and cones there has to be some kind of internal linkage which connects the activated rhodopsin inside the cell with the surface membrane. The position is clearest in rods where a single photon absorbed anywhere inside the outer segment can stop the movement of about 10 million sodium ions per second for a period of one to two seconds.

For some time there were two main candidates for the internal messenger. In 1975 Hagins and Yoshikami suggested that light released calcium ions from disks, and that these ions then blocked channels. The rival theory, now thought to be correct, is that cyclic GMP is present at a fairly high concentration and keeps the light-sensitive channels open in the dark. Rhodopsin activated by light catalyzes a G-protein which in turn activates the enzyme phosphodiesterase that hydrolyzes cyclic GMP. The turnover number of this enzyme is high, about 2,000/second, so that a strong flash causes a rapid fall in cyclic GMP and hence a rapid decrease in the inward current of sodium ions.

In 1985 opinion swung strongly against calcium and in favor of the cyclic GMP theory. There were several kinds of evidence but the one that I found most convincing was that of E.E. Fesenko, S.S. Kolesnikov, and A.L. Lyubarsky, who submitted an article to *Nature* in the summer of 1984. The Russian workers showed that the concentration of an isolated patch of membrane was not reduced by raising calcium, but that it was increased in a rapid and reversible manner by applying a physiological concentration of cyclic GMP to the inner surface membrane obtained from a rod outer segment. Cyclic GMP appears to act directly on the ionic channels rather than by turning on a cascade of phosphorylating enzymes as biochemists originally thought. Details of the mechanism and of the names of some of those who worked it out can be found in the excellent review by Stryer (1986).

Apart from the positive evidence that cyclic GMP is the internal transmitter, there were good reasons for thinking that all was not well with the calcium theory. For example Yau and Nakatani (1984) showed that a light flash decreased rather than increased internal calcium. Another result obtained by McNaughton and Nunn (1985), which is incompatible with the calcium theory, was that transferring the rod to isotonic calcium chloride caused a large transient increase in light-sensitive current. A further strong objection to the calcium theory was the demonstration that the introduction of the calcium chelator BAPTA had little effect on the rising phase of the response (Lamb, Matthews, and Torre, 1986).

The conclusion from these and other experiments was that a rise in internal calcium did not close channels, but acted indirectly, perhaps blocking guanylate cyclase and interfering with the supply of cyclic GMP.

Ionic Movements and the Cyclic Nucleotide Cascade

Although calcium ions are no longer considered to be the internal transmitter it is clear that they play an important part in controlling the ionic currents underlying photoreception. Some of my experiments with Brian Nunn are concerned with this subject and are summarized in a review written shortly before his death (Hodgkin, 1988; Hodgkin and Nunn, 1988).

I entered this field with some trepidation as I knew little modern biochemistry, and it is hard to learn anything new when you are over 70. However, I cheered up when I found that our experiments would involve the sodium/calcium exchange mechanism on which Baker, Blaustein, and I had worked at Plymouth some years before. This system maintains a low internal calcium ion concentration at the expense of the sodium and potassium gradients, which are themselves maintained by the sodium/potassium pump (Cervetto et al., 1987; McNaughton, 1990).

The main chemical and electrical events in the cascade that follows the absorption of a quantum of light are summarized by the highly simplified diagram in Figure 14. With a salamander rod in the dark there is an inward sodium current of about 50 pA, which is only 5 percent of the maximum light-sensitive current that the cell is capable of producing. This effect occurs because a large number of channels are closed, some by external calcium and others because the concentration of cyclic GMP is not high enough to keep the whole population open. At first it seems wasteful to have most of the channels closed, but it may be helpful to stabilize cyclic GMP at a low level. If there were a high concentration of cyclic GMP, many molecules would need to be hydrolyzed and the system would be insensitive to light.

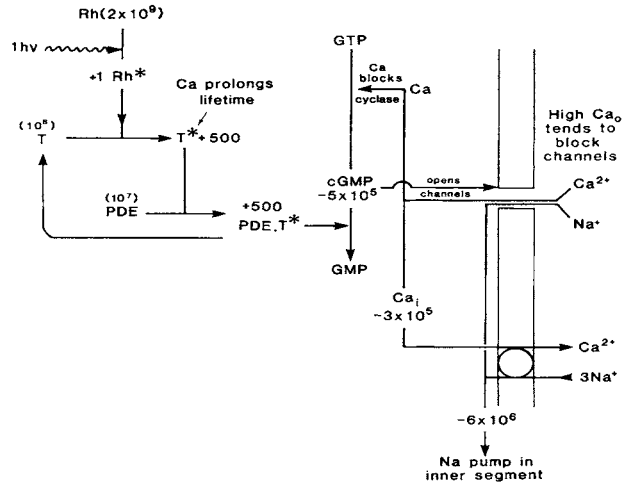

Figure 14. Scheme showing possible interactions of Ca^{2+} with ionic channels and with cyclic nucleotide cascade. Rh is rhodopsin, Rh* is rhodopsin activated by light. T is transducin, a G-protein, and T* is the activated form produced by GTP replacing GDP in the G-protein in a cyclical reaction catalyzed by Rh*. PDE is the phosphodiesterase which, when activated by T*, catalyzes the hydrolysis of cyclic GMP to GMP. The figures in brackets give the number of rhodopsin, transducin, or PDE molecules in a toad rod; other figures give the number per photoisomerization. Instead of prolonging the life of activated PDE, Ca^{2+} might act by increasing the number of T* per Rh*, perhaps by prolonging the life of Rh*. For further details see Stryer, 1986.

In a toad or salamander rod there are about 2×10^9 molecules of rhodopsin. Absorption of a light quantum by a rhodopsin molecule causes its retinal chromophore to isomerize from the 11-*cis* to the all-*trans* form, a change that leads neighboring parts of the molecule to become enzymatically active and catalyze the production of activated trans-

ducin, a G-protein. Considerable amplification occurs at this stage and roughly 1,000 active transducin molecules may be produced by one photoisomerization. Activation of transducin involves the replacement of GDP by GTP in the G-protein and is a cyclical process driven by GTP. *In vivo*, the activated transducin has a lifetime of one or two seconds in rods and less in cones. However, the quenching of transducin is still the subject of active research (see reviews by McNaughton (1990) and by Lagnado and Baylor (1992)). From transducin, activation is handed on to phosphodiesterase, which can rapidly hydrolyze cyclic GMP and close channels in a fraction of a millisecond. The number of cyclic GMP molecules hydrolyzed by one quantum is the order of 10^3, which suppresses the entry of between 10^6 and 10^7 sodium ions—this being the overall amplification of the system in ions per quantum. The amplification in terms of energy is less because the system transforms down from 2.5 electron volts—the energy of a quantum of 500 nm light—to about 0.1 electron volts—the energy saved by stopping one sodium ion from moving down its electrochemical gradient.

Lagnado and Baylor (1992) and others have pointed out that if the high gain of the transduction mechanism were constant, a steady background of moderate intensity would close all the light-sensitive channels and prevent any additional signals from being encoded. However, a gain-control mechanism automatically reduces sensitivity so that some channels remain open in the presence of a background. The drop in sensitivity depends to a considerable extent on the fact that the light-sensitive channels are permeable to calcium as well as sodium ions. Measurements with a rapid solution change method suggest that calcium is about 10 times more permeable than sodium. The internal calcium level depends on the balance of entry through light-sensitive channels and extrusion through the sodium/calcium potassium exchanger. When calcium influx is blocked by closure of channels by light, internal calcium is pumped down by the exchanger with the result that many channels reopen and the eye becomes light-adapted. The same mechanism helps to keep the response to a flash short, as was shown later by Brian Nunn and myself (Hodgkin and Nunn, 1988). Further evidence that the drop in internal calcium is partly responsible for light-adaptation, is that clamping the internal calcium with buffers blocks the reduction in sensitivity normally associated with background light (Yau and Nakatani, 1985; Lamb et al., 1986).

In 1986 McNaughton, Nunn, and I came across the interesting phenomenon illustrated by Figure 15. We found that raising external calcium immediately before a flash had the effect of sensitizing the rod, in that recovery from the flash was delayed by an amount equivalent to a 2.3-fold increase in flash strength. If the same pulse of raised calcium was given more than about 1 second before the flash, the effect disappeared, presum-

ably because internal calcium was pumped out with a time constant of 0.5 second or so. If given on top of the response the effect again disappeared, probably because all calcium channels were closed and no calcium could get in. Later as channels reopened, calcium had a rapid and reversible effect in shutting off the current, but there was no prolongation of the current, such as that observed immediately after the flash.

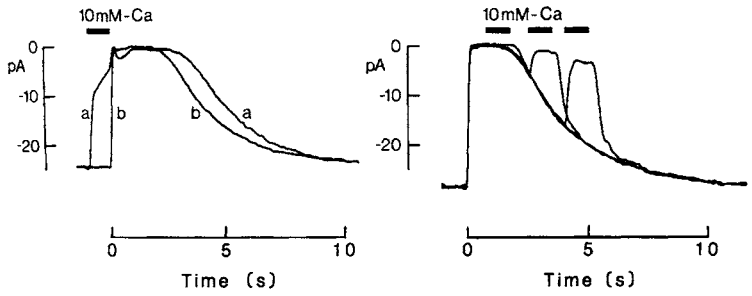

Figure 15. Effect of one second pulse of raised external calcium in lengthening the response of a salamander rod when applied immediately before a strong flash. Record *b* (left) shows the effect of the flash by itself, applied at time 0. Record a shows the effect of preceding the flash (and in practice overlapping it) with a one second pulse of raised calcium (10 mM instead of 1 mM) applied from –1 to 0 seconds; note the prolongation of the response. The right-hand records show the effect of the flash by itself and with the pulse of raised calcium applied on the plateau and during the falling phase; note that there is no prolongation of the response (Hodgkin, McNaughton, and Nunn 1986).

These effects are consistent with a sensitizing effect of elevated calcium at an early stage in the transduction chain. It also seems that the levels of ionized calcium and cyclic GMP must be in rapid equilibrium during recovery from the flash.

Just before Brian Nunn left Cambridge we obtained evidence that reducing internal calcium accelerates recovery in two ways: (1) by turning on guanylate cyclase and accelerating the supply of cyclic GMP, and (2) by reducing the lifetime or number of active transducin molecules and decreasing the activity of phosphodiesterase, so lowering the rate of hydrolysis of cyclic GMP.

At the Helmerich conference in 1986 I wrote the following:

> . . .it will be aesthetically pleasing when the various interactions between ions and the nucleotide cascade can be summarized in a set of differential equations that describe the complicated responses to light or chemical and ionic changes. At one time I had hoped to be in on this myself but as things have turned out, all I can do is to gaze from Pisgah to the promised land where I hope you will enjoy yourselves.

Although much has been discovered during the last 10 years we are still a long way from fully understanding how the retina transforms visual into neural signals.

Retrospective

To my great sorrow Brian Nunn died in September 1987, which put an end to some plans we had made for future research. Our last paper was published in 1988 and since then I have devoted much of my energy to writing, in particular to *Chance and Design*, an autobiography dealing mainly with the first part of my life.

Royal Society Presidency, 1970–1975

In 1970 when I became president, the Royal Society had been in Carlton House Terrace, London, for three years and the former president and his wife, the Blacketts, had furnished and lived in the president's flat on the third floor. This flat contained one large room with a splendid view looking across St. James Park to Westminster. David Martin, the executive secretary, thought that after I took office I would need to spend two or three nights in London—an estimate which proved about right. At that time my wife, Marni, was running children's books at Macmillan and usually commuted to London four days a week from Cambridge. She welcomed the idea that the Royal Society should be our London pied-a-terre and we lived there happily in the midweek for the next five years. I was keen to keep my experimental work going in Cambridge, both because it was going well and because unless I have some research to think about, I become too obsessively involved with administration—and too upset when things go wrong, as they often do. With the help of Denis Baylor and other visiting scientists I managed to do my research reasonably successfully, though it often meant working for much of the weekend.

When I had become president, David Martin had asked me rather nervously whether I had a policy. I said I had not but thought that my predecessors, Lord Florey and Lord Blackett, had formulated objectives which would keep us busy for the next five years. Briefly, these objectives were that the Society should take a greater part in promoting research, particularly in its international aspects or in connection with appointments of outstanding distinction, such as Royal Society research professorships; also that the Society should aim to make its meetings more interesting and accessible to all concerned with pure and applied science. This had been difficult at the Society's former home, Burlington House, but would be much easier in our new premises in Carlton House Terrace with its large lecture hall. When asked what I had enjoyed most during my five years as president, my answer was "entertaining friends and col-

leagues in this beautiful building." Next to that, and on a more serious plane, I put the sense of historical continuity and of taking part in scientific discussions in a Society that counted Robert Boyle and Sir Isaac Newton among its earliest members.

International relations were prominent in the Society's activities, and I found myself bombarded with invitations from different countries. During the next six years I visited Japan, India, Canada, Australia, China, Kenya, and Iran (the last two after my presidency but on Royal Society business). A delegation was going to Moscow in 1975 but at the last moment was postponed to a date that I could not manage. However, I had already spent May 1967 in Russia and the neighboring country, Georgia, and did not particularly mind missing this trip.

The Royal Society attached high priority to restoring the links with Chinese science which had flourished before the Cultural Revolution but disappeared completely after it. One or two Fellows did manage to go to China, and we helped them to get visas. But the Chargé d'Affaires hated to put anything on paper and preferred to make a solemn declaration that it was perfectly in order for Dr. X to visit China.

Eventually the Chinese Academy of Science invited a small delegation from the Royal Society to visit China and discuss scientific exchanges. In May 1972, Kingsley Dunham (our new foreign secretary), Martin, and I accepted at once and booked tickets on the overland air route through Siberia. However, at the last minute we were told by the Chargé d'Affaires that permission was withdrawn and we must cancel our visit. This we refused to do, cabled the Academy that we were coming, and went ahead on the flight through Moscow, Omsk, and Irkutsk to Beijing. In Beijing we were greeted in a friendly way, put up in a comfortable hotel, taken sightseeing and shown various university departments, which seemed more disorganized by the Cultural Revolution than most other institutions in China. This was not surprising because one of the aims of the Cultural Revolution was to prevent the re-emergence of an intellectual elite.

The sightseeing was interesting, but not what we came to accomplish. After several days it became evident that the Cultural Revolution was still much in force, and that members of the Chinese Academy were frightened of arranging any sort of meeting with our delegation. After consulting the British ambassador we sent a letter asking for a meeting to the right man at the Chinese Academy. This was written in the grandest handwriting and phrased in the politest language we could manage. It did the trick. An evening meeting was arranged, and an exchange arrangement between Britain and China was discussed and supported on the understanding that it would be developed later by a Chinese delegation to the Royal Society—an event that took place in October and formed the basis of the numerous visits that have been made since by both British and Chinese participants.

On our last evening in Beijing we went to a formal banquet in the Hall of the Peoples, where we were received by the president of the academy, Ko-Mo-Jo, with whom gifts of books were exchanged, and where he stated that the academy looked to United Kingdom scientists for help in developing the study of fundamental sciences in China.

Trinity College, Cambridge, 1978–1984

As a Trinity College scholarship in 1931 was the event that opened up a career in science for me, there was something appropriate about ending my academic life as Master of Trinity, the college where so many distinguished scholars had found interest and happiness. So, in 1978, I had no hesitation in accepting the Mastership, although it meant a great change in our way of life. My wife gave up her publishing job with Macmillan, and we sold our over-large but much loved house in Newton Road. This saddened our children and grandchildren, who were deeply attached to our old home although they no longer lived there. However, they soon came round to the view expressed by an American friend that the Master's Lodge in Trinity was "not a bad pad."

Even if you do not love grandeur, you would have to be unromantic not to feel the charm of living in the splendid house described by the historian G.M. Trevelyan as "built by Nevile's love and Bentley's pride." It is true that in summer the courts are full of tourists, and one wishes that more visitors would accept Baedeker's advice that "Cambridge is less attractive than Oxford and may be omitted altogether if the visitor is short of time." But even at the height of the tourist season, peace returned in the evening, and in the early morning a kingfisher or a heron could occasionally be seen on the river wall at the end of the Master's garden.

Transcending these details was the feeling that the Master's Lodge was part of Trinity College and belonged to its history, or even its prehistory. In the Comedy Room wall, to quote Trevelyan again, "the bees have made their hives in blocked-up windows that once looked out on the Wars of the Roses."

Most country houses or palaces are lived in for only months of the year and are often empty for long periods of time. But Trinity Lodge has been lived in more or less continuously for nearly four centuries and must have seen some 50,000 undergraduates come and go in Trinity Great Court. Partly for that reason we adopted the practice of keeping the picture-lights on in the lodge, so that on winter evenings undergraduates crossing Great Court could catch glimpses of the portraits of Elizabeth I and famous Trinity men like Isaac Newton and the poet Andrew Marvell.

One change that I remember with satisfaction was the coincidence of my Mastership with the entry of female undergraduates to Trinity College in 1978. I believe that this change, about which many people were nervous, has been a resounding success and will be of enduring benefit to the college.

Another satisfying development was the continued growth of the Trinity Science Park on land given to Trinity's precursor, King's Hall, in 1443. Both the creation and development of this major enterprise were the work of the senior burser of Trinity, John Bradfield. I am glad that I was able to help him with this project which is important in bridging the gap between science and industry—not only in Cambridge but in the country as a whole.

We were told that on leaving a master's lodge in Cambridge, one must either move into the country or stay as near the center of the city as possible. We chose the latter course and found an oldish house between the Fitzwilliam Museum and the Botanical Garden. Although quite unlike our previous homes, it suits us down to the ground.

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