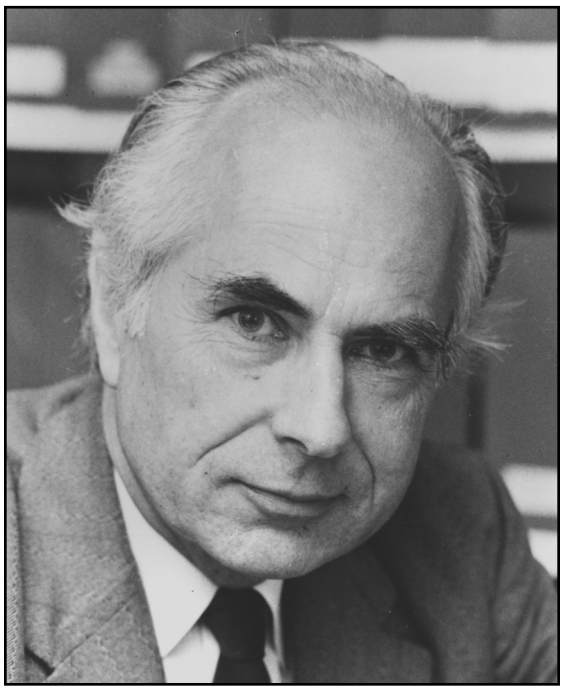
SIR ANDREW FIELDING HUXLEY



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ANDREW FIELDING HUXLEY was an exceptionally distinguished physiologist, renowned for his outstanding research in the physiology of nerve and muscle cells. He came from an illustrious English family, several of whom were prominent in science and literature. Andrew read physical sciences at Trinity College, Cambridge starting in 1935, and later specialized in physiology. His knowledge of physics and mathematics served him well in his subsequent physiological research, which was known for brilliant experimentation as well as for penetrating and exacting biophysical analysis of the results. Huxley spent his entire professional life at Cambridge University and University College London. He was named a fellow of the Royal Society in 1955 and served as its president from 1980 until 1985. He also received the Nobel Prize for Physiology or Medicine in 1963, was knighted by Queen Elizabeth II in 1974, and was appointed to the Order of Merit in 1983.

Andrew Huxley will long be remembered both for the "Hodgkin-Huxley" model for the nerve action potential, which initiated and set a standard for the field of cellular electrophysiology, and for his pioneering research on several aspects of muscle contraction. In each of these areas, he first identified major questions to be addressed and then developed imaginative experimental approaches toward answering them. Through the many collaborators who were fortunate to have worked with him over many decades, his contributions will continue to be felt for years to come.

Family History

Andrew Huxley's grandfather was the zoologist and comparative anatomist Thomas Henry Huxley (1825–1895), a contemporary of Charles Darwin who was known as "Darwin's Bulldog" for his ardent support for Darwin's theory of natural selection as the basis for evolution, and his grandmother was Henrietta Anne Heathorn Huxley (1825–1915). Their fourth child was the author Leonard Huxley (1860–1933), whose first marriage was to Julia Arnold (1862–1908). Leonard and Julia had four children, including biologist Julian Sorrell Huxley and novelist Aldous Leonard Huxley, both of whom became famous in their own fields. Leonard Huxley's second marriage to Rosalind Bruce (1890–1994) produced two sons, the financier and lawyer David Bruce Huxley (1915–1992) and Andrew Fielding Huxley.

Early Life and Education

Huxley was born in Hampstead, London, on 22 November 1917. He

attended University College School and then was a King's Scholar at the Westminster School in central London until 1935. After school, he went up to Trinity College, Cambridge to read for the Natural Science Tripos, choosing physics, chemistry, and mathematics for Part I. After a year of anatomy to qualify in medicine, he read Part II physiology from 1938–39, with Alan Hodgkin as his tutor. In Hodgkin's laboratory, Huxley learned to measure electrical potentials inside the axons of nerve cells from crabs, both when the cells were at rest and when they were conducting action potentials, which are the electrical signals that spread rapidly along nerve fibers for long distances. Following standard practice at the time, they placed a reference electrode in the fluid outside the axon and a measuring electrode adjacent to an intentionally damaged region of the axon to make electrical contact with the inside of the cell. This allowed them to follow changes in the electrical potential difference across the thin surface membrane of the cell. Because of the damage, this method leads to some uncertainty in the measured potentials, but early results suggested that during the action potential the inside of the axon goes from being negatively charged with respect to the exterior of the cell, as it is at rest, to being positively charged. This reversal of sign didn't agree with the then prevalent theory, which predicted that the negative electrical potential inside the axon at rest would be reduced in magnitude during the action potential, but should not "overshoot" zero and become positive. Their new result indicated that better measurements of internal electrical potentials in nerve cells during action potentials would be needed, and that if this observation were confirmed, the existing theory would need modification.

Scientific Research on the Action Potentials of Neurons

At the end of the term in 1939, Hodgkin invited Huxley to join him at the laboratories of the Marine Biology Association in Plymouth during the summer to experiment on some "giant" neurons of squids, which occasionally were caught by local fishermen. Hodgkin had learned about these very large neurons from Kenneth Cole at the Marine Biological Laboratory in Woods Hole, Massachusetts, the previous May. Their axons can be fifty times larger in diameter than those of crab neurons, and that makes them considerably easier to work with. At first, Huxley set out to study some physical properties of the axoplasm, which fills the interior of axons. For this, he dissected single giant axons from a squid, tied one cut end over a hollow glass cannula, and suspended them vertically in seawater. His intention was to measure how quickly small drops of mercury, introduced through the cannula,

would descend through the axoplasm, as a measure of its viscosity. The results he got were unexpected. The mercury drops didn't descend at all, indicating that the axoplasm is a gel, not a viscous liquid. But Andrew quickly realized that, with this setup, he could insert a fine glass tube filled with saline and carrying a fine silver wire through the cannula into the axon past the damaged end, and use it as a truly internal electrode to measure more accurate values for internal potentials in a healthy region of the axon.

He quickly found that inserting this electrode was not easy. If it touched the inside of the delicate membrane surrounding the axon, the axon instantly died. He then found that he could avoid this by observing the electrode inside the axon from the side using a microscope and a small mirror to get both frontal and side views of the electrode as it descended. He and Hodgkin then measured internal potentials in axons at rest of about –50 mV, as expected. Then, when a propagating action potential passed by the tip of the electrode, they observed a swing in internal potential of almost +100 mV, confirming that the internal potential actually did reverse in sign, reaching about +50 mV at the peak of the action potential. They repeated this experiment several times to confirm the result before they returned to Cambridge at the end of the summer. Unfortunately, a few days later, Germany invaded Poland and further experiments were prevented by the beginning of World War II. They published a brief report on their summer's results in *Nature* that fall, and then went to work in the war effort, Alan on radar and Andrew in gunnery.

Hodgkin and Huxley returned to Cambridge in 1945 and published a more extensive report on the 1939 work in the *Journal of Physiology*. Their central observation, that the potential inside the axon reverses sign during the action potential, had been confirmed in the U.S. in 1940 by Cole and H. J. Curtis. Hodgkin did some further experiments at Plymouth in the summer of 1947, without Andrew, who was about to get married. Hodgkin explored the effects on the action potential of alterations in the external sodium ion concentration, and found that the size of the action potential was reduced at lowered sodium concentrations and was completely abolished in sodium-free conditions, suggesting there was an important role for sodium ions in the action potential mechanism.

Cole wrote to Hodgkin in 1947, telling him about a "voltage-clamp" method he had used to record the electrical current through the membrane of a stimulated axon while an electronic feedback circuit held the membrane voltage constant. This made interpretation of the results much simpler than when both voltage and current changed simultaneously, as they do during a normal action potential. In August of

1948, Huxley joined Hodgkin and Bernard Katz from University College London in Plymouth for preliminary experiments using this new method.

After refining their experimental setup during that winter, Hodgkin and Huxley returned to Plymouth in the summer of 1949. They began by identifying three ions—sodium, potassium, and chloride—as the carriers of electrical charge (current) across the membrane by altering the concentrations of each of these ions in the sea water bathing the axons and observing the effects on the membrane currents during action potentials under voltage-clamp conditions. Then they collected large sets of current records after rapidly changing the membrane potential from its resting value to various levels, and clamping it there for a time equal to the duration of an action potential. These experiments indicated that when the membrane potential is brought above the threshold for stimulation of an action potential, the electrical conductance of the membrane rapidly changes in three phases. First there is a rapid increase in conductance for sodium ions. Second is a decrease in sodium conductance, and third is a slower increase in conductance for potassium ions. These three conductance changes seemed to Hodgkin and Huxley to be the keys to understanding how the action potential worked. In one month of intensive work at the end of that summer, they obtained the experimental records they felt they would need to explore that idea.

After considering various ways that ions might pass through the membrane, they concentrated on a simple model with three independent conducting pathways across the surface membrane of the axon, one for each ion. They neither knew nor speculated on the nature of these pathways; they simply were specialized "pores" through the membrane through which specific ions could flow. Hodgkin and Huxley further proposed that the electrical conductances across the membrane for sodium ions and for potassium ions would be independently controlled by the membrane voltage, while a third "leakage" conductance that did not change with membrane voltage was thought to be primarily due to chloride ions. Their model required that the conductance changes in these "pores" would have to be triggered by changes in the electrical potential difference across the surface membrane, and they reasoned that there must be something within the membrane itself that "sensed" those changes. Little was known at that time about the composition of the membrane, but they realized that any free electrical charges within the membrane would sense the changes in the electrical field across the membrane and be drawn toward one or the other surface of the membrane, depending on the strength and direction of that electrical field. To formalize this idea, they postulated a particular number of

mobile charged particles whose distribution across the membrane would adjust to changes in the electric field within the membrane according to the well-known Boltzmann equation in physics. The new distribution of these charged particles would, they proposed, lead to the observed changes in membrane conductance for sodium and potassium ions. If there was a single key moment or step in the evolution of their model for the action potential, this probably was it. Many years later, in looking back at this period, Hodgkin gave much credit to Huxley for this insightful and critical introduction of simple physical principles early on in their analysis.

Their task then became one of finding a physically plausible set of mathematical relationships to represent the movements of their postulated charged particles within the membrane and then to refine those equations until they would account quantitatively for the conductance changes they observed. To match the steepness and shape of the experimentally determined relationships between ion conductances and time, they had to assume that each conductance change depended on multiple charged particles all moving to a certain position in the membrane under the influence of the new electric field to cause the observed conductance changes. Other equations would then be needed to describe the time dependence of the movements of the charged particles in the membrane. This required repeated calculations and adjustments to the equations after comparison of the results with the data. By March of 1951, they had a set of equations that led to conductance curves that closely matched those from the voltage-clamp records.

Huxley performed all the necessary calculations for this huge task using a hand-cranked Brunsviga Model 20 mechanical calculator, spending hours or even days to fit even a few experimental records. After fitting the equations to the voltage-clamp data, his final task became one of using the equations to calculate a propagating action potential, in the absence of the voltage-clamp assumption and to compare the results to an actual recording of an action potential from a live axon. Andrew had hoped to do these calculations using an early digital computer in Cambridge University, but that machine was down for modification. It took him three weeks of intensive effort on the Brunsviga to compute just one action potential, a task that he later characterized as being "particularly laborious." Furthermore, he had to do this many times over, making adjustments to parameters in the equations, before achieving a completely satisfactory match between computed and real action potentials. The final results, also in Andrew's words, "were satisfyingly similar to real action potentials," and Alan later wrote, "[W]e began to feel that we had not wasted the many

months that we spent in analyzing records." While they still had little idea what these charged particles were, or what the pathways the ions took through the membranes were like, they did have a physically plausible theory that could predict the actual phenomenon of an action potential very accurately. That was a major step forward and led subsequent research in the right direction.

Hodgkin and Huxley published very little on their experiments and the associated calculations while they were in progress during the years following 1948. Then, in 1952, they published a set of five papers in the *Journal of Physiology* in which they first summarized their experimental data, then presented their model, and finally showed how the computations based on that model fit the data remarkably well. This work eventually led to the Nobel Prize in Physiology or Medicine in 1963, a prize they shared with Sir John Eccles for his related work on synapses, the junctions between neurons that transfer signals from one neuron to others.

After Hodgkin and Huxley's analysis was published in 1952, it appeared that no more work would be needed on the action potential for some time in the future. In a biographical memoir of Alan Hodgkin written by Andrew Huxley in 2000, he recalled that "[w]hen we had completed the work on the squid fibre that we published in 1952, we could not see what could be done next to take the understanding of the excitation process to a deeper level." Of course this was not the end of research on the action potential, but many of the relevant advances in the decades after 1952 came from areas other than electrophysiology. For example, in 1952 Hodgkin and Huxley had written, "At present the thickness and composition of the excitable membrane are unknown. Our experiments are therefore unlikely to give any certain information about the molecular events underlying changes in permeability." By 1976, Neher and Sackmann had voltage-clamped tiny areas of a membrane using small glass pipettes and recorded currents through single ion channels. They showed that individual channels are either open or closed and, when open, carry "microscopic" currents of a fixed size. The "macroscopic" currents measured by Hodgkin and Huxley and others in real neurons would be the sum total of the currents through a statistically determined number of open channels in a larger area of membrane. This is reminiscent of and not unrelated to the statistical distribution of charged particles in Hodgkin and Huxley's equations. Molecular biologists now have discovered the molecular structure of several kinds of ion channels, including sodium channels, and shown that they consist of assemblies of protein subunits surrounding a water-filled pore extending across the thickness of the membrane. These are Hodgkin and Huxley's proposed pores.

Additionally, these protein subunits contain charged amino acids in regions of the molecules that, when mutated by substitution of uncharged amino acids, result in channels with reduced or missing voltage sensitivity. These must be the charged particles that Hodgkin and Huxley proposed as the voltage sensors in their model. Direct evidence for movement of charged particles in the membrane has come from observation of small "gating" currents, which immediately precede the changes in ionic currents.

After 1952, Hodgkin turned his attention to studies of action potentials in skeletal muscle cells and then to vision, and Huxley shifted his focus from neuron biology to mechanisms of contraction in muscle cells.

Scientific Research on Muscle after 1952

The shift of Huxley's interest to skeletal muscle cells allowed him to indulge a long-time fascination with optics and microscopes. Aware of confusion in the scientific literature for many decades about the nature of the "light" and "dark" bands that form the striations of skeletal muscle cells, and about changes in the appearance of these bands during contraction, Huxley explored possible optical artifacts in imaging of such structures in thick specimens. He then designed and built an interference microscope that avoided these problems in an optically understandable way. He and Rolf Niedergerke used that microscope to show definitively that the dark A-bands in a muscle fiber stay constant in length during shortening of the fiber, while it is the lighter I-bands that shorten. This observation was a keystone in the formulation of the sliding filament mechanism for contraction put forth by Andrew Huxley and others in the 1950s and now widely accepted.

Next Huxley turned his attention to the question of how the depolarization of the surface membrane of a muscle cell during its surface action potential, which is similar to a nerve action potential, leads to activation and shortening of the contractile fibrils deep inside the cell. True to form, Huxley devised a novel and direct experimental approach to explore this excitation–contraction problem. In collaboration with Robert Taylor, he selectively depolarized small areas of the surface membrane of an isolated frog muscle cell using a tiny glass electrode pressed against the surface membrane of the cell. The contractions that this produced were highly localized to small regions of the cell just under the depolarized patches of membrane. Interestingly, these local contractions were seen only when the depolarized spot was adjacent to the center of an I-band in the striation pattern of the fiber, a region called the Z-line. At about the same time, Keith Porter and

George Palade, at the Rockefeller Institute for Medical Research in New York, described a membranous network inside striated muscle cells, which they named the *sarcoplasmic reticulum* (SR). Their electron micrographs showed that the SR in amphibian muscle fibers has a particular "triad" configuration at the Z-lines, exactly where Andrew's local activation experiments led to contractions. Because the SR is a three-dimensional network of membranes that extends throughout the muscle fiber, this suggested that these triads might somehow be involved in the coupling of surface membrane depolarization to mechanical contraction deep within the cell.

When Huxley came to Rockefeller in 1957 to lecture about his work on muscle cells, I was a graduate student working in Keith Porter's laboratory doing comparative electron microscopic studies of the SR in several kinds of muscles, including frog muscle cells. After Huxley described his "local-activation" experiments, I became very interested in his approach and in a possibility of further correlations between experimental and structural studies with regard to the possible role of the SR in muscle cell activation. This led to a plan that I would spend some time working in Huxley's laboratory in England, to learn more about experimental physiology and to more directly correlate my "structural" studies with his "functional" ones. Fortunately, trips for graduate students to work abroad were encouraged at Rockefeller, and this plan became reality the next year.

When I arrived in Cambridge to work with Andrew in 1958, we set out to repeat his local activation experiments on a different type of frog skeletal muscle fiber, one that contracts more slowly than the more common twitch type of fiber that he and Taylor had studied. First, and not surprisingly, the local activation in these slow fibers resulted in slower contractions. What was more interesting was that the "sensitive spots" where contraction could be activated in the slow fibers were not specifically localized opposite the Z lines, but were found at various positions in the striation pattern. My electron microscopy showed that overall there was much less SR in this fiber type, and also that the few triads that were present were more randomly located, not specifically at the Z-lines as in the faster fibers. While this observation fell far short of proving that the SR or its triads were involved in the coupling process, neither did it discourage that thought.

Because there are very few slow muscle fibers in frog muscles, Huxley and I sometimes found that after hours of dissecting a whole muscle with hundreds of fibers down to a single muscle fiber, we often got one of the fast, twitch type. Huxley suggested that we should have a second set of experiments to do on these twitch fibers when we got them. We decided to explore the maximum length to which a muscle

cell could be stretched and still produce tension when it was stimulated, as a test of the sliding filament theory of contraction. Evolving thought on contraction had focused on two kinds of short protein filaments alternating in bundles along the length of the fiber. Indeed, this alternation of "thick" and "thin" filament bundles is the source of the repeating striation pattern of A-bands and I-bands. Tension was thought to arise where these two types of filaments overlapped and thus could interact. If we were to stretch a muscle fiber enough that the bundles of filaments were pulled apart, then there would be no overlap, and active tension should drop to zero. At first, we found that a small amount of tension persisted, even at extreme lengths. But we also found that the muscle fiber didn't stretch uniformly along its length. The two ends of the fiber always stretched less than its central portion. These ends still had overlapping filaments and produced tension, even when the center was stretched well beyond where tension should have dropped to zero. Characteristically, Huxley quickly saw a solution. We needed to hold the fiber under constant tension, not constant length, and to look for cessation of shortening in the central region of the fiber's length, independent of what was happening at its ends.

One Sunday, after dinner at his house in Grantchester, near Cambridge, we sat down to talk about how to do these experiments. We would need to observe the results at the middle of a stimulated muscle fiber using a microscope at high enough magnification to show us even very small amounts of shortening of the striations. We had already tried this with one end of the fiber fixed and the other attached to a spring to hold the tension on the fiber constant, but the movement of the middle of the fiber toward the fixed end always led to blurred images at its center. Andrew then sketched a clever device with a pivoted lever at each end of the fiber, linked with crossed strings so that when the fiber shortened, the levers would move toward each other by equal amounts. This should allow the ends to shorten with minimum movement at the center of the fiber. The following week Andrew showed this design to one of the laboratory staff in physiology, who happened to have as a hobby collecting and repairing old watches. With considerable delight, he built the required device for us, using jeweled bearings and springs from an old pocket watch. It worked a treat. We could always find a place near the middle of the fiber where the striations stayed still enough during stimulation that we could film the contraction and measure the amount of shortening on the developed films. We found that the shortening at the center went to zero when the repeat length of the striation pattern there was 3.65 micrometers or greater. Later, after I had returned to Rockefeller, I measured the lengths of the filaments in the same kind of muscle fibers using electron microscopy,

and found that the length of the striations where overlap between the two types of filaments became zero also was close to 3.65 micrometers. This indicated that overlap was necessary for tension production, in agreement with the emerging sliding filament hypothesis.

Huxley continued working for many years on the contraction mechanism in skeletal muscle cells with a variety of collaborators, including Clay Armstrong, Fred Julian, Bob Simmons, Vincenzo Lombardi, Hugo Gonzales-Serratos, Yale Goldman, Al Gordon, and myself. Attention became focused on the mechanism that caused the sliding between filaments and therefore was the basis of muscle shortening. Andrew had formalized his ideas in a model in 1957, which he further elaborated in 1971 in collaboration with Simmons. Just as he had proposed unspecified "charged particles" moving in the neuron membrane and controlling ionic currents through the membrane, he developed a muscle model with cyclic action of unspecified "cross bridges" exerting forces between thick and thin filaments to generate tension and shortening in muscle fibers, and he showed that this model fit with available information on muscle energetics. In 2000 he wrote of this model in a review: "It was purely kinetic in character, i.e. it did not make specific postulates about the structural and biochemical events underlying the interactions between myosin and actin sites." Much as with the action potential mechanism, subsequent physiological experiments and results from molecular biology have provided detailed information on the proteins that form the "cross-bridge" links between thick and thin filaments and how they change shape to generate forces.

Personal Memories of Working with Andrew Huxley

Working with Andrew Huxley in the laboratory was exciting and instructive. As already made clear, he was the consummate experimentalist. Almost every day, he came into the laboratory with a new thought. Sometimes it just popped out, but sometimes I suspected that it had resulted from much careful consideration. It was not Andrew's style to think about an experimental approach he already knew, and then ask what he might do next using that same approach. Instead he first asked what problem needed to be solved next, and then thought about possible solutions, always based on sound physical principles. Then he figured out how to test those ideas with precise measurements and observations in the laboratory, using whatever experimental means were necessary. Thus, many of his studies led to new and novel devices or methods. The local activation experiments were a good example of that. What more direct way to study the link between surface membrane depolarization and contraction inside a muscle cell than to

depolarize small patches of its surface membrane and watch through a microscope just inside that patch for signs of contraction?

Over the years, beginning in 1958, Andrew Huxley and I developed a close friendship that has been a highlight of my scientific career as well as my personal life. In addition to working together in Cambridge and later at University College in London, he came to Columbia University to deliver the Jessup Lectures for 1964 and to help me with local activation experiments on crab muscle fibers. He also paid several visits to my laboratory at the University of Pennsylvania, after I moved there in 1965. He and his wife, Richenda, stayed with Helen and me at our house during some of his frequent trips to the United States for lectures and other events. They attended a retirement party organized by some colleagues and friends of mine in Philadelphia, where Andrew paid me a nice compliment by saying, "Lee could solve most any problem in the laboratory." I do remember two occasions when I did contribute to our experiments in a way that made me feel worthy of working with him. The first time we worked together, I mounted a phonograph cartridge on the foot-operated lathe that Andrew's parents had given him when he was a boy, and used it to hold the fine glass electrodes while we ground their tips to an appropriate size for use in local activation experiments. That thus amplified the very faint sounds made in the grinding process, by which we judged its progress, and greatly improved our success rate. A second time I felt technically "worthy" came the last time we worked together, at University College London in 1980. Andrew came in with an idea, more theoretical than practical, for converting longitudinal movements of the striations in an image of a muscle fiber into an electronic signal. While home in Philadelphia that Christmas, I cobbled together a small electronic circuit and, when back in London, added some optical bits to a microscope to test his idea. Somewhat to my surprise, and his, it actually worked.

I last visited Andrew for a few days at his home in Grantchester in March 2006. While there, I inquired about the Brunsvega calculator that he had used to do the action potential calculations in the 1950s. He remembered that it was in his office, and after dinner one evening at Trinity College, when we found it. He sat down and became totally engrossed in remembering how to enter numbers, when to turn the crank, and when to flip the lever that moved the carriage to the left or right. He remarked that a major advance in this particular calculator over earlier ones had been that you could transfer the contents of the "current register" into a "storage register." Then, after using the "current

register" for another task, you could bring the number in the "storage register" back to the "current register" without having to write it down and reenter it manually. Amazing—in modern computer terms, this would be a single memory location! It is no wonder that it took him so long to do the action potential calculations.

Academic Positions

Andrew Huxley was appointed research fellow at Trinity College, Cambridge in 1941, a position he didn't take up until after the war in 1946, when he also became a demonstrator in the university physiological laboratory (a post held until 1950). He was assistant director of research from 1951–59, and reader in experimental biophysics from 1959–60, as well director of studies at Trinity College beginning in 1952. In 1960, Huxley left Cambridge to become the Jodrell Professor and head of the Department of Physiology at University College, London, and then Royal Society Research Professor in 1969, a position he held until 1983. He then returned to Cambridge, as master of Trinity College, from 1984 until 1990 and as honorary fellow from 1990 until his death.

Personal Life

Andrew married Jocelyn Richenda Gammel Pease (1925–2003) in 1947. "Chenda" was the daughter of the geneticist Michael Pease and Helen Bowen Wedgwood, the eldest daughter of Josiah Clement Wedgwood, MP for Newcastle-under-Lyme for thirty-six years and the first Baron Wedgwood of Barlaston. She became a justice of the peace and was active in a variety of public work activities in and around Cambridge and Grantchester, where they lived. They had one son, Stuart Leonard Huxley (1949), and five daughters, Janet Rachel Huxley (1948), Camilla Rosalind Huxley (1952), Eleanor Bruce Huxley [Vajrasalchi] (1959), Henrietta Catherine Huxley (1960), and Clare Marjory Pease Huxley (1962), six children of whom Andrew was justifiably very proud.

Elected 1975

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Selected Bibliography of Sir Andrew Huxley

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Clockwise from upper left: The author with Richenda and Andrew Huxley at the author's home in Merion Station, Pennsylvania, 13 August 2002; Helen and Lee Peachey with Andrew Huxley at a "bash" for Andrew in Bar Harbor, Maine, in August 1992; Andrew, at Trinity College, Cambridge on 9 March 2006, reacquainting himself with the Brunsviga Model 20 mechanical calculator that he had used in the 1950s for the action potential calculations; Andrew and Richenda at a lobster banquet for the 1992 "bash."