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HLA Antigens in Multiple Sclerosis

Central to all mammals investigated is a group of closely-linked genes which relates to a number of different immunological processes. In man this genetic region has been designated the HLA complex, which consists of a variety of different genes; it is known to be located on a segment of Chromosome 6 (Lamm *et al.* 1974). Several different *in vitro* techniques have been used to identify some of the gene products present on the cell surfaces.

The HLA-A and -B as well as the HLA-C antigens are detected by the microlymphocytotoxic test. These specificities, considered loosely to be the HLA antigens, are expressed on cells of most tissues, although only weakly – if at all – on red cells (Fig 1).

The mixed lymphocyte reaction (MLR) is based on the ability of specific antigens on the lymphocyte surface controlled by the HLA-D locus to elicit a proliferative response in allogeneic lymphocytes (Yunis & Amos 1971). Until recently it was only possible to test for D-locus identity between two individuals. More recently, by the use of homozygous typing cells (Bradley *et al.* 1973, Jorgenson *et al.* 1973, DuPont *et al.* 1973) and sperms (Halim & Festenstein 1976), it has proved possible to type for individual D-locus specificities. The tissue distribution of the D-locus antigens is more restricted than that of the HLA-A, -B and -C antigens.

Additional antigens have been detected, almost exclusively on B cells and not T cells, by B-cell serological techniques. These antigens are considered analogous to the original Ia genes found in the I-A region of the murine H-2 system which controls antigens detected predominantly on B cells (Sachs & Cone 1973). At least two genes controlling B-cell antigens in humans have been established in the HLA complex but not yet mapped.

Several features mark the gene products of the closely linked HLA-A, -B, -C, -D and B-cell genes. They are highly polymorphic; more than twenty each of HLA-A and HLA-B, five HLA-C and eight HLA-D antigens have been identified (Kissmeyer-Nielson 1976). Also, some specificities, but not others, of the different systems occur together more frequently than can be explained by chance, e.g. HLA-A1 and HLA-B8 occur together in about 10% of individuals. Since their respective frequencies are approximately 20% and 15%, they should occur together, if randomly distributed, in only 3% of individuals. This phenomenon, known as linkage disequilibrium, also explains why, for instance, HLA-DW2 is more closely associated with HLA-B7 and HLA-DW3 with HLA-B8. In addition, the HLA complex controls genes whose products are involved overtly in *in vivo* phenomena. A number of different components of complement are controlled by genes within the HLA complex – both the C^2 and C^4 polymorphisms and their serum levels have been shown to be determined by genes located in the HLA complex (Möller 1976).

Antigens of major importance in kidney graft rejection have also been shown to be products of

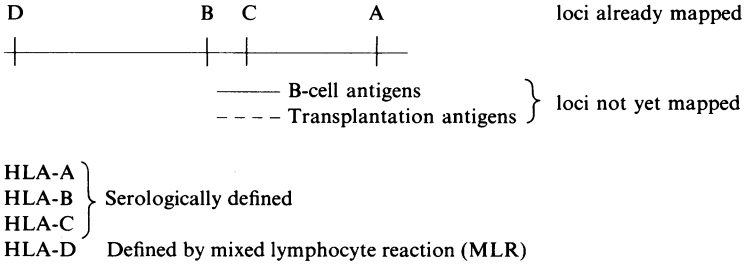

Fig 1 *HLA region of Chromosome 6*

genes within the HLA complex, based on the high success rate of grafts between HLA identical siblings compared with grafts between siblings differing for one or both haplotypes (Singal *et al.* 1969).

The association of a variety of diseases with certain HLA specificities is of special interest to clinicians. This association was firmly established when it was observed that 95% of individuals with ankylosing spondylitis have HLA-B27, which is normally found in 10% of healthy individuals (Brewerton *et al.* 1973, Schlosstein *et al.* 1973). Associations between the HLA antigens and multiple sclerosis were noted earlier and the purpose of this article is to demonstrate the altered HLA specificities in this disease and indicate certain clinical and genetic implications.

Jersild *et al.* (1972) clearly established that certain HLA frequencies – HLA-B7 particularly – differed in multiple sclerosis, and earlier in that year Naito *et al.* (1972) had already shown an increased frequency of HLA-A3. Since the HLA system is so heterogenous, there is always the possibility that associations between HLA antigens and disease may be found by chance. It is therefore interesting to note that Cazzullo & Smeraldi (1972) in Italy found a higher frequency of HLA-A9 and not -A3 or -B7.

When D-locus typing became possible, an even higher association between patients with multiple sclerosis and the HLA-DW2 (LD-7a) specificity was shown (Jersild *et al.* 1973), i.e. 70% of patients were observed to have -DW2 compared to 16% in controls. More recently, a number of laboratories have shown a very high incidence of the particular B-cell antigen in linkage disequilibrium with -DW2 in patients with multiple sclerosis (Winchester *et al.* 1975, Compston *et al.* 1976, Terasaki *et al.* 1976). A summary of the frequencies of the HLA-A3, -B7, -DW2 and the B-cell antigen associated with DW2 is given in Table 1, based on collated data from different centres mentioned above. It has not been definitely established that the B-cell antigen, BT 101 (Compston *et al.* 1976), and Group IV (Terasaki *et al.* 1976) are one and the same, although they are both in strong linkage disequilibrium with -DW2. Nevertheless, the high association of multiple sclerosis in both series with a specific B-cell antigen is apparent.

Since the siblings or offspring of patients with multiple sclerosis who inherit the same haplotype rarely also acquire the disease, it is evident that the disease is multifactorial in origin. The gene product in the HLA complex which induces susceptibility to multiple sclerosis appears to be in strong linkage disequilibrium with the specific B-cell antigens mentioned earlier. The association of multiple sclerosis with -A3, -B7 and -DW2 can thus be seen to be due to their linkage disequilibrium with the specific B-cell antigen. Terasaki *et al.* (1976) suggested that the multiple sclerosis susceptibility was due to a mutation of a gene closely linked to the B-cell antigen system and this mutation occurred originally in an individual with a classical multiple sclerosis haplotype -A2, -B7, -DW3 and Type IV antigen. The various possibilities on the role played by the gene product have been reviewed recently by McDevitt & Bodmer (1974).

Certain clinical implications arise from the association of multiple sclerosis with the particular HLA haplotype. Two groups, Jersild *et al.* (1973) and Bertrams *et al.* (1973), have suggested that the correlation between the possession of HLA-DW2 and -B7 in patients with multiple sclerosis affects the progression coefficient of the disease in these individuals unfavourably.

The presence or absence of the B-cell antigen associated with multiple sclerosis in a patient suspected of having the disease may be of aid in diagnosing multiple sclerosis. This test cannot yet be established on a simple routine basis. The B-cell antigen is present in 20–30% of individuals without multiple sclerosis and approximately the same proportion of multiple sclerosis patients lack it.

Table 1
Distribution of some HLA antigens in multiple sclerosis (MS)

		% positive		
		MS	*Control*	*Reference*
HLA-A3		33	20	Compston *et al.* (1976)
		50	32	Terasaki *et al.* (1976)
		48	25	Jersild *et al.* (1973)
HLA-B7		57	33	Compston *et al.* (1976)
		39	33	Terasaki *et al.* (1976)
		49	26	Jersild *et al.* (1973)
HLA-DW2		50	20	Terasaki *et al.* (1976)
		70	16	Jersild *et al.* (1973)
B-cell antigen	BT 101	83	32	Compston *et al.* (1976)
	Group IV	83	33	Terasaki *et al.* (1976)

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The Evidence Justifying Immunosuppression Therapy in Multiple Sclerosis

It is a rather difficult task to elaborate on the existing evidence justifying immunosuppressive treatment in patients with multiple sclerosis (MS). The main obstacle to the removal of this difficulty lies in the still unresolved question of whether immune mechanisms are decisively involved in the natural history of MS and, if so, in what way and to what degree. Thus, in any attempt to justify immunosuppression one must first scrutinize the validity of the evidence for a major role of the immune system in this disease.

If someone unbiased by any particular school of thinking and methodological expertise were to work his way through the vast amount of available information about the possible cause of MS, he might well end up with the picture of a multifactorial ætiology as shown in Fig 1.

There is good evidence for the involvement of metabolic factors, modified by diet (Mertin & Meade 1977); for a viral infection (Johnson 1975), presumably taking place at a certain age; and for immune reactions to cause the symptoms of the disease or perpetuate it once central nervous system (CNS) tissue damage has been brought about by other factors (Paterson 1973). If the assumption of a multifactorial cause of MS were to prove correct, then subsequently any curative regimen would have to include a combination of different therapeutic approaches. This may perhaps be one of the reasons why all therapeutic trials, aiming usually for an interference with only one of these possible factors, have been so unsatisfactory up to date.

Immune mechanisms in MS

In recent years the notion of immune deviation has been discussed increasingly in MS research. A congenital defect or a viral infection may impair the function of certain cells of the immune system, the thymus-derived T cells (which are the agents of the cell-mediated immune response), and thus make possible a continued virus infection of the CNS. The viruses thought most likely to be responsible are those of the paramyxo group; for

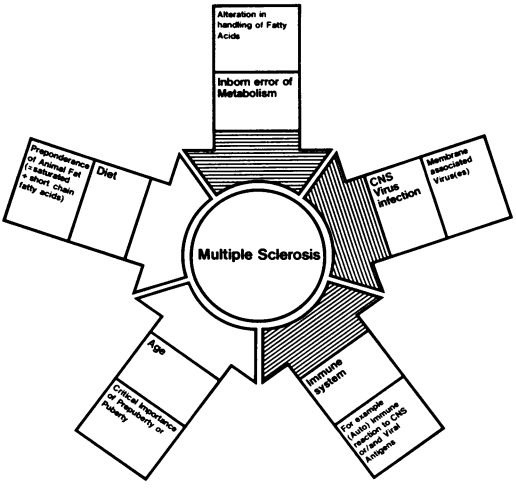

Fig 1 *The multifactorial ætiology of multiple sclerosis. Shaded areas indicate involvement of genetically determined or influenced membrane functions*