Cambridge University Press
978-0-521-41774-7 - Muscular Contraction
Edited by Robert M. Simmons
Excerpt
More information

1

A. F. Huxley: an essay on his personality and his work on nerve physiology

ROBERT STÄMPFLI

This article was originally written in 1970 for an Italian editor who intended to publish a book about the Nobel Prize winners for Physiology and Medicine (which has never been published). Having had the privilege of collaborating with Andrew Huxley for most of the period of his work with Alan Hodgkin which finally was awarded the Nobel Prize, a colleague thought that I probably had a very personal experience of this historical event and might be the right author to describe this period. In doing so, this chapter gives my personal impressions of the personality of Andrew Huxley during the early part of his and my own scientific career. It also provides an account of his contribution to research in nerve physiology which preceded his very successful work in muscle physiology and biophysics which is the main subject of this book.

Parentage and life before World War II

Andrew Fielding Huxley was born in Hampstead, London, on November 22, 1917. His father Leonard Huxley was a son of the famous nineteenth-century biologist, educator, and writer Thomas H. Huxley who, in his book *Man's Place in Nature,* first popularised the view that human beings evolved from other animals.

Andrew Huxley wrote in his curriculum vitae:

> My father Leonard Huxley was for a time a classics master at Charterhouse School and later took up a literary career, writing a number of biographies and being the editor of the *Cornhill*

Cambridge University Press
978-0-521-41774-7 - Muscular Contraction
Edited by Robert M. Simmons
Excerpt
More information

> magazine. The children of his first marriage included Sir Julian Huxley, the biologist, and Aldous Huxley, the writer. After his first wife's death, my father married Rosalind Bruce, and I am the younger of the two sons of this marriage. My father died in 1933.
>
> I was educated at University College School (1925–30) and Westminster School (1930–5; King's Scholar); and went up to Trinity College, Cambridge, in 1935 with a major entrance scholarship. I had turned over to science from classics in 1932 and went to Cambridge expecting that my career would be in the physical sciences: I have always been mechanically minded, and I was inspired at Westminster by the physics teaching of the late J. P. Rudwick. I naturally took physics, chemistry and mathematics in my part I at Cambridge, but the rules required me to take another science, and I picked physiology, largely on the recommendation of an old friend B. Delisle-Burns, now of the Physiology Department, McGill University. I found Physiology interesting, partly for its subject matter and partly through contact with Adrian, Roughton, Rushton, Hodgkin and the late G. A. Millikan (all Fellows of Trinity) and others in the department, and decided to specialise in it. I spent 1937–8 doing Anatomy with the intention of qualifying in medicine, and 1938–39 doing the part II course in physiology. In August 1939, I joined Hodgkin at the Marine Biological Laboratory at Plymouth for my first introduction to research.

Until his undergraduate days, Huxley had been a rather shy boy and kept to himself, to his thoughts, and his books. He lived with his parents and his older brother in Hampstead, a protected family life. His two famous half-brothers Aldous and Julian were so much older that he considered them rather as uncles than as brothers. Up to the age of 15, when his father died, he had certainly learnt many things from him and had felt the importance of his grandfather's work, as his father had written a biography on Thomas H. Huxley – T.H. as he used to be called.

Alan Lloyd Hodgkin was at that time already established as a top-class experimentalist in electrophysiology. He had been one of Andrew Huxley's teachers at Trinity College. When Hodgkin took him to Plymouth for their first work in collaboration – Huxley's introduction to research – they actually made the discovery that formed the basis for the work that led to their Nobel award. Hodgkin had already performed several sets of experiments with K. S. Cole in the United States, using the "giant axon" of the squid described by the Oxford zoologist J. Z. Young. These animals possess fast-conducting, very thick nerve fibres which enable them to extrude seawater from their hollow muscular mantle system by a fast contraction and to withdraw suddenly by this squirting action from an attacking animal or any danger they recognise. These quick reactions, which have to occur at relatively low temperature, have led to the development of the thickest single nerve fibres known in the animal kingdom – reaching a diameter of about 1 mm. In Plymouth the species *Loligo forbesi* was readily available. Its giant fibres frequently reached a diameter of half a millimeter. They could be separated from the mantle muscle by careful dissection without losing their property of conducting fast nervous impulses if they were kept in seawater.

The experiment attempted by Hodgkin and Huxley consisted of measuring the viscosity of the axoplasm by dropping mercury down the inside of the vertically mounted fibre from the cut end. Having suspended the fibre vertically from the cannula, they realised that it would be possible to put a concentric capillary through the cannula and use it as an electrode, recording for the first time the absolute value of the membrane potential difference between the inside and the external seawater. They found in the resting fibre a negative value of about −50–60 mV, of the inside with respect to the outside. During the nervous impulse, elicited by electrical stimulation of the fibre, this membrane potential reversed, for a fraction of a millisecond, to a value of +45–50 mV (inside positive), and then recovered within about one millisecond to its original resting value. The "action potential" – that is, the electrical signal revealing excitation of the nerve membrane – consisted thus of an impulse of about 110 mV amplitude, starting from the negative resting potential towards zero and "overshooting" this value by 40–50 mV. Overshoots of action potentials over the resting potential value had been observed previously, but had never been accepted as an experimental fact, as all observations had been obtained with external electrodes. The observation of Hodgkin and Huxley (1939), obtained by measurement of the membrane potential with an internal electrode, was direct evidence which invalidated the theory of Bernstein (1902) which suggested that nervous activity consisted of a breakdown of the resting potential to zero. Bernstein had anticipated the origin of the resting potential. He assumed a selective permeability of the resting membrane for potassium ions, and the existence of a diffusion potential due to the differential concentration of potassium – about 20-fold higher in the interior as compared to seawater. A sudden loss of selectivity and an increase of permeability to all ions during the nervous impulse would temporarily bring the membrane potential to zero. For 30 years this was a widely accepted explanation of the action potential, since no one had succeeded in measuring its absolute value. The result of the experiment of Hodgkin and Huxley, which was confirmed one or two years later by the independent measurements of H. J. Curtis and K. S. Cole (1940, 1942) in the United States, meant a revolution in the physiology of excitation. However, this revolution was seriously delayed by the political events of the time. All investigations were hindered by the outbreak of World War II. During the first year of the war, Huxley was a clinical student in London. "But when medical teaching in London was stopped by air attacks", he says in his curriculum vitae, "I changed to work of more immediate application, and spent the rest of the war on operational research in gunnery, first for Anti-Aircraft Command and later for the Admiralty". Nevertheless, he was elected to a research fellowship at Trinity College, Cambridge, in 1941, which he took up at the beginning of 1946.

During World War II

During the war, his military duty seemed not particularly demanding for his well-trained brain. He decided to keep it alert by designing three-dimensional models of stellated forms of the regular polyhedra (during some of his free hours). They had, if possible, to be designed to be cut out from one single piece of cardboard. It was then folded and stuck together to give a three-dimensional model. He then sketched a different drawing of the model for each eye, so that each drawing could be looked at with the appropriate eye at the appropriate distance to give a stereoscopic image. All these models are masterpieces of invention and mathematical planning. They represent an example of the kind of exercise which he imposed on his brain in the moments of leisure.

This occupation reveals some of the particularities of Huxley's personality. He is by no means a man who does not appreciate relaxing – "popping off for a holiday" – as he calls it. But even in his free moments his remarkable brain needs occupation: whereas other people try to do nothing, he switches to some "good old mathematical problem" that requires logical treatment and a high degree of organised thought. I suppose that Huxley, during the war period, discovered his wonderful gift of a perfect intelligence and a perfect hand.

CAMBRIDGE

Cambridge University Press
978-0-521-41774-7 - Muscular Contraction
Edited by Robert M. Simmons
Excerpt
More information

At Trinity College, Cambridge

His research fellowship at Trinity was given under war conditions, which meant that he did not have to submit a voluminous experimental and theoretical project to be admitted. During the war, Hodgkin and Huxley met several times to write up the full paper concerning their discovery of the overshoot of the action potential. Hodgkin, who wrote the paper almost entirely, had been wondering whether their observation could mean that during activity the membrane became permeable to sodium ions; but since researchers assumed that the higher resting permeability to potassium than to sodium was due to the smaller size of the hydrated potassium ion, it did not seem plausible to suggest that there was a "pore" that would admit sodium ions more freely than potassium ions. Furthermore, the intracellular sodium concentrations reported by other authors mentioned a ratio of only about 2:1 for the external/internal sodium concentration. In addition, Cole and Curtis had found an overshoot of about a 100 mV in one case, which made a diffusion potential for sodium unlikely. This explains why the full paper submitted to the *Journal of Physiology* on February 20, 1945 (Hodgkin & Huxley, 1945) does not even discuss such a possibility. (*Editor's note:* The background to this work is described more fully by Hodgkin, 1977.)

But the discussion of the overshoot continued between Hodgkin and Huxley, and also Bernard Katz, from the Biophysics Department of University College, who had come back from Australia after the war. Hodgkin had considered the possibility of dipoles in the membrane, which by turning around could possibly produce an overshoot. This hypothesis was shot down by Huxley because it could not be tested. They had started measuring the amount of potassium accumulating in a thin layer of fluid outside a crustacean nerve fibre. Hodgkin had also conducted a preliminary experiment (unpublished) with sodium-deficient solutions which, when applied to crustacean axons, decreased the amplitude of the action potential and seemed to argue in favour of a sodium mechanism for generation of the overshoot. He decided to do additional experiments with sodium-deficient solutions, in collaboration with Bernard Katz in Plymouth in 1947.

Marriage to Richenda Pease

Andrew Huxley had made the acquaintance of Richenda Pease, daughter of the geneticist Michael Pease, who worked for the Agricultural

Research Council in Cambridge. She had been to a dance given by the Barlow family after the war, and Andrew had been invited to it by his contemporary at Trinity, Andrew Barlow, a cousin of Richenda. Richenda's mother was a daughter of Lord Wedgwood, the famous Labour politician. Richenda had become an undergraduate at Newnham Women's College, where she studied physics, chemistry, and physiology. Huxley taught her in part I classes and was invited to Girton, where the Pease family had built a house.

Michael Pease, Richenda's father, had developed a reputation in the genetics of poultry by developing an autosexing breed, a particular cross where the plumage differs according to sex. Like his wife, he came from a family with considerable sympathy for Labour politics. His father Edward Pease was one of the founders of the Fabian Society.

Both parents liked to invite to their home a large number of young people. They had expanded their house, which had been built soon after the first war, by adding two first-war army-surplus huts to the existing house on their grounds. One of them contained a library and working room for Michael Pease. The other served as a children's room, dining room, and dancing floor according to the needs of the moment. They had a big garden, and in one of the trees the children had built a tree house, where Andrew and Richenda hoped to retreat from the family crowds. Richenda's brother, however, discovered them and tried to take away the steps that gave access to the tree house. This event was noticed by the family and marked the beginning of more and more frequent meetings and rising sympathy between Richenda and Andrew. They became engaged in the summer of 1946 and were married in July 1947. During their engagement, Andrew lived at Trinity College.

A presumed diffusion pathway for sodium

Hodgkin and Huxley frequently discussed the current–voltage relation of an excitable membrane and the physical basis of the permeability changes that were obviously involved in the generation of the action potential. Hodgkin who according to Huxley was far ahead in his understanding of physical chemistry (which is denied by Hodgkin), was actively elaborating theories of ways in which the permeability of a lipid membrane might vary with membrane potential. Huxley began to calculate action potentials under the assumption that depolarisation of the membrane produced an immediate increase of sodium permeability; but

Cambridge University Press
978-0-521-41774-7 - Muscular Contraction
Edited by Robert M. Simmons
Excerpt
More information

his first try showed that on this assumption alone, there would be a potential rise to a peak without recovery. Hodgkin proposed the presence of a negatively charged sodium carrier that might bind other cations, such as hydrogen, at the inside of the membrane after carrying sodium into the fibre. This would represent an inactivation process which could be included in the mathematical treatment.

In early 1947, Huxley began to compute action potentials, first without and then with inactivation of the presumed diffusion pathway for sodium ions which was opened by depolarisation of the membrane by an electrical stimulus to or above the threshold level. He computed membrane action potentials and also conducted action potentials. Each calculation took at least a week to ten days. He accomplished them mostly during his free hours. His computations made the work of both Hodgkin and Huxley tremendously exciting. Hodgkin wrote to me in a personal letter, “All the action potentials were computed by Andrew and I don’t know anyone else who could have done them”.

During this period, Hodgkin and Huxley also measured the potassium release due to activity of the nerve membrane by recording the membrane resistance (Hodgkin & Huxley, 1946). “In this I was very much a learner”, admits Huxley. Hodgkin went to Plymouth for one month (June 20 to July 19), to do sodium experiments on squid fibres from July 4 to 12. These experiments gave clear evidence of the linear dependence of the overshoot on the logarithm of the external sodium concentration $[\mathrm{Na}]_o$ and supported the idea, which had so far been rejected, of a specific pathway for sodium across the membrane – a pathway made available only during the action potential. Hodgkin included some of these results in his presentation of the Hodgkin and Huxley communication at the International Congress of Physiology, Oxford, entitled “Potassium leakage and absorption by an active nerve fibre” (Hodgkin & Huxley, 1947a,b). Huxley, who during this period had been on his honeymoon with Richenda, came to the Congress directly from Scotland.

Experiments with single myelinated nerve fibres at Cambridge

It is then that I met both Hodgkin and Huxley for the first time. I presented a paper on single nodes of Ranvier, and Professor Alexander von Muralt, my teacher in Berne, introduced me to them. Together with Professor E. D. Adrian, he had already planned a research stay of six months for me in Cambridge as a temporary guest in the Rockefeller

Unit at the Physiological Laboratory. Hodgkin had written a letter in April of the same year, suggesting that we use this stay to demonstrate saltatory conduction in myelinated fibres by showing that longitudinal currents within one internode occurred simultaneously, but showed a delay from one internode to the next: "This means that the time relations of an action potential recorded with a pair of electrodes spaced about 0.5 mm apart should not alter when the electrodes are slid along an internode. Hence instead of getting a straight line relation between conduction distance and conduction time one should get a series of steps". A drawing was added which corresponded very well to what Huxley and I found later during our common experimental work. The only prediction that was not yet adequate was the method suggested by Hodgkin, but, as will be shown later, he helped afterwards by proposing an important modification.

Hodgkin asked me to come first to Plymouth for a few days to see the work he was doing with Katz at that time. They were determining the temperature dependence of the squid action potential: "cooking fibres", as they called it.

After the Oxford Congress, Huxley was committed to two visits to introduce his wife to relatives – the reason why he was absent during some important first experiments to prove the sodium theory. As always in Plymouth during good weather, a trawler went out in the early morning to catch the fish and squid. Only in the early afternoon were the animals unloaded and put into the seawater tanks of the laboratories of the Marine Biological Association. The experiments began in the evening after careful dissection of the giant fibres of the biggest animals and went on for most of the night, often until the early morning hours of the next day. I was deeply impressed by the beauty of this experimental work and by the very critical attitude of Hodgkin and Katz. I was given a little side job – to try dissecting nerve fibres from the ventral cord of shrimps. I did my best but was not successful. Nevertheless, both Hodgkin and Katz were extremely kind and let me ask many questions, some of them showing clearly how little I knew and understood about the physiology of excitable membranes. During these few days in Plymouth, I began to realise how privileged I was to have an opportunity to work in England, where physiology was at its best and where these relatively young men represented the top researchers in this field. After approximately a week at the end of September, Hodgkin and I went to Cambridge, where I was expecting to meet Huxley at the Physiological Laboratory.

First impressions

When I went there in the early morning, after having become one of the guests at the Hermitage Guest House, and spent the first night in my room in an attic of Newnham Grange next door, the house of the physicist Sir Charles Darwin, I had great expectations of starting some fascinating work as soon as possible. However, at the department, nobody seemed to be "in", as I could gather from the board at the entrance, where all the people doing research were listed, from Professor E. D. Adrian to the newest postgraduate. I made myself known to Miss Elton, the secretary, and was told that most people would probably arrive at about 10 o'clock. Andrew Huxley arrived at this time in an excellent mood and took me to the basement of the building, where the rooms of the Rockefeller Unit occupied by Hodgkin, Huxley, and myself were. At the end of the corridor was E. D. Adrian's laboratory. I discovered later that it had a red light above the door, which was turned on when he was in. This meant that he was not to be disturbed. I was told that he escaped through the window if insistent visitors wanted to see him. At present, the light was not on; I was therefore allowed to have a glimpse of the many pieces of old-fashioned-looking apparatus, mostly rather untidy, and to see the dusty windows and the very big loudspeaker with a beautiful big trumpet.

Hodgkin, who had also arrived, tried an experiment with a single myelinated nerve fibre with me which was inconclusive. He was then very busy working out the results of his two consecutive stays in Plymouth. As Huxley got interested in dissecting single nerve fibres, Hodgkin then decided to put his laboratory at our disposal and to work mostly at home. We were thus able to use his excellent electronic equipment and Huxley's laboratory for dissection and for constructing nerve chambers. The most important tool for this was a foot-operated lathe which was Huxley's preferred instrument.

We began by building a suitable dissection stand for single nerve fibres with good dark-field illumination. Huxley, who turned out to be an expert optician, designed a dark-field condenser from a lens of an old war-surplus projector. Nylon threads that were used to tie single nerve fibres came from a parachute rope. When particularly fine threads of less than 20-μm diameter were required, we used the hair of Hodgkin's daughter Sarah, who was then a baby.

I soon realised the importance of the daily tea in the common room of the Physiological Laboratory. Huxley was usually hungry at this time of the day and stopped in the midst of an experiment when tea time came. We went to the common room, where a big kettle of water was boiling and tea was available. Several paintings on the wall, particularly the one of Sir Joseph Barcroft, gave a college atmosphere. Huxley, then about 30 years old, was known to come in regularly for tea and to eat "buns" with margarine and jam. All those in the laboratory and others from outside, who wanted to make use of his remarkable intelligence, came and waited respectfully until his second helping before asking questions. He would at first listen and continue chewing. Then, instead of answering directly, he usually reformulated the question much more precisely and to the point than others had been able to put it. He then gave a quick answer if the problem had become a pseudo-problem by his new formulation. But quite often he took a pencil and a sheet of paper and began to develop the adequate mathematical expression. The general belief of the audience was that no one could ever find a mistake in the work of his brain. This explained why so many who had difficulties getting their problems straight used Huxley as a human computer. Working with him was thus a great privilege. Not only I, but also Hodgkin and Katz, appreciated his unfailing logic and mathematical talent. On such occasions, Huxley not only proved to be a brilliant thinker, but also showed an amazing knowledge of biology, physics, and chemistry and an excellent memory as well.

Saltatory conduction

Our work went on very well. We got a good idea of how to measure longitudinal currents along a myelinated nerve fibre from Hodgkin. He came one morning with a piece of transparent plastic tape, folded in two. If oil was put in between the folded tapes, he argued, a vertical "oil gap" could be used to separate two compartments of saline. A nerve fibre could then be pulled through fine openings across the oil. The potential difference between two troughs of physiological solution on both sides of the oil gap would be proportional to the longitudinal current. By moving the fibre, one could measure the longitudinal current produced at any place by the conduction of a nervous impulse and conclude whether transmission of impulses is saltatory – that is, occurring by jumps from one node of Ranvier to the next, through the purely passive cable properties of the internodes – or continuous. The idea was excellent, but the transparent plastic tape, however, was inadequate.