SCHISTOSOMIASIS

The mouse that wasn't immune

F. E. G. Cox

OVER the past few years it has become clear that humans can acquire some kind of immunity to schistosomiasis. Although the mechanisms involved are not clear, we do have a vast amount of information about immunity to schistosome infections in laboratory animals, of which the mouse is one of the most widely used. However, a series of recent reports[1-3] has pointed to some of the dangers inherent in attempting to draw too many conclusions from the schistosome–mouse model, adding fuel to the debate as to whether any of the existing laboratory models are realistic ones.

Schistosome infections begin when the aquatic larval stages of the parasite, the cercariae, penetrate the skin. The cercariae remain there for 4–5 days, acquiring a coating of host antigens before entering a blood vessel to be carried, as schistosomula, to the heart, lungs, gut and liver. During this passage, they gradually mature into egg-laying adults that normally reside in the blood vessels of the gut or bladder. *Schistosoma mansoni* is the best studied species and its hosts can be classified as permissive, in which the whole life cycle as far as egg-laying adults is completed, or non-permissive, in which the life cycle is curtailed *en route*. The rat is a non-permissive host whereas humans, baboons and mice are permissive. In immune animals, the immune response, mediated by a variety of antibody-dependent cell-mediated cytotoxic mechanisms, is directed against the migrating schistosomula and attrition occurs mainly in the skin and lungs. In attempting to unravel the response, it is highly desirable to have a laboratory model in which immunity in permissive and non-permissive hosts can be compared. Such a model appeared to be mice belonging to the 129 strain; in a proportion of animals, the life cycle progresses to the adult stage, whereas in the rest attrition occurs as a loss of worms from the portal system 3–4 weeks after infection[4,5]. It now appears, however, that the outcome of the infection depends not on differences in immune responsiveness but on the architecture of the blood vessels associated with the lungs and liver[1-3].

It has been known for some time that the portal system of mice chronically infected with *S. mansoni* becomes 'leaky'[6] and that this phenomenon can be investigated by injecting latex beads into a mesenteric vein. The technique has now been applied to uninfected 129 mice[1,2], and in a proportion of such animals the beads were not retained in the liver, as happens in most strains of mice, but became lodged in the lungs. Other studies confirmed the relocation of worms in the lungs of some 129 mice[1,2,5]. It therefore seems that there is a way in which latex beads — and by implication worms — can migrate from the liver to the lungs. This problem was approached by making latex moulds of the vasculature of 129 mice[2,3]. Experiments with the moulds showed that in some animals the vasculature was normal, but that in others there was a considerable truncation of the blood vessels of the liver and lungs which correlates with non-permissiveness[3]. The findings do not explain the migration of worms to the lungs. But an independent study, also using a latex mould[2], has shown that in permissive 129 mice there are connections between the hepatic portal system and the vena cava.

Three groups[1-3] have now demonstrated that the non-permissiveness of 129 mice is due to anatomical abnormalities and is not the result of an acquired immune response. But what actually happens? In normal mice the worms migrate to the liver and cannot get back to the lungs, whereas in some 129 mice they are able to do so, presumably through the connections demonstrated. Once in the lungs, there is a powerful antibody-dependent cell-mediated cytotoxic response, involving eosinophils, which kills the parasites and terminates the infection. The killing mechanism probably involves antibody against schistosome glutathione-S-transferase, a mechanism that drew attention to the 129 mice in the first instance[1], although whether this is a cause or an effect of the parasite killing is not clear. Other possibilities such as the presence of Sendai virus[1], to which 129 mice are particularly sensitive, have now been ruled out[3].

The nature of the connections between the hepatic portal system and the vena cava have not been discussed, but the connections appear to correspond with the ductus venosus; in the embryo, the ductus venosus conveys blood from the umbilical cord directly to the common hepatic vein. Normally, this vessel disappears at birth but whether it persists in 129 mice and, if so, whether its persistence is correlated with the poor vasculature of the lungs and liver of these animals are questions yet to be answered. This series of observations, however, does serve as a warning not to postulate immunological mechanisms where simple anatomical or physiological explanations might suffice. □

F. E. G. Cox is in the Division of Biomolecular Sciences, King's College London, Campden Hill Road, London W8 7AH, UK.

1. Mitchell, G. F. *Parasite Immun.* **11**, 713–717 (1989).
2. Coulson, P. S. & Wilson, R. A. *Parasitology* **99**, 383–389 (1989).
3. Elsaghier, A. A. F. & McLaren, D. J. *Parasitology* **99**, 377–381 (1989).
4. Garcia, E.G. *et al. J. Parasitol.* **69**, 613–615 (1983).
5. Elsaghier, A. A. F. *et al. Parasitology* **99**, 365–375 (1989).
6. Wilson, R. A., Coulson, P. S. & McHugh, S. M. *Parasite Immun.* **5**, 595–601 (1983).

COMPUTING

In search of higher powers

Colin Upstill

THE solution of many important scientific problems requires computer power far beyond that offered by general-purpose machines. One way around this is to connect general-purpose processors together in a parallel computer; another is to build special-purpose hardware that achieves a particular computation as effectively as possible. Common examples of such hardware 'accelerators' include graphics co-processors, FFT (fast Fourier transform) engines, and, most recently, neural-network simulators. On page 33 of this issue, Sugimoto *et al.*[1] outline a hardware accelerator, called GRAPE (for gravity pipe), for force calculations for the gravitational many-body problem. Such calculations require enormous computer power: realistic simulations of the dynamics of astrophysical systems would take up to a teraflops year of calculation[2] (equivalent to a Vax 11/780 running for one million years).

Special-purpose hardware like that proposed by Sugimoto *et al.* can be used to solve many other N-body problems, such as calculating Coulomb and van der Waals forces for molecular dynamics simulations. Many other types of scientific computation require vast computer power, for example, solving the equations of quantum chromodynamics, key to our fundamental understanding of the nature of matter. This sort of computation is only going to be feasible in the foreseeable future by using special-purpose hardware, parallel computing or both.

Advances in semiconductor technology have benefited both approaches. Sugimoto *et al.* propose a GRAPE chip using custom LSI (large-scale integration; tens of thousands of transistors per chip) clocked at 30 MHz. A multi-chip parallel processor could be realized fairly easily, because the many-body forces are simply additive. Today's ultimate hardware solution is custom VLSI (very-large-scale integration) clocked at many tens of MHz, which, with feature sizes down to 1 μm or less, can pack hundreds of thousands of