News and Comment

Nobel Prize: 1963 Award Honors Three for Research on Nerve Functioning

Two Britons and an Australian were named last week to receive the 1963 Nobel Prize in Physiology and Medicine for their studies of nervous system functions. The recipients are Alan Lloyd Hodgkin, a 49-year-old biophysicist, of Cambridge University; Andrew Fielding Huxley, 45, Jodrell professor of physiology, University College, London, and Sir John Carew Eccles, 60, professor of physiology, Australian National University, Canberra. The following is a description and appreciation of their work by M. G. F. Fuortes, chief of the section of neurophysiology, ophthalmology branch, National Institute of Neurological Diseases and Blindness.

The early observations made by Luigi Galvani at the beginning of the 19th century and the interpretations advanced by Galvani himself and by Alessandro Volta made it clear that some relation exists between electricity and the activity of nerves. Later work showed that nerves can be brought to a state of activity by electrical stimuli and that they can produce electric currents under certain conditions; but it was only at the start of the present century that some interpretation of the experimental findings could be proposed.

W. Nernst suggested that the electrical properties of nerves should be ascribed to accumulations and to movement of ions across a barrier permeable to some ions only. A more specific hypothesis was proposed during the same period by J. Bernstein, who suggested that nerves are surrounded by a membrane permeable to potassium ions and that a different concentration of potassium inside and outside the nerve fiber creates a voltage gradient across the membrane. Bernstein supposed that, during activity, the membrane lost temporarily its property of selective permeability with consequent "short-circuit" and production of an electric current.

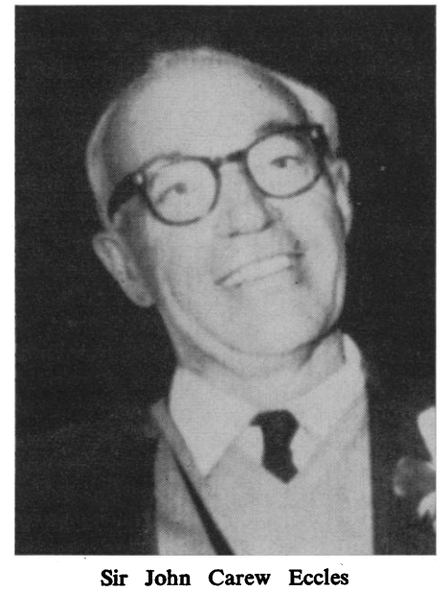
Keith Lucas, E. D. Adrian, J. Erlanger, H. H. Gasser, and many others gave new impetus to the studies on nerve cell function when they discovered that the electrical changes accompanying nerve activity consist of rapid impulses having all the same size and shape (all-or-none law) and when they described many properties of these impulses, including refractoriness, accommodation, conduction velocity in relation to fiber size, and others.

A major effort (culminating in W. A. H. Rushton's analyses) was also made to deduce the properties of nerve fibers from measurements of the electric currents required to evoke propagated activity, but still no satisfactory interpretation of the physicochemical events underlying the nerve impulse could be proposed.

An important advance was made shortly before World War II, when K. S. Cole and H. Curtis, working on the isolated giant axon of squid, obtained evidence that the "active" potential change accompanying a propagated impulse correlates with decreased impedance of the axonal membrane. In the same year (1939) a brief note in *Nature* brought the announcement of a new and surprising observation. Using glass pipettes so fine that they could be inserted inside an axon without damaging its function, Hodgkin and Huxley were able to measure directly the potential across the membrane at rest and during activity and found that at the peak of the nerve impulse the membrane potential does not go to zero, but reverses its sign.

The same observation was made independently and almost at the same time by Cole and his co-workers. This finding disproved Bernstein's view that the action potential is a consequence of a short-circuit of a membrane normally permeable to potassium only, and it raised some doubts about the basic idea originated by Nerst, that electric potentials and currents in biological tissues bear simple relations to ionic concentrations and ionic movements. Some degree of uneasiness persisted until Hodgkin and Katz showed that the experimental observations could be explained if one assumed that during activity the nerve membrane becomes highly permeable to sodium ions so that, for the short time occupied by the nerve impulse, the potential across the membrane is controlled mainly by the difference of concentration of sodium, in accordance with Nernst's relation. Hodgkin and Huxley reported on the findings on which the new hypothesis was based at the 17th International Congress of Physiology, and their report was acclaimed by *Nature* as one of the most significant communications at the Congress.

Two independent methods were later used to confirm the "sodium hypothesis." Using radioactive isotopes, Hodgkin, Keynes, and co-workers measured the amounts of various electrolytes entering and leaving the nerve fibers at rest and during activity. The results proved to be in agreement with the view that the membrane is permeable mostly to potassium when it is at rest and mostly to sodium during activity.



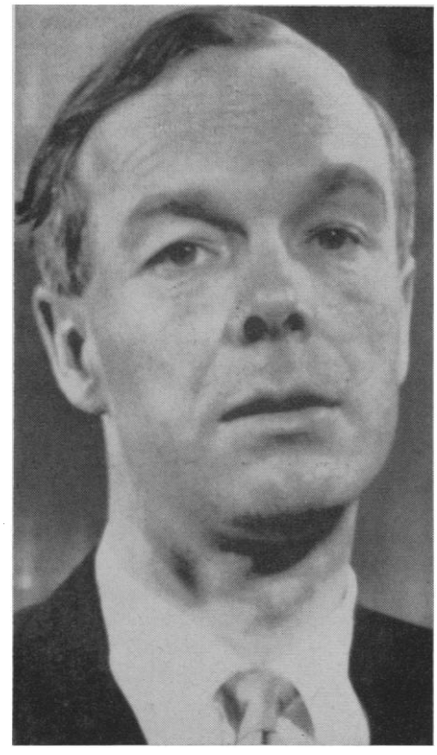
Sir John Carew Eccles

The other method was derived from a technique originally introduced by Cole and his associates. It made use of a control system which made it possible to set the membrane potential of the squid giant axon to any desired level. The current required to maintain the voltage at different levels was measured, and the course of membrane conductance at various membrane potentials was deduced from these measurements.

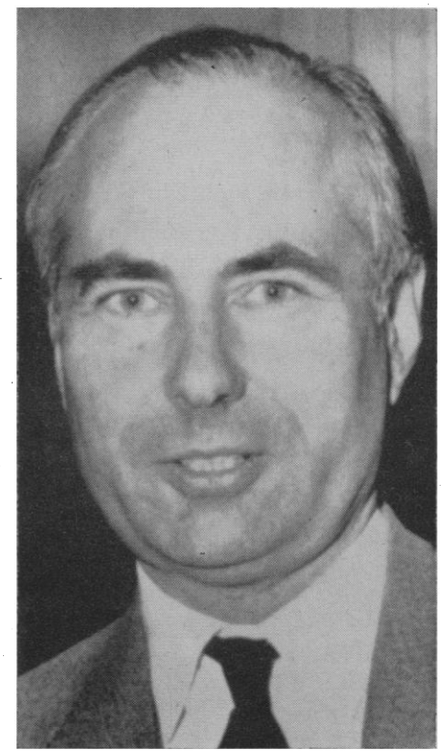
The result of these studies led to a precise formulation of the sodium theory of the nerve impulse, which states that the permeability of the nerve membrane to potassium and to sodium is a function of membrane potential and time. The mathematical formulation of these relations is so complete that it permits not only a reconstruction of the course of the conducted action potential but also includes terms adequate to explain threshold, refractoriness, accommodation, anodal stimulation, and so forth. It is now known that the formidable task of fitting theoretical curves to the experimental records of propagated action potentials was performed by Huxley with only the aid of a desk calculator, since the electronic computer was not available at the time.

Both experimental findings and theory were described in a group of five admirable articles published by Hodgkin and Huxley in 1952, and a detailed summary of the new ideas was given by Hodgkin at a memorable meeting held in the same year at Cold Spring Harbor.

The same meeting was attended also by J. C. Eccles, who reported on his recent experiments on spinal cord activities, showing how the views developed by Hodgkin and Huxley could be applied to the study of central nervous system physiology. Eccles had worked for a long time with C. S. Sherrington in Oxford and had contributed most effectively to the well-known studies conducted there on reflex activities. The work performed in Oxford had been of great value for the interpretation of those features of reflex responses which depend upon the structural organization of the central nervous system and further important progress was made in this field when D. P. C. Lloyd clearly differentiated monosynaptic from plurisynaptic reflex pathways. Still, the basic question of how impulses entering the central nervous system can evoke or prevent excitation of central neurones was not settled.



Alan Lloyd Hodgkin



Andrew Fielding Huxley

Some workers thought that the events responsible for transmission across synapses are similar to those responsible for conduction of excitation along nerve fibers, and considered that central neurones are brought into activity by the action currents of impulses reaching the terminals of presynaptic fibers. It was very difficult to explain inhibition with this hypothesis.

Other workers thought instead that the processes responsible for transmission at synapses were analogous to those occurring at the junction between nerves and muscles. The experiments of O. Loewi, H. H. Dale, and their coworkers had shown that the effects of nerve excitation upon heart or skeletal muscles are due to liberation of a chemical substance which could be identified with acetylcholine. Extending this work, B. Katz showed that acetylcholine is liberated by the terminals of motor nerve fibers when membrane potential is decreased and that acetylcholine decreases membrane potential of the muscle fiber by increasing its permeability to ions. The mechanisms of inhibition could also be interpreted when it was found that impulses from inhibitory nerves (present in some muscles of invertebrates) liberate a different chemical, and that this as yet unidentified substance evokes a change of permeability resulting in stabilization or increase of the resting membrane potential of the muscle fiber.

Eccles's results on spinal cord reflexes showed that synaptic transmission is analogous to transmission from motor nerves to muscles: impulses from excitatory nerves increase permeability of the motoneurone membrane to ions which tend to decrease membrane potential. The action of inhibitory nerves is exerted through interneurones and results in increase of permeability to ions which tend to augment membrane potential. As in the squid axon, impulses are generated by motoneurones when membrane potential is sufficiently decreased. The basic mechanisms of reflex activities were thus satisfactorily clarified.

In the last decade, the views put forward by Hodgkin, Huxley, and Eccles have been subjected to rigorous test in many laboratories all over the world and have stimulated fruitful research which promises to continue for some time to come. Although contributions of great importance were made by many other scientists, there is no doubt that the recent advances in our under-

standing of the function of nerves and synapses are largely due to the work of the three scientists who were honored this year by the award of the Nobel prize.

Space: Senator Fulbright Steps Into Lunar Landing Controversy

The much-battered space program received a new blow last week when Senator J. William Fulbright delivered a critique that landed right on the preselected impact area.

As chairman of the Foreign Relations Committee in a highly compartmentalized legislative chamber, Fulbright exercises little or no direct influence on the Senate's space deliberations. But he has won a place for himself as perhaps the most scholarly and thoughtful senior member of that body, and when he chooses to express himself on areas outside his primary concern, the legislative climate is affected by at least a little bit.

The object of the Senator's critique was the two-pronged argument that is frequently offered in behalf of rapid expansion of the space effort: (i) that national security and prestige require the United States to surpass the Soviets in space, and (ii) that, because of political problems, the money allotted for space would not be made available for domestic welfare measures.

The first argument, Fulbright said in an address on the floor, "can be challenged on two grounds: first, it is not at all clear that the Russians are trying to beat us to the moon; second —and more important—it is even less clear that it would be an irretrievable disaster if they did. . . .

"What if they did get there first? Would that be an unmitigated disaster and disgrace for America? Would it make us a second-rate people, shamed in the eyes of the world, and in our own eyes, as well? I do not think so. I think it would be a temporary embarrassment and annoyance, but not a calamity. It would hurt our pride, but not our lives as free men in a free society. Most emphatically, it would not change the course of history. . . .

"The competition between freedom and dictatorship is a great deal more than a competition in technological stunts. The real issue is between two conflicting concepts of man and of his life in organized societies. It is on this level that the contest between freedom and communism will ultimately be resolved. . . . If, at the end of this decade, the Russians should have reached the moon, and we should not, but if we, instead, have succeeded in building the best system of public education in the world, in the renovation of our cities and transport, in the virtual elimination of slums and crime, in the alleviation of poverty and disease, who would then be ahead in the worldwide struggle for the minds and allegiance of men?"

Fulbright then went on to the argument that a reduction in the space program would not mean increased support for welfare programs. "It is frequently said that we did not provide adequate funds for education and other vital domestic needs before we had a space program, and that there is no assurance that we would increase our efforts in these areas if the space program were abandoned or reduced. This, I am bound to concede, may well be true, although the Congress has come close, several times, and very close last year, to adopting a meaningful program of Federal aid to education, and it is possible that the reduction of our space expenditures would provide the impetus for the enactment of a really good education bill. In any case, I see little merit in the view that since we will not spend money, anyway, on things we urgently need, we might as well spend it on things we do not need. If it comes to that, I, for one, would rather not spend the money at all."

No direct reply to the Senator's argument has yet been delivered, and in the nature of things it is quite possible that the speech will go unanswered by NASA supporters. But a few days after the Fulbright address, NASA officials, testifying on Capitol Hill, quite accurately pointed out that, to a large extent, the moon program has been the victim of some misleading bookkeeping. The figure $20 billion is often associated with the moon program, but it is reasonable to assume, they argued, that even without the moon objective we would have the massive missile effort and space exploration program that are major components of the lunar effort.

Although the NASA officials didn't agree on a figure, the consensus seemed to be that perhaps only a few billions of the overall space budget could be directly charged to the moon landing. This isn't at all far-fetched, but it comes rather late in the game, and since NASA itself has been using the $20 billion figure for the moon program, it is going to have a hard time convincing the Congress that the real price is considerably lower.—D. S. GREENBERG

Senator Seeks Views on Drug Policies

Senator Hubert H. Humphrey is soliciting the judgments of medical and other scientists on means of improving the clinical testing and evaluating of new drugs, and on related issues of federal drug policy. Responses should be sent to the Subcommittee on Reorganization and International Organization of the Committee on Government Operations, Room 162, Old Senate Office Building, Washington 25, D.C. The subcommittee will hold replies in confidence if requested to do so.

UNESCO: Director General Stakes Out Broader Responsibilities In Applying Research to Development

The United Nations Educational, Scientific, and Cultural Organization (UNESCO) plans to put a substantially increased portion of its next biennial budget into science. UNESCO officials are seeking bigger appropriations, and a large part of the requested increase would be used for applying science to the problems of economic development.

Up to now, UNESCO activities in education have been much better financed than those in scientific research, and the new budget, if accepted, would narrow the gap significantly.

Pressures for more strenuous U.N. efforts to foster economic development have been building quite naturally in the international body in recent years as many new countries joined—countries which shared colonial origins and development problems.

The United Nations Conference on the Application of Science and Technology for the benefit of the Less Developed Areas (UNCAST), held in Geneva last February, probably marked the point at which R&D for development was generally recognized as a major concern for the U.N. However, after the UNCAST conference—a qualified success—no clear policy appears to have emerged on what the U.N. could and should do about develop-