in gas in the galaxies that lie between us and the quasar. The strengths of these lines may be used to infer both the relative gas-phase abundances of the ions responsible, and, through some corrections for relative populations of different levels of ionization, the relative element abundances in the interstellar gas.

There is a major complication that has to be considered if one wishes to infer the true abundances from the gas-phase abundances. In the interstellar medium in the Galaxy, much of the material for the common elements (such as carbon, oxygen, silicon and iron) goes into the formation of interstellar dust grains, so that the true abundances of these elements are somewhat higher than the gas abundance would indicate. Only for a few relatively rare elements, notably zinc, is there negligible depletion onto dust, and only through measurement of the abundances of these are we likely to obtain an accurate picture of the heavy-element abundances in high-redshift systems.

Detecting the zinc lines is difficult because of the weakness of the lines even for abundances typical of those in our Galaxy, and the possibility of lower abundances at high redshift increases this difficulty. Despite this, two groups have recently reported measurements of lines from singly ionized zinc which allow them to determine its abundance relative to hydrogen at redshifts $z = 2.8$ and $z = 2.3$ (refs 1, 2). Thus, depending on the rate of slowdown of the expansion of the Universe, they are examining the chemical content of material which existed when the Universe was something like 15–30 per cent of its present age. In both cases, the heavy-element abundances relative to hydrogen, as measured by Zn^+, are roughly an order of magnitude down on the value near the Sun. The straightforward interpretation of these results is that nucleosynthesis in these high-redshift systems has led to the production of only about one-tenth of the heavy elements we see today, and so the objects are in an early stage in their chemical evolution.

In both studies it was possible to compare the zinc abundance with chromium, another species that is depleted onto grains, and in both cases the chromium abundance is closer to the true value than in the Galaxy. As a consequence, it seems likely that these high-redshift regions are relatively dust free. If this is true in general, abundance analyses based on the stronger lines of more common elements that are depleted in a galaxy should provide reasonably reliable estimates for the true abundances. This is encouraging for those wishing to probe higher-redshift, and possibly lower-abundance, systems to obtain a fuller picture of the chemical history of material in the Universe. □

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MULTIPLE SCLEROSIS

Hopeful genes and immunology

Dale E. McFarlin and Peter J. Lachmann

ALTHOUGH both environmental and genetic factors are believed to contribute to the pathogenesis and etiology of multiple sclerosis (MS), it is the genetic contribution which is attracting most attention in research laboratories at present, and which was the main focus of a recent workshop*.

The evidence for a genetic contribution to MS is derived from studies of the disease in families and ethnic groups. Recent population-based studies of large numbers of patients have confirmed earlier impressions that up to 18 per cent have affected family members (A.D. Sadovnick, University of British Columbia) and that there is a higher concordance in monozygotic (MZ) than in dizygotic twins (G.C. Ebers, University of Western Ontario). Also, some clinically normal MZ twins have abnormalities on magnetic resonance imaging consistent with subclinical disease. Moreover, environmental factors do not explain why the disease is absent in Hutterites residing in western Canada, a region of high prevalence (W.J. Hader, University Hospital, Saskatchewan) or why in Kuwait, the prevalence is approximately three times greater in Palestinians than in Kuwaitis (A.S. Al-Din, Kuwait University).

The epidemiology of MS is consistent with a polygenic disorder and a number of genes were discussed as possibly contributing to susceptibility. Emphasis was placed on genes related to immune function because of the prevailing opinion that an immunopathologic process gives rise to the disease. Associations between MS and HLA class II molecules, particularly the DRw2 and DQw1 serotypes, are well known. Extensive analyses of HLA class II genes in MS have been conducted and a *DQβ1* gene that encodes polymorphic sequences in DR2, DR4 and DRw6 was found in 97 per cent of Norwegian patients and in 70 per cent of controls by using a sequence-specific oligonucleotide probe (F. Vartdal, University of Oslo). Another new finding was that a recently recognized DQα polymorphism correlates with the disease (R. Heard, Hammersmith Hospital). So far, however, no specific HLA class II sequence related to susceptibility or resistance to MS, analogous to that described in insulin-dependent diabetes, has been identified.

The possible role of genes other than those of the *HLA-D* locus on chromosome 6 was discussed, particularly those encoding TNF-α, TNF-β and complement components. Some products of these genes can lead to damaged myelin and secretion of TNF-β by myelin basic protein-specific T-cell clones, discussed below, correlates with the production of experimental allergic encephalomyelitis (EAE), a possible animal model of MS (L. Steinman, Stanford University). Complement activation has been implicated in the pathogenesis of MS and EAE (D. A. S. Compston, University of Cambridge), and it was suggested that genetic deficiency of late-acting complement components could be protective in populations with low frequency of MS.

Three independent groups of investigators presented new findings linking MS to T-cell receptor (TcR) genes. One study showed that haplotypes for germline V beta genes in $DR2^+$ MS patients differed ($P < 0.002$) from those in $DR2^+$ controls (W.E. Biddison, NIH). In the second study, *TcRβ* haplotypes defined by polymorphic markers were compared in MS sibling pairs, and haplotype sharing was found to be significantly more frequent ($P < 0.004$) than expected (S.L. Hauser, Harvard University). The third study reported linkage of MS to a TcRα gene polymorphism and described amplification of this gene by polymerase chain reaction (PCR) from MS brain (J.R. Oksenberg, Stanford University).

The influence of genes at other loci was also considered. The previously described association between MS and genes on chromosome 14 including *GM1* and the α-antitrypsin gene were debated and now seem less convincing to some investigators (G. Stewart, University of Sydney; B. De Hooghe, University Hospital, London, Ontario). No new information on the previously reported association with *GM3* was described. Various clinical observations provoked discussion of genes related to gender: the prevalence is higher in females than males; in like-sex MZ twins, the concordance is higher in females than males, and in families in which parent to child 'transmission' occurs, the father to son 'transmission' is lower than other possibilities (Sadovnick). A resistance gene on the Y chromosome or a recessive resistance gene on the X chromosome could explain the findings, but data supporting such possibilities are lacking.

New findings from a variety of auto-

* *Genes and Susceptibility to Multiple Sclerosis*, Cambridge, 25–29 July 1989.

immune animal diseases were presented, from whence a common theme with implications for MS emerged. This is that the spontaneous occurrence of autoimmune disorders, such as thyroiditis, insulin-dependent diabetes and systemic lupus crythematosus — and so, by implication MS — requires the interaction of three or more genes, one of which is usually an *MHC* gene. When fewer than the required number of genes are present, pathological abnormalities may occur in the absence of clinical disease. For example, at least three genes are required for the expression of insulin-dependent diabetes in NOD mice, but if only two are present as in NOD.H2^b congenic strain, abnormal accumulations of mononuclear cells occur in the pancreas (L. Wicker, Merck, Sharp and Dohme). Multiple genetic influences are clearly operative in experimentally induced demyelinating diseases that serve as possible models for MS, including EAE (F. Lublin, Thomas Jefferson University, Philadelphia) and encephalitis associated with coronavirus in rats and Theiler's murine encephalomyelitis virus (TMEV) in mice. A gene that confers resistance to subacute demyelinating disease in rats has been identified (H. Wege, Universität Wurzburg). Recent experiments indicate that the demyelination produced by TMEV is the consequence of a T-cell response to a viral antigen (S.D. Miller, Northwestern University). Such immunologically mediated processes require recognition of antigen in association with MHC molecules, but in the central nervous system, MHC is expressed in relatively low amounts, if at all. This has led to considerable interest in the capacity of residual cells of the central nervous system, such as astrocytes, microglia and capillary endothelial cells, to function as antigen-presenting cells and to participate in immunopathological processes.

The findings in MS and animal models provide a clear rationale for future studies. One approach will be to define the disease susceptibility genes related to MS in greater detail. Such efforts will benefit from recently developed approaches such as 'micro-satellite' probes and the use of PCR in conjunction with specific oligonucleotide primers for the genes of interest. Assessment of multiple genes in well-characterized families will be essential. This will be laborious and progress will be enhanced by cooperation among different investigators. It was particularly encouraging, therefore, that considerable discussion, including an unscheduled evening session, was devoted to future collaborative efforts. As such genetic studies proceed, there will be parallel efforts to characterize immune reactivity in MS. Extensive studies in a few patients indicate that such findings will be complicated. For example, T-cell reactivity to myelin basic protein is heterogeneous both in terms of epitope specificity and *TcR* gene usage (J.R. Richert, Georgetown University).

Another line of investigation that received encouragement is the development of therapeutic strategies that involve immunological manipulation. Studies of EAE and immune reactivity to myelin basic protein provided the basis for five approaches affecting either T cells or antigen presentation. One is treatment with antibody to CD4. This inactivates the subset of T cells that bear this protein (H. Waldmann, University of Cambridge) and is beneficial in EAE. Another approach is the use of antibody to the TcR. Support for this approach is derived from experiments with encephalitogenic T-cell clones. In PL mice, these preferentially use Vβ8.2, and the administration of antibody to this *TcR* gene product blocks EAE (Steinman). An alternative is the use of antibody to MHC class II molecules, which suppresses EAE in some species.

Finally, there are two approaches that make use of peptides and which were explored recently in News and Views by Charles Janeway (*Nature* **341**, 482–483; 1989). In one case, the plan is to immunize with TcR peptides. Recent data indicate that encephalitogenic T cells from mice and rats share germline *TcR* genes despite difference in peptide specificity. A conserved sequence has been identified and vaccination with a corresponding synthetic nonapeptide induces resistance to EAE in the highly sensitive strain of Lewis rats (M. Howell, Immune Response Corporation, San Diego). The other possibility is to block MHC class II molecules with specific peptides. Assessment of synthetic polypeptides with single amino-acid substitutions in the nonapeptide that causes EAE in PL mice has identified one that binds with high affinity to MHC class II molecules (J. Rothbard, ImmuLogic Pharmaceutical Corporation, Palo Alto) and inhibits the induction of EAE (D. Wrath, Stanford University).

Collectively, these experiments provide an elegant demonstration that recently acquired knowledge in fundamental immunology can be used to modify an immunologically mediated disease such as EAE. This produced considerable excitement for extending such efforts to MS patients. Implicit in such reasoning is that a T cell-mediated process contributes to the pathogenesis of MS and that humans will respond in the same manner as rodents. Neither of these is yet certain. Nonetheless, it is clear that the workshop has provided the basis of a variety of new approaches for studying MS. □

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DAEDALUS

Sound of silence

A PORTABLE radio or tape player with loudspeakers is essentially an offensive weapon; its chief function is to annoy other people. The socially responsible music lover uses a personal tape player driving earphones, so as to deafen himself without disturbing anyone else. Sadly, this noble intention is seldom achieved. The soft, tinny, rhythmic leakage from earphones has a unique annoyance value of its own. So Daedalus is developing a truly private listening system. His idea is to vibrate the user's eardrums directly, without ever generating any sound at all.

To couple the eardrum directly to a mechanical transducer would require the most delicate surgery, and would permanently affect normal hearing. But Daedalus recalls a magnetic ear-lacquer he once invented. Sprayed into the ears, it coats the eardrums so that they can be vibrated by an oscillating magnetic field. It was intended as the sensing component of a magnetic metal-detection system; but Daedalus now sees it as the ideal way to create an entirely private sound sensation. With his eardrums coated with ferromagnetic lacquer, the user will directly hear the audio field of a nearby induction coil, mounted perhaps on his collar or spectacle frame. Feed the coil from his personal tape player, and he will hear its music in wonderful high fidelity — all the distortions and limitations of small earphones will be eliminated. Nobody else will hear a thing. The lacquer should last for several days, until displaced by the ear's natural waxy secretion.

This splendid technology can easily be extended. The deaf-aid industry will surely welcome such a simple way of generating subjective sound, free of all the limitations of small ear pieces and the problems of acoustic feedback. Buses and aircraft will be able to radiate a music channel magnetically, and charge patrons for the use of a discreet ear-spray to listen to it. And magnetic tape recordings will become far more accessible — just wind them past your lacquered ear and hear them directly, with no electronics needed at all!

But the uses of ferromagnetic ear-lacquer should extend far beyond sound reproduction technology. Electricians could listen directly to motors, transformers and relays to diagnose their ills. They could track wiring through a house, and estimate the current flowing in it by sound alone. And health worriers could monitor the general environmental level of a.c. magnetic fields, which over time are feared to depress the human immune system. With the malign tones of overhead power lines, military radars, and badly shielded video-display terminals ringing in their ears, they could assess the hazards directly, and adopt the appropriate level of worry. David Jones