# Memories of Hugh E. Huxley (1924–2013)

**James Spudich**
Department of Biochemistry, Stanford University School of Medicine, Stanford, CA 94305

The field of structural biology lost a giant on July 25, 2013, when Hugh E. Huxley passed away at age 89. At the time of his death, he was professor emeritus of biology at Brandeis University. But for much of his career, he was at the Medical Research Council (MRC) Laboratory of Molecular Biology (LMB) in Cambridge, United Kingdom. Huxley joined the American Society for Cell Biology in 1982. In 1983, along with Joseph Gall, he won the prestigious E. B. Wilson Medal, the highest honor awarded by the society.

My first meeting with Hugh Huxley was in January 1969. When I arrived at the LMB to begin a postdoctoral fellowship with Hugh, I met Linda Amos in the front entrance hall. After introducing myself, I asked Linda where I might find Hugh Huxley. She replied that I was most likely to find him in the basement at the rotating anode for collecting low-angle, x-ray diffraction data on muscle fibers. I was to look for "an elegant man with white hair." Her description was perfect, and Hugh was easy to find. He welcomed me to Cambridge, and after a brief discussion, we agreed to meet the next day. Thus began a memorable two years of work in Hugh's laboratory. My training in structural biology at the LMB was pivotal for what my laboratory was able to accomplish over the next four decades.

Huxley's career represents intense training in physics. In 1941, he entered Christ's College, Cambridge, to study physics. After his first two years, his studies were interrupted by service in the Royal Air Force as a radar officer from 1943 to 1947. During that time, he worked on the development of improved airborne radar devices, and he found his passion in developing mechanical and electrical devices. He was to continue in that path for his entire career.

Huxley then returned to Cambridge to finish his physics studies, and, in 1948, he joined an extraordinary adventure in Cambridge by becoming the first PhD student of a newly formed small MRC unit founded by Max Perutz and John Kendrew, housed in a temporary hut outside the Cavendish in Cambridge and named the "Laboratory of Molecular Biology." As Kendrew's PhD student, Huxley began his lifelong interest in exploring the structural basis of muscle contraction. For his PhD thesis, he used low-angle, x-ray scattering of live muscle fibers to reveal a fascinating pattern of reflections in resting (precontraction) versus "rigor" (postcontraction) muscle. His PhD thesis, completed in 1952, was entitled "Investigations in Biological Structures by X-Ray Methods. The Structure of Muscle" (Huxley, 1952).

To put Huxley's work in perspective: Albert Szent-Györgyi and his colleagues had shown in the 1940s that both actin and myosin were needed to give artificial fibers that would contract in ATP, and the general conclusion at that time was that the contractile apparatus in the muscle involved composite filaments of colloidal actomyosin that underwent some form of ATP-dependent phase transition. An

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Address correspondence to: James Spudich (jspudich@stanford.edu).

early pivotal contribution from Huxley, which derived from the changes in equatorial reflections from his low-angle, x-ray patterns between muscles at rest and in rigor, was his conclusion that actin and myosin were present as separate sets of filaments in a double hexagonal array (Huxley, 1952, 1953a).

Those were the years when electron microscopy entered the world of biology as a tool to reveal details of organelles and molecular assemblies in ways that were impossible to see using light microscopy. Huxley was determined to understand the molecular basis of the diffraction patterns he was observing in muscle preparations, and, not having an electron microscope readily available in Cambridge, he went to MIT in the late summer of 1952 as a postdoctoral fellow on a Commonwealth Fellowship to work in F. O. Schmitt's laboratory. There, he quickly obtained electron micrographs of cross-sections of plastic-embedded muscle (a very new technique then) and clearly saw the double hexagonal arrays of thick and thin filaments in end-on view (Huxley 1953b), presumably myosin and actin, respectively, just as he had deduced from the equatorial x-ray diffraction patterns of living and rigor muscles.

Then, in early 1953, Jean Hanson arrived at MIT, and she and Huxley began a very fruitful collaboration. This soon led to their finding, by phase-contrast light microscopy, supported by electron microscopy, that the myosin filaments were confined to the so-called A-band, whereas arrays of actin filaments, attached to Z-lines, ran through the I-bands and continued on into the A-bands, interdigitating there with the myosin filaments. Because of the existing evidence for the double hexagonal array (which they could now recognize as coming from the region of overlap of the thick and thin filaments), they put forward with some confidence the partially overlapping arrays of filaments model in a letter to *Nature* in 1953 (Hanson and Huxley, 1953). They learned by a chance encounter in Woods Hole, Massachusetts, that Andrew Huxley (unrelated) and Ralph Niedergerke were also exploring the mechanism of muscle contraction at the time, and the two groups published seminal back-to-back papers in *Nature* in 1954 in which they proposed the sliding filament theory of muscle contraction (Huxley and Hanson 1954; Huxley and Niedergerke, 1954). A good read is the extensive review that Hanson and Huxley published of the work done to this point (Hanson and Huxley, 1955). This theory was considered heretical by many and was not fully embraced by muscle biologists for some time to come. All theories of muscle contraction before this time involved some form of phase transition of an actomyosin matrix.

Hugh Huxley returned to Cambridge in the late spring of 1954, going back to the MRC unit and a research fellowship that his old college, Christ's, had awarded him. The MRC unit was flourishing, but various factors, including the lack of easy access to an electron microscope, led Huxley, in 1955, to join Professor Bernard Katz's biophysics department at University College London, which was equipped with a new electron microscope bought for Huxley with money from the Wellcome Trust. Controversy continued as to whether there were two sets of overlapping filaments or continuous filaments presumably consisting of a composite of actin and myosin. The basic problem was that the "thin" sections of muscle that electron microscopists were using at that time were 600 Å or more in thickness, and longitudinal sections showed only a confused image of superimposed filament layers. Huxley's next contribution was to build an improved version of an existing thin-sectioning microtome, and he achieved sections of only 100–150 Å in thickness. These sections clearly showed single layers of thick and thin filaments lying side by side, with the thick (myosin-containing) filaments terminating at the ends of the A-bands, and the thin (actin-containing) filaments continuing on into the I-bands and attaching to the Z-lines (Huxley, 1957). Cross-bridges could be seen very clearly between the myosin and actin filaments; these occurred at an average axial spacing of ~400 Å between a given thick and thin filament, and there appeared to be three sets of cross-bridges arranged helically on the myosin filaments within the ~400-Å interval. The cross-bridges appeared to be attached over a range of angles of tilt.

These micrographs convinced a great many people of the correctness of the overlapping filament model, but a lot of skepticism remained as to whether the actual sliding model driven by cross-bridge movement was valid and whether filament lengths did stay constant during contraction.

Huxley's further electron microscopy studies involved isolated thin and thick filaments from disrupted muscle fibers. By "negative staining" technologies on isolated thin actin filaments and introducing in particular 2% uranyl acetate solution as an excellent negative stain, he revealed remarkable features of the thin and thick filaments isolated from disrupted muscle fibers. In the case of the actin filaments, addition of heavy meromyosin (the soluble actin-binding part of myosin), produced a "decorated" actin (or "arrowhead") structure that revealed the structural polarity of actin filaments and how those filaments are organized in muscle (Huxley, 1963). Myosin thick filaments formed in vitro (by diluting myosin solutions at higher salt concentrations into lower salt) showed a reversal of polarity at the center of each filament (Huxley, 1963), which was a requirement of the sliding filament, moving cross-bridge mechanism that he and Jean Hanson had proposed.

Huxley's scientific accomplishments led to his election as a fellow of the Royal Society in 1960, the youngest fellow at that time (he was 36). In 1962, the Cambridge MRC LMB Unit had moved into a fine, large, new building on the outskirts of Cambridge. Huxley was invited back there, with a research fellowship at King's College for five years and then a more permanent one at Churchill College. Huxley later became joint head of the Structural Studies Division of the LMB in 1975 and deputy director in 1978.

From 1962 to 1987 at the MRC LMB, Huxley carried out higher-resolution studies using low-angle, x-ray scattering that further contributed to our understanding of the structural basis of muscle contraction. This involved constant improvements in rotating anodes for generation of x-rays, and improvement of camera design that made it possible to record axial diffraction patterns from contracting muscles (Huxley and Brown, 1967). Eventually, the use of synchrotron radiation allowed such a powerful x-ray source that it became possible to follow the reflection changes that occur during muscle contraction with millisecond time resolution. Huxley and others capitalized on this development to obtain extraordinary resolution of the likely structural changes involved in muscle contraction.

In 1969, on the basis of his work over more than 15 years, Huxley formally proposed the swinging cross-bridge hypothesis of muscle contraction (Huxley, 1969). Four decades of subsequent biochemical, biophysical, and structural work by others with purified proteins verified Huxley's swinging cross-bridge hypothesis as the molecular basis of muscle contraction.

In recognition of his immense contributions, Huxley was awarded numerous honors, including the Louisa Gross Horwitz Prize, the Gairdner Award, the Antonio Feltrinelli Prize, and the Copley Medal from the Royal Society, the highest scientific award in the United Kingdom.

When Huxley was nearing retirement age in the United Kingdom, he was invited to join the Rosenstiel Basic Medical Sciences Research Center at Brandeis University, which importantly extended his scientific life by nearly another 25 years. He served as the director of the Rosenstiel from 1988 to 1994. He worked on muscle

research until the end. Hugh Huxley's contributions were always marked by major insights, incredible precision, and a scientific and personal integrity to be emulated. His passing is an end of an era in muscle biology.

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