RESUME

Soft core

To test whether your egg is hard boiled or uncooked, spin it and see what happens. J. L. Hilton proposes something similar for Mars to see if it has a solid core (*Astr. J.* **102**, 1510–1527; 1991). Disturb a spinning body and its axis will continue to oscillate, or 'nutate', the Earth's 'Chandler wobble' being an example of this effect. But the exact response depends on whether the interior is rigid or not. Earth's molten core is just discernible in this way. Hilton calculates the effect of the torques exerted on a completely solid Mars by the Sun, Jupiter, its moons Phobos and Deimos, and its varying orbit; the effects of a liquid core are to be added in a subsequent paper. The test for a liquid core could, in principle, be applied to any planet, but only Mars gives us the clear view necessary to see its tiny nutation of 7 arcseconds a year.

Not in the blood

THE powerful disruptive biochemical effects of ozone, the three-atom allotrope of oxygen, may come to the assistance of those seeking to prevent transmission of the human immunodeficiency virus through blood products. K. H. Wells *et al.* report in *Blood* (**78**, 1882–1890; 1991) that the viral activity of HIV-infected blood samples treated with 1,200 parts per million of ozone is reduced 100-billionfold *in vitro*, without seriously affecting the plasma component factor VIII. Why this happens is unclear; perhaps the ozone attacks the fatty viral envelope and destroys the virus's capacity to infect cells, the authors speculate. Whether the treatment will make a feasible alternative to screening remains to be seen. Tests of the infectivity of treated blood in sensitive animal models will be an essential next step.

Malignant diagnosis

THE last thing one needs during an operation is a serious reaction to the general anaesthetic, but for sufferers of the rare disorder malignant hyperthermia (MH), the resulting sudden paralysis can be fatal if unchecked. Linkage studies have incriminated the ryanodine receptor (RYR1), which controls release of calcium ions in muscle cells, but a putative mutation has only just been identified. E. F. Gillard *et al.* (*Genomics* **11**, 751–755; 1991) describe a point mutation in the RYR1 gene in affected members of one out of 35 MH families, which substitutes an arginine residue for cysteine. The analogous mutation is found in five strains of pig that suffer the related porcine stress syndrome. However, the molecular basis of most MH cases remains to be determined, and may not be confined to the RYR gene.

VIRAL PROTEASES

Molecular metamorphosis

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NEVER throw away your wide ties, for one day they are certain to come back in style. This is a useful tip in science as well — today's backwater is often tomorrow's hot field, the proteases being a good example. Enzymology began with these digestive enzymes, but by the 1970s they were considered *passé*. Now they are centre-stage once more, figuring prominently in the design of drugs against AIDS, emphysema, arthritis and hypertension. On page 37 of this issue[1], a new Achilles' heel is presented for antiviral agents: the three-dimensional structure is described of a viral protease that in effect shoots itself in the foot so that it can assume a new identity as a structural protein.

Because they seem to come in a small number of families, with well-defined structures and modes of action, proteases are everyone's favourite molecules for model building from sequence similarity. Proteases act as cutting tools to tailor proteins and their precursors to fit their context in the execution of cellular processes. From the three-dimensional structure of the core protein of Sindbis virus, an enveloped virus of the alphavirus family, it now seems that some proteases are also capable of metamorphosis[1]. Choi *et al.* find that the principal domain of the core protein has a polypeptide fold similar to that of the serine protease chymotrypsin. It possesses a complete catalytic triad, but its own C-terminal amino acid, a tryptophan, is lodged in its primary substrate specificity site, rendering it inactive. Thus, Sindbis-virus core protein is an enzyme designed to carry out a single turnover, cleaving itself from the viral polyprotein precursor and simultaneously changing itself into a structural protein.

Most single-stranded RNA viruses code for proteases of the chymotrypsin family, although some of these enzymes have cysteine replacing serine as the active site nucleophile. (Human immunodeficiency virus protease is a not able exception — it belongs to the structurally and chemically distinct family of aspartyl proteases.) These enzymes cleave the individual viral proteins from the giant polyprotein precursor in the first step of viral assembly. But they are not incorporated into the finished virus particle, and their function can sometimes be replaced by endogenous cellular proteases.

It has long been suspected that Sindbis virus and other members of the insect-transmitted alphavirus family are different. Simmons and Strauss showed in 1974 that the virus core protein, which forms the coat surrounding the RNA, is responsible for its own release from the polyprotein[2]. Sequence analysis[3] and mutagenesis experiments[4–6] indicated that Sindbis core protein has a catalytic triad of Asp 163, His 141 and Ser 215, similar to the Asp/Glu-His-Ser triad found in all serine proteases and in many esterases[7,8].

But this active-site similarity did not in itself establish that the three-dimensional structure of the Sindbis core protein is similar to that of, say, chymotrypsin, because many different polypeptide chain folds (for example, that of subtilisin) possess this same catalytic triad as a result of convergent evolution to a common function[9]. Moreover, the usual polypeptide chain fold for viral coat proteins is an eight-stranded 'jellyroll' antiparallel β-barrel which does not resemble any serine protease[10]. Indeed, it has been suggested, on the basis of a low level of sequence similarity, that Sindbis core protein should adopt the jellyroll fold, with a catalytic triad arising by convergent evolution[11]. This prediction seemed reasonable as no structural protein was known to be folded like a serine protease.

The three-dimensional structure of the Sindbis core protein was determined by Choi and co-workers by X-ray crystallography, which establishes that the molecule possesses the chymotrypsin fold[1]. The catalytic triad is in the same position as in the mammalian or bacterial chymotrypsin-like enzymes. There are, however, some significant and intriguing differences. There are no disulphide bridges. The 'methionine loop' is missing and so is the C-terminal helix; as already mentioned, the C terminus is folded back into the active site. The 'second serine' found in all other chymotrypsin-like proteases, which hydrogen-bonds to the side chain of the catalytic aspartate, is a non-hydrogen-bonding leucine in Sindbis core protein. The loops that form the P2 and P3 substrate-binding pockets in other serine proteases are completely absent. And finally, the catalytic aspartate 163, whose counterpart is buried in all other serine proteases, is exposed to solvent.

Ordinarily, deployment of a protease as a structural protein would be like using termites to construct a hardwood floor. Sindbis virus solves this problem by having the core protein inactivate itself. The *cis* and *trans* cleavage of a protein from a viral precursor cannot normally be distinguished, but in the case of Sindbis core protein the X-ray structure shows that autocatalytic scis-