insulin but to some other protein that is involved in its biosynthesis and exocytosis, candidates being protein disulphide isomerase, hsp 70, the sorting receptor or the protease that cleaves proinsulin. There is a precedent for one protein's changing the pathway of exocytosis and maturation of another. In this case it is the class I MHC molecule that falls victim to the E3/19 protein during adenovirus infection. The complex stays in the endoplasmic reticulum, preventing cell surface expression of class I MHC and presentation of virus-derived peptides to the immune system of the host. The binding of E3/19 to HLA-A,B,C molecules shows polymorphism which maps to the α_1 and α_2 domains[14]. Reminiscent of MHC restriction, this is surely not chance and encourages the hypothesis that a relatively flexible, unstructured part of E3/19 is binding into Bjorkman's groove.

The binding site of MHC molecules lacks the singular specificity of an antibody molecule. It is more analogous to that of a proteolytic enzyme such as trypsin, which is capable of binding and clipping most proteins but shows sequence preferences in the choice of sites. Given the broadness of specificity one should expect and be looking out for additional molecules that perturb, regulate or exploit MHC molecules by latching on to their binding sites. This mechanism could provide the basis for all the non-immunological functions attributed to MHC molecules.

An example, which is doubly relevant to this discussion, is the association of class I MHC antigens with the insulin receptor[15]. Experiments from many laboratories show reciprocal precipitation with antibodies against these two molecules and differences due to polymorphism in the class I MHC molecules. Could this effect, which is not found with class II MHC molecules, contribute to the dramatic loss of β-cell viability in the H–2K^b transgenic mice? Uncontrollable up- or down-regulation of functional receptors for insulin or related growth factors by increased class I MHC expression may perturb the metabolism of β-cells to the point where they become non-viable.

β-cell death

The degeneration of β-cells in these transgenic mice is a variable and relatively slow process, suggestive not of an acute toxicity but of metabolic handicap that gradually wears the cells down. In searching for guidance one immediately thinks of the clathrin-minus mutants of yeast. Although not always lethal, this mutation disrupts the organization of membranous organelles and severely increases the generation time. Coordinated metabolism is incapacitated and away from the rich media and intensive care of the laboratory these cells would surely give up their life without clathrin[16]. And it is in the recycling and marshalling of clathrin pools in the pancreatic β-cells that there might lie some clues. Orci and co-workers show that cleavage of proinsulin to insulin occurs in the coated vesicles that bud off from the transgolgi[10]. Prevention of proteolysis by either monesin treatment or introduction of non-cleavable analogues of lysine and arginine into insulin also stop disassembly of the clathrin coat.

These authors hypothesize that generation of the C peptide provides the signal for clathrin disassembly. I have already discussed how binding of proinsulin by MHC could prevent conversion to insulin. Another possibility is for MHC to be incorporated into the coated vesicles and bind the connecting peptide once it has been cleaved. In both situations clathrin would accummulate; locked up in its own cage and unavailable for other functions. Even a partial reduction in receptor-mediated endocytosis could spell disaster for cells and the eventual cause of death could be as unrelated to histocompatibility as the deprivation of iron.

From these[1–3] and from other[5] studies it is apparent that transgenic mice will be instrumental in unravelling thymic education and the questions of tolerance. In contrast to previous experimental systems, they allow introduced components to be present throughout ontogeny. It was perhaps the unanticipated importance of this difference that led Allison *et al.*[1] and Lo *et al.*[2] to be unprepared for the results they obtained. The value of transgenic mice for research on, if one can say it, 'normal' diabetes is at best unclear. Unfortunately, these transgenic mice have not delivered a valid test for the role in this disease of increased expression of MHC molecules by pancreatic cells. However, study of these mice should further understanding of exocytosis and secretion and perhaps the perturbations caused by intracellular MHC molecules. □

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Daedalus

Blow up the Earth!

TUNNELLING is a slow, hazardous and very costly business, as demonstrated by the proposed Channel Tunnel between Britain and France. And yet, muses Daedalus, it could be so easy. The Earth's crust is actually quite plastic. The roof of a coal-mine tunnel, for example, slowly subsides; its floor, freed of its previous overburden, comes up. An abandoned tunnel is soon squashed flat. So Daedalus plans to reverse this geoplastic process. His idea is to adapt standard oil-well techniques to horizontal drilling, so as to bore a full-length pilot tunnel a few centimetres across. He will then apply an internal pressure, and simply pump the tunnel up to the required diameter.

This appealing scheme faces several difficulties. Most tunnels and boreholes leak; groundwater gets into them. In Daedalus's pressurized tunnel, the hydraulic fluid will leak out. His pilot bore will have to be filled initially with some sort of muddy grouting, pumped in till the leaks are sealed. And although many surface rocks, like clay and chalk, are fairly plastic at room temperatures, harder ones like granite only deform at a useful rate when heated. Because their creep rate typically goes up tenfold for every ten-degree Celsius rise in temperature, quite modest heating should suffice.

So DREADCO's engineers are working on a plan to thread an electric cable through the pilot borehole, fill the hole with water, seal it and pass a heavy current. The trapped, heated water will reach and exceed its critical state, attaining many hundreds of degrees Celsius and many hundreds of atmospheres pressure. This neat method of hot pressurization has other advantages. Water greatly weakens all rocks, perhaps by lubricating small cracks. And supercriticial water is a powerful solvent for many rock components, especially silica. Under this supercritical assault, the rock will not only yield plastically; it will dissolve away. Daedalus estimates that a few megawatts of electrical power per kilometre should pump up quite a respectable tunnel in a year or so — neatly, painlessly and relatively cheaply.

The final product, however, will not be the straight, parallel hollow cylinder that engineers dream of. The softer and less loaded areas of the tunnel (near the entrances, for example) will have been inflated into huge caverns long before the tough and overburdened rocks in the middle have expanded to design size. And geological anisotropies will cause much wandering from the central line. Furthermore, all the heat put into the rocks will still be there, and for several years travellers will find the tunnel passage rather a tropical experience. David Jones