gain weight and increase the production of heat from brown adipose tissue. Because adult animals tend to lose brown fat, its function in fully grown humans has been debated. Now Enerbäck *et al.*[1] present a new look using molecular genetics.

The protein that is responsible for uncoupling combustion and ATP synthesis in brown adipose tissue is the mitochondrial uncoupling protein (UCP1; formerly UCP). The structure of the *Ucp1* gene is known, so a DNA construct was developed containing the regulatory elements of this gene, along with the coding sequence for the A chain of diphtheria toxin. Transgenic mice containing this so-called 'toxigene' had greatly reduced amounts of UCP in their brown adipose tissue[5]. One transgenic strain developed obesity by increasing food intake, rather than by a reduction of energy expenditure alone. Enerbäck *et al.* have now gone one step further, by producing a *Ucp1* knockout mouse. These mice show the expected inability to keep warm in the cold but, surprisingly, they do not become obese.

This would seem to be the end of luxus consumption, but to the rescue comes the finding that there is another UCP — the mouse *Ucp2* gene was described by Fleury *et al.*[6] in the March issue of *Nature Genetics*. It has marked homology with a human *UCP2* gene, and it is found not only in brown fat, but in white fat as well. Moreover, expression of *Ucp2* is upregulated in white adipose tissue when the mice are fed a high-fat diet. The obvious next steps are to make knockouts of *Ucp2* and to determine whether UCP2 is normally involved in burning away extra calories, and whether it is dysfunctional in the obese.

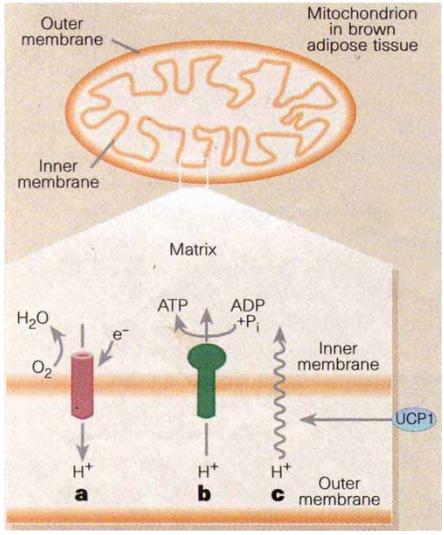

Figure 1 **Oxidative phosphorylation takes place in the inner membranes of mitochondria in brown adipose tissue.** a, **An excess of protons is generated on one side of the membrane as electrons move along a 'respiratory' chain.** b, **The proton excess leads to 'coupled' oxidation, which results in the formation of ATP.** c, **The mitochondrial uncoupling protein (UCP1) creates a 'leak', dissipating the proton excess to yield heat.**

In spite of these findings, the long search to find the heat producer that keeps its lucky possessors svelte is far from over. We may soon learn how UCP1 is involved in caloric exchange, but its roles in obesity treatment and pathogenesis are uncertain. Previous efforts to treat obesity by uncoupling oxidative phosphorylation using thyroid hormone, dinitrophenol or massive doses of sympathetic agonists ended in doing more mischief than good because mitochondrial uncoupling occurred at unwanted, as well as at desired, sites.

Concentrating on calorie intake or expenditure alone may also be misleading. The caloric inequalities that produce obesity are probably small and, when obesity is achieved, there may be re-equilibration to maintain it at a fixed level. This could indicate the existence of an 'equalizer' that maintains a given level of fat storage. Examples of known equalizers include the collection of elements that maintain constant blood pressure or blood glucose levels. Within the equalizer system there may be luxus consumption, which could act interdependently with all other factors. Notably, both obese and non-obese people at their usual body weight require roughly the same number of calories per unit of metabolic mass[7]. But when these people are experimentally raised 10 per cent above or below their usual weights, there is induced caloric inefficiency at the high weight (which tends to restore them to their initial state), and increased caloric efficiency at the lower weight.

Caloric wastage after weight increase is a form of luxus consumption. However, obese people behave exactly the same as the non-obese when they are changed from their obese weight — the equalizer system ordains what the level of fat storage will be, rather than this single element. Thomas and Palmiter[2] take this further and suggest that the equalizer has redundancy. They have generated knockout mice that lack the gene for dopamine β-hydroxylase (*dbh*), so they cannot synthesize noradrenaline or adrenaline. The effect of this is to paralyse the sympathetic nervous system, which is believed to be an essential regulator of energy metabolism. However, the authors find that knocking out the *dbh* gene has no effect on fat storage. So if the concept of the pathogenesis of human obesity is correct, examining all components in the regulatory system remains the only way to approach an understanding of the entire system. But, as of this moment, stick to your diet, keep up your jogging, and wait for the continuation of this fascinating story. □

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Daedalus

The kindest cut of all

Metal cutting is a brutal process. Lathes, drills and milling machines all force a cutting edge through a resistive workpiece. That edge rapidly wears from the enormous friction of the metal flowing past it under extreme pressure. Furthermore, the flow is quite unlubricated. The fiercest spray of cutting fluid cannot reach the point where the edge is parting the metal. All it can do is absorb the resulting heat.

Daedalus hopes to change all this. On a microscopic scale, he says, a cutting edge is very rough and blunt, with a highly uncertain radius. As it is driven forward, the metal shears in front of it, so that there is always a tiny gap ahead of its rounded nose. Daedalus wants to pump lubricant into that gap. Flowing back along the faces of the cutting tool, it will lubricate the twin streams of sheared metal. So he is applying modern microfabrication methods to chips, not of silicon, but of tool steel and tungsten carbide.

His new photo-etched tool chips have cutting edges of precisely defined radius. Along each edge is a series of etched holes a few micrometres across. When the chip is cemented onto its matching support, a channel in the latter reaches the holes in the chip. The resulting drill bit, lathe tool or milling cutter can be fed with lubricant through its shank. The fluid will weep through the holes and emerge along the cutting edge of the tool, into that minute gap where the metal of the workpiece is being parted. For the first time, the cutting edge itself will be lubricated.

The lubricant poses problems of its own. To leak at a useful rate from such tiny holes, it must combine the highest density with the lowest viscosity. A supercritical fluid should fill this bill — carbon dioxide, say, or nitrous oxide. An edge exuding some 70 atmospheres of an almost incompressible but readily expansible fluid should practically eliminate frictional contact at the cutting edge. A little oil dissolved in the fluid would precipitate out as it expanded, giving more conventional lubrication downstream. The strong cooling of expansion would be useful too.

The new tools will transform engineering. Lathes and milling machines will carve effortlessly through the toughest metal on a fraction of their previous power. The tools, protected by supercritical lubrication, will not wear; their products, formed by edges of optical quality, will themselves have a precision mirror finish. Metal cutting will become a delicate, quiet, contemplative form of industrial sculpture.

David Jones