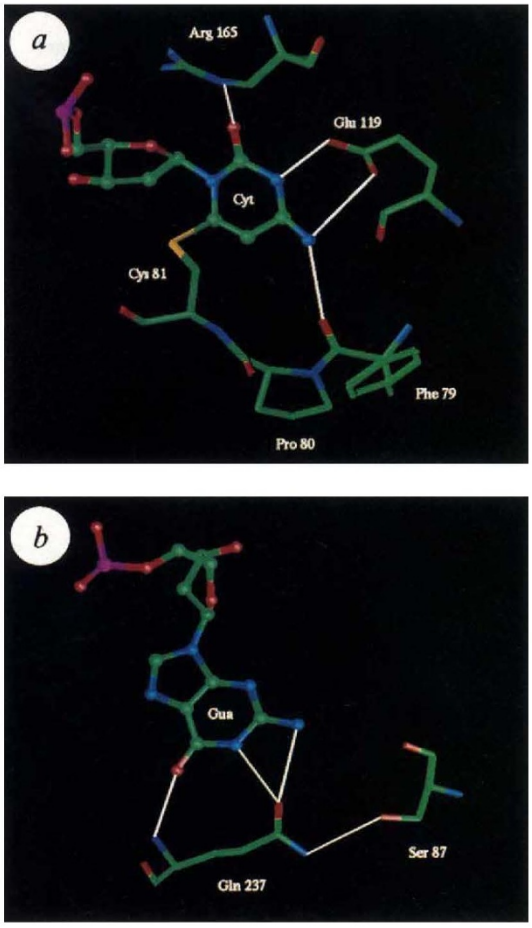

FIG. 3 Intermolecular hydrogen-bonding interactions involving the active-site cytosine and guanine residues in the ternary complex. *a*, The looped-out cytosine is covalently linked through its C6 position to the sulphydryl of Cys 81, and is anchored through hydrogen bonds to its Watson–Crick pairing edge with the backbone and side-chain atoms of the invariant Phe 79, Glu 119 and Arg 165 residues. *b*, The Gln 237 side-chain on the recognition loop penetrates into the cavity generated by the looped-out cytosine and forms backbone and side-chain hydrogen bonds with the Watson–Crick pairing edge of the orphan guanine residue.

Cys 81 and AdoHcy positioned on opposite sides of the slightly nonplanar dihydrocytosine residue. The polar groups along the Watson–Crick pairing edge of the dihydrocytosine ring are all involved in intermolecular hydrogen bonds with invariant residues of the m5C-MTase in the complex (Fig. 3*a*). These interactions that define substrate specificity anchor the dihydrocytosine in its binding pocket through pairing with both side-chain and backbone groups on the enzyme.

The cavity generated by the looped cytosine is occupied by Gln 237 (white in Fig. 2*a*) from the small-domain, glycine-rich recognition loop, and by Ser 87 (blue) from the large-domain, active-site loop, which penetrate into the DNA helix from opposite directions in a pincer movement. The polar groups along the Watson–Crick pairing edge of the orphan guanine are all involved in intermolecular hydrogen bonds with the backbone and side-chain atoms of Gln 237, whose alignment is stabilized through hydrogen-bond formation with Ser 87 (Fig. 3*b*). Interestingly, neither Gln 237 nor Ser 87 are conserved residues in m5C-MTases, meaning that hydrophobic interactions must also contribute to these intermolecular alignments.

Quite different positions are occupied by the AdoMet cofactor in the binary complex and the AdoHcy cofactor product in the ternary DNA complex. The AdoHcy is tightly bound in its cofactor-binding pocket, the site being accessible to solvent. One can surmise a sequence of steps leading to ternary-complex formation involving initial binding of m5C-MTase to the DNA followed by subsequent binding of the cofactor.

The structure of the cofactor–m5C-MTase–DNA ternary complex discussed here defines one step (**2** in Fig. 1) on the reaction pathway for cytosine C5 methylation on DNA. Other issues that need to be addressed include a structural dissection of the enzyme–DNA contacts in the initial binding event that accounts for the observed sequence-specific recognition (**1** in Fig. 1), and elucidation of the pathway for the return of the methylated cytosine into the DNA helix (**3** in Fig. 1). It should be possible to tackle these questions by choosing suitable cytosine and cofactor analogues, and by creating mutations in the enzyme that would trap the required intermediates for structural characterization.

Finally, we can expect that the opening of the DNA helix observed in the ternary complex in the m5C-MTase system will be but the first example of motifs in other protein–DNA complexes that involve helix disruption. Variants of this structural theme may well turn up in DNA complexes ranging from those formed by replication-origin-binding proteins to enzymes catalysing recombination events. □

Dinshaw J. Patel is in the Cellular Biochemistry and Biophysics Program, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.

1. Wolberger, C. *Curr. Opin. struct. Biol.* **3**, 3–10 (1993).
2. Travers, A. A. *Curr. Opin. struct. Biol.* **2**, 71–77 (1992).
3. Klimasauskas, S., Kumar, S., Roberts, R. J. & Cheng, X. *Cell* **76**, 357–359 (1994).
4. Cheng, X. *et al. Cell* **74**, 299–307 (1993).
5. Wu, J. C. & Santi, D. V. *J. biol. Chem.* **262**, 4778 (1987).
6. Erlanson, D. A., Chen, L. & Verdine, G. L. *J. Am. chem. Soc.* **115**, 12583–12584 (1993).
7. Osterman, D. G. *et al. Biochemistry* **27**, 5204 (1988).

DAEDALUS

Fat and fancied

DIETING and jogging make millions miserable, most of them women. They claim to be in it for health and fitness; but what they really want, of course, is sexual desirability. For the Western world thinks that slim is sexy. Some people denounce this as culturally imposed 'sizeism'; but Daedalus claims it is genetic. He argues that we have evolved to be sexually attracted by people who, in current conditions, are most likely to rear successful offspring. In societies where food is limited, fat women tend to be fancied — their fat reserves should see them through the metabolic challenges of pregnancy and lactation. In rich societies, food isn't critical, so slim women are desirable — their slimness implies that they are young and not pregnant already. Earlier in this century, even the West was so poor that heavy figures were popular, and many people tried to put on weight.

How does this come about? After all, nobody can choose to be attracted by this or that style of figure. Many forms of instinctive and sexual behaviour, human and animal, are imprinted by some crucial experience which occurs during a brief time-window of susceptibility. Daedalus reckons that there must be a critical period, probably quite early in infancy, when a baby 'decides', in effect, whether it is growing up in an over-fed or a starving society. If starvation seems to loom, it will be imprinted to fancy the fuller figure; if not, its sexual ideal will be slim.

Modern Western clinics and baby-care organizations judge the health of a baby by the speed with which it gains weight. Babies are given as much food as possible all the time, so they inevitably get fat. At the same time, of course, they become imprinted with extreme slimness as their sexual ideal. Hence the universal tragic mismatch between desire and reality which is sizeism.

So Daedalus proposes the experiment of inserting a controlled period of near-starvation into the feeding regime of otherwise well-fed babies. The age of onset and the duration of this period will be varied; when the infants mature, the figures they find attractive will be noted. This will reveal the crucial period for imprinting size preference. Western baby-feeding schedules will then be able to starve the next generation for just this critical period, while happily overfeeding it all the rest of the time. The blissful result will be a society of fatties, all programmed to fancy other fatties. Sizeism will vanish; dieting and jogging will perish unmourned. Health and fitness will decline, of course, but nobody cares about that. David Jones