50-Year Anniversary of Sliding Filament

In this issue of the *Journal* we mark a milestone in physiology, the 50th anniversary of the publication in *Nature* on May 22, 1954 of two papers (Huxley, A.F., and R. Niedergerke. 1954. Structural changes in muscle during contraction; interference microscopy of living muscle fibers. *Nature*. 173:971–973; Huxley, H., and J. Hanson. 1954. Changes in the cross-striations of muscle during contraction and stretch and their structural interpretation. *Nature*. 173:973–976) which formulated the sliding filament hypothesis of muscle contraction. Two historical reviews remind us of the significance this early work. One, by Andrew Szent-Györgyi of Brandeis University, describes the struggles that established the biochemistry of actin and myosin and how this knowledge was meshed into the sliding filament hypothesis. The other, by Roger Cooke of the University of California, San Francisco, describes how this knowledge has become the basis for atomic models of muscle contraction. Three of the four authors of those 1954 papers are still active, and Sir Andrew Huxley, while retired, still attends all the important muscle meetings. Unfortunately, Jean Hanson died prematurely in 1973.

As often is the case for articles that later become landmarks, the sliding filament hypothesis did not find immediate acceptance. The then current view was that myosin was a long negatively charged polypeptide without much structure, which shortened on addition Ca\(^{2+}\) ions. That there was no evidence to support this model did not detract from its wide acceptance. It was argued that the cross striations of skeletal muscle could not be of great significance because smooth muscle contracted without having them. Moreover, it was not widely accepted that myosin was an ATPase. Myosin was a structural protein and had no business being an enzyme. This point of view was held by no less than O. Meyerhof and A.V. Hill. However, H.E. Huxley’s superb electron microscopy showed beyond reasonable doubt that, when cross-striated muscle contracts, the two sets of interdigitating filaments (made of myosin and actin) slide past each other without either significantly altering its length. Moreover, about the same time soluble fragments of myosin were prepared that contained ATPase activity. These myosin fragments were shown to contain the myosin cross-bridge, an entity that cyclically binds and releases the actin filament while hydrolysing ATP. In fact, this fragment undergoes a conformational change during its combination with actin, which “rows” the actin filament past the myosin filament—the swinging cross-bridge.

Most of the basic facts were known by the time of the Cold Spring Harbor Symposium on Muscle in 1972 and forms the substance of A. Szent-Györgyi’s review (in this issue, pp. 631–641). Once the implications of the model were appreciated, the prevailing view became: just a few remaining details and muscle would be finished—and 50 yr later we’re still busy. Many techniques, including X-ray crystallography and single molecule mechanics, have contributed enormously to the present understanding of muscle contractions. The swinging cross-bridge has become a swinging lever arm, and muscle contraction and many aspects of cell motility have become unified, in the sense that they all rely on ATP-induced conformation changes in the myosin cross-bridge. R. Cooke’s narrative (in this issue, pp. 643–656) covers these developments. Many of us feel that a complete description of muscle contraction in physico-chemical terms is just round the corner. It will be interesting to see how muscle research is doing in 50 yr time!

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