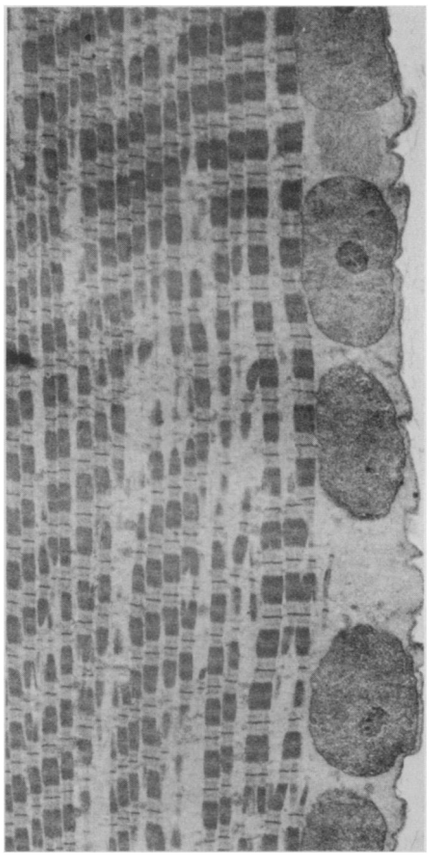
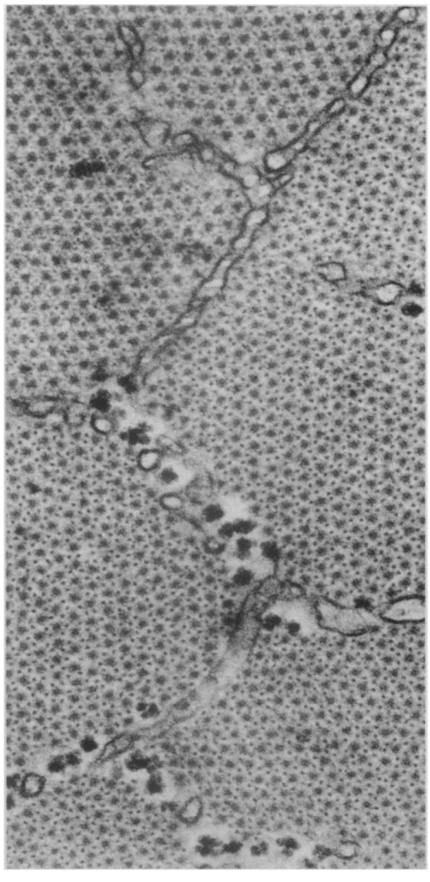


Above: Longitudinal view of muscle.

H. E. Huxley

Below: Horizontal view of muscle.



Science shows its muscle

Muscle contraction is generally understood; now it must be grasped at the molecular level

by Joan Arehart-Treichel

Movement, at least with purpose, is a hallmark of living things. Life oozed from the primordial deep by cytoplasmic streaming. Man and other animals have crawled, floundered, stalked and galloped their way through the centuries. Heart muscles, visceral muscles, voluntary muscles have made this progress possible.

During the past few decades, scientists have obtained intimate knowledge of the composition of muscle, at least of the voluntary (striated) kind. The generally accepted theory of voluntary muscle contraction, which is supported by ample experimental evidence, is that the muscle filaments do not shorten. Rather they slide past each other. This sliding is possible thanks to ATP, the universal energy-releasing molecule of all cells and tissues. But how the sliding filaments work, and how ATP energy molecules interact with the filaments to cause contraction is not known for sure, and it could easily be 20 years before they are, according to Hugh E. Huxley of Cambridge University in England, a pioneer investigator in how muscles contract at the microscopic level.

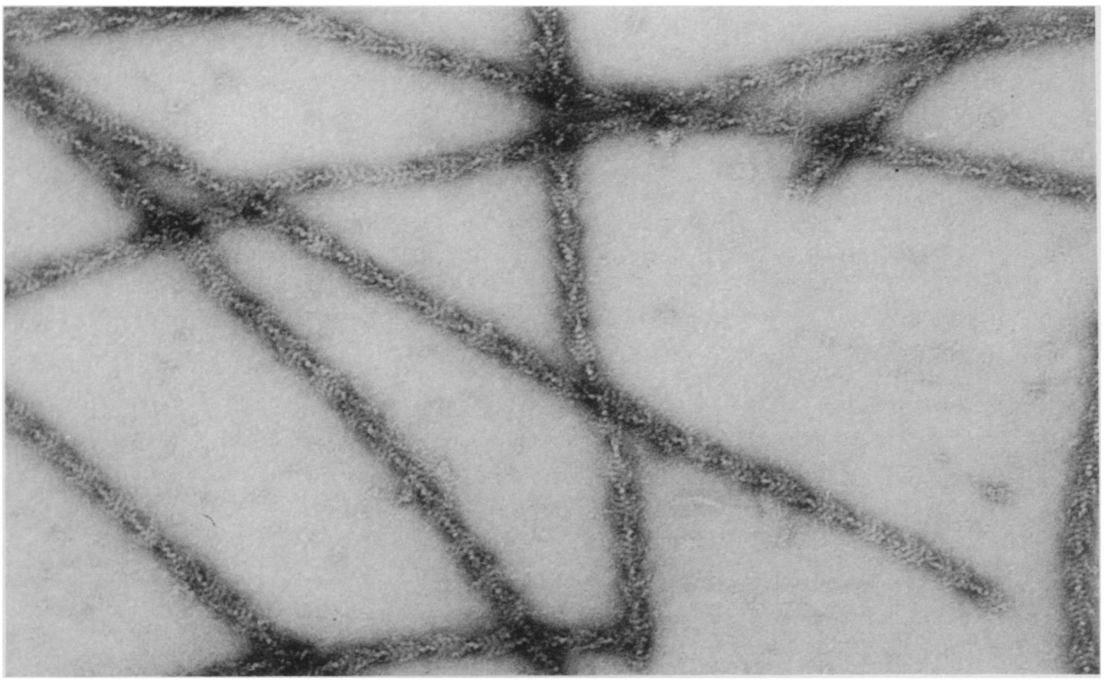
"In 1952," Huxley says, "we learned how to fix muscle preparations for visualization under the electron microscope. As a result we made considerable progress in subsequent years in identifying the components of muscle and in delineating the general structural changes during contraction. During the past couple of years, though, we've come up against the boundary of available techniques. Unraveling muscle contraction at the molecular level is a slower process."

Nonetheless investigators, like Huxley and his colleagues at Cambridge, are making progress. In an interview at Cambridge with SCIENCE NEWS, Huxley told of the latest findings to come out of his laboratory. Most, but not all, muscle investigators agree with the results.

The filaments of voluntary muscle are made of thin protein molecules called actin and thick protein molecules called myosin. In the muscle, the thick and thin filaments alternate: A myosin filament lies next to an actin filament, the actin filament is flanked by another myosin filament, and so on. One of Huxley's major efforts is to pinpoint the role of myosin molecules in contraction. He and his co-workers are calling on the electron microscope, X-ray diffraction, a computer technique of image analysis designed in their laboratory, and other molecular biology techniques.

They have found that during contraction, myosin molecules, making up myosin filaments, bridge over to actin filaments sandwiched between the myosin filaments. The tails of the myosin molecules provide the backbones of the myosin filaments. It is the heads of the molecules that do the bridging. These heads are believed to attach in a perpendicular configuration onto the actin filaments and then to tilt in a unilateral (about a 45-degree) direction, drawing the actin filaments along. Under the electron microscope, heads from two myosin filaments, bridging the actin filament sandwiched between them, look like a string of arrowheads. This is because the heads on each side of the actin filament attach to the actin at similar angles.

Yet, in bridging to an actin filament, myosin heads rotate in such a manner that—could the electron microscope give three-dimensional pictures—the heads would look not so much like ar-

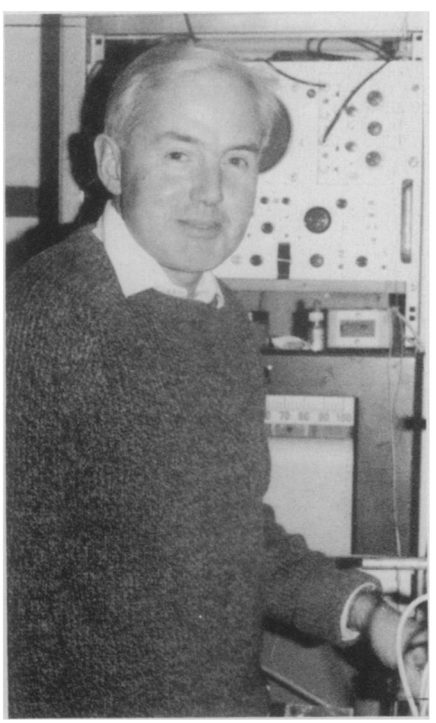


Myosin filaments bridging actin filaments look like strings of arrowheads.

H. E. Huxley

rowheads but like crooked fingers poking into the actin filaments. A technique devised by Aaron Klug in Huxley's laboratory—computer calculations of the electron density of actin and myosin molecules—allowed them to determine these three-dimensional contours. "So we are pretty confident, in a rough way," Huxley says, "that our print-outs are representative of how the cross bridges attach."

Huxley and his colleagues take this evidence as support for the theory that myosin heads (filaments) attach and reattach to the actin filaments sandwiched between them, always tilting in the same unidirectional manner. Consequently the actin filaments are moved. Myosin filaments on one end of a muscle segment (technically called a sarcomere) move actin filaments to the center of the segment. Myosin filaments on the other end of the segment move actin filaments to the center of the segment. This coming together (interdigitation) of actin filaments from opposite ends of the segment is what makes the total segment of muscle contract.



Joan Arehart-Treichel

Huxley: Now going after the atoms.

"Particularly intriguing," Huxley points out, "is the discovery that myosin molecules bridging over to actin molecules may be involved not only in mammalian muscle fiber movement, but in movement in lower organisms and in embryo cells undergoing differentiation (assuming specialized capacities). Because actin and myosin have been isolated from all kinds of cells, including one-celled organisms and embryo cells, Huxley and his colleagues put actin molecules from the slime mold with myosin molecules taken from the rabbit. Although the molecules were from different species, they still combined in the same arrowhead pattern identified in mammalian muscle.

The Cambridge investigations into the details of myosin bridging began three years ago, and they are still going on. Meanwhile Huxley and his co-workers are probing the role of a muscle protein that they believe keeps muscle fibers from contracting during the resting state of muscle. This protein is tropomyosin.

Huxley and his colleagues hypothesized that when myosin heads bridge to actin, they actually project into the groove of the actin filament. By occupying a particular position in the groove during the resting stage, tropomyosin keeps myosin heads from attaching to actin molecules. Klug's computer technique showed them that myosin heads bridge into the groove of the actin filament. X-ray diffraction studies showed that tropomyosin occupies one position in the groove of the actin filament during rest and moves to a different position during contraction. These discoveries, they feel, are strong support for their hypothesis—that tropomyosin keeps myosin away from actin when the muscle is at rest.

"The real challenge," Huxley declares, "is to get a handle on the atomic structures of actin and myosin molecules. That way, the molecules' interactions with contraction regulator proteins like tropomyosin, with each other and with ATP can be determined. For example, we would like to know where all the atoms in the myosin heads are and how the configurations of atoms change when the heads tilt and ATP splits."

The way to gain this structional picture at the atomic level is through X-ray analysis of crystals of purified actin and myosin molecules. Huxley and his colleagues have been trying to crystallize some preparations of purified muscle proteins for some time now. Such a feat is possible, Huxley is convinced, because other protein molecules—hemoglobin, myoglobin (muscle hemoglobin) and enzymes—have been crystallized in recent years.

He admits, however, that it is hard to say when he'll get the crystals. "It could be tomorrow," he says, "or it might take another 10 years." Some American investigators believe they might beat him to it. □