RÉSUMÉ

Tell tails

ICARUS, legend alleges, burned out by coming too close to the Sun. So did Icarus the comet, according to D. K. Yeomans (*Astr. J.* **101**, 1929–1928; 1991). Icarus and Apollo are two of several minor planetary bodies, studied by Yeomans, previously identified as stray asteroids owing to their eccentric Earth-crossing orbits. But it has always been recognized that some of these wayward inhabitants of the inner Solar System may be extinct comets, exhausted of volatile ices after countless orbits. Yeomans compared the orbits of several of these bodies with those to be expected if they were moving solely under the influence of gravity. Most behave as expected, but Icarus and Apollo do not. It seems they contain residual traces of ices that evaporate in rocket-like jets as they approach the Sun.

The eyes have it

A PARAMECIUM studied by Y. Nakaoka *et al.* (*J. Cell Sci.* **99**, 67–72; 1991) knows light from shade and makes an avoiding response when the wick is turned up or down. In both cases a measurable membrane depolarization ensues. Deciliated paramecia by contrast respond only to an intensity increase, which implies that the cilia, as well as the cell body, must be light sensitive. The creatures were known to possess retinal, but now it has been found that an antibody against frog rhodopsin labels all the membranes, including those of the cilia. Even if the antigen has a higher molecular weight than animal opsin, the cilium might be seen as a sort of proto-rod or cone and a fit model for vertebrate vision.

Anything goes

THE recently identified heavy '17-keV' neutrino may be just what theoretical physicists have been waiting for. Seen as an annoying anomaly for the standard model of particle physics, the neutrino could solve an even older anomaly, the charge of the electron, or so suggest R. Foot and S. F. King (*Phys. Lett.* B**259**, 464–468; 1991). There are insufficient constraints in the standard model to show why the electron has the precise charge it does, or why neutrinos have none. Foot has previously shown that making certain assumptions about the exact character of the various types of neutrino solves that difficulty. Foot and King now show that this works if one of the neutrino types has just the mass (17 keV) seen in several experiments. The idea introduces fresh oddities – including a further neutrino several million times heavier. But without proper experimental constraints, anything goes in this story.

BCG

Rebirth of a star performer

M. J. Colston

A NEW twist in the long and chequered career of the human tuberculosis vaccine BCG is heralded by the reports by Stover and colleagues, and Aldovini and Young, that appear on pages 456[1] and 479[2] of this issue. Both sets of authors have used BCG (bacille Calmette–Guérin) as a vehicle to express antigen-encoding genes from other pathogens, including the human immunodeficiency virus (HIV), and demonstrate that such constructs are able to induce humoral and cell-mediated responses to the recombinant antigens. So one of the oldest vaccines still in use may well take on a fresh lease of life, the old stager re-emerging as a star performer.

Albert Calmette and Camille Guérin first produced BCG in the early 1920s, by growing a strain of the virulent bovine tubercle bacillus on a medium containing potatoes, bile and glycerine. After many passages it was found to have lost virulence, being unable to produce tuberculosis in animals, and in 1924 it was declared to be a *virus fixe*. Several decades of controversy ensued, with disputes about its effectiveness against tuberculosis and even scandal surrounding its safety (from which it was subsequently exonerated).

Widespread administration of BCG became accepted policy in many countries in the 1950s and 1960s, following the demonstration of its powerful protective effect against tuberculosis in British schoolchildren[3]. It has even found a part in cancer therapy, where its remarkable immunostimulating properties have been used for immunotherapy. The recent observations of its poor efficacy against tuberculosis and leprosy in southern India[4,5], and the questioned cost-effectiveness of continued vaccination against tuberculosis in some Western countries, had led some to argue that its days were numbered. But BCG is safe, cheap and undoubtedly has a significant impact on the incidence of tuberculosis in some populations, particularly when administered early in life, and it is likely to remain part of the vaccination armoury for the foreseeable future.

The stimulus for the fresh activity centring on BCG has been the application of molecular genetics to the mycobacteria. These are particularly difficult organisms to work with, being slow growing (experiments with *Mycobacterium tuberculosis* often take three to four weeks, compared to 24 hours for similar experiments with *Escherichia coli*), and until recently they have been avoided by bacterial geneticists. But their importance as pathogens in their own right and as models for other intracellular infectious agents has led to the development of methods for introducing DNA into mycobacteria, and the propagation and expression of such foreign genes[6–8].

Aldovini and Young[2] have now introduced genes encoding HIV proteins (Gag, Pol and Env) into BCG, using a promoter from a mycobacterial heat-shock protein (Hsp 70) to drive expression of the genes. Stover and colleagues[1] have also employed mycobacterial heat-shock promoters to drive expression of the foreign genes, and have developed two different systems for propagating foreign DNA in mycobacteria – a multicopy plasmid system for extrachromosomal replication of the foreign DNA, and a system which uses the attachment site and integrase gene of a mycobacteriophage to achieve site-specific integration into the mycobacterial chromosome. These systems have been used to express β-galactosidase, HIV proteins (Pol, Gag, reverse transcriptase, gp20 and gp41) and tetanus toxin in BCG.

Both groups report that, when mice are immunized with recombinant BCG, antibody and cell-mediated responses against the foreign antigens are readily detectable. Both helper and cytotoxic T-cell responses were induced, and preliminary results indicate that the recombinant antigens can be recognized by T cells in association with both class I and class II molecules of the major histocompatibility complex. Thus all the immunological components required for generating immunity against a wide range of pathogens could be detected.

The success of BCG as a vaccine has been thought to be due to its ability to survive for long periods of time in the vaccinated host, thereby providing constant antigenic stimulation; this notion is supported by the observation of Stover *et al.* that killed BCG expressing tetanus toxin failed to generate an immune response against the recombinant antigen, whereas viable recombinant BCG did so. Paradoxically, this phenomenon might represent a limitation of the approach, at least in the short term; the many millions of people throughout the world who have received conventional BCG may eliminate a second (recombinant) vaccination too quickly to permit adequate priming of the immune response to the recombinant antigen.

If BCG is to be successfully developed as a recombinant 'carrier' of genes of other pathogens, a number of other issues remain. First, it will be necessary to identify the essential protective components of the pathogens, so that the appropriate genes can be transferred; for many pathogens, although a great deal is known about their immunological recognition, our understanding of the way that recognition is translated into a protective response is meagre. Second, many organisms undergo rapid changes as a means of avoiding immunological recogni-