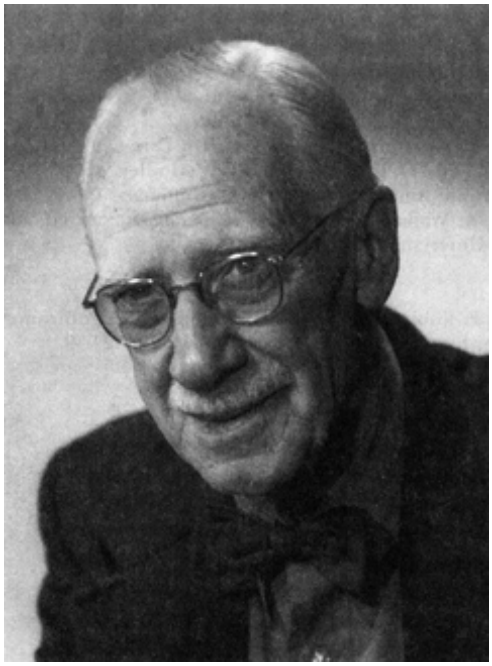

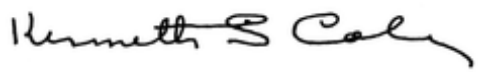

# Kenneth Stewart Cole

*July 10, 1900 — April 18, 1984*

By Sir Andrew Huxley

KENNETH STEWART COLE's training was in classical physics and electrical engineering but he turned his skills to the investigation of the electrical properties of living tissues. Through an impressive combination of theoretical and experimental approaches, he made major contributions to our understanding of the surface membranes of many types of cells, and especially of the changes undergone by the electrical properties of the membranes of excitable cells when activated. In particular, his demonstration in 1938 (with H.J. Curtis) of a large increase in membrane conductance during the passage of a nerve impulse, without change of capacitance, was a major landmark.

## PERSONAL HISTORY

Kenneth Cole, known to his wife as Ken but to all his friends as Kacy, was born on 10 July 1900 at Ithaca, New York. His father, Charles Nelson Cole, was at that time an instructor in Latin at Cornell University; two years later the family moved to Oberlin, Ohio, as his father took a post at Oberlin College, of which he later became Dean. Cole's mother was Mabel Stewart; both his parents came from Urbana, Illinois. There was one younger brother, Robert, with whom he remained very close throughout his life despite a large difference in age; they were joint authors of four papers published between 1936 and 1942.

In 1932, Cole married Elizabeth Evans Roberts, an attorney. Later, her work was mostly concerned with civil rights and in 1956 she joined the staff of the new Civil Rights Commission; in this work she made many journeys to the South investigating the validity of racial segregation complaints. She died in 1966. They had one son and one daughter, both still living.

From his early years he had strong interests in electricity: he records that as a youngster he 'produced sparks and shocks with worn out parts from the telephone company and put together a licensed wireless station with a Ford spark coil and galena (for a detector) begged from the head of the Geology Department' (Cole 1979). He majored in physics at Oberlin College, but delayed completion of the course by working for more than a year in the General Electric Research Laboratory at Schenectady. Here he met, and was much influenced by, Irving Langmuir, whose famous work on surface films at an air-water interface may well have been one of the origins of Cole's interest in the surface membranes of living cells. For his Ph.D. he moved to Cornell where he developed an electron spectrograph and studied the photographic action of electrons under the supervision of F.K. Richtmyer, at the same time as holding an instructorship (1922-1926).

His switch of interest to biological objects that could be investigated by physical, especially electrical, techniques was kindled by summer visits that he made during this period. In 1923 he spent some weeks at the Cleveland Clinic with H. Fricke, who was just completing his epoch-making measurements of the electrical capacitance of the surface membrane of red blood corpuscles, using a high-frequency alternating current bridge (Fricke 1923, 1925). He records (Cole 1979) that he became committed to biology after spending the next summer at the Marine Biological Laboratory at Woods Hole on Cape Cod, Massachusetts, where he worked on heat production by the eggs of the sea urchin *Arbacia* under C.G. Rogers. His interest in the electrical properties of

living things was probably stimulated by his lifelong friendship with W.J.V. Osterhout, which began during this visit to Woods Hole.

After completing his Ph.D. Cole was awarded a postdoctoral fellowship by the National Research Council to use Fricke's method to determine the membrane capacity of sea-urchin eggs. He held this fellowship (1926-1928) at Harvard, and went to Woods Hole for his experiments. During this period he also did important theoretical work on the impedance of a suspension of spherical cells and on the representation of impedances by plotting reactance against resistance.

He spent the year 1928-29 in theoretical work on cell membranes at Leipzig in the laboratory of Debye, supported by a fellowship from the General Education Board. He made himself familiar with the theory, due to Nernst and Planck, of the potential differences generated by diffusion between two different electrolyte solutions--very relevant to the potentials across biological membranes. During this time, L.E. Sutton, F.R.S., was also in Debye's laboratory, and he and Cole jointly made suggestions for the improvement of the centrifuge microscope developed by E. Newton Harvey, whom Cole had met at Woods Hole.

Cole returned to the U.S.A. to take up two posts associated with Columbia University, New York: as Assistant Professor (later Associate Professor) in the Department of Physiology (1929-46) and as Consultant Physicist at the Presbyterian Hospital (1929-42). His duties were varied: calibrating radiotherapy machines; advising on safety when using cyclopropane as an anaesthetic (there had been an explosion in an operating theatre); overhauling a medical physiology teaching laboratory; and giving a few lectures. He collaborated with surgeons in developing an operation for aortic aneurysm using an electrically heated wire. In his own research, he continued his investigations, both theoretical and experimental, on the electrical properties of animal and plant tissues, using at first what he describes as a 'crude' bridge; in 1935 he settled down to designing and building a high-precision alternating current bridge which could be used quickly over a wide range of frequencies and which he used in his famous demonstration of the decrease in membrane resistance of nerve during the passage of an impulse. He also built an apparatus with which he measured the surface tension and elasticity of the surface membrane of sea-urchin eggs, following up observations that Newton Harvey had made with the centrifuge microscope that Cole had helped to design.

Cole spent most of his summers working at Woods Hole on sea-urchin eggs, on the fresh water alga *Nitella* and, after 1936 when he met its discoverer J.Z. Young, on the giant nerve fibre of the squid. One summer was spent with Fricke at the Cold Spring Harbor Laboratory on Long Island Sound, where he worked on the electrical impedance of the marine alga *Laminaria*, and another summer at the marine biology station on Bermuda.

Early in 1936, Cole was joined by Howard J. Curtis, who had previously worked with Fricke and was thus familiar with alternating current methods of investigating the electrical properties of biological objects. Most of Cole's scientific work from that date until Curtis moved to a post at Johns Hopkins in 1942 was done in collaboration with Curtis, including the demonstration of membrane impedance changes in the nerve membrane during an impulse. Also in 1936, Cole visited Britain and met A.L. Hodgkin, who later spent a year (1937-38) at the Rockefeller Institute in New York, during which he joined Cole for a short spell at Woods Hole to measure the D.C. resistance of the membrane of the squid giant nerve fibre in the resting state (a quantity that could not be determined by the A.C. methods then being used by Cole and Curtis). In 1939 they began using internal electrodes inside the giant nerve fibre of the squid.

Cole spent 1941-2 on leave from Columbia as a Guggenheim Foundation Fellow at the Institute for Advanced Study at Princeton, studying literature on non-linear systems. From 1942 to 1946, still on leave from Columbia, he was Principal Biophysicist at the Metallurgical Laboratory, University of Chicago with Curtis as his next-in-line; here he was in charge of research on the biological effects of radiations and radioactive materials produced by the uranium fission chain reaction process and was responsible for biological aspects of safety in the Manhattan project (atomic weapon development). D.E. Goldman told me that Cole and Szilard were among those who voted against the decision to drop the first bomb.

In 1946, the University of Chicago set up a new Institute of Radiobiology and Biophysics and Cole accepted appointment as Professor of Biophysics and Physiology and head of the Institute; he was re-joined by George Marmont, who had joined him at Columbia in the early 1940s. On a suggestion from J. Savage, Marmont made an internal electrode to be inserted into a squid giant fibre, with long conducting surface so as to ensure that the internal potential was uniform within this length; current would be fed to the electrode under feedback control and Cole added an arrangement by which alternatively the potential of the electrode could be controlled electronically. In the latter mode of operation, this was the first 'voltage clamp' (a phrase that Cole did not like). This was the method by which great advances were made in the years after the war; unfortunately Cole contributed little to those advances largely, it seems, because Marmont had a strong preference for operating the equipment in the 'current clamp' mode which turned out to be far less informative than the 'voltage clamp' (Cole 1982, p. 316).

The first experiments with this equipment were made in the summer of 1947. Cole told Hodgkin about these experiments in a letter later that year, and gave him full details in a visit that Hodgkin made to the U.S.A. next spring; at this meeting Hodgkin also told Cole of the experiments on squid nerve that he and Katz had done in 1947 establishing that the action potential is generated by sodium ions moving down their concentration gradient. Hodgkin had already been thinking of making a voltage clamp, but the information he was given by Cole and Marmont was a great help and stimulus towards developing the equipment that he used, together with Katz and myself, in the summers of 1948 and 1949.

In 1949 Cole moved again, to become Technical Director of the Naval Medical Research Institute at Bethesda, Maryland, close to Washington D.C. Although he had an intellectually powerful team, including Manuel Morales, David Goldman, Terrell Hill and John Moore, Cole's time at NMRI appears from his own account (Cole 1979, p. 17) not to have been happy, partly on account of Senator McCarthy's activities; nor was it scientifically very productive. As a result, Cole moved once more, in 1959, to set up a new Laboratory of Biophysics in the National Institute of Nervous Diseases and Blindness, National Institutes of Health, just across the road from the NMRI. He took John Moore with him, got an improved voltage clamp running, and produced a series of

valuable papers in 1960. He stepped aside from the headship of the laboratory in 1966, shortly after reaching the age of 65, but continued working there as Senior Research Biophysicist (part time from 1971). For the first semester of 1963-64 he was Regents' Professor at the University of California at Berkeley; there he gave a course of lectures which became the foundation for his book *Membranes, ions and impulses*, published in 1968.

Cole exerted a great influence on the development of membrane research, not only by his discoveries, his techniques and his precise measurements but also through his book and many general articles; through personal guidance of many, both in his laboratory and elsewhere; and through the Training Program on Excitable Membranes at the Marine Biological Laboratory, Woods Hole. In a broader field, he was one of the prime movers in establishing the Biophysical Society and the International Union of Pure and Applied Biophysics.

## RESEARCH ON CELL MEMBRANES

By far the greater part of Cole's published scientific work was on electrical aspects of cell membranes. This originated as an extension of the measurement of the capacitance of suspensions of red blood corpuscles by H. Fricke, with whom Cole had spent part of the summer of 1923. Fricke (1925) found a value of 0.81 μF $cm^{-2}$ for the capacitance of the surface membrane of these cells, in close agreement with more recent determinations; he took the dielectric constant of the lipid material of the membrane to be 3 and deduced a thickness of 3.3 nm, implying a monomolecular layer. By the time Cole began his work on membranes, in 1926, Gorter & Grendel (1925) had shown that the area of the monomolecular film formed on a Langmuir trough by the membrane lipids was double the surface area of the red blood corpuscles from which the lipids had been extracted, showing that the membrane was a bimolecular, not a monomolecular, layer, and that Fricke had underestimated the dielectric constant. Thus, the outline of present-day ideas of the basic structure of cell membranes was established just before Cole's work began.

Up to 1936, Cole explored the linear, passive electrical properties of cell membranes. At first, in place of the alternating current bridge used by Fricke, he adopted the method of Philippson (1921) and measured the ratio of mean square voltage to mean square current as a function of frequency when the output of an oscillator was applied to the cell suspension, using vacuum thermocouples as detectors. His first measurements were on the eggs of the sea urchin, *Arbacia punctulata*, which he chose largely because these were the objects whose heat production he had measured in the summer of 1924 and there were suggestions that heat was liberated by the superficial part of the cell when it was fertilized. These eggs also had the advantage of being spherical, so that the theoretical treatment was much simpler than for red blood corpuscles with their shape of biconcave discs. He analysed his results by means of an original theoretical treatment which was a great advance on the simplified theory used earlier by Fricke and others. His results, which turned out later to be misleading, was that the surface capacitance of the cells varied inversely with the square root of frequency, and he concluded that the apparent capacitance was a 'polarization capacitance', i.e. that it was due to accumulation of ions on the two sides of the interface between cell contents and the surrounding solution as current flowed, rather than to a dielectric layer separating the two conducting phases. The dependence of apparent capacitance on frequency was not a surprise as similar effects had been found by Philippson and others when measuring the electrical properties of various animal and vegetable tissues.

Cole's next contribution (7)* was a theoretical treatment of the bulk electrical properties of a cell suspension in which the surface of the cell had a frequency-dependent capacitance with loss such that the ratio *m* of the equivalent series resistance to the capacitative reactance was independent of frequency ('constant phase angle'). He proved a result that he had stated in a previous paper (5), namely that when (capacitative) reactance is plotted against series resistance for a suspension of cells with membranes showing this property, the locus as frequency is changed in an arc of a circle with centre below the resistance axis. Cole presented almost all his observations on the passive electrical properties of cells in graphs of this form. In this paper (7) he stated that many sets of observations on a wide range of tissues, some by himself and others from the literature, could be fitted in this way with various values of the ratio *m*.

Cole's next measurement on sea-urchin eggs (21) used a different species, *Hipponoë esculenta*. To his surprise, the reactance plots were semicircles with the centre on the resistance axis (phase angle 90 ° ), implying that the membrane capacity showed no loss and was independent of frequency, i.e. it was an ideal capacitance. The same result was found with the eggs of the starfish *Asterias* (22) and also on re-investigation of the eggs of the sea-urchin *Arbacia* (23). The reason for the low phase angle found previously with this material was not resolved at that time; in a later review (93, p. 32) Cole hints that it may have been due to using mixed batches of eggs from different individuals, as both the diameter of the eggs and the apparent capacitance vary substantially between individuals.

These experiments clarified the situation greatly as regards uniform cells in suspension (mammalian red blood corpuscles as well as echinoderm eggs) in showing that their membranes had a nearly perfect capacitance such as would be expected from a thin lipid surface membrane, but created a discrepancy between cell suspensions and whole tissues, which gave phase angles between 55 ° and 78 ° . Cole returned to the theory of constant phase angle behaviour in two papers written jointly with his brother Robert H. Cole and published in 1941 and 1942 (44,48). They show that the transient response of a circuit element of this type is a power function of time, and they discuss several possible underlying causes for such behaviour without reaching a definite conclusion.

Meanwhile, Cole turned his attention from cell suspensions to excitable tissues, mostly the fresh-water alga *Nitella* which has long cylindrical cells capable of propagating a long-lasting (approximately one second) action potential, and the giant nerve fibre of the squid to which he was introduced by its discoverer J.Z. Young in 1936; there is also one paper (20) on muscle. From 1936 to 1942, the greater part of this work was done jointly with H.J. Curtis; their principal tool was the A.C. bridge that Cole designed and built in 1935 (26).

Measurements of the resting electrical characteristics of *Nitella* cells (28) and of the giant nerve fibre of the squid (32) showed membrane properties not unlike those of other cells: a capacitance of around 1μF $cm^{-2}$ with a constant phase angle a little less than 90°. These measurements were made with the current flow perpendicular to the long axis of the cell. In this situation, the cell is shunted by the low resistance of the solution in which it is immersed, and the resistance of the cell membrane in parallel with its electrical capacity is so high as to be effectively infinite and its actual value cannot be determined by this technique. However, when current flow is parallel to the fibre axis, between electrodes separated by a good many millimetres, a substantial fraction of the current flows through the surface membrane even at low frequencies or with direct current, and the membrane resistance can be measured by either A.C. or D.C. methods. *Nitella* being a fresh-water organism, Blinks (1930) had been able to make the external resistance high enough so that its shunting effect was slight and a D.C. measurement of longitudinal resistance gave the membrane resistance with only small corrections; he found values of the order of $10^5$ ohm $cm^2$. The situation is much more complicated in the case of the squid giant nerve fibre as it has to be surrounded by a layer of salt solution of high conductivity and the passage of current through the membrane is not uniform and is distributed over an appreciable length of the fibre; Hodgkin had worked out a possible method and he and Cole (36) did the experiments during Hodgkin's visit to the U.S.A. in 1938; they found a value around $10^3$ ohm $cm^2$.

The most widely accepted theory of excitation and conduction in excitable cells at that time was that of Bernstein (1902) according to which the resting potential (inside 50-100 mV negative relative to the external solution) was a concentration potential due to the membrane being appreciably permeable to potassium (but not to sodium) ions while the concentration of potassium inside was around 50 times that in the external solution; excitation consisted in a great increase of the permeability of the membrane to all ions so that the membrane potential would fall nearly to zero. Current would then flow from adjacent regions of the cell, causing a decrease in the absolute value of the membrane potential there and this in turn was assumed to cause a similar increase of permeability, which thus travelled along the cell as a self-propagating wave. There were already hints from the work of Lullies, Dubuisson, and especially of Blinks (1936) that the propagated impulse was accompanied by a decrease in impedance but their results were not quantitative and they could not distinguish fully between changes in the capacity and the resistance of the membrane, though Blinks's result (on *Nitella*) clearly showed that there was a substantial decrease in the membrane resistance.

Cole and Curtis made a major advance in 1938 by demonstrating, first in the long excitable cells of *Nitella* (33,34) and then in the giant nerve fibre of the squid (33,35) that the change in impedance was due to a very large drop in the resistance in parallel with the membrane capacity while the latter hardly changed in value. In both cases, the membrane resistance fell to a few percent of its resting value, and the change began rapidly at the moment of the point of inflexion half way up the rising phase of the action potential. This is the moment when the EMF of the membrane must be undergoing a rapid change, so the simultaneity of the resistance drop implied that it was closely related to the change in EMF. The result was therefore a strong confirmation of one of the essential features of Bernstein's theory. It was important from the theoretical point of view not only for this reason but also because it showed that the drop in resistance, presumably due to an increase in permeability of the membrane to ions, took place without any drastic change in the basic structure of the membrane.

These measurements were made with transverse current using the A.C. bridge that Cole had constructed. Both in *Nitella* and in the squid nerve fibre, the membrane resistance fell during the action potential to a value low enough to be measured with fair accuracy by this method. It was a technical triumph to have obtained so clear a result, especially in the case of the squid nerve fibre whose action potential lasts for less than a millisecond: Cole and Curtis recorded the out-of-balance signal from the bridge on a cathode-ray oscilloscope, altered the resistance and capacity values in the balancing arm of the bridge, and noted the two times, within the action potential duration, when the out-of-balance signal fell to zero. In the case of *Nitella*, with an action potential lasting about one second, they had been able to photograph the Lissajous figures created by the out-of-balance signal at a series of times within the action potential.

The next step forward was to take advantage of the great size of the squid fibre to put an electrode inside so as to measure directly the potential difference across the membrane and its change during the impulse. This was done in the summer of 1939, simultaneously and independently by Curtis & Cole (39) at Woods Hole and by Hodgkin and the present writer (1939, 1945) at the laboratory of the Marine Biological Association at Plymouth. Curtis and Cole found action potentials averaging 50 mV with some reaching 80 mV. In this series of experiments they used platinized metal electrodes and an amplifier without satisfactory D.C. response and were therefore unable to measure the resting potential. For these reasons it was not until the next season's work, with improved apparatus, that they confirmed (49) the observation that was the most important outcome of the measurements by Hodgkin and myself, namely that the action potential (around 90 mV in our experiments) was much larger than the resting potential (inside about 45 mV negative to external solution) so that the internal potential became positive at the peak of the action potential by some 40 or 50 mV whereas according to Bernstein's theory it should have approached but not passed zero potential difference. The origin of the EMF was not identified until after World War II when Hodgkin & Katz (1949) showed that it was due to the permeability increase being specific for sodium ions and not a generalized 'breakdown' of the membrane as had been proposed by Bernstein and widely accepted.

The measurements by Curtis and Cole in 1940 and 1941 were not only more extensive than those of Hodgkin and myself in 1939 but their electrodes allowed a better estimate of the junction potential where they made contact with the interior of the nerve fibre, an important point when considering the difference between resting and action potential. Their paper (49) did, however, contain two unfortunate errors which, after the War, contributed to the delay in acceptance of the idea that the 'overshoot' of the action potential (interior of fibre becoming positive relative to external solution at the peak of the action potential) was due to entry of sodium ions moving under the influence of their concentration difference. The first was that they used a variable inductance in their amplifier to compensate for the lag caused by the high resistance of their internal electrodes combined with the input capacitance of the amplifier; Cole (1968, p. 145) admitted later that they must have over-compensated because they obtained much larger action potentials than have been recorded in later years with equipment not subject to this source of error. The action potential illustrated in their paper had a total amplitude of 168 mV and an overshoot of 110 mV, which could have been produced by the sodium mechanism only if the internal sodium concentration had been many times lower than the measured value. The other error was the statement that the action potential as well as the resting potential was 'not

appreciably affected' by replacing the external solution with an almost ion-free solution (isosmotic dextrose), which again would have been impossible if the overshoot had been due to entry of sodium ions. All subsequent work has shown that the action potential is abolished when the fibre is surrounded by a solution free from sodium ions or a few other ions (e.g. lithium) which are able to substitute for sodium; it is not clear how Curtis and Cole came to make this statement.

Two important papers from the early war years showed that the membrane of the squid fibre rectifies strongly, having a much higher conductance for outward than for inward current. This was demonstrated by changes in the transverse impedance during current flow (42) and by direct measurement of the current-voltage relation using an internal electrode for the potential measurement (43). The current was applied through a narrow external electrode and consequently the current density through the membrane and the potential difference across the membrane were not uniform along the fibre; Cole deduced a relation, sometimes known as Cole's theorem, by which they obtained current density $I_m$ at membrane potential $V_m$ from the measured total current $I_o$ : $I_m = I_o dI_o/dV_m$. The resistance values at the resting potential were very low in these experiments (23 ohm $cm^2$ as against 1000 ohn $cm^2$ found by Cole & Hodgkin (36)). This was evidently due to damage to the fibre resulting from impalement by the internal electrode: when the membrane potential was raised by inward current flow the resistance rose to several hundred ohm $cm^2$.

Another observation made at this time (45) with longitudinal current flow was that at low frequencies (a few hundred hertz), the membrane had the characteristics of an inductance in parallel with the capacitance. This was puzzling because, as Cole pointed out in a paper (46) discussing these two phenomena of rectification and inductance, it is not reasonable to suppose that the apparent inductance is due to creation of a magnetic field. However, Cole drew attention in that paper to known physical systems which have inductive characteristics unrelated to magnetism and one of these was important because it suggested the mechanism shown later to underlie the inductive behaviour of the nerve membrane. This was the carbon filament lamp, in which the electrical resistance falls with rise of temperature so that when a constant voltage is applied and the filament heats up, the current rises slowly just as it does through an inductance in series with a resistance.

During the War, it became clear both to Cole and to Hodgkin that an understanding of the excitation process would be greatly helped by an experiment in which the potential difference across the membrane was controlled by the experimenter and the time course of current through the membrane was measured; the unstable character of the membrane which underlies the 'all-or-none' character of the propagated impulse would be overcome if the impedance of the circuit controlling the potential were low enough. Experiments on the squid nerve were necessarily postponed until after the War, but in 1941 Cole suggested to J.H. Bartlett that he should do the analogous experiment on the 'iron wire model': it had been known for many years that an iron wire, passivated in strong nitric or sulphuric acid, would propagate a short-lived period of reactivity on electrical stimulation in a way that had many analogies with nerve conduction. Bartlett (1945) used a low-resistance potentiometer to apply step changes of potential to a piece of iron with a small surface exposed to sulphuric acid of appropriate concentration and recorded the current using a D.C. amplifier and cathode-ray oscillograph.

The first apparatus for making this type of measurement on nerve (the squid giant fibre again) was built shortly after the War by Marmont in Cole's Institute. He used a long internal electrode so that the internal potential was held almost uniform over its length and the current passing from the electrode through the membrane was controlled by a feedback circuit; at Cole's suggestion he arranged that it was also possible to control the current by feedback from the potential on the internal electrode. In the latter mode, the time course of current could be recorded when the membrane potential was caused, by a command signal, to undergo a step change to a new constant level, a device that came to be known as the 'voltage clamp'. The only full account of their experiments with this equipment (in 1947) is a paper under the authorship of Marmont alone (1949); it gives detailed descriptions of the apparatus and of one type of experiment performed with it, in which a stimulating pulse of current was passed through the membrane via the internal electrode and subsequently the membrane current was held at zero by the feedback circuit. The result was an action potential in which the time course was not complicated by longitudinal current flow; however, it was not very different from an ordinary propagated action potential.

Despite Marmont's preference for the controlled-current mode, a few records were taken in the voltage-clamp mode; these were reported briefly by Cole (57) at a conference held in Paris in the spring of 1949. Strikingly, these records did not show an all-or-none response to reduction of the potential difference across the membrane, but over a certain range of membrane potential there was a phase of inward current that clearly would have generated an action potential if the feedback from recorded potential had not prevented it. The records showed qualitatively all the main features that Hodgkin and I found in our experiments in 1948 and 1949, except that the late outward current was not well maintained. This was due to polarization of the electrode by the rather large current density that had to be passed through its surface; this error was avoided in our experiments by using two internal electrodes, one for potential measurement and the other for passing current. The main difference between their work and ours was, however, that they did not use solutions with altered sodium concentration and therefore were unable to analyse the current into components carried by sodium and by potassium ions.

In one respect, Marmont's records of 1947 were better than ours of 1948: they showed an appreciable lag between the step of membrane potential and the rise of the transient inward current (due to sodium entry). At the Paris meeting, Cole cited this as evidence against the theory that we tentatively proposed at that meeting (which made sodium current an instantaneous function of membrane potential) whereas we attributed the lag to instrumental delays. Later we fully confirmed the existence of the lag as a genuine feature of the membrane response, and it was an important factor in determining the formulation that we finally adopted in our mathematical representation of the permeability changes (Hodgkin & Huxley 1952).

Cole made many investigations on voltage-clamped squid fibres in the following years, in collaboration with J.W. Moore and later R.E. Taylor, but this work was not published until 1960 and 1961 (72-78). They used a second electrode for potential measurement, thus eliminating errors due to polarization of the current electrode, but, unlike the potential electrode used by Hodgkin and myself, this was a glass micropipette, with the advantage that the potential was recorded from just below the surface membrane but also the disadvantage that the high resistance of the electrode, together with its capacitance and that

of the input stage of the amplifier, put a limit to the speed of response of the feedback system. They recorded much larger ionic currents (up to 5 or 10 mA $cm^{-2}$ peak inward current) than had been obtained by Hodgkin and myself or by Cole in his experiments with Marmont; an unwanted result of this improvement (due partly to better condition of the nerve fibres and partly to the use of applied current to raise the resting potential) was that the feedback was not always able to control the membrane potential fully, and 'notches' and oscillations appeared in the current traces. These were taken by some critics as invalidating the conclusions drawn from voltage-clamp records, but Cole and his colleagues showed by their extensive experimental and theoretical investigations that these irregularities were instrumental artifacts, arising only when the surface resistance of the long internal electrode was not low enough to ensure that at each instant the potential difference across the fibre membrane was uniform over the length from which the current was being recorded. It is fortunate that the fibres used by Marmont and Cole in 1947, and by Hodgkin and myself in 1948-49, did not produce large enough inward currents to cause instabilities of these kinds.

Cole & Moore (75) also investigated the delay with which the current carried by potassium ions rises following a sudden depolarization of the fibre (interior of the fibre made positive from its resting negative potential). It was already known that this delay increased when the resting potential was artificially raised by means of applied current, but Cole & Moore found that when the resting potential was raised to an extreme level, the increase in the delay was greater than could be plausibly explained by the mechanism that Hodgkin and I (1952) had proposed; this effect has not yet been given a satisfactory explanation. Cole & Moore (75) confirmed however that our formulation gave a satisfactory fit within the range of membrane potential that occurs in a living fibre.

Cole's last major contribution was his book *Membranes, ions and impulses* (93), published in 1968. This book gives a very full account of work in the field covered by its title, putting Cole's own work into relation with that of others. As regards Cole's own work, it not only collects his contributions in a consecutive and readily accessible form, but presents much of his thinking and theory that do not appear in his papers published in the scientific journals. More about the origins of his interests is to be found in his autobiographical chapter in the 1979 issue of the *Annual Review of Physiology* (Cole 1979) and in an article in the *Annual Review of Neuroscience* (Cole 1982). Two collections of essays in his honour have been published (Agin 1972, Moore 1976).

## ACADEMIC HONOURS

Member, US National Academy of Sciences, 1956

Hon. Doctor of Science: Oberlin College 1959; University of Chicago, 1967

Hon. Doctor of Medicine, University of Uppsala, 1967

National Order of the Southern Cross, Government of Brazil, 1966

National Medal of Science, 1967

Foreign Member of The Royal Society, 1972

In 1973, the Membrane Section of the Biophysical Society (U.S.A.) established an annual 'Cole Award' in his honour.

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I AM INDEBTED TO COLE'S daughter Sally for most of the particulars of his early life and of his family.

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