infection with the human immunodeficiency virus-1 (HIV-1). These authors observed an increased risk of rapid disease progression with a reduction in the number of HLA-A, -B and -C types.

These studies support a pathogen-driven theory for variation (or 'polymorphism') of the MHC. Other mechanisms for the maintenance of polymorphism are also gaining credence. Rodents use MHC-determined odour preferences to select mates⁷, and preliminary behavioural studies involving sweaty T-shirts indicate that some human students may use comparable cues⁸. Also, HLA homozygosity (where people have only one HLA type per locus) might impair fetal survival through an unknown mechanism⁹.

Association studies of infectious diseases have often been too small to assess typically low-frequency HLA variants — a problem that is compounded by the extensive diversity at these loci. The more convincing infectious disease associations have usually been with HLA class II antigens¹⁰, such as HLA-DR2, which increases susceptibility to leprosy and tuberculosis in Asia. Jeffery *et al.*⁴ confirm a previous association between the class II antigen HLA-DR1 and disease susceptibility in HTLV-1 infection, and speculate that this may relate to a pathogenic effect mediated by CD4-positive T cells. There is also strong evidence that HLA-DR13 and HLA-DR11 are associated with clearance of infection by the hepatitis B and C viruses, respectively¹⁰. The first evidence for a protective effect of HLA heterozygosity was also found in persistent hepatitis B virus infection but, again, only for HLA class II antigens¹¹.

Why have HLA class I associations been more difficult to identify? Peptide epitopes (the sequences that T cells focus on) tend to bind to a greater variety of class II than class I molecules, suggesting that clearer class I associations with disease should be found. Technical issues may be part of the answer — molecular typing for the many low-frequency class I variants was introduced relatively recently. Indeed, Jeffery and colleagues detected the HLA-A*02 protective association with HTLV-1 owing to the unusually high frequency of this allele. The protective effect of HLA-B*53 against severe malaria¹² was discovered for the same reason. A large variety of alleles also minimizes the number of homozygotes, reducing the power of most studies to evaluate heterozygote advantage.

Most HLA associations with infectious disease probably represent small effects, yet they are important in evolutionary terms. For commonly fatal infectious diseases, modest odds ratios are enough to select and maintain polymorphism. Genetic variation in the infectious pathogen may also be significant. There is substantial sequence variation in HIV, and it may change its immunodomi-

nant epitopes repeatedly during an infection, as viral mutants are selected by immune pressure¹³. Such viral polymorphism may explain the differing results in many HLA studies of HIV and AIDS. In human papillomavirus and malarial infections, HLA associations with molecularly defined strains of pathogen have been identified^{14,15}.

Heterozygote advantage has now been documented for HLA in only two viral diseases^{5,11}, and it was absent in a large malaria study¹². Perhaps it is undermined by the tendency of cellular immune responses to focus on just one or a few major epitopes. The switching of such epitopes in HIV infection¹³, and the tiny size of the hepatitis B virus genome (which leads to a paucity of epitopes), may explain why heterozygote advantage has been observed in these infections. But, in general, other forms of balancing selection might be more important¹⁶. One is frequency-dependent selection, where rare alleles have a selective advantage — possibly because they arose more recently, giving pathogens less time to adapt to them. Another is fluctuation in selection pressures (produced, for example, by intermittent epidemics), which may also maintain polymorphism. Finally, in the presence of numerous infectious diseases, different alleles, protecting against individual pathogens, could make heterozygosity advantageous overall.

The elegant studies of Jeffery *et al.*⁴ and Carrington *et al.*⁵ document the evolutionary selection pressures that viruses can exert on HLA types. They also support the still controversial view that killer T cells are mainly protective, rather than pathogenic, in these diseases. The challenge now is to design vaccines that will allow the host to strike back — and exert new selection pressures for viral diversification. □

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Daedalus

Spiritual matters

The connection between matter and spirit has been debated for millennia. The central mystery is that certain material objects (human beings) contrive to be conscious and to possess a spiritual dimension. This implies that matter itself has some rudimentary spiritual character.

Daedalus reckons that the spiritual world occupies the same space as the material one, but at most points is very weakly coupled to it. Nonetheless, over cosmological space and time, this weak coupling must have brought the two realms into thermodynamic equilibrium. So the spirit world will have acquired the average temperature of the physical universe — 3 K, the temperature of the microwave background. (This explains why a ghost, an invasion of the material world by the spirit one, tends to cool the room.)

So Daedalus is looking for the weak thermodynamic coupling between the two worlds. A warm material object, even in a perfect vacuum and surrounded by a perfect reflector, should slowly cool down by thermal leakage into the spiritual world. The experiment will test modern thermometry and high-vacuum techniques to their limits; but success would open a whole new field of discovery.

Daedalus is already planning his exploration of it. He hopes to discover whether holy relics and ritual objects, imbued with spiritual significance, cool faster than more mundane ones. He expects that biological materials, especially the neurotransmitters and proteins of brain chemistry, will cool faster still. They are part of the secret of human consciousness, and should be quite tightly coupled to the spiritual world. This coupling might take the form of strong spectroscopic emission at the 3 K black-body peak in the millimetre-wave region, or it might be far more subtle. But detailed experiments, aided by such insights, should reveal the spiritual capacity of a wide range of objects and substances.

Perhaps the most interesting objects for testing will be semiconductors, either as bulk solids or in the form of integrated circuits and microprocessors. If they cool no faster than common minerals, this will demonstrate their lack of a spiritual dimension — in which case no computer, however powerful, could be conscious. But if they turn out to cool as fast as the neurotransmitters, then conscious technological monsters like Hal and Deep Thought should indeed be possible.

David Jones