

## MULTIPLE SCLEROSIS

ments, is consistent with an early mammalian radiation always retaining something of the ancestral sprawling gait. Two complete humeri from the Eocene have been published as stereophotographs and show features to support this<sup>8</sup>, including a marked residuum of the primitive torsion between humeral head and elbow condyle. Sereno and McKenna<sup>2</sup> now argue from the features of their beautiful specimen of a small, Late Cretaceous multituberculata forelimb that it was very like that of therians and it was swung parasagittally over a considerable range. A corollary is that therians and multituberculata share this advance, not shown by monotremes. Non-palaeontologists should note that the methods used in these studies are not speculative descriptions of how the dead bones may have articulated and moved: a considerable number of osteological features are scored objectively to evaluate functional and phylogenetic correlations. However, many fossil specimens show cracks and distortions which can make biometrics inexact.

There is need for caution in relation to these new conclusions. The detail is obtained from one or two species in a long-lived radiation that must have adapted to a variety of niches. How likely is it that all multituberculata over this huge time span were restricted to low-frequency hearing? If the forelimb was advanced in a Cretaceous form and primitive in an Eocene form, from the same taeniolauid group, how secure is any assumption about the timing of the advance? We derive from marsupials and placentals knowledge of a broad range of adaptations, but the monotremes, platypus and echidna, are very specialized in locomotion and hearing, and we still only guess at the primitive ancestral form. With important new material coming from the efforts of Australian palaeontologists and from the recent American–Mongolian expeditions, we can hope that more well preserved skeletal finds will provide both interesting answers and surprises within this somewhat neglected part of our family history. □

Robert Presley is in the School of Medical and Molecular Biosciences, University of Wales, Box 911, Cardiff CF1 3UA, UK.

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## More genes versus environment

Byron H. Waksman

ON page 150 of this issue<sup>1</sup>, Ebers *et al.* describe the results of a painstaking study of 15,000 patients suffering from multiple sclerosis (MS). Their conclusion is that the aggregation of MS cases within families is determined entirely by genetic factors and is not influenced by shared environmental factors like infection. This vexing genes-versus-environment issue has been convincingly resolved as a result of the authors' comprehensive screening of adoptive first-degree 'relatives' of a large, fully ascertained and well studied population of MS patients from fourteen clinics across Canada.

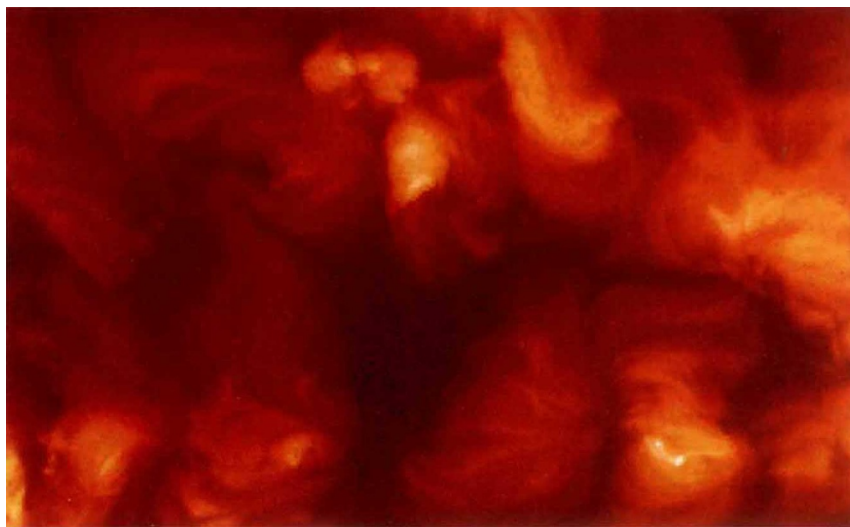
In a sense, these findings are not surprising. It is now widely thought that MS is the result of an immunologically mediated, quite possibly autoimmune, process. Susceptibility to MS seems to be determined, in part, by the genes that encode elements of the trimolecular complex involved in recognition by T cells. These

include the major histocompatibility complex (MHC), certain T-cell receptor peptide sequence polymorphisms and encephalitogenic peptides of brain protein antigens; also implicated are genes governing elements of the immunologically determined inflammatory process. The high concordance of MS in monozygotic twin pairs and in first-degree relatives of individuals with MS, cited by Ebers *et al.*<sup>1</sup>, is an expression of these genetic influences.

But although Ebers and co-workers were unable to detect any effect attributable to shared environment, things may not be quite so simple. These authors only addressed the question of MS prevalence among non-biological 'relatives' living with an MS case, most of whom do not carry genes for MS susceptibility. But shared environment undoubtedly does play a part in the induction of disease among biological relatives who live with

## SOLAR PHYSICS

## Coils of flame



J. Klimchuk/Yohkoh

THESE fiery coils would have been the delight of any Renaissance painter, could he only have seen them. But the image shown here is not a snippet from the head of some Titian beauty. Instead, the arching, twisted loops are an X-ray telescope's view of the solar corona, where the gas — fiery indeed — is at a temperature of several million kelvin. How the gas is heated to this extent was the question exercising James Klimchuk and Lisa Porter, whose research is reported on page 131 of this issue and in a paper to appear in the *Astrophysical Journal*. From observations of long-lived coronal loops made with the soft X-ray telescope aboard the Japanese Yohkoh

satellite (the name means 'sunlight'), they have determined the temperatures and densities of individual loops, and from this derived a scaling law for loop length with gas pressure. The various theories for the mechanism of coronal heating make different predictions for what this scaling law should be, so — an unusual feat in this area of research — Klimchuk and Porter have supplied an observational means of discriminating between rival theories. To untangle the tale further will, they suggest, best be done by making direct measurements of the magnetic field strength in the loops.

Lindsay Nightingale

the index case, and who are susceptible to MS.

Data obtained in an earlier study by Ebers' group, which looked at sibpairs in MS families, supported a role for genes and for shared exposure to environmental agent(s) in determining the age and year of onset of MS in the members of each pair<sup>2</sup>. The incomplete penetrance of susceptibility genes in identical twin pairs also points to the importance of environmental influences in the occurrence of disease among those with the appropriate genes.

Ebers and his colleagues express the hope that their findings "may . . . divert the search for environmental clues away from specific uncommon viruses to a broader category of events occurring early in life which are applicable to regional populations"; this comment is presumably aimed at Kurtzke and those sharing his view<sup>3</sup> that existing epidemiological data point to a specific infectious (presumably viral) agent as a direct cause of MS. No such agent has ever been successfully linked to MS, however, either by direct isolation or by indirect (for example, serological) means, despite claims for some twenty different viruses. The epidemiological data<sup>4</sup> fit equally well with a model of disease induction in genetically susceptible individuals by common viruses and mediation by a secondary process, such as autoimmunization against myelin or other brain antigens.

The situation in MS is reminiscent of that in poliomyelitis, in which there is a clear relation between the age at which viral transmission occurs and the age at which attack by the virus on the central nervous system commences. The incidence of neurological disease increases in individuals of higher socioeconomic status within a population (because this tends to be associated with viral transmission delayed to late childhood or early adolescence) and in populations living at temperate latitudes (these, in general, enjoy a better standard of living, again with later transmission of common childhood infections). A similar requirement in MS for late viral transmission has been demonstrated in a well controlled, population-based study that showed an almost tenfold increase in the risk of contracting MS as the age (up to puberty) of infection with common childhood viruses (such as measles) increased<sup>5</sup>.

The ability of viruses to cause autoimmunization is not in doubt. It was shown over a decade ago<sup>6</sup> that measles in humans occasionally results in T-cell sensitization against myelin basic protein (MBP) and this sensitization is associated with an inflammatory demyelinating 'post-infectious' encephalomyelitis. The same relationship has been demonstrated in rats and mice infected with suitable strains of coronavirus or measles virus<sup>7,8</sup>. Such

cross-immunization is usually attributed to molecular mimicry<sup>9</sup>. A recent report establishes that T-lymphocyte clones from MS patients specific for a single encephalitogenic MBP peptide recognize configurationally similar peptides of several common viruses equally well<sup>10</sup>. These cells are stimulated by either viral or MBP peptides to proliferate and secrete inflammatory cytokines.

The factors responsible for inducing MS, the thrust of Ebers and co-workers' contribution, must be strictly distinguished from the factors that trigger relapses (or exacerbation) of this disease once it has been induced. Here upper respiratory and gastrointestinal virus infections appear to play a key part, as first reported by Sibley *et al.*<sup>11</sup> and dramatically confirmed more recently by Panitch<sup>12</sup>. The interval before relapse, however, is measured in days or weeks, whereas initiation of the process that leads to MS may span a period of years — Kurtzke, in his Faeroe Island studies, calculated an average interval of six years<sup>3</sup>. Also, although new T lymphocytes with pathogenic potential may be generated at each relapse, other factors may predominate, such as systemic release of inflammatory cytokines like  $\gamma$ -interferon, as part of the viral infection. This would result in upregulation of the MHC on vascular and glial elements in the central nervous system, which in turn would allow new lesion formation. Administration of  $\gamma$ -interferon in quiescent MS patients does in fact provoke symptoms of the disease, which correlate with MHC expression on circulating monocytes<sup>13</sup>.

Time will tell whether other (non-infectious) agents also play a role in inducing MS. The infectious/autoimmunity hypothesis has proved remarkably fruitful, but other influences, such as climate, general levels of infection and neuroendocrine processes call for deeper investigation. □

Byron H. Waksman is in the Department of Pathology, New York University. He can be reached at 300 East 54th Street, New York, New York 10022, USA.

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DAEDALUS

## Hard water

**ENGINEERING materials must not only be strong: they must be stiff as well. Indeed, stiffness is often more important than strength. Plastics, for example, are excluded from many engineering uses not because they would break, but because they would bend.**

In this connection Daedalus recalls that the stiffness of a tube can be increased by pumping a fluid through it. At a critical flow rate it even becomes infinitely stiff. Any deflection is then perfectly opposed by the internal flow. Increase the flow further, and 'negative stiffness' sets in — the pipe will react against a load. At higher flows still, oscillations occur. This is what makes a fire hose wriggle under a fast flow.

DREADCO's engineers are now exploiting these facts. Aircraft and rockets, for example, have to be very light but stiff structures; they also depend on liquid fuels pumped at high velocities. The DREADCO workers hope to achieve the first requirement with the aid of the second. Many aircraft already store their fuel in compartments in their wings, and little modification should be needed to pump it to the engines through the hollow spars of the wing structure. Indeed, this trick has already been proposed for supersonic aircraft to allow the flowing fuel to absorb frictional heat from the leading edges.

A light and flimsy aircraft or rocket, stiffened in flight by its flowing fuel, should be supremely efficient. More cunning still, its stiffness and damping could even be altered in flight by redistributing the fuel flow between different spars of the structure. The various flutters and instabilities which plague aerodynamics could be played off against each other, shifted away from dangerous resonances, or otherwise made harmless. The computing power already built into all modern aircraft and rockets could implement such strategies in real time with great aplomb.

Another application is more earthbound. Daedalus is designing a large, light building with a structural frame of plastic piping. This will be stiffened by pumping water continuously through it. Some of the water will be used by the normal domestic and heating or cooling requirements; the rest will be recirculated. The idea is to withstand earthquakes. A severe shock to the structure will stop the pumps. The building will then lose, not its strength, but its stiffness. It will absorb the battering in a flexible, rubbery manner, neither falling down nor injuring the occupants. When the danger is past, it can be pumped back to normal structural rigidity.

David Jones