These were unknown and, as is customary, Suzuki *et al.* took an averaged value for their effect on transfer efficiency. Their Fig. 4 (page 382), however, shows that they assume a large change in the relative angular positions of the two fluorophores during the working stroke, so the estimated distances are subject to uncertainty.

Using a variant of FRET, Getz *et al.*⁸ also showed that the working stroke is accompanied by a conformational change. The donor was a molecule containing a terbium atom which is luminescent rather than fluorescent, making a combination that operates over greater separations than ordinary FRET and has other advantages⁹. The fragment of myosin used included the catalytic domain and the whole of the lever. The donor was attached close to the tip of the lever and the fluorescent acceptor to the catalytic domain; actin was present so rigor attachments were formed. On adding ATP (myosin dissociates from actin and recovery stroke occurs), an increase in transfer was found, although sufficient change in separation between donor and acceptor would not be expected from the presumed recovery stroke of the lever. Getz *et al.* concluded that the decrease of transfer was the result of a change in orientation of the acceptor, although other explanations are possible. Their result is a timely warning that FRET results do not unambiguously indicate a change in separation between donor and acceptor.

These observations^{1,8} confirm that a conformational change within the myosin molecule does accompany the working stroke, but do not indicate its extent. The results of Dobbie *et al.*² are complementary: they provide a value for this extent without giving further evidence for a conformational change. An intact fibre from frog muscle was stimulated and a small length oscillation was imposed at a frequency (about 3 kHz) too high for the conformational changes to follow, so that the tension and length changes were in phase. The intensity of the meridional X-ray reflection corresponding to the spacing (14.5 nm) of myosin molecules along their filaments was also recorded and its fluctuations were exactly in opposite phase to the length changes. However, when a similar experiment was done on a fibre in rigor (that is, without ATP so that all cross-bridges were presumably in the state corresponding to the end of the stroke), the X-ray intensity fluctuations were exactly in phase with the length changes.

These results confirm those of Yagi *et al.*¹⁰ at a lower frequency (500 Hz) where phase shifts are appreciable. They imply that the long axis of the cross-bridge swings from one side to the other of the perpendicular to the fibre axis during a working stroke (Fig. 1). This agrees with results from fluorescent probes attached to the lever arm but contradicts a conclusion¹¹ reached (on a scallop

muscle) from electron-paramagnetic-resonance spectra, a method that cannot distinguish between angles on the two sides of the perpendicular.

Dobbie *et al.* explain these X-ray intensity changes quantitatively. In their model (Fig. 3, page 385) the tip of the lever moves by about 9 nm during the working stroke, a little less than the 10–12 nm (suggested by X-ray structures^{6,7}) which matches the amount deduced from sudden length changes (see above). If this 9 nm turns out to be correct it will therefore be necessary to postulate some movement in addition to that from the swing of the lever, perhaps from tilting of the catalytic domain on the actin filament³ or shortening of the connection of the myosin head to the shaft of its filament¹².

All of this is impressive support for the lever-arm hypothesis, but many questions remain. How many of the myosin heads are active at any one time? Is the working stroke a single event or does it go in two or more steps? Answers may come from measurements of the force and amount of movement between a single myosin molecule and an actin filament. But the time resolution of such experiments is inferior to that of experiments on whole fibres, the results are affected by compliance in the actin filaments, and there are big discrepancies between the results from different laboratories. Moreover, experiments are done with myosins from different animals, and at low temperatures where the behaviour of the intact muscle is unknown.

Many will echo Holmes's remark⁶: "The fact that these results fit so nicely with other experiments supporting the lever-arm hypothesis points to their significance". Perhaps so, but results that agree with one's preconceptions need to be scrutinized with especial care. I readily admit that I am inclined to accept results that fit with a working stroke of at least 10 nm suggested long ago by experiments on living muscle⁵, rather than values in the 4–6 nm range that were widely accepted a year ago¹³. □

A. F. Huxley is at Trinity College, Cambridge CB2 1TQ, UK.

1. Suzuki, Y., Yasunaga, T., Ohkura, R., Wakabayashi, T. & Sutoh, K. *Nature* **396**, 380–383 (1998).
2. Dobbie, I. *et al.* *Nature* **396**, 383–387 (1998).
3. Diaz Baños, F. G., Borda, J., Lowy, J. & Svensson, A. *Biophys. J.* **71**, 576–589 (1996).
4. Raymont, I. *et al.* *Science* **261**, 58–65 (1993).
5. Ford, L. E., Huxley, A. F. & Simmons, R. M. *J. Physiol.* **269**, 441–515 (1977).
6. Holmes, K. C. *Curr. Biol.* **7**, R112–R118 (1997).
7. Dominguez, R., Freyzon, Y., Trybus, K. M. & Cohen, C. *Cell* **94**, 559–571 (1998).
8. Getz, E. B., Cooke, R. & Selvin, P. R. *Biophys. J.* **74**, 2451–2458 (1998).
9. Selvin, P. R. & Hearst, J. E. *Proc. Natl Acad. Sci. USA* **91**, 10024–10028 (1994).
10. Yagi, N. *et al.* *J. Synch. Rad.* **3**, 305–312 (1996).
11. Baker, J. E., Brust-Mascher, I., Ramachandran, S., LaConte, L. E. W. & Thomas, D. D. *Proc. Natl Acad. Sci. USA* **95**, 2944–2949 (1998).
12. Harrington, W. F. *Proc. Natl Acad. Sci. USA* **68**, 685–689 (1971).
13. Howard, J. *Nature* **389**, 561–567 (1997).

Daedalus

Fat is a feminist issue

Fat causes a multitude of miseries these days, mainly to women. Emaciation is intensely fashionable. The sub-text of this fashion, says Daedalus, is sexual, but not in the obvious way. Many cultures consider obesity to be sexy; George Orwell commented on the rotundity of the Englishman's secret ideal. This makes good biological sense. Fat is itself a source of oestrogen, so fat women are likely to be sexually enthusiastic — a fact celebrated by a famous English cartoon duo. Conversely, thin women should have a weaker sexual drive. Anorexic women often even cease to menstruate.

So Daedalus reckons that fashionable slimness is really about power. A slim woman hopes to arouse strong desire in the opposite sex, while being immune to it herself — a position of great power. The age-old sex war, augmented by the modern feminist battle, therefore decrees that slimness should be fashionable.

This unstated *realpolitik* of modern fashion leaves fat women in a sorry plight. For not only does fat release sex hormones; sex hormones encourage fat to accumulate, in its usual sites around the female frame. By positive feedback, a fat woman may get ever fatter, more sexually needy, but less fashionably desirable. Meanwhile her slim sisters, sexually switched off by their emaciation, can denounce men for harassing them with unwanted attentions.

Daedalus wants to break this vicious cycle. Many chemicals said to damage animal reproduction (such as DDT) concentrate in body fat. So DREADCO chemists are seeking a drug which dissolves in the fat, but stimulates rather than sabotages its biochemistry. It must boost not only the production of oestrogen (so that even women with little fat will feel sexy) but also leptin — the feedback-control protein which counters obesity by damping production of further fat. Arsenic may give a clue; in low doses it can lead both to emaciation and hypersexuality.

The biochemical development may be long and tortuous. But the final product will splendidly counter the malign influence of modern fashion. With DREADCO's 'Slim and Sexy' fat-activator, fat women will shed their girth without damping their ardour; slim women will no longer sacrifice sexual feeling to fashion; post-menopausal women building their middle-age spread may not need HRT. Militant feminists, of course, will find good reasons to avoid and denounce the product.

David Jones