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Jan Bures · Jean Pierre G. Changeux

John E. Dowling · Oleh Hornykiewicz

Andrew F. Huxley · JacSue Kehoe

The History of Neuroscience in Autobiography

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James L. McGaugh · Randolf Menzel

Mircea Steriade · Richard F. Thompson

Volume 4

Edited by Larry R. Squire

The History of Neuroscience in Autobiography

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Contents
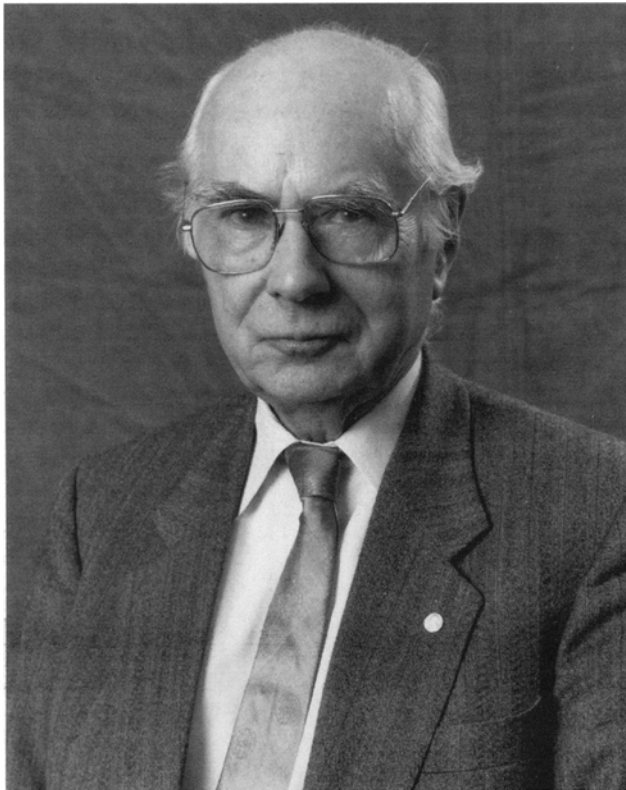
Andrew F. Huxley

BORN:

Hampstead, London, UK
November 22, 1917

EDUCATION:

University College School, London (1925)
Westminster School, London (1930)
Cambridge University, Trinity College, B.A. (1939)

APPOINTMENTS:

Operational Research, Anti-Aircraft Command (1940)
Fellow Trinity College, Cambridge (1941–1960, 1990–)
Operational Research, Admiralty, London (1942)
Physiology Department, Cambridge, Demonstrator (1945)
    Assistant Director of Research (1951)
    Reader in Experimental Biophysics (1959)
Jodrell Professor and Head of Department of Physiology,
   University College London (1960)
Royal Society Research Professor (1969–1983)
President of the Royal Society (1980–1985)
Master of Trinity College, Cambridge (1984–1990)

HONORS AND AWARDS:

Fellow of the Royal Society (1955)
Nobel Prize in Physiology or Medicine (1963)
Copley Medal, Royal Society (1973)
Knight Bachelor (1974)
Honorary Sc.D., Cambridge (1978)
Foreign Associate, National Academy of Sciences USA
   (1979)
Order of Merit, UK (1983)
Grand Cordon of the Sacred Treasure, Japan (1995)

*Andrew Huxley studied nerve conduction in the squid giant fiber jointly
with Alan Hodgkin and in myelinated fibers with Robert Stampfli. Later,
he turned to muscle contraction, proposing the sliding-filament theory
simultaneously with H.E. Huxley and contributing to both theoretical and
experimental studies.*

Andrew F. Huxley

T he Huxley family into which I was born is well known for three of its members: my grandfather Thomas Henry Huxley (1825–1895), the 19th-century biologist, and two of my half-brothers, Julian Huxley (1887–1975), biologist, and Aldous Huxley (1894–1963), novelist. Huxley is not a common surname, but it is also not very rare; it is the name of a village in Cheshire in northwestern England. I am not detectably related to Dr. Hugh Huxley, and it is pure coincidence that, in the same year, he and I independently got onto the idea that muscle contraction takes place by relative sliding motion of two sets of filaments. Leonard G.H. Huxley, a physicist who became Vice-Chancellor of the Australian National University in Canberra, was my third cousin.

> T.H. Huxley wrote a short autobiography which includes the following passage:
>
> As I grew older, my great desire was to be a mechanical engineer, but the Fates were against this; and, while very young, I commenced the study of Medicine under a medical brother-in-law. But, though the Institute of Mechanical Engineers would certainly not own me, I am not sure that I have not, all along, been a sort of mechanical engineer in *partibus infidelium*.... The only part of my professional course which really and deeply interested me was Physiology, which is the mechanical engineering of living machines.

Much of the same could be said of me: my boyhood interests were mainly mechanical, and I entered Cambridge University with the intention of specializing in physics and becoming an engineer. My subsequent interest in physiology is exactly described by the phrase "the mechanical engineering of living machines," and a substantial part of my work has been the design and construction of instruments needed for my research.

T.H. Huxley is best remembered as "Darwin's bulldog," on account of his vigorous defence of the theory of evolution by natural selection after the publication of Charles Darwin's *Origin of Species*. His interest in physiology continued throughout his life. Although he never did any original research in physiology, he was influential through lectures and a small textbook and

especially through stimulating the development of physiology as an independent subject in England. It was on the strength of his advice that Trinity College in 1870 started Cambridge physiology by appointing Michael Foster as a teaching Fellow in the subject, thus establishing a strong tradition in physiology which I found when I entered the college as an undergraduate in 1935. It was also on his advice that T.J.P. Jodrell gave money to University College London to establish a full-time professorship of physiology (the first in England); I held that post from 1960 to 1969. T.H. Huxley's own research was in comparative anatomy and palaeontology; he was also very influential as a promoter of science and education and through his many lectures and essays on a wide variety of topics.

T.H. Huxley coined the word "agnostic" to describe his own position in relation to the existence of a deity. He was explicitly not an atheist, taking the view that there was no way of getting reliable knowledge of the existence or the nature of any deity. My father followed him in this respect and so have I.

My father Leonard (1860–1933) was the second of his three sons; the eldest died at the age of four and the youngest became a doctor who made a successful career as a first-rate physician and general practitioner, but was not responsible for any particular advance in medicine. His son Michael was in the Foreign Office, but left in order to found the Geographical Magazine. Of the daughters of T.H. Huxley, the eldest married an architect, Frederick Waller. Sir Crispin Tickell (formerly Ambassador to Mexico and British Permanent Representative to the United Nations, and Warden of Green College, Oxford 1990–1997) is their great-grandson. The second was herself a talented painter and married the well-known painter John Collier, but died after having one daughter; Collier later married T.H. Huxley's youngest daughter and their son Laurence was in the Foreign Office and became Ambassador to Norway. Another daughter married Alfred Eckersley, an engineer and builder of railways in Mexico and South America. Their three sons were all important figures in the early days of radio: Thomas was elected as a Fellow of the Royal Society for his theoretical work on transmission and reflection of radio waves, Peter was chief engineer to the British Broadcasting Corporation, and Roger was on its programme side.

My father was a classical scholar and for some years taught Latin and Greek, first at St Andrews University and then at Charterhouse School, a well-known boy's school in Surrey, south of London. He then turned to a literary career, writing several biographies, notably, the standard *Life and Letters* of T.H. Huxley (published in 1900), followed by a similar life of Joseph Hooker, one of the leading botanists of the 19th century and a very close friend both of Charles Darwin and of T.H. Huxley. He then worked for the publishers Smith Elder until that firm came to an end in 1916 with the suicide of its head, Reginald Smith (son-in-law, not son, of the George Smith who had built the reputation of the firm in the 19th century). The business was taken over by another long-standing publishing firm, John Murray, and

my father worked for them until the end of his life as a reader and later as editor of the *Cornhill*, a literary magazine. Although in no way a professional scientist, he was very knowledgeable about science, not only the biology that he had learned from his father and from writing his father's life, but he was familiar with physics and chemistry at an elementary level. He was a lover of the countryside and knew most of the birds and wild flowers that we came across when out for a walk. He was a keen gardener.

Much about the Huxley family is to be found in *The Huxleys* by Ronald Clark.

My father and his first wife, Julia Frances Arnold, were married in 1885. She was a granddaughter of Thomas Arnold who, as Headmaster of Rugby School, had set a new standard for schooling in England early in the 19th century. Her eldest sister was Mary Ward (Mrs. Humphry Ward), novelist and social reformer, whose daughter Janet became the wife of the historian George Trevelyan. This connection was very important to me, since I came to know them and other members of the Trevelyan family closely as a result of it.

The eldest son of my father's first marriage was Julian Huxley, another biologist whose interests were mainly in animal behavior, in animal development, and in evolution, but who also became well known for his essays on a wide range of public questions. His interests in biology were very different from mine, and I do not think that I was much influenced by him in that respect. Their third son was Aldous Huxley, the novelist. Julian and Aldous were a generation older than myself, so they were like uncles to me and to my one full brother David (1915–1992, later a lawyer who spent his working life in Bermuda and in the United States). I saw them often until Aldous's move to the United States in 1939 and Julian's death in 1975. Both were very good company, though in different styles: Julian was full of stories and very entertaining; Aldous was quieter, but his conversation was always full of interest.

Julia Huxley died in 1908, and four years later my father married Rosalind Bruce as his second wife. She was 30 years his junior and survived him by more than 60 years, dying in 1994 at the age of 104. Her father William Wallace Bruce, who died in 1907, had been a successful London merchant, importing from the West Indies and the Mediterranean and with interests in shipping. He retired at the age of 45 and devoted himself to social matters. He was elected as a member of the London County Council, serving on its Finance Committee and its Housing Committee. He was deeply involved in slum clearance, notably, in the Seven Dials district of London. He was also a Major in the Artists' Corps of Volunteers. His father was born in Northern Ireland and had come to London after spending several years as a merchant in Demerara, where he became a member of the government and Councillor of the Supreme Court of Civil and Criminal Justice. His forebears had included several Presbyterian and Unitarian ministers distinguished enough to be included in the Dictionary of National Biography. My mother's

maternal grandfather was Thomas Fielding Johnson, who owned and ran a spinning mill in Leicester. He gave the land and the initial building (previously a lunatic asylum) for the University College of Leicester (later Leicester University) and was also a notable benefactor to the Leicester Infirmary.

My mother had strong native intelligence, but was not of an intellectual turn of mind and had not been at a university. She was very skillful with her hands, particularly in wood-carving and needlework, and she encouraged my brother and myself in woodwork and metalwork, which stood me in good stead during my research career. She was brought up as a Unitarian, but did not continue as a churchgoer after her marriage.

Boyhood

I was born (1917) and brought up in Hampstead (north London). My interests were mainly mechanical. My brother and I played a lot with a set of wooden bricks; we made things with Meccano, a toy consisting of metal strips and plates with holes through which they could be joined with nuts and bolts, together with rods, wheels, and cogs so that an unlimited range of working models could be constructed; and we played with clockwork trains ($1\frac{1}{4}$ in. gauge). I made things for the railway from wood and metal. My parents bought for us a metal-turning, screw-cutting treadle lathe (Drummond 4 in. round-bed) which I still possess; I have used it throughout my career for making my own apparatus. In my teens, I added several features to it: divisions on the movements, two four-start worm gears to obtain finer automatic feeds, and a clutch on the main shaft so that a screw-cutting tool would automatically return to the correct position to deepen the thread it was cutting after disconnecting and re-engaging the clutch.

Microscopes were another boyhood interest. When I was about 12, my parents gave my brother and me a small microscope (top magnification of about 200X), and later, I had the use of two 19th-century microscopes that had belonged to members of my mother's family. I learnt about microscopes and microscopy from *The Microscope: A Practical Handbook* by L.H. Drew & L. Wright which was given to me by my half-brother Julian. Toward the end of my schooldays, I chose as a prize *Applications of Interferometry* by W. Ewart Williams, by which I was introduced to the concept of an interference microscope (this bore fruit later when I developed an interference microscope for the research on muscle which I started when Hodgkin and I had finished our work on nerves). I do not think I began taking photographs down a microscope until my student days at Cambridge.

For many years, I collected butterflies and moths (often rearing them from caterpillars), both on weekend expeditions, in our Hampstead garden, and when we were on holiday. This was, I think, a pure collector's instinct. In the same way, one summer I collected ferns, and another summer, I collected grasses, sedges, and rushes. I did not have much interest in living

things as such; for most of my childhood we had no pets, though later on we had a cat. I was once given a nest of ants between two sheets of glass, so that one could watch their activities; I kept this for some years, feeding the ants with sugar solution. I watched them with interest, but not systematically. I remember reading *Ants, Bees and Wasps* by Sir John Lubbock (Lord Avebury).

We spent our summer holidays at Connel Ferry, near Oban, on the west coast of Scotland, where my mother's mother owned a holiday house; sometimes we stayed in that house, but sometimes it was occupied by other branches of the family and we then rented another house in the same village. We had a rowing boat with an outboard motor on Loch Etive, but did not sail. Our main occupations were picnicking with boat(s) or car(s), often jointly with uncles, aunts, and cousins; climbing the hills (no rock climbing); and coarse fishing in the loch. At Easter, we often went to other houses that my grandmother rented for use by her daughters and their families, first at Thorpeness near Aldeburgh on the east coast of England and later at Felpham near Bognor on the south coast. At Easter 1931, my grandmother took my parents, my brother, and myself on a Hellenic cruise during which we visited cities on the Dalmatian coast and most of the famous sites in Greece and Sicily, preceded by a few days in Venice and finishing with a few days in the south of France. Until my father's death in 1933, my parents regularly spent a couple of weeks in Switzerland each winter for skating (English-style figure skating) and another two weeks in May touring in the northwest of Scotland.

We often drove out of London for the day at weekends, usually either to the parts of Surrey that my father had known when he was a Master at Charterhouse and when his first wife was Headmistress of the girls' school Prior's Field that she had founded (and where we often dropped in for tea) or to Ivinghoe and Ashridge on the Chiltern Hills, northwest of London, near Albury where Mrs. Humphry Ward, sister of my father's first wife, had lived.

Schooling

I was never at a boarding school. Before going to school, I was taught for about a year (1924–1925) by a governess, who came because my brother was kept at home after an attack of measles followed by pneumonia. I then went to University College School in Hampstead, junior branch 1925–1929 and senior branch 1929–1930. My parents then moved me (as they had moved my brother) to Westminster School, where I had the main part of my secondary schooling (1930–1935). It had originated as a school attached to the monastery of which Westminster Abbey was the church, and after the monastery was dissolved by Henry VIII, the school was refounded by Queen Elizabeth I and became one of the leading schools in Britain. I was elected to a non-residential scholarship at the end of my first year.

For my first two years (including one year after taking School Certificate) I did classics and reached the point of enjoying much of the Latin and Greek literature that we read, but my real interests were clearly in the sciences and my parents persuaded the headmaster (with some difficulty) to allow me to switch to the science side. I was extremely well taught in physics by J.S. Rudwick (father of M.J.S. Rudwick, well known as a historian of geology); I was also well taught in mathematics. I did not find chemistry interesting and had only a small amount of biology. I was not particularly good at games; we played soccer in the winter and I played tennis in the summer. I also played a good deal of Eton fives (a ball game in which the players hit the [hard] ball with their hands in a court modeled on the space between two buttresses of a building at Eton School). I was often the youngest in my form. I won several book prizes for being top of my form and also several prizes for pieces of good work, in the shape of Maundy money (silver penny, twopenny, threepenny, and fourpenny pieces, not in general circulation but minted primarily for distribution by the King or Queen to the poor at an ancient ceremony on Maundy Thursday, the day before Good Friday).

University Education, 1935–1939

In those days, there were closed scholarships from Westminster School to Christ Church, Oxford, and closed exhibitions to Trinity College, Cambridge (all such awards have since been abolished). My brother went to Christ Church in 1934 with one of the scholarships to read PPE (politics, philosophy, and economics), but I went to Trinity, Cambridge in the next year with one of the exhibitions and a major open scholarship, won in examinations in physics, chemistry, and mathematics. My father and all my half-brothers had also been at Oxford (Balliol College), but the choice of Cambridge for me was partly because of its higher reputation at that time for science, partly because my mother (this was after my father's death) thought it would be better for me to be at a different place from my elder brother and partly because of our friendship with George Trevelyan, he being then Regius Professor of Modern History at Cambridge and a Fellow of Trinity College. The choice turned out to be of great importance for my career as I went up with the intention of specializing in physics; if I had gone to Oxford I would not have had the opportunity of switching to physiology, as I did with no difficulty at Cambridge.

At Cambridge University, the courses for degrees ("triposes") are divided into two parts, with much flexibility allowing for change after Part I. For Part I (the first two years of the course in natural sciences) it was natural for me to take physics and chemistry as whole subjects (two-year courses) and mathematics as a half-subject. The regulations required me to take a third experimental science, and I chose physiology on the advice of Ben Delisle Burns (1915–2001, later a distinguished neurophysiologist) who

had been a boyhood friend in Hampstead and was then an undergraduate at King's College, Cambridge: he told me that physiology was a lively subject in which even in the first year newly discovered things, and things still controversial, were taught, unlike the situation in physics or chemistry. At Cambridge (as also at Oxford) an important part of the teaching consists of spending an hour a week, either alone or with one or two other undergraduates, with a member of the teaching staff of the College. Most of these "supervisions" that I was given were in physiology, and these were given by William Rushton and F.J.W. (Jack) Roughton, both Fellows of the Royal Society and well known for their research, respectively, in nerve conduction and color vision and in the carriage of gases by the blood. I found the subject much more stimulating than physics or chemistry, partly because of their teaching and partly because the course in physics did not take me far beyond what I had learned at Westminster. Another Fellow of Trinity College and Lecturer in the Department of Physiology who influenced me toward switching to physiology was Glenn A. Millikan, son of R.A. Millikan who determined the charge on the electron by the oil-drop experiment. He was an exceptionally friendly and lively person who was extremely good to many undergraduates of my generation. He allowed me to assist him in a small way with his experiments, measuring changes in the oxygenation of myoglobin in active muscles by a photoelectric method and later in the development of a spectrophotometer for biochemical use (never completed on account of the war). Millikan married the elder of the two daughters of George Mallory who was killed on Mt. Everest. At the outbreak of war they moved to the United States, where he held a post at Vanderbilt University. He developed a photoelectric device for measuring the oxygenation of the blood of aircraft pilots. Sadly, he was killed in a climbing accident shortly after the war.

My interest in physiology was also stimulated by other members of Trinity College a few years older than myself whom I met socially through living in the same college, notably, Alan Hodgkin (1914–1998; a Junior Research Fellow from October 1936 and Master of the College, 1978–1984) and David K. Hill, an undergraduate one year senior to me who followed his father A.V. Hill as a distinguished muscle physiologist. Others were R.L.M. Synge (inventor of partition chromatography with A.J.P. Martin, Nobel Prize, 1952); John Kendrew (collaborator of Max Perutz in the determination of protein structure, Nobel Prize, 1962); J.H. Humphrey, M.R. Pollock, and P.G.H. Gell (all of these later became Fellows of the Royal Society); A.H. Gordon and B.M. Wright (later of the National Institute for Medical Research); and E.D. Barlow (later psychiatrist, Head of the London Zoo, and Chairman of Cambridge Scientific Instrument Co., founded by his grandfather Horace Darwin).

As a result of these influences, I decided toward the end of my second year to do Part II of the Tripos in physiology, not physics. I was advised by

E.D. Adrian (later Lord Adrian, President of the Royal Society and Master of Trinity College) to become medically qualified, largely for career reasons since at that time nearly all University posts in physiology were held by medically qualified persons. My Part I work covered the requirement for preclinical study in physiology, but I had not studied anatomy, so I spent the academic year 1937–1938 dissecting the human body. I had one year of clinical study (1939–1940), but this was stopped by the bombing of London and that was when I started my war work. As I shall tell later, this was in anti-aircraft and naval gunnery; this came about through the influence of A.V. Hill, whom I had gotten to know through his son David. A.V. Hill was a leading figure in muscle research throughout the first half of the 20th century (Nobel Prize, 1923); he influenced my career in several ways.

I spent part of the summer of 1938 in the laboratory of Jack Roughton, helping with experiments on his rapid reaction apparatus. Britton Chance was also in the same laboratory at the time. He spent part of his time adding a photoelectric detector to Roughton's apparatus and the rest of it in developing a servo pick-off from a magnetic compass as part of an automatic pilot for a sailing boat; both of these activities led on to fields in which he later became world famous.

I took the Part II course in physiology in 1938–1939. There were only 12 of us taking that course; 3 of us later became Fellows of the Royal Society (J.A.B. Gray, later Head of the Medical Research Council, J.C. Waterlow, later Professor of Nutrition at the London School of Hygiene and Tropical Medicine, and myself). Our main lecturers were E.D. Adrian (who had become Head of the Department in 1937), William Rushton, Jack Roughton, Bryan Matthews, Basil Verney, Nevill Willmer, and Wilhelm Feldberg, who were members of the departmental staff. Members of other departments from whom we had occasional lectures included G.S. Adair, J. Hammond, F.H.A. Marshall, and D. Keilin. All of these either already were or later became Fellows of the Royal Society.

At the end of my Part II year (summer of 1939), I had invitations to join in research work both from Nevill Willmer, distinguished both in cytology and in vision studies, and from Alan Hodgkin, who had already carried out several important pieces of research on nerve conduction. Although considerably attracted to Willmer's work on account of my interest in microscopy, I accepted Hodgkin's invitation, partly because I had gotten to know him personally and he was nearer to me in age and partly because nerve conduction was a field in which my knowledge of physics would be useful.

First Research, Summer 1939

Hodgkin moved his equipment to the Marine Laboratory at Plymouth early in the summer vacation of 1939 with the intention of doing experiments on the giant nerve fibers of squids, and I joined him in early August. He first

suggested that I should measure the viscosity of the axoplasm by suspending the fiber from a cannula and dropping mercury down; this was abortive because the mercury drops stopped as soon as they entered the fiber, the axoplasm being a gel and not a liquid as we had supposed. Having gotten the fiber suspended in this way, Hodgkin suggested pushing an electrode down inside so as to record the membrane potential directly between axoplasm and external fluid. We used a saline-filled glass tube containing a chlorided silver wire to make a non-polarizable electrode and Hodgkin's direct-coupled amplifier with cathode-follower input, so that the steady resting potential could be recorded as well as the action potential. We immediately found that the amplitude of the action potential was much greater than the resting potential, so that the internal potential went considerably positive at the peak of the action potential. This was contrary to the then current belief, although Hodgkin already had hints of an "overshoot" from external recordings on single fibers from crabs and lobsters, but this was not published until later.

The outbreak of war seemed imminent, so we left Plymouth on August 30, two days before Hitler invaded Poland. We wrote a short note that was published as a letter to *Nature* reporting the result, but with almost no discussion of its significance. I wrote a slightly longer account which I submitted to Trinity College as a dissertation for a junior Research Fellowship; wartime regulations allowed the Electors to award these Fellowships without the usual full-length dissertation. I was awarded one in 1941. A full-length paper written almost entirely by Hodgkin, but under both names appeared in the *Journal of Physiology* in 1945; in it we suggested four possible explanations for the overshoot, all of them wrong. We were both familiar with the experiment carried out in the United States in 1937 by K.S. (Kacy) Cole and Howard Curtis which showed a great increase in the conductance of the membrane during the action potential, implying an increase in permeability to ions, and we ought to have realized that this increase in permeability was highly specific for sodium ions, allowing them to enter by diffusion down their concentration gradient, carrying their positive charge inwards. If either of us had known the paper of Overton (1902: On the indispensability of sodium (or lithium) ions . . .), I am sure that we would have reached this conclusion immediately in 1939.

Curtis and Cole also recorded the action potential internally from giant fibers of squid in the summer of 1939 at Woods Hole, MA, but they used a bare platinum electrode with indeterminate junction potential and a capacity-coupled amplifier, so they could not record the resting potential and therefore did not recognize the overshoot.

Medical Studies

When I finished undergraduate work in 1939, I was intending to do a couple of years' research before going to a hospital for my clinical studies. With

the outbreak of war, however, it seemed right to go ahead at once toward a medical qualification, but I had not gotten a place at a clinical medical school. Several others in Cambridge were in the same situation, so John Ryle, then Regius Professor of Physic at Cambridge, ran an introductory clinical course for us at Addenbrooke's Hospital, Cambridge, for the first six months of the war. My other main teacher was the nutritionist R.A. McCance; for the first three months of the war, he and his colleague Elsie Widdowson ran an experiment on rationing and I was one of their subjects. Our diet was similar to the ration diet that was available throughout the war: not restricted for total calories (bread and potatoes were not rationed in Britain until after the end of the war), but the amounts of meat, fats, milk, and sugar were much more severely restricted in our experiment than in wartime rations. Healthy young males like myself stayed perfectly fit on this diet; at New Year in 1940 some of us, including McCance, Widdowson, and myself, spent a week in the Lake District taking very vigorous exercise, which we were perfectly able to do. The only disadvantage of the diet was that we had to chew bread much of the time while we were walking and climbing.

I then spent six months as a clinical student at University College Hospital in London, under the surgeon Gwynne Williams and the physician and clinical scientist Sir Thomas Lewis, famous for his studies of cardiac arrhythmias and of pain. Teaching there stopped at the end of September 1940 on account of the bombing of London, and I was moved into operational research for the Anti-Aircraft Command. I found clinical study very interesting, and I do not know whether I would have returned to physiology if I had completed a medical course or whether I would have made a career in clinical work. As things turned out, most of my life has been spent in posts where I was teaching medical students, and I am very glad to have had even that single year of clinical study since it enabled me to see how different the attitude of a clinician has to be from that of a scientist: the clinician has to make immediate decisions, often on slender evidence, while the scientist has (almost) unlimited time.

War Work

A.V. Hill had led the team that developed anti-aircraft gunnery in World War I. With this background, he was in touch with General Pile, C-in-C AA Command in the summer of 1940, and felt that Pile needed scientific advice. Hill introduced Patrick Blackett (discoverer of the positron; Nobel Prize, 1948) to Pile, who appointed him as Scientific Adviser. Blackett needed assistants. All physicists and mathematicians were already busy on war work so Hill provided him with a team of physiologists: Leonard Bayliss, a lecturer in physiology at University College London and son of the famous Sir William Bayliss; Hill's son David; and through him, myself. We had all taken physics

in Part I of the Natural Sciences Tripos at Cambridge, which was very ade-
quate for dealing with the sort of problems that we were faced with, and our
acquaintance with biology was probably a better background than physics
for trying to deal with the huge uncertainties of war. Radar sets working on
a wavelength of 3 m were already deployed at most of the gunsites around
London, and most of our work was devising ways of using the very impre-
cise data from these radars for controlling the guns, with all the predictors
being designed on the assumption that enemy aircraft would be picked up
in searchlight beams and could be tracked with high precision with optical
telescopes.

    Blackett moved from AA Command to Coastal Command of the Royal
Air Force, where he was busy with anti-submarine warfare, and Basil Schon-
land, a South African famous for his studies of lightning, took over our unit.
Blackett moved again, to the Admiralty, where he was Chief Adviser on Oper-
ational Research and was again engaged mostly on anti-submarine warfare.
In 1942, he got me transferred to the Admiralty to work in the Gunnery Divi-
sion of the Naval Staff. I was nominally under Sir Ralph Fowler, famous as
a pioneer of statistical mechanics, but he had already had a stroke and only
came in occasionally; nevertheless, he was still a formidable character. Much
of my work was scientific advice to the gunnery officers of whom the Divi-
sion was composed, but there was a certain amount of what could properly
be called operational research: I was on board several warships while they
were carrying out gunnery trials, and I crossed the English Channel four
days after the invasion of France to examine the damage done to defences
by the naval bombardments. I stayed on at the Admiralty for a few months
after the end of the war, writing up my wartime activities for my succes-
sors, and returned to Cambridge at the beginning of 1946. I found my war
work interesting, and I benefitted afterwards from experience that I had
gained in statistics and numerical solution of equations and in the theory of
servo mechanisms which I had come across in connection with the automatic
control of gun turrets.

    For some years after the war, I was an Associate Member of the Ordnance
Board, the body responsible for the design and testing of guns.

Marriage

At a dance in January 1946 I met my future wife, Jocelyn Richenda Gammell
Pease (she uses the name Richenda), who was then a second-year undergrad-
uate at Newnham College, Cambridge. She had spent three years during the
war in the United States, with the family of Charles Dunbar (later Secre-
tary of the Brookhaven Research Laboratory) in Cambridge, MA. There she
attended the Buckingham School as a day girl. We became engaged in the
summer of 1946, but did not marry until July 1947 when she had finished
as an undergraduate.

Her father was Michael Stewart Pease (1890–1966), a geneticist who worked on poultry and was well known for developing autosexing breeds (breeds in which the plumage was noticeably different in the two sexes immediately after hatching). His father was Edward Reynolds Pease, a founding member of the Fabian Society and for many years its Secretary, who came from a Quaker family but became an atheist and left the Quakers (Richenda is a Quaker name). Joseph Pease, a direct ancestor, was a notable figure in the development of railways in the mid-19th century.

My wife's mother's maiden name was Helen Bowen Wedgwood (1895–1981), the eldest child of Josiah, 1st Baron Wedgwood and previously for many years M.P. for Stoke-on-Trent, and Ethel Bowen, daughter of Judge Bowen. She had been an undergraduate at Newnham and was, for many years, a Justice of the Peace and a County Councillor. Through the Wedgwoods, my wife was connected with the Darwins, a circumstance that led to our meeting: the dance at which we met was at the home of Sir Alan and Lady Barlow, she being a granddaughter of Charles Darwin. Richenda's mother had known her as a distant cousin, while I knew two of the Barlow sons as undergraduates at Trinity College.

My wife's elder brother is the nuclear physicist R. Sebastian Pease, F.R.S.

Although my wife read Natural Sciences at Cambridge, she did not make a career in science. She has been active in many voluntary capacities, for many years as a Justice of the Peace, a chairman of school governors, and Chairman of the Bedfordshire, Cambridgeshire and Peterborough Wildlife Trust, etc. We have six children: our one son Stewart (born 1949) is an engineer, one of our daughters is a botanist, and another is a molecular geneticist. My wife is an excellent hostess, and I have depended greatly on her in the periods when I had to do a lot of entertaining as President of the Royal Society and as Master of Trinity College, Cambridge.

Research on Nerve at Cambridge and Plymouth, 1946–1952

I returned to Cambridge to take up my Fellowship at the beginning of 1946 and joined Hodgkin again; he had returned immediately after the end of hostilities. The idea that the overshoot of the action potential might be due to entry of sodium ions had come to me as a result of hearing the Croonian Lecture by August Krogh (famous mainly for his studies of the capillary circulation) at the Royal Society in October 1945; he reported work in Scandinavia during the war using radioactive tracers which had shown that cell membranes were not totally impermeable to sodium ions as had been generally supposed (Krogh, 1946). From then on, the sodium hypothesis was under active discussion between Hodgkin and myself. There were several difficulties in the idea. First, Curtis and Cole in the United States had repeated

their intracellular recordings, but used a non-polarizable electrode and a direct-coupled amplifier. They recorded an overshoot much too large to be explained by sodium entry (later admitted to be due to overcompensation for lag due to resistance and capacitance of the electrode and input circuit). Second, they had stated that resting and action potential were unchanged in a solution which did not contain sodium. Third, it was then believed that the selective permeability to potassium ions, responsible for the resting potential, was due to the hydrated potassium ion being smaller than the hydrated sodium ion, and this made it difficult to imagine that a membrane could be more permeable to sodium than to the smaller potassium ions.

We did not attempt direct tests of the sodium theory at once because it was clear that these would be best done on the giant nerve fiber of the squid, which was available in Britain only at Plymouth; the laboratory there had been badly damaged by bombing in the war so experiments were not possible in the summer of 1946. The relevant experiments were done by Hodgkin with Bernard Katz in the summer of 1947; I did not join them because I was married that summer and was occupied with our honeymoon and with visits to members of the family. Meanwhile, in 1946, 1947, and the early part of 1948, I computed (with a hand-cranked Brunsviga calculator) several action potentials on a variety of assumptions about the way in which the ions penetrated the membrane, either as free ions or in combination with a "carrier" anion confined to the membrane. In some cases the carrier was buffered by combination with another ion (Ca^{2+} or H^+) present at a higher concentration on one side of the membrane than the other, causing either inactivation of the sodium permeability or a delay in the rise of the potassium permeability. We did not consider the possibility to which we were later led by our voltage-clamp work and that has since been confirmed by more specific experiments, namely, that the ions pass through "gates" that are opened or closed by change of membrane potential.

This work was not published at the time, but it was a useful guide when we did our experiments with the voltage clamp in 1948 and 1949. I have recently (2002) published an account of the speculations and calculations that we made in 1946–1948. They included several propagated action potentials as well as the simpler "membrane action potentials" in which the potential change is constrained to have the same time course at all points in the area of membrane considered. Strictly, the equations governing a propagated action potential are partial differential equations since distance along the fiber and time are both independent variables. It would not have been practicable to compute the solution to such equations with a hand calculator, so we converted them into a set of simultaneous ordinary differential equations by assuming a constant velocity. The solution for the internal potential would then go toward plus infinity or toward minus infinity according to whether the guessed velocity was greater or less than the true value, which was approached by successive approximation.

After our first season's work with the voltage clamp, I calculated one more action potential assuming that the ions crossed the membrane combined with a carrier, but with parameters adjusted to match the voltage-clamp results. This was published in our contribution to a meeting in Paris in 1949 (Hodgkin, Huxley, and Katz, 1949).

Later, in 1947, I was joined by Robert Stämpfli from Bern, who had been introduced to Hodgkin and me by Professor Alex von Muralt. He had taught himself to dissect single myelinated nerve fibers from the nerves of frogs, as had been done in the 1920s by Kato in Japan. Together, we gave strong additional evidence for saltatory transmission in those fibers. We also measured their resting and action potentials, finding an overshoot similar to that in the squid fiber and showing the dependence of the overshoot on the external sodium concentration.

Hodgkin and I (1947) used an indirect method to estimate the amount of potassium leaving a nerve fiber per impulse conducted, showing that it was sufficient for the charge carried to restore the resting potential after the action potential. Our publication contained the first mention of the idea that the rise of the action potential is due to the entry of sodium ions.

The Voltage Clamp

Both Hodgkin and Cole suspected that the all-or-none character of the nerve action potential was due to a current-voltage relation in the membrane that was continuous but included a region of negative slope which caused positive feedback and therefore instability. Such a feature would make it difficult to measure the current-voltage relation. I remember a discussion with Hodgkin, probably in 1945, in which he pointed out that it would be necessary to use electronic feedback to an internal electrode so as to control the internal potential ("voltage clamp") and to make it undergo stepwise changes. I replied that it would be just as good to feed current from a low-impedance source, but Hodgkin had realized that this would be an imperfect arrangement since the electrode would become polarized by the high current density that would be needed.

Early in the war, Cole suggested to J.H. Bartlett that he should perform an experiment of this type on the "iron wire model": it was well known that iron wire made passive by immersion in strong nitric or sulfuric acid would propagate an electric change when electrically stimulated in a way that had close analogies with nerve conduction. Bartlett (1945) used a low-resistance potentiometer to apply step changes of potential to a piece of iron made passive in this way and recorded the current with a D.C. amplifier and cathode-ray oscillograph; the experiments were only moderately successful.

Cole, together with M. Marmont, was the first to make experiments of this type on the squid giant fiber in the summer of 1947 (Cole, 1949). However, their experiments were limited: Marmont had originally devised

the apparatus with the intention of controlling the membrane current and Cole had made an addition which made it possible to use it to control the internal potential. Using it in this voltage-control mode, they did show that the current-voltage relation is continuous with a region of negative slope (Cole, 1949), but they did not analyze the current into components carried by different ions; further, their apparatus was not a true voltage clamp since they controlled the current by feedback from the same internal electrode by which current was injected. This effectively provided a low-impedance source from which potential changes were applied to the internal electrode and the results were therefore distorted by electrode polarization, as Hodgkin had foreseen: the long-lasting outward current during what should have been a constant raised internal potential declined because the potential of the axoplasm did not follow perfectly the potential applied to the wire.

Hodgkin and I, together with Katz in the initial experiments, had our equipment running in 1948 (Hodgkin, Huxley, and Katz, 1952), but made our final series of measurements in 1949. By varying the external sodium concentration, we separated the membrane current into an inward component due to sodium entry and an outward component that we attributed to the exit of potassium ions. We further analyzed the mechanism of the permeability changes by applying a second step of potential. We fitted equations to the time courses of the permeability changes as functions of time and membrane potential and solved the resulting differential equations representing the behavior of the membrane when not controlled by feedback. EDSAC I, the first electronic computer in Cambridge (and one of the first in the world), was not available at the time because it was being upgraded, so I did the computations by hand as I had done in 1946–1948. The final result was satisfactorily similar to the action potentials recorded from the actual fibers. The results were published in 1952 (Hodgkin and Huxley, 1952a,b,c,d) and were the basis on which Hodgkin and I received shares in the Nobel Prize for Physiology or Medicine in 1963. Sir John Eccles also received a share in the prize for establishing that synaptic transmission depends on changes in ionic permeability; neither Hodgkin nor I ever worked with Eccles.

We confirmed that the outward component of membrane current is carried by potassium ions by comparing a steady outward current with the outward movement of radioactive potassium using fibers from the cuttlefish Sepia.

After analyzing and publishing the work with the voltage clamp, we could not see how to carry the analysis of excitation and conduction to a deeper level. We looked for "gating currents," i.e., the small currents now known to be carried across the membrane by movement of charged structures that open gates in response to membrane potential change, permitting the small ions to pass through. We could not detect them, partly because our measurements were not precise enough and partly because the very small gating currents were overlaid by the much larger currents carried by the

ions and blockers such as tetrodotoxin were not yet available. The huge advances that have been made since have depended on advances in electronic techniques and in other branches of biology, notably, molecular genetics. Hodgkin and I therefore turned to other lines of work. Hodgkin turned to other aspects of nerve function such as the active transport of ions across the membrane by which the ion movements during activity are reversed and, later, the excitation of the rods and cones of the retina by light. I moved into investigations of muscle contraction. I did, however, continue with a small amount of theoretical work about nerve conduction (Huxley, 1959).

The set of equations that Hodgkin and I had produced was first put onto an electronic computer by Cole, Antosiewicz, and Rabinowife (1955). The result showed a discontinuity between stimuli that led only to a small active response by the fiber and stimuli that led to a full-sized action potential. It was clear to Hodgkin and me that the equations required that the response should be continuous, and I remember a conversation with Cole in which I failed to convince him of this. Later, however, he admitted that the apparent discontinuity was due to a computer error: the program asked it to divide zero by zero at a certain point in one of the equations describing the ionic permeabilities (Cole, 1958).

Research on Muscle at Cambridge, 1952–1960

I had become interested in muscle through being asked to take over the lectures on muscle to the final-year course in Physiology from David Hill, who moved from Cambridge to Plymouth in 1948. From the lecture notes that I inherited from him, I learned about the phenomenon known as the "reversal of striations," well described by 19th-century microscopists such as Engelmann (1881), but almost completely neglected since 1900. During contraction of fibers from limb muscles from insects, the region with highest refractive index changed from the A band to the vicinity of the Z line. This seemed to me to be something that might give a clue to the intimate mechanism of contraction, and it was attractive to me because of my interest in microscopy. The 19th century work did not show whether the phenomenon was related to activation or to development of tension or to shortening, because the insect fibers that had been studied (satisfactory for microscopy because of their small diameter and very broad striations) were not fully excitable. From the work of Ramsey and Street (1940), it was known that single fibers could be dissected from muscles of frogs in a fully excitable state, but these fibers were thick and had narrow striations and, therefore, it was virtually impossible to obtain a satisfactory image of their striations by ordinary light microscopy. Polarized light, with high-aperture illumination, does give a satisfactory optical section, but the 19th-century work had shown that the phenomenon does not show up with polarized light. Phase contrast shows refractive index differences well on thin specimens, but not on thick

specimens such as these muscle fibers. What was needed was an interference microscope in which the light that had passed through the specimen was combined with coherent light that had bypassed the fiber; the path differences due to the refractive index differences in the fiber would then be converted to intensity differences by interference and could be observed by eye or by photography.

As mentioned in connection with my boyhood interests, I already had an idea for making such an instrument, based on a polarizing microscope, but incorporating a Wollaston prism below the condenser to separate the incident polarized light into two components with electric vectors at right angles and a second Wollaston prism above the objective to recombine the two beams, with the specimen being placed so that one of the beams passed through it while the other passed through an empty space in the field nearby. I took the idea to the microscope makers Messrs R. & J. Beck, who told me that the idea had already been patented by F.H. Smith (1947); commercial development was therefore impossible, but they were ready to make a single set of the necessary components for me. A low-power instrument of this type, with the objective and condenser each consisting of a simple doublet, was easily made by adding the Wollaston prisms to a standard polarizing microscope, but it did not have sufficient resolving power to be useful for studying the striations of frog muscle. With a high-power condenser and objective, however, the ideal positions for the prisms are inside the condenser and objective, so they have to be placed outside them with the result that the two beams are displaced laterally when they emerge from the upper prism, causing the image to be crossed by finely spaced interference fringes. It was therefore necessary to add further birefringent components to bring the two beams into superposition. The resulting instrument, with an objective of numerical aperture 0.9, functioned very well, even with white light (Huxley, 1954, 1957a). I made the parts for holding and adjusting the prisms myself, using the lathe that my parents had given to my brother and myself when I was about 12 years old. The movements had to have high precision: appreciable intensity changes were caused by a change of path difference between the two beams of 10 nm, corresponding to a displacement of the lower Wollaston prism by 1 μm.

In the work on frog muscle fibers with this microscope, I was joined by Rolf Niedergerke from Göttingen. Before we got around to stimulating a fiber to look for the reversal of striations, we noticed that when we stretched a fiber passively, all or nearly all the change of length took place in the I bands, the reverse of what was in the textbooks of that date. There was no visible change in the striations during isometric twitches or short tetani. These observations immediately suggested that the material that gave the high refractive index and birefringence to the A bands was in the form of rodlets which did not change their length when the fiber was stretched; the reversal of striations would then be attributable to crumpling or overlapping

of the ends of these rodlets when the fiber shortened and they collided with the rodlets of the adjacent sarcomere. We recorded cinematographically the changes in the striations when strong local shortening was induced by application of steady current, and on one occasion the distinction between A and I bands became very indistinct and a narrow dense line appeared where the center of the A band had been; the reversal of striations did occur with further shortening when a second set of dense lines appeared at the positions of the Z lines. A natural interpretation of the first set of dense lines was that they were due to collision or crumpling of the ends of a second set of filaments in each I band and the outer parts of each adjacent A band, which slid into the A bands during shortening; this was the observation that suggested to us the idea of sliding filaments. However, in most of the contractions that we observed, this sequence of changes did not occur, but both A and I bands appeared to become progressively narrower. We therefore delayed publishing the result; it turned out later that the reason for the difference was that, in most cases, only the myofibrils near the surface were activated and the inside of the fiber shortened passively and the fibrils were thrown into waves so that the striations were foreshortened in the image (Huxley and Gordon, 1962). This was in the early part of 1953; I was not able to give much time to research as I was then Press Editor of the *Journal of Physiology* and also Secretary of the College Council, as well as having teaching duties (not very heavy).

I spent the summer of 1953 at the Marine Biological Laboratory at Woods Hole, supported by a Lalor Fellowship. There I met H.H. Weber of Tübingen (later of Heidelberg), who told me of the experiments by Wilhelm Hasselbach (1953) in his laboratory. He had dissolved away the myosin from fragmented muscle and examined the residue with the electron microscope, finding that the actin was in the form of filaments held together at their centers by the Z line. This immediately suggested that the second set of filaments that we postulated were composed of actin. A little later during that visit, I met Hugh Huxley (from the Cavendish Laboratory, Cambridge) and Jean Hanson (from the Department of Biophysics at King's College London), who had come to Woods Hole from MIT, where they were working in the laboratory of F.O. Schmitt. I told them of our observations with the interference microscope and our idea that length changes in muscle took place by relative sliding movements of two interdigitating sets of filaments. They showed me the electron micrographs of transverse sections of frog muscle that established the existence of two sets of filaments and that were published by Hugh Huxley later the same year, with a brief mention of the sliding-filament theory. They also showed me their phase micrographs of separated myofibrils treated with various solutions that showed, in agreement with Hasselbach's observation, that the additional material in the A bands was myosin. The main accounts of the evidence for sliding filaments by H.E. Huxley and Hanson (1954) and by myself with R. Niedergerke (1954)

appeared alongside in *Nature* the following year. Details of my work with Niedergerke were published in 1958.

In our 1954 article, we proposed that relative force between filaments of the two sets was generated by independent force generators distributed throughout the region of overlap between the filaments. The basis for this suggestion, which has been amply confirmed, was the observation by Ramsey and Street (1940) that, over much of the range of initial length at which isometric contractions could be recorded, the tension developed was roughly proportional to the amount of overlap of the two sets of filaments. However, the lengths of the filaments were not accurately known, so it remained uncertain how close the proportionality between overlap and force was. I returned to this problem several years later (see below).

In the summer of 1954 I spent a lot of time brooding on the nature of the mechanism by which the independent force generators that we postulated in each overlap zone produce force or sliding movement. A clue was provided by Dorothy Needham (wife of biochemist and sinologist Joseph Needham), who pointed out that the relation between rate of energy liberation and speed of shortening found by A.V. Hill (1938) implied that repeated interactions took place at each active site during a single contraction (Needham, 1950). Such cyclic action is difficult to fit into the idea, universally accepted at that time, that contraction takes place by shortening of continuous filaments, which may be the reason why this suggestion did not immediately attract much attention. In a sliding-filament process, however, it is natural to think in terms of cyclic mechanisms since one cannot imagine a single interaction between active sites on the filaments operating over a distance approaching 1 μm such as can occur in a single contraction. So I thought out a mechanism in which a "side-piece," attached to the backbone of the thick filament by an elastic connection, was able to attach to a site on the thin filament with a rate constant that was moderate when the relative positions of the filaments were such that the connection gave a positive contribution to overall tension, and the rate constant for detachment was large after sliding motion had brought it to a position where its contribution was negative. With a suitable choice of parameters, this theory gave a good approximation to the relationships established by A.V. Hill (1938). However, it was so speculative that I did not consider publishing it until Bernard Katz, one of the editors of *Progress in Biophysics and Biophysical Chemistry*, suggested that I write a contribution to one of its issues. I accepted this invitation, and in early 1955, I submitted a typescript containing the theory. I was very disappointed that the article did not appear until nearly two years later (Huxley, 1957c).

The theory has remained useful, as its main kinetic assumptions are probably roughly correct. It is now clear, however, that much or all of the generation of force is due to more specific changes in the cross-bridge than merely attaching in a position where the elastic element is stretched, but this need not alter the kinetics greatly.

The theory was undermined when A.V. Hill (1964) showed that the rate of energy liberation did not increase with shortening speed over the whole range, as described in his 1938 paper, but passed through a maximum. However, I showed later that this feature can be explained if the initial attachment involves two steps.

Before leaving Germany, my colleague Rolf Niedergerke had become aware of some of the 19th century microscopy of muscle. I followed this up using the wonderful collection of reprints made by Michael Foster, which was then in the library of the Physiological Laboratory at Cambridge (it is now in the library of the Whipple Museum of the History of Science in Cambridge). I found that most of our observations had been well known in the latter part of the 19th century, though no one seems to have proposed a sliding-filament process. The old observations had been lost after 1900, chiefly because of a switch of interest to biochemical events and the argument that contraction must be a molecular process: molecules are not visible with the light microscope and, therefore, nothing important will be learned from what can be seen. This is set out in the small book that I published in 1980.

The Inward Spread of Activity in a Muscle Fiber

In late 1953, I was joined by Bob Taylor from the University of Illinois. We set out to look for changes in the light scattered and diffracted by frog muscle fibers activated by electric current under conditions where no action potentials are set up. We made a trough with a shape designed so that current was drawn uniformly from the fiber over a substantial length and set up a drum camera for recording the diffraction spectrum continuously. Nothing of great interest was emerging, so we switched to the question of how a change of potential difference across the surface membrane activates the contractile material at distances up to several tens of micrometres. This had become an acute problem in 1949 when A.V. Hill showed that the whole cross-section of each fiber began to contract within a few milliseconds after an action potential, a time too short to allow a hypothetical activator substance liberated at the membrane to reach the center of the fiber by simple diffusion.

With my interest in muscle structure, I was aware of papers showing that the Z lines in adjacent myofibrils were united to form a membrane ("Krause's membrane") that connected with the inside of the surface membrane (Enderlein, 1899). This suggested that this structure might conduct an influence (of unspecified nature) inward from the membrane. We tested this idea by reducing the membrane potential of a very small area of membrane by applying a saline-filled micropipette (tip diameter about 1 μm) to the surface of an isolated fiber from frog muscle and then applying a negative electric potential to the fluid in the pipette. We watched the fiber under a polarizing microscope so the anisotropic A bands were clearly visible; the Z lines were not visible, but their position was recognizable because it is at

the middle of the non-birefringent I band. The result was just as we hoped: when the pipette was placed over an I band, we often saw a contraction, completely localized to that I band; but when the pipette was over an A band, we never saw a contraction. We recorded these local contractions with a cine camera, and we published a letter in *Nature* entitled "Function of Krause's Membrane."

We showed the film at a meeting of the Physiological Society. The electron microscopist J.D. Robertson was in the audience. He produced from his pocket a slide showing an electron micrograph of a longitudinal section of muscle which clearly showed a pair of tubules penetrating the fiber on either side of each Z membrane, so he suggested that inward conduction took place along these tubules and that our pipettes were not small enough to distinguish between the two members of each pair. However, his micrograph (Robertson, 1956) was from a muscle of a lizard, while our experiments were on fibers from frog muscle, so it was possible that both of us were right—as happens in many controversies in biology.

To resolve this problem, it was necessary to repeat our experiment using an optical system that shows the Z membranes. The interference microscope that I had developed for study of the changes in the striations did this, so Taylor and I repeated the experiment under this microscope on frog fibers and also on fibers from crab muscle with much broader striations. In a frog fiber, the Z line always remained central in the I band, even when the pipette was applied just to one side of it; however, in a crab fiber, the Z line was pulled across toward the side on which the pipette was placed. Later, in collaboration with Ralph Straub from Geneva, I repeated the experiment on fibers from lizard muscle and saw the same result as in crab muscle—not what one might have expected from the evolutionary relationships of those animals. If we had known of the paper of Golgi's pupil Veratti, published in 1902, we would have been aware of these differences in the system of transverse tubules, but it had been completely forgotten until rediscovered and reprinted in English translation (Veratti, 1961).

Indications of membrane structures inside muscle fibers were seen with the electron microscope at about the same time as our observations of local contractions, but the structures in frog muscle at the level of the Z line seen by Porter and Palade (1957) consisted of a row of vesicles, not a continuous structure. The Wellcome Trust provided an electron microscope for our department in 1957, and I studied the membrane systems of frog muscles with it, finding that, in some preparations, Porter's vesicles were replaced by a tubule (Huxley, 1959). At about the same time, Andersson-Cedergren demonstrated continuous tubules in mouse muscle, but they were in pairs flanking each Z line, like the tubules seen by Robertson in lizard muscle.

Thus, it became clear that inward conduction was taking place along these tubules, and the title of our letter to *Nature*, "Function of Krause's Membrane," was inappropriate. This is an example of the danger of relying

on an apparent confirmation of a preconceived hypothesis, as emphasized in Karl Popper's book *Conjectures and Refutations*.

With the electron microscope, I looked for openings of these tubules to the extracellular space, but could not see any. Even now, such openings have rarely been seen in the skeletal muscles of frogs or mammals. In 1964, however, Makoto Endo in my laboratory showed that a fluorescent dye enters the tubules from the extracellular space, and Sally Page and Hugh Huxley independently showed with the electron microscope that large molecules can enter the tubules. It was only later that I found evidence from the late 19th century that Indian ink particles can enter the tubules of heart muscle (Nyström, 1897). These observations made it clear that changes of membrane potential can spread up the membranes of the tubules, causing liberation of the activator (calcium ions) close to the contractile material. These and other confusing observations are set out (Huxley, 1971) in my Croonian Lecture to the Royal Society.

For the local-activation experiments, I designed a micromanipulator; for electron microscopy, I designed an ultramicrotome. In both, I used crossed-strip hinges for the levers that gave the fine movements. These allow rotation about a single axis with no friction and no backlash, unlike ordinary pivots. I was pleased with myself for thinking up this type of pivot, but later found that there had been controversy about 1900 between the Cambridge Scientific Instrument Company and the National Physical Laboratory as to which of them had invented it first. Initially, both instruments were made for me by the workshop of the Engineering Department of Cambridge University; in both cases they also made a number of copies for other laboratories. The ultramicrotome was later manufactured by the Cambridge Scientific Instrument Co., which provided an important additional income when we were paying fees for the education of our six children.

The Maximum Length for Contraction

In 1958 I was joined by Lee Peachey, who had just completed his Ph.D. at the Rockefeller University under the pioneer electron microscopist Keith Porter. We returned to the problem of the relation between the tension generated by an isolated muscle fiber and the amount of overlap between the thick and thin filaments. As soon as we stretched an isolated fiber under a light microscope, we noticed that there were regions at both ends where the sarcomeres (the units of the striation pattern) were much less extended than in the middle of the fiber. This made measurements of tension ambiguous, but we were able to show that the middle part of the fiber was unable to shorten if it was stretched so far that there was no overlap as seen in our electron micrographs. There was, however, still overlap in the end regions, and if the tendon ends were held stationary, tension rose because the regions with overlap shortened, stretching the middle still further.

This showed that the relation between length and isometric tension could be found reliably only if precautions were taken to keep constant the length of a selected region in the middle of the fiber. This was the first problem to which I addressed myself after moving from Cambridge to University College London in 1960.

Move to University College London, 1960

Early in 1960, I was invited to accept the Chair of Physiology at University College London. I was then very comfortably established at Cambridge, with a teaching Fellowship at Trinity College and a Readership in the Physiology Department at University College London (both tenure positions), and we were living in an extremely attractive house in the picturesque village of Grantchester, a couple of miles outside Cambridge. Therefore, there was a strong temptation to stay where I was.

However, I also received a letter from A.V. Hill, whom I had gotten to know through his son David, as I said earlier. He was then working at University College London in his retirement. In this letter, A.V. said that he had been in a similar position in 1919, comfortably established in Cambridge following his return after World War I, when he was offered the Chair of Physiology at Manchester University. Lord Rutherford, the physicist, had just returned from Manchester to Cambridge, so A.V. asked his advice. He quoted this advice to me, saying that he had followed it and had never regretted doing so. The advice was: "Cambridge is a splendid place when you are young and Cambridge is a splendid place when you are old, but for the middle of your life for God's sake get out." So I entered into negotiations with University College and London University.

The only serious obstacle was that we wished to stay living in our Grantchester home, but this was over 50 miles from London and London University had a rule that its staff must live within 30 miles (in those days, professors and readers were appointed by the University, not by the College). Further, I was told that the University readily relaxed this rule in any direction except toward Oxford or Cambridge. The rule had been introduced because Oxford and Cambridge dons used to accept a chair in London University, but stay living in Oxford or Cambridge and turn up in London only occasionally for a lecture or a committee meeting. I assured them that I had no intention of behaving like that, and it was agreed that I could stay in our Grantchester home provided that I also had a London address and spent some nights there each week. I did not get a flat in London, but slept Monday, Tuesday, and Thursday nights in bed-and-breakfast places within walking distance of the College. I always traveled by train to London early on Monday, home Wednesday evening till Thursday morning, and home again on Friday evening. On this basis I saw at least as much of my family as I did when working in Cambridge, since in term time I gave tutorials from 6:00

till 8:00 PM three days each week and often dined in the College on those evenings, and at weekends I sometimes had teaching duties and often went to work in my laboratory. When I was staying in London in the routine that I adopted, I would get some supper and return to my office or my laboratory until nearly midnight, walk back to my bed-and-breakfast, and walk back to the department early next morning. In this way, I spent more hours in the department each week than anyone else. I am sure it is the best way of doing a London job.

Like A.V. Hill, I did not regret the move: University College London was a very friendly place, and I had opportunities there which I would not have had if I had stayed in Cambridge, as a relatively junior member of the department. As a former Fellow of Trinity College, I still had the right to take meals in the College and to bring guests to the college's "feasts," as guest nights are called in Cambridge.

I retired from headship of the department in 1969, when I was awarded one of the research professorships of the Royal Society. This provided not only my salary, but also generous allowances for research expenses, a secretary, and a technician. I still gave a few lectures, but I had no administrative duties. I stayed on at University College London until I was appointed Master of Trinity College, Cambridge, in 1984, as I shall tell later.

Research on Muscle at University College London, 1960–1984

As I have already mentioned, I returned once again to the problem of the length-tension relation in isolated muscle fibers from frogs. As Lee Peachey and I had found in our experiments at Cambridge, it was necessary to arrange that the middle region of a fiber was held at constant length during a contraction so as to avoid the extra tension that is given by sarcomeres with greater overlap near the ends of the fiber if the ends are held stationary. This required continuous measurement of the length of the selected region and feedback from this measurement to a motor which moved one tendon of the fiber so as to keep the length signal constant. I was joined for two years by Al Gordon who had just completed a Ph.D. in physics at Cornell, and we developed a device ("photo-electronic spot-follower") which detected the positions of two small pieces of gold leaf stuck to the isolated muscle fiber at the ends of a selected region within which the striation spacing was uniform. This gave a length signal from which we used feedback to a galvanometer movement to which one tendon of the fiber was attached. This development was completed in collaboration with Fred Julian from the Naval Medical Research Institute at Bethesda (1962–1965). We were then able to show a close proportionality between filament overlap and the tension developed on stimulation with the fiber held a series of lengths above that which gave the maximum tension (at shorter lengths, the tension fell away because

the filaments of adjacent sarcomeres collided). We also showed that, over
the same range, the speed of unloaded shortening was almost independent
of overlap, as would be expected if the movement was being generated by
independent active sites in the overlap zone.

The situation was confused for many years by the measurements by
G.H. Pollack and his collaborators, who omitted to use feedback control of
sarcomere length and found that substantial tension developed even when
the fiber was stretched considerably beyond the length at which there ceased
to be any overlap in most of the length of the fiber. When at last they did
control the sarcomere length, they obtained results in close agreement with
what we had published a quarter of a century before (Granzier and Pollack,
1990).

In 1967 I was joined by Bob Simmons. Originally trained in physics, he
had been with David Phillips at the Royal Institution doing X-ray crystallog-
raphy on enzymes, but came to University College to take a course designed
to give some biological background to physicists and chemists who wished
to make a career in biological research. For his project in this course, he
worked with me, and our collaboration continued until he moved to King's
College London 12 years later.

We settled down to investigating the mechanism of force generation in
muscle by applying step changes of either tension or length to a fiber during a
contraction. The first studies of transient responses of muscle had been made
by Dick Podolsky using steps of tension. He had found that the response was
a heavily damped oscillation of length, superposed on the steady shortening
that followed the drop in tension. At first, we too tried to use tension steps
so as to avoid complications due to changes in length of series elastic ele-
ments that would occur after the step itself if tension were not kept constant.
We used negative feedback from a tension signal to the motor attached to
one of the tendons to control the tension. We found an oscillatory response
superposed on steady length change, as Podolsky had done, but under some
conditions the oscillation was only very lightly damped (Armstrong, Huxley,
and Julian, 1966). However, we found it too difficult to obtain satisfactory
performance during the first few milliseconds after the step because of the
non-linearity of the muscle properties. That was the immediate reason why
we switched to steps of length, though in retrospect the results from length
steps were easier to interpret. The response to a step decrease in length
consisted of a series of decaying exponential terms, which indicated that the
response of the contractile system is more directly related to length changes
than to tension changes since the latter generate an oscillatory response.

We found that the response to a shortening step was composed of four
phases: Phase 1, an almost linear decrease in tension simultaneous with the
length; Phase 2, recovery in a few millseconds much of the way toward the
original tension; Phase 3, a delay or actual reversal of the tension recovery;
and Phase 4, slow recovery to the original tension.

Phase 2 appeared to represent the actual working stroke of the cross-bridges, and we found that its time course became more rapid the larger the shortening step was applied, and therefore the smaller the tension during Phase 2. We produced a theory of this acceleration on the basis that the working stroke in a cross-bridge consisted of one or a few stepwise events which stretched the elastic element in the cross-bridge and that the work done against this elasticity formed part of the activation energy for the step(s) (Huxley and Simmons, 1971). This theory is still useful, although it has had to be modified in its quantitative aspects as a result of improved measurements and evidence that there is appreciable compliance in the filaments themselves (Huxley and Tideswell, 1996).

We were joined in 1971 by Lincoln Ford, with a two-year fellowship from the NIH. After improving our equipment so as to obtain much better time resolution, we obtained our final series of measurements. We published four papers on the responses to length steps under various conditions: first, during the tension plateau of fibers at their normal length; second, on fibers stretched to various lengths; third, during steady shortening at various speeds; and fourth, during the rise of tension at the start of stimulation (Ford, Huxley, and Simmons, 1977, 1981, 1985, 1986). Lincoln returned for a month or so each year to help in preparing these papers, but our close collaboration ended with Ford's return to the United States in 1973, Simmons's move to King's College in 1979, and my becoming President of the Royal Society in 1980. As a result, we did not achieve what I had hoped for, namely, making a synthesis of our results into a comprehensive theory, as Hodgkin and I had done for nerve conduction in our papers of 1952.

Another very productive collaboration has been with Vincenzo Lombardi of the University of Florence and later with his colleague Gabriella Piazzesi. It began in October 1979 when Lombardi came to University College London for a nine-month visit. Lee Peachey was also with me at the time. Much of our work was developing a new device for obtaining a signal representing change in length of the selected segment of an isolated muscle fiber. We used the light diffracted by the striations, but not in the way that is commonly used, which is to estimate the spacing from the angle of the first diffraction line, since that method is subject to numerous artifacts. We devised a circuit which signaled the longitudinal displacement of an image of the striations, and the difference between the outputs of two of these circuits, one at each end of the selected segment of the fiber, gave the change of length. This apparatus turned out to be much more satisfactory than other methods and became the standard method in my laboratory and in Lombardi's. It gives a precision of about 1 in 10^5 of segment length, with a time lag of about 1 μs.

During that first visit, we also did one experiment on living fibers. This was designed to detect compliance in the thin filaments, and it appeared to confirm the conclusion reached by Ford, Simmons, and myself that such compliance was negligible. Perhaps fortunately, we did not publish it: more

recent experiments by much more direct methods have shown clearly that the compliance is quite appreciable.

Since then, Lombardi came to collaborate for periods of a few weeks, usually twice each year. This continued throughout the period when I was President of the Royal Society or Master of Trinity and into my retirement until 1998, when I gave up my laboratory and sent my equipment to Florence for his use. We made further improvements to the equipment, including a miniaturized loudspeaker-type motor for changing the fiber length, which I made on the lathe that I have owned since boyhood. This gave steps complete in about 30 μs, as compared to 150 μs with previous motors. With these sharp steps, the effects of reflection of the traveling wave set up by the step were noticeable, and we devised circuits for shaping the command signal in order to reduce these effects.

Throughout, we have also had a continuous correspondence about his experimental work at Florence and drafts of his papers based on it.

Other Workers in My Laboratory

While I was Head of the Department at University College London, I usually had two or three others in my laboratory, working more or less independently on problems connected with muscle. A few of these were working for a Ph.D. and the others were postdocs. In contrast with present-day custom, I did not put my name on the papers reporting their work unless I had taken a very substantial part in the experiments. They included Saul Winegrad, Hugo Gonzalez-Serratos, Lucy Brown, Makoto Endo, Clara Franzini-Armstrong, Reinhard Rüdel, Stuart Taylor, Peter Heinl, Jan Lännergren, Russell Close, and Lydia Hill.

Resonance in the Cochlea

My father had received as an undergraduate prize a copy of Helmholtz's book on hearing (*Die Lehre von den Tonempfindungen...*), and I read parts of it when I was an undergraduate. I was impressed by his evidence for a resonance mechanism for pitch discrimination, and this impression was strengthened by Thomas Gold's dissertation which won for him a junior Research Fellowship at Trinity College (Gold and Pumphrey, 1948; this was the same Gold who later became well known in cosmology and geochemistry). Gold also argued that the sharpness of resonance would only be possible if there is a positive feedback process to counteract the damping due to the fluids in the cochlea. In the late 1950s, I contemplated switching my main line of research from muscle to the mechanism of the cochlea and I asked the advice of Bryan Matthews, then Head of the Physiology Department at Cambridge, who had done some experiments on the ear. He replied that the problems had been definitively solved: von Békésy had shown that the

movements of fluids in the cochlea were not sharply tuned so that pitch discrimination must be done in the brain, and his conclusions had been confirmed by the electrical recordings of Hallowell Davis and Tasaki. I therefore stuck to my muscle work and was duly surprised when Nelson Kiang (1965) showed extremely sharply tuned responses in fibers of the auditory nerve when the blood circulation in the preparation was well maintained.

I never did any experimental work on the ear, but I did publish one theoretical paper (1969) in which I showed that true resonance might occur in a structure resembling the cochlea provided that the cochlear partition (basilar membrane plus organ of Corti) had appropriate mechanical properties. I do not believe that the suggestions in that article have been followed up. There is much emphasis now on the movements generated by the outer hair cells of the cochlea. These no doubt counteract damping as suggested by Gold more than half a century ago, but I am not aware that they have other effects on possible resonance.

My other contribution to the theory of hearing was to draw attention (1990a) to the beautiful experiments of Ernst Bárány (1938). Bryan Matthews had drawn my attention to his paper, which had shown beyond doubt that the important function of the ossicles is to reduce bone-conducted sound relative to air-conducted sound. This had been completely neglected, and all the textbooks stated that the function of the ossicles was to improve the matching between air and the fluids of the cochlea. This matching is achieved almost entirely by the large ratio of the area of the eardrum to the area of the footplate of the stapes, and it is beyond belief that evolution would have produced the elaborate system of ossicles when the same result could have been achieved by a small reduction in the area of the footplate of the stapes.

President of the Royal Society

The Royal Society is the equivalent in Britain of the National Academy of Sciences (NAS) in the United States, though of course much smaller. It supports and promotes science in many ways. It receives a substantial grant each year from the government, but this is spent on professorships, research fellowships, etc. awarded by the Royal Society. The Royal Society has sufficient funds of its own to remain independent of government with regards to its policy and the reports that it produces—nothing like as many as the NAS. Outside Britain, it has an important function in promoting international contacts through exchange schemes.

I did not have time for consecutive research while I was President of the Royal Society or Master of Trinity College, Cambridge, especially during the year when I held both of those offices (1984–1985). Work at the Royal Society took up about three days a week, and I made several trips abroad visiting the national academies of other countries. Although I gave up a few

memberships of other bodies, I also had responsibilities in the International Union of Physiological Sciences, the Muscular Dystrophy Group of Great Britain, the Natural History Museum, the Science Museum, the Nature Conservancy Council, and the committee that advises the Home Office on experiments on living animals. Such time as I could find for research was mostly spent in finishing the analysis of the results that Bob Simmons, Lincoln Ford, and I had obtained and in writing the last two papers on that work, but, as I have already mentioned, I did occasionally get into the laboratory with Vincenzo Lombardi.

The one important innovation that was made during my time was the establishment of the junior research fellowships known as University Research Fellowships. At that time, very few vacancies were coming up for positions in the universities in Britain, partly because of cuts in government funding, but also because of the age structure in the universities that had been established in the 1960s. These fellowships are awarded to scientists, mathematicians, or engineers with a few years' postdoctoral experience and are tenable for up to 10 years, with the expectation that many of the holders will obtain university posts within that time. There are now over 300 holders of these appointments.

Another matter that took up a good deal of my time was resisting pressure from politically minded groups to break off scientific contacts with countries with totalitarian governments. For example, scientists from South Africa and from China had been prevented from attending certain international congresses, and the two most senior Soviet scientists wishing to attend the International Congress of Biochemistry in Australia in 1982 were denied visas (not for scientific reasons). This was the main topic of my annual address to the Royal Society in November 1982. My other addresses were concerned with unjustified criticisms of Darwinian evolution (1981); ethical questions such as experimentation on living animals (1983); government support of science and the universities (1984); and the fragmentation of biology (1985).

Master of Trinity College, Cambridge, 1984–1990

At most of the colleges in the universities of Oxford and Cambridge, the Head is elected by the Fellows of the college. In Trinity, however, our founder, King Henry VIII, laid down that its Head should be appointed by the King or Queen of England. The Fellows are consulted on the appointment, but they have no veto, and as a result they give the Master very much less power than in most other colleges, in case an unwelcome appointment might be made. Much of the work that heads of other colleges have to do is performed in Trinity by the Vice-Master, who is elected by the Fellows from among their number. The Master of Trinity is therefore to some extent a figurehead, though he is Chairman of the College Council and of any meeting of the

Fellows at which important decisions may be taken. He would be expected to take a leading part in dealing with any crisis that might arise in the College; fortunately, nothing of that sort happened during my tenure.

The Master when I was an undergraduate before the war was the physicist J.J. Thomson, who had discovered the electron in 1897. He was the last Master who was not subject to a retiring age, and he remained Master until his death in 1940 at the age of 83. His successors included George Trevelyan and Lord Adrian, whom I have mentioned in other connections, and my immediate predecessor was Alan Hodgkin, my mentor. As is customary, we moved into the Master's Lodge, which is a part of the college buildings. It is a splendid residence (and also very comfortable). The main entertaining rooms date from the beginning of the 17th century and provided a wonderful setting for the considerable amount of entertaining that we were expected to do, both of undergraduates and of senior members of the University, as well as one visit by the Duke of Edinburgh (Chancellor of the University); one by Princess Margaret, sister of the Queen; and two by the Princess Royal in her capacity as President of the British Olympic Committee when it held fund-raising dinners in the College.

Diffraction of Light by the Striations of Muscle

A very convenient way of estimating changes in the length of a segment of an isolated muscle fiber is to measure changes in the direction of one of the first-order beams in the diffraction pattern of laser light created by the striations. This technique is widely used on account of its simplicity, but, unless additional precautions are taken, it is subject to artifacts due to differences in the spacing and orientation of the striations in different "domains" within the fiber. During a visit to Lee Peachey in Philadelphia, I developed an optical device to recognize these domains. They diffract in slightly different directions and therefore cause fine structure within each diffracted beam. By using a mask with a hole to select a particular spot in this pattern, individual domains could be made visible and recorded photographically. This work led me to look into the theory of light diffraction by a thick striated structure. Several conclusions emerged, such as the existence of particular thicknesses at which the intensity of a diffracted beam drops to zero. However, these results are of only limited use in interpreting the diffraction pattern from a muscle fiber since the theory assumes a perfectly regular structure.

Retirement, 1990–

When I retired from the Mastership, we moved back to our house in Grantchester, where I am now writing this. I continued a little experimental

work in collaboration with Vincenzo Lombardi and his colleague Gabriella Piazzesi from Florence, but I did not have a full-time collaborator. For some years, I had as a research assistant, Simon Tideswell, who was skilled in computers, and we published two papers based on simulations of transient responses. The first paper (1996) gave a fairly good simulation of the tension time course after step changes of length. The second paper (1997) dealt with a phenomenon discovered by Lombardi and known as the rapid recovery of the power stroke and provided a fresh explanation based on the attachment of the second head of myosin molecules of which only one head had previously been attached to the actin filament.

When Lincoln Ford, Bob Simmons, and I were analyzing our records of the tension changes in response to stepwise shortening, we needed four exponential terms to fit the early phase of tension recovery (Phase 2), but the simulations in the 1996 paper by Tideswell and me gave a time course much closer to a single exponential term. Julien Davis, however, fits Phase 2 with only two exponential terms, and he has recently suggested to me that the reason for the difference is that we took Phase 2 as being represented by deviations from a straight line fitted to the beginning of Phase 3, while he takes deviations from the curve obtained by fitting exponential terms to Phases 3 and 4. His procedure is probably better justified than ours, and I am planning to re-analyze some of our records by his method.

I remain very busy, refereeing papers submitted to journals, grant applications, and proposals for promotion or for prizes. I am writing obituaries and a few articles, largely historical such as this one. I try to keep up with the progress on muscle contraction by reading, by visiting to former colleagues, and by attending conferences and symposia in the field, though I am restricting the amount of long-distance travel that I undertake.

Many things are still uncertain about the way in which a myosin molecule pulls on an actin filament to make a muscle contract, and I still spend time thinking about this problem. It remains to be seen whether I shall have any ideas that are worth publishing.

Selected Bibliography

Bárány E. A contribution to the physiology of bone conduction. *Acta Oto-Laryngol* 1938;Suppl. 26:1–223.

Bartlett JH. Transient anode phenomena. *Trans Electrochem Soc* 1945;87:521–545.

Cole KS. Dynamic electrical characteristics of the squid axon membrane. *Arch Sci Physiol* 1949;3:255–258.

Cole KS, Antosiewicz HA, Rabinowitz P. Automatic computation of nerve excitation. *J Soc Ind Appl Math* 1955;3:153.

Cole KS. Membrane excitation of the Hodgkin-Huxley axon. Preliminary corrections. *J Appl Physiol* 1958;12:129–130.

Enderlein G. Beitrag zur Kenntniss des Baues der quergestreiften Muskeln bei den Insekten. *Arch Mikrosk Anat* 1899;55:144–150.

Engelmann TW. Ueber den faserigen Bau der contractilen Substanzen, mit besonderer Berücksichtigung der glatten und doppelt schräggestreiften Muskelfasern. *Pflügers Arch Gesamte Physiol* 1881;25:538–565.

Gold T, Pumphrey RJ. Hearing. I. The cochlea as a frequency analyser. Hearing. II. The physical basis of the action of the cochlea. *Proc R Soc Lond Ser B* 1948;135:462–491 and 492–498.

Granzier HLM, Pollack GH. The descending limb of the force-sarcomere length relation of the frog revisited. *J Physiol* 1990;421:595–615.

Hasselbach W. Elektronenmikroskopische Untersuchungen an Muskelfibrillen bei totaler und partieller Extraktion des L-Myosins. *Z Naturforsch* 1953;8b:449–454.

Hill AV. The heat of shortening and the dynamic constants of muscle. *Proc R Soc Lond Ser B* 1938;126:136–195.

Hill AV. The abrupt transition from rest to activity in muscle. *Proc R Soc Lond Ser B* 1949;136:399–420.

Hill AV. The effect of load on the heat of shortening of muscle. *Proc R Soc Lond Ser B* 1964;159:297–318.

Huxley HE, Hanson J. Changes in the cross-striations of muscle during contraction and stretch and their structural interpretation. *Nature* 1954;173:973–976.

Kiang NY-S. *Discharge patterns of single fibers in the cat's auditory nerve.* MIT research monograph no. 35. Cambridge, MA: MIT Press, 1965; Chap. 7.

Krogh A. The active and passive exchanges of inorganic ions through the surfaces of living cells and through living membranes generally. *Proc R Soc Lond Ser B* 1946;133:140–200.

Needham DM. Myosin and adenosinetriphosphate in relation to muscle contraction. *Biochim Biophys Acta* 1950;4:42–49.

Nyström G. Ueber die Lymphbahnen des Herzens. *Arch Anat Physiol (Anat Abt)* 1897:361–378.

Overton E. Beiträge zur allgemeinen Muskel- und Nervenphysiologie. I Mittheilung. Ueber die Unentbehrlichkeit von Natrium-(oder Lithium-)Ionen für den Contractionsact des Muskels. *Pflügers Arch Gesamte Physiol* 1902;92:346–386.

Porter KR, Palade GE. Studies on the endoplasmic reticulum. III. Its form and distribution in striated muscle cells. *J Biophys Biochem Cytol* 1957;3:269–300.

Ramsey RW, Street SF. The isometric length-tension diagram of isolated skeletal muscle fibers of the frog. *J Cell Comp Physiol* 1940;15:11–34.

Robertson JD. Some features of the ultrastructure of reptilian skeletal muscle. *J Biophys Biochem Cytol* 1956;2:369–380.

Smith FH. 1947 British provisional patent specification no. 21996.

Veratti E. Investigations on the fine structure of striated muscle fiber. *J Biophys Biochem Cytol* 1961;10(Suppl.):1–59.

Selected Publications by A.F. Huxley

Book

Huxley AF. Reflections on muscle (based on the Sherrington Lectures, 1977). Liverpool: Liverpool University Press, 1980. Reprinted by Princeton, NJ: Princeton University Press.

Chapter in Book

Huxley AF. Looking back on muscle. In Hodgkin AL, Huxley AF, Feldberg W, Rushton WAH, Gregory RA, McCance RA eds. *The pursuit of nature. Informal essays on the history of physiology.* Cambridge, UK: Cambridge University Press, 1977;23–64.

Papers in Journals

Armstrong CM, Huxley AF, Julian FJ. Oscillatory responses in frog skeletal muscle fibres. *J Physiol* 1966;186:26–27P.

Brown LM, Gonzalez-Serratos H, Huxley AF. Structural studies of the waves in striated muscle fibres shortened passively below their slack length. *J Muscle Res Cell Motil* 1984;5:273–292.

Elliott GF, Huxley AF, Weis-Fogh T. On the structure of resilin. *J Mol Biol* 1965;13:791–795.

Ford LE, Huxley AF, Simmons RM. Tension responses to sudden length change in stimulated frog muscle fibres near slack length. *J Physiol* 1977;269:441–515.

Ford LE, Huxley AF, Simmons RM. The relation between stiffness and filament overlap in stimulated frog muscle fibres. *J Physiol* 1981;311:219–249.

Ford LE, Huxley AF, Simmons RM. Tension transients during steady shortening of frog muscle fibres. *J Physiol* 1985;361:131–150.

Ford LE, Huxley AF, Simmons RM. Tension transients during the rise of tetanic tension in frog muscle fibres. *J Physiol* 1986;372:595–609.

Gordon AM, Huxley AF, Julian FJ. Tension development in highly stretched vertebrate muscle fibres. *J Physiol* 1966a;184:143–169.

Gordon AM, Huxley AF, Julian FJ. The variation of tension with sarcomere length in vertebrate muscle fibres. *J Physiol* 1966b;184:170–192.

Hodgkin AL, Huxley AF. Action potentials recorded from inside a nerve fibre. *Nature* 1939;144:710.

Hodgkin AL, Huxley AF. Resting and action potentials in single nerve fibres. *J Physiol* 1945;104:176–195.

Hodgkin AL, Huxley AF. Potassium leakage from an active nerve fibre. *J Physiol* 1947;106:341–367.

Hodgkin AL, Huxley AF. Currents carried by sodium and potassium ions through the membrane of the giant axon of Loligo. *J Physiol* 1952a;116:449–472.

Hodgkin AL, Huxley AF. The components of membrane conductance in the giant axon of *Loligo*. *J Physiol* 1952b;116:473–496.

Hodgkin AL, Huxley AF. The dual effect of membrane potential on sodium conductance in the giant axon of *Loligo*. *J Physiol* 1952c;116:497–506.

Hodgkin AL, Huxley AF. A quantitative description of membrane current and its application to conduction and excitation in nerve. *J Physiol* 1952d;117:500–544.

Hodgkin AL, Huxley AF. Movement of radioactive potassium and membrane current in a giant axon. *J Physiol* 1953;121:403–414.

Hodgkin AL, Huxley AF, Katz B. Ionic currents underlying activity in the giant axon of the squid. *Arch Sci Physiol* 1949;3:129–150.

Hodgkin AL, Huxley AF, Katz B. Measurement of current-voltage relations in the membrane of the giant axon of *Loligo*. *J Physiol* 1952;116:424–448.

Huxley AF. Applications of an interference microscope. *J Physiol* 1952;117:52–53P.

Huxley AF. A high-power interference microscope. *J Physiol* 1954;125:11–13P.

Huxley AF. An ultramicrotome. *J Physiol* 1957a;137:73–74P.

Huxley AF. Das Interferenz-Mikroskop und seine Anwendung in der biologischen Forschung. *Verh Ges Dtsch Naturforscher Aertze* 1957b:102–109. Berlin: Springer-Verlag.

Huxley AF. Muscle structure and theories of contraction. *Prog Biophys Chem* 1957c;7:255–318.

Huxley AF. Ion movements during nerve activity. *Ann NY Acad Sci* 1959;81:221–246.

Huxley AF. A micromanipulator. *J Physiol* 1961;157:5–7P.

Huxley AF. A theoretical treatment of the reflexion of light by multilayer structures. *J Exp Biol* 1968;48:227–245.

Huxley AF. Is resonance possible in the cochlea after all? *Nature* 1969;221:935–940.

Huxley AF. The activation of striated muscle and its mechanical response (The Croonian Lecture for 1967). *Proc R Soc Lond Ser B* 1971;178:1–27.

Huxley AF. A note suggesting that the cross-bridge attachment during muscle contraction may take place in two stages. *Proc R Soc Lond Ser B* 1973;183:83–86.

Huxley AF. Muscular contraction (review lecture at meeting of the Physiological Society, Leeds University, 14–15 Dec. 1973). *J Physiol* 1974;243:1–43.

Huxley AF. Address of the President at the Anniversary Meeting, 30 November 1981. *Proc R Soc A* 1981;379:v–xx; *Proc R Soc Lond Ser B* 1981;214:137–152.

Huxley AF. Address of the President at the Anniversary Meeting, 30 November 1982. *Proc R Soc A* 1983;385:v–xvi; *Proc R Soc Lond Ser B* 1983;217:117–128.

Huxley AF. Address of the President at the Anniversary Meeting, 30 November 1983. *Proc R Soc A* 1984;391:215–230; *Proc R Soc Lond Ser B* 1984;220:383–398.

Huxley AF. Address of the President at the Anniversary Meeting, 30 November 1984. *Proc R Soc Lond Ser A* 1985;397:183–196.

Huxley AF. Address of the President at the Anniversary Meeting, 30 November 1985. *Science Public Affairs* 1986;1:1–2.

Huxley AF. Muscular contraction (prefatory chapter). *Annu Rev Physiol* 1988;50:1–16.

Huxley AF. A theoretical treatment of diffraction of light by a striated muscle fibre. *Proc R Soc Lond Ser B* 1990a;241:65–71.

Huxley AF. Bone-conducted sound. *Nature* 1990b;343:28.

Huxley AF, From overshoot to voltage clamp. *Trends Neurosci* 2002;25:553–558.

Huxley AF, Gordon AM. Striation patterns in active and passive shortening of muscle. *Nature* 1962;193:280–281.

Huxley AF, Niedergerke R. Interference microscopy of living muscle fibres. *Nature* 1954;173:971–973.

Huxley AF, Niedergerke R. Measurement of the striations of isolated muscle fibres with the interference microscope. *J Physiol* 1958;144:403–425.

Huxley AF, Peachey LD. The maximum length for contraction in vertebrate striated muscle. *J Physiol* 1956;156:150–165.

Huxley AF, Simmons RM. Proposed mechanism of force generation in striated muscle. *Nature* 1971;233:533–538.

Huxley AF, Stämpfli R. Evidence for saltatory conduction in peripheral myelinated nerve fibres. *J Physiol* 1949;108:315–339.

Huxley AF, Stämpfli R. Effect of potassium and sodium on resting and action potentials of single myelinated nerve fibres. *J Physiol* 1951;112:496–508.

Huxley AF, Taylor RE. Local activation of striated muscle. *J Physiol* 1958;144: 426–441.

Huxley AF, Tideswell S. Filament compliance and tension transients in muscle. *J Muscle Res Cell Motil* 1996;17:507–511.

Huxley AF, Tideswell S. Rapid regeneration of power stroke in contracting muscle by attachment of second myosin head. *J Muscle Res Cell Motil* 1997;18:111–114.

Huxley AF, Lombardi V, Peachey LD. A system for recording longitudinal displacements in a striated muscle fibre during contraction. *Boll Soc Ital Biol Sper* 1981;57:57–59.

Slawnych MP, Seow CY, Huxley AF, Ford LE. A program for developing a comprehensive mathematical description of the crossbridge cycle of muscle. *Biophys J* 1994;67:1669–1677.

Sundell CL, Peachey LD, Goldman YE, Gonzalez-Serratos H, Huxley AF. Visualization of domains in spatially filtered images of skeletal muscle. *Biophys J* 1986;49:262a.