age plants of California that have replaced the native bunch grasses. Captain Cook on his second expedition in 1773 introduced pigs to New Zealand (where they are still called "Captain Cookers") (9). Recently a predacious terrestrial planarian from New Zealand has appeared in Scotland; this planarian may cause problems because its preferred diet is earthworms (*10*). Is this New Zealand's revenge? New Zealand itself has had its share of introduced species. Somebody planted those Port Orford cedars at the Christchurch airport. Those Monterey cypresses that adorn the town square of Punta Arenas around the statue of Magellan must have also had some help. Earnest bird lovers, wanting to feel at home in the New World, brought us English sparrows and starlings, and we have returned the compliment with the gray squirrel and raccoon. Some of these introductions are pleasant reminders of faraway places, but many are detrimental to their new ecosystems. It is to be hoped that all our bays and estuaries will not become so much alike in their flora and fauna that there is no interest in traveling to see strange and interesting things (like little blue soldier crabs in Australia). But we must also hope that the bureaucrats do not spin a web of regulations more entangling than the ornithologist's mist nets and thereby defeat their own good intentions.

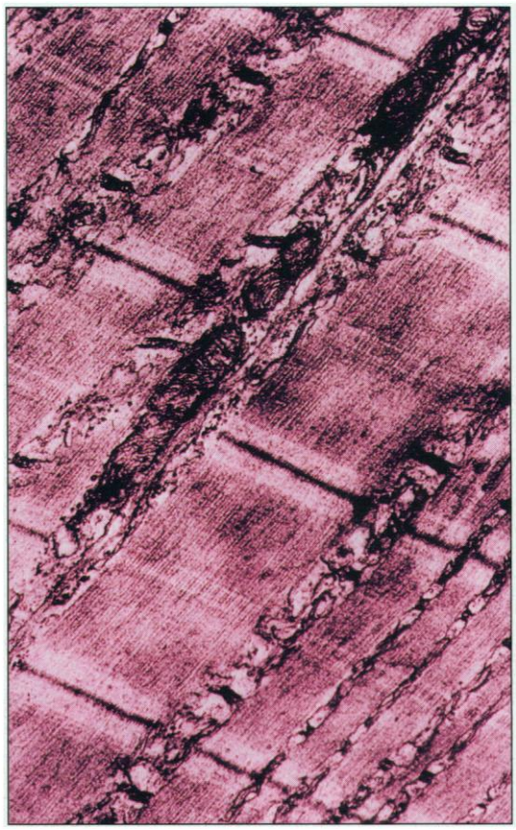
References and Notes

1. J. T. Carlton and J. B. Geller, *Science* **261**, 78 (1993).
2. J. T. Carlton, thesis, University of California, Davis (1979).
3. J. T. Carlton *et al.*, *Mar. Ecol. Prog. Ser.* **66**, 81 (1990).
4. W. C. M. Klein Breteler, in *Ecology of the Wadden Sea*, W. J. Wolff, Ed. (Balkema, Rotterdam, 1981), vol. 1, pp. 119–121.
5. J. Kear, *Man and Wildfowl* (Poyser, London, 1990).
6. W. Stolzenburg, *Nature Conservancy* **42**, 16 (1992).
7. The problems that have been caused by the *Dreissena* invasion stirred the National Oceanic and Atmospheric Administration into arranging a workshop from 20 to 22 April 1993, in Seattle to discuss nonindigenous estuarine and marine organisms. There were 60 participants, including visitors from Belgium, Finland, Tasmania, and the Australian mainland. In addition to the scientists, there were also speakers from industry, aquaria, and aquaculture, as well as administrators. The workshop did not ask for recommendations or pass resolutions, but did agree that the magnitude of the distribution of exotic organisms in coastal waters had been greatly underestimated. Nonindigenous estuarine and marine organisms are causing ecological change in coastal waters, and it may be only a matter of time before something as bad as the zebra mussel arrives in our estuaries. More careful and thorough analyses of the taxonomic status of introduced organisms are needed. The tone of the meeting was that additional regulation will not help much, but that all industries should become more aware of this problem of transferring organisms from one part of the world to another.
8. S. Lewis, *Cane Toads, An Unnatural History* (Dolphin Doubleday, New York, 1989).
9. J. Druett, *Exotic Intruders: The Introduction of Plants and Animals into New Zealand* (Heinemann, Auckland, 1983).
10. D. MacKenzie, *New Scientist* **131**, 31 (1991).

Molecular Muscle

Edwin W. Taylor

It is almost 40 years since the sliding filament model of muscle contraction (in which muscle filaments move past one another) was proposed independently by A. F. Huxley and R. Niedergerke (*1*) and by H. E. Huxley and J. Hanson (*2*). There followed 20 years of progress in structural, mechanical, and biochemical studies—the synthesis of which led to the idea that the thick and thin filaments slide past one another by means of rotating crossbridges (*3*). Thin filaments consist mainly of the globular protein actin, and thick filaments mainly of myosin, a long protein with a prominent "head." This model has been considered to be basically correct, with perhaps only a few details to be filled in, and certainly suitable for entry into standard textbooks. Now in this issue of *Science*, Rayment and co-workers take our understanding of muscle contraction to a new level of sophistication by reporting the three-dimensional structure of the myosin head at 2.8 Å and then using this structure and other existing data to propose a model of the actomyosin complex that begins to explain the molecular movements that underlie muscle contraction.



Striated muscle. Magnification, x23,800. [Photograph by D. W. Fawcett/Visuals Unlimited]

The essence of the sliding filament model is that the myosin head binds to the actin filament in one orientation, rotates to a second orientation, possibly a 45° change, and then detaches. The cycle is driven in one direction by coupling these transitions to the steps of adenosine triphosphate (ATP) hydrolysis. The rotation need not involve the whole head but requires only a part, which could be accomplished by a bending of the protein structure. In either case, part of the free energy of ATP hydrolysis is stored mechanically as a "stretched spring" in the head or, alternatively, in the connection of the head to the myosin filaments.

In the 20-year effort to fill in these details we have learned a great deal about muscle contraction and cell motility, but we have been unable to satisfactorily determine how actin and myosin actually interact. What has been lacking is the three-dimensional structures of the proteins. In 1990, the structure of the actin monomer was obtained, and a model was proposed for the packing of monomers in the actin filament (*4*, *5*). Now that Rayment *et al.* have described the three-dimensional structure of the myosin head at 2.8 Å resolution (*6*), they have also been able to propose a model of the actomyosin complex in which the conformational changes during contraction can be discussed in terms of the molecular structure (*7*).

We have waited a long time for this structure of myosin and the model of actomyosin. Now that we have these, what can we expect to learn? First, we should now be able to synthesize the information that has been accumulated on actin and myosin. Indeed, a test of the correctness of the structure is its consistency with this extensive evidence. The new results pass this test easily. Affinity labeling, crosslinking, energy transfer, and image reconstruction of the actomyosin complex had provided a low-resolution model in which the substrate and actin binding sites and the relative positions of some side chains had been determined (*8*, *9*). There is surpris-

The author is in the Department of Molecular Genetics and Cell Biology, University of Chicago, 920 East 58 Street, Chicago, IL 60637.

ingly good agreement of this older model with the new molecular structure (although some use of this older information was made in aligning the actin and myosin). The substrate pocket and the actin binding regions are on opposite sides of myosin separated by 3 to 4 nm, as expected. The reactive thiols Cys^{697} and Cys^{707} are roughly at the expected distance from the ATP binding site. The region from amino acid 626 to 647, which contains six lysines, can make contact with the amino terminal of actin, which has a high negative charge. Crosslinking studies had predicted that these regions could be in contact (*10*).

The structure also reveals a new feature that can explain previous observations. In addition to the contact of myosin with the amino terminal of actin, the alignment predicts a second binding region between actin and myosin with more specific hydrophobic contacts in the sequence from Pro^{529} to Lys^{553}. This feature fits nicely with the evidence that the binding of myosin to actin is a two-step reaction (*11*); the first step depends on ionic strength, whereas the second is a conformation change that is relatively independent of ionic strength but is highly temperature-dependent (*12*).

The fundamental problem with the rotating crossbridge model has been the failure to obtain convincing evidence for a large-scale change in the structure that could account for a movement of the crossbridge of 5 to 10 nm in the direction of motion. It was expected that such a large movement would be detected by low-angle x-ray diffraction and the use of fluorescent and electron-spin resonance probes. Although resting, contracting, and rigor muscles show differences in diffraction patterns and in the orientations of fluorescent and spin labels, the results have been inconclusive. Because the crossbridges are not synchronized, diffraction in the steady-state reports average orientation, and only recently has evidence for a change in orientation been found during tension redevelopment after a release (*13*). Spin-labeling of the heads on the reactive Cys^{707} showed that some of the heads in the active cycle are oriented at the rigor angle, which might be the end of the rotation, but most of the attached heads were disordered and in rapid motion (*14*). A possible explanation is that the head bends during the power stroke and that the probes were unfortunately placed in a region that did not move. However, if the protein bends, there is at most a very small change in the mass distribution upon binding nucleotide or actin (*15*).

The new molecular structure suggests a way out of this problem. The myosin molecule is unique in having an 8.5-nm α helix running down the middle and ending at the base. It is apparently stabilized by the two light chains, since a bare α helix is rarely found in proteins in aqueous solution. Removal of the light chains does not inhibit adenosine triphosphatase activity but does eliminate motility (*16*). It is proposed by Rayment *et al.* that the binding of substrate could cause the large substrate pocket to close and move the tip of the molecule 5 nm. This would require a relatively small change in the mass distribution, and it might explain why probes on Cys^{707} did not detect a change in orientation.

The structure may also give us some new insights into the mechanism of energy coupling. An unexpected feature is a narrow cleft that extends from under the substrate binding pocket and separates the two halves of the 50-kD domain. Apparently this cleft must close to fit the proteins together in the actomyosin complex, and it could be opened by substrate binding, which weakens the interaction with actin. A model of the contraction cycle is proposed in which closing of this cleft releases phosphate and triggers the power stroke. Although the structure does not immediately solve the coupling problem, but only suggests a solution, it has initiated a new direction in the study of motile systems. Myosin really does look like a protein designed to bend through a large angle. The proposed coupling model is still largely speculative, but it can be readily tested by experiment.

Where do these new findings lead? The determination of the structure of a 150-kD protein was a formidable task. A second structure with nucleotide bound in the pocket will be awaited with great interest. And now that the structure of one of the motor proteins has been solved, we can ask whether other motor proteins that move organelles along microtubules (*17*) share common features of structure and coupling mechanism. Kinesin and other proteins in this group are much smaller than myosin (they have 40- to 50-kD heads), and they do not require light chains to function. Crystallization and structure determination should be much simpler than for myosin, and the relative ease of expression of active protein in bacteria should facilitate a study of the coupling mechanism by molecular genetics. Although biochemical studies are still at an early stage, these proteins appear to be significantly different than actomyosin (*18,19*). The next big step in this field is to learn the principles of the design and construction of molecular motors.

References

1. A. F. Huxley and R. Niedergerke, *Nature* **173**, 971 (1954).
2. H. E. Huxley and J. Hanson, *ibid.*, p. 973
3. H E. Huxley, *Science* **164**, 1356 (1969).
4. W. Kabsch, H. G. Mannherz, D. Suck, E. Pai, K C Holmes, *Nature* **347**, 37 (1990).
5. K. C. Holmes, D. Popp, W Gebhard, W. Kabsch, *ibid.*, p. 44.
6. I. Rayment *et al., Science* **261**, 50 (1993).
7. I Rayment *et al., ibid.*, p. 58.
8. K. Sutoh, M. Tokunaga, T. Wakabayashi, *J. Mol. Biol.* **206**, 357 (1989).
9. J. Botts, J. F. Thomason, M. F. Morales, *Proc Natl. Acad. Sci. U.S.A.* **86**, 2204 (1989).
10. K Sutoh, *Biochemistry* **22**, 1579 (1983).
11. M A Geeves, R. S. Goody, H. Gutfreund, *J. Muscle Res. Cell Motil.* **5**, 351 (1984).
12. E. W Taylor, *J. Biol. Chem.* **266**, 294 (1991).
13. M Irving, V. Lombardi, G. Piazzesi, M. A. Ferenczi, *Nature* **357**, 156 (1992).
14. P G Fajer, E. A. Fajer, J J. Matta, D. D. Thomas, *Proc. Natl. Acad. Sci. U.S A.* **87**, 5538 (1990).
15. K. Wakabayashi, *Science* **258**, 443 (1992).
16. S. Lowey, G S. Waller, K. M. Trybus, *Biophys. J.* **64**, A7 (1993).
17. R. D. Vale, *Trends Biochem. Sci.* **17**, 300 (1992)
18. D. D. Hackney, *Philos Trans. R. Soc. London Ser. B* **336**, 13 (1992).
19. A Sadhu and E. W Taylor, *J Biol. Chem.* **267**, 11352 (1992).