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Immune disease and HLA associations with myasthenia gravis

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SUMMARY In the late 1950's laboratory and clinical evidence suggested that myasthenia gravis was an autoimmune disorder. Since then a voluminous literature has developed documenting the many immunological abnormalities that occur in this condition. Recent findings point to a central disorder of immunoregulation. It is postulated that the disease occurs as a result of host genetic and environmental influences—the latter being, as yet unidentified and possibly a virus.

It was first suggested by Smithers in 1959[1] that myasthenia gravis might be an autoimmune disease because of the histological similarities he noticed between the thymus gland in myasthenic patients and the thyroid gland in patients with thyroiditis. Within a short period of time several other workers reported immunological features in the disorder: Nastuk and co-workers[2 3] provided the first laboratory evidence of an immunological abnormality when they enlarged on work first reported in 1956[4] and recorded changes in the serum complement levels of myasthenic subjects; at the same time Strauss et al[5] reported the presence of complement-fixing antibody, binding *in vitro* to skeletal muscle, in the serum of these patients. Simultaneously, Simpson[6] described a very large series of cases of myasthenia gravis and drew attention to the increased incidence of other illnesses thought to be autoimmune. Thus the attention of the early investigators of myasthenia gravis was drawn to the immune system and since then a voluminous literature of immunological observations has accrued in this disorder.

A wide variety of immunological abnormalities have been demonstrated including evidence of thymus-derived (T cell) malfunction *in vivo* and *in vitro,* changes in the distribution of T and bursa-derived (B) lymphocytes in the thymus gland, a wide variety of autoantibodies with, in particular, antibodies to the nicotinic postsynaptic acetylcholine receptor, fluctuations of certain serum complement components, and the presence of circulating immune complexes.

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A genetic contribution to the pathogenesis of the disease has also been clearly demonstrated by family studies and, more recently, by the discovery that certain histocompatibility antigens are over-represented in these patients. Finally, a laboratory model, experimental allergic myasthenia gravis (EAMG), produced by immunising susceptible animals with postsynaptic nicotinic receptor, has been described.

It is stressed in this article that immunoregulation, which is dependent on the proper interaction of genetic and extrinsic factors, is abnormal in myasthenia gravis and the plethora of immunological abnormalities found can thus be interpreted as due to a central defect in immune regulation.

T lymphocyte function

It seems appropriate to begin this section with restatement of the fact that led Simpson[6] to formulate his theory that myasthenia gravis was an autoimmune disorder: that is, there is an association of myasthenia gravis with several other diseases considered to have an autoimmune aetiology. The association appears strongest with thyroid diseases and rheumatoid arthritis but table 1 shows the many other immunological disorders reported as occurring in myasthenic patients. There is also an increased incidence of neoplastic disorders, including chronic lymphocytic leukaemia[7] and lymphosarcoma.[6] Patients with myasthenia gravis in general do show an increased risk of developing malignancy, a risk which is lessened if thymectomy is performed.[8]

The fundamental abnormality which results in autoimmunity is as yet unknown but a variety of

Table 1 *Diseases reported in association with myasthenia gravis*

Autoimmune haemolytic anaemia
Carcinoma
Coeliac disease
Complication of penicillamine therapy
Dermatitis herpetiformis
Disseminated lupis erythematosus
Epilepsy
Immune complex nephritis
Pemphigoid
Pemphigus
Pernicious anaemia
Polymyositis
Pure red-cell aplasia
Rheumatoid arthritis
Sarcoidosis
Scleroderma
Sjogren's syndrome
Thymoma
Thyroiditis
Thyrotoxicosis
Ulcerative colitis

clinical and laboratory observations have led to the formulation of several theories of causation. A study of these theories shows that the features invariably stressed as representing the development of autoimmunity, are found in myasthenia gravis. Thus it is to be expected that investigation of the nature of the autoimmune process in this disease will be of great importance in explaining the nature of autoimmunity and the importance of host-viral relationships.

The original investigators of autoimmune diseases studied the serum autoantibodies detectable; in most of the present theories of autoimmunity however, it is the thymus-derived (T) lymphocytes which are allocated the most important role. In 1949 Burnet and Fenner[9] had suggested that mutant cells might give rise to the poetically termed "forbidden clones", producing self-reacting antibodies. This theory was questioned by Fudenberg[10] who pointed out that, clinically, there is an increase in autoimmune diseases in patients with immune deficiency—an observation in direct contrast to that predicted. Allison[11] and Weigle[12] suggested that the basic lesion in autoimmunity was a disturbance in one of the functions of T cells, that is, that of the recognition of self. Following this, the T lymphocyte co-operated with B lymphocytes which had been stimulated by autoantigens and autoantibodies were produced. Allison[11] argued cogently that this particular T lymphocyte function (that of self-recognition) could be by-passed under a variety of conditions, including virus infections, drug administration, or after partial degradation of autoantigens. A detailed account of this theory and its implications has been given recently by Allison.[13]

Early clinical studies suggesting a T cell defect in myasthenia gravis were reported by Adner *et al.*[14] Myasthenic patients were shown to have an impaired ability to become sensitized to skin testing with dinitrochlorobenzene (DNCB). Immunoglobulin A (IgA) deficiency has also been shown to occur with disproportionate frequency[15]: there is good evidence that IgA production is related to intact thymic function[16] and IgA deficiency therefore reflects T cell dysfunction.

The occurrence of thymic pathology in myasthenia gravis was one of the first, and is one of the best, documented features of the illness.[17] Recent investigations have revealed changes in the distribution of T cells in this organ: it has been reported that although the percentage of T lymphocytes is the same in the normal thymus, in the hyperplastic thymus and in the thymoma associated with myasthenia gravis, the cells are distributed differently in the normal and abnormal glands. In the normal thymus they are detected mainly in the cortex, while in thymic hyperplasia or thymoma they are diffusely arranged in both cortex and medulla.[18–20] Increased numbers of certain subsets of intrathymic B cells have also been reported by some workers.[18 20–22] Birnbaum and Tsairis[23] were unable to confirm these findings but it is probable that the contrasting results are due to different methods of assay.

The ratio of T to B cells in the peripheral blood of myasthenics is normal[18 20 24] but reactivity can be demonstrated between peripheral blood lymphocytes and syngeneic thymocytes.[18 21 22 25] This latter finding suggests that neoantigens are present in the thymus of patients with myasthenics gravis and it led Datta and Schwartz[26] to postulate that myasthenia gravis was an infectious disease.

A general impairment of T cell function has been revealed by *in vitro* studies of the disorder.[27–29] The last-named workers claimed that *in vitro* responses were most severely depressed during myasthenic crises.

The T cell population, however, is composed of several distinct subpopulations, each with unique functions. A delicate balance between regulatory cells and effector cells is required for normal immune homeostasis (fig). The function of the regulatory subgroup called suppressor cells is attracting much interest at the moment. It can be seen from the figure that these suppressor cells can act on effector T cells, on helper T cells and on B cells: an increase or a decrease in the effectiveness of suppressor lymphocytes can thus lead to immunological disturbances. It

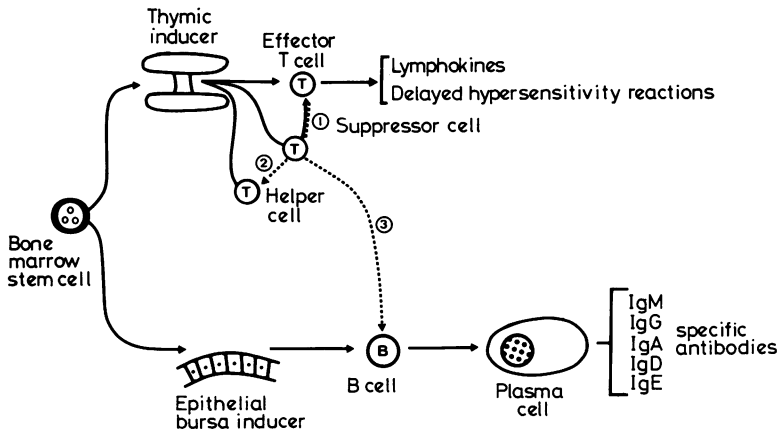

Fig *Lymphocyte System Development. This shows diagramatically first how bone marrow cells are processed in the thymus and the Bursa equivalent to give rise to the different subpopulations of T and B lymphocytes and secondly the postulated pathways of suppressor cell interactions.*

has been suggested in fact that defective functioning of this subgroup underlies autoimmune disease.[30]

There have been some studies of suppressor cell activity in myasthenia gravis and an increase in the number of these cells has been reported.[31] As explained however, theoretically one would expect a decrease in the suppressor cell population.[32 33]

Work has been done on other subgroups of T cells in childhood myasthenia gravis: investigators have detected a serum factor directed at a subpopulation of the T lymphocytes and associated with a decrease in the total number of T cells, as identified by the E-rosette technique.[34] Their results are in direct contrast to those of the numerous other workers who have not found any significant difference in the proportion of E-rosetting cells found in adult myasthenics or normal controls.[18 20 21 23 24]

Animal studies have helped to illuminate the major role played by suppressor cells in the immune system and it is these studies which have suggested that autoimmunity is due to a functional deficiency of such lymphocytes. Conditions which cause impairment of central T cell regulation result in hyperactivity of B cells and the production of autoantibodies.

One of the most extensively studied models of such a disorder is the autoimmune condition found in New Zealand black (NZB) mice, or in the hybrid produced by crossing New Zealand black and white (NZB/W) mice. The murine model of autoimmunity which develops is very similar to human systemic lupus erythematosus, with hyperglobulinaemia. Coombs-positive haemolytic anaemia, antinuclear and lymphocytotoxic antibodies and immune complex glomerulonephritis.[35] Autoimmune phenomena develop with age and it has been shown that when old mice are injected with the T cells of young mice there is some reduction in the severity of the immunological disorders.[35]

Since it has been suggested that this development of autoimmunity reflects loss of suppressor cell activity, confirmation of the hypothesis was sought by treating mice, from the first month of age, with the soluble products of concanavallin A stimmulated suppressor T lymphocytes. The treated animals were shown to have hypogammaglobulinaemia, no antinuclear or antierythrocytic antibodies and the immune complex nephritis found was very much milder than in the untreated group, that is "whereas 96% of the untreated animals developed pathologic glomerular lesions, of 2 to 4+ severity, only 4% of the treated animals developed a renal abnormality of this magnitude".[33] A marked prolongation of survival in the treated mice was also noticed.

Autoantibodies

As discussed in the preceding paragraphs there is now conclusive evidence of T cell abnormalities in patients with myasthenia gravis. These abnormalities, especially those of immunoregulation, lead to the vast array of immunologic aberrations found in the disorder. Numerous autoantibodies have been detected in myasthenic serum with the recent demonstration of antibody to the postsynaptic nicotinic acetylcholine receptor affording us a major insight into the pathogenesis of the disease (see table 2).

Whether or not this autoantibody is solely responsible for the clinical weakness in myasthenia gravis is unknown. Since the first report[4] of immunological involvement in myasthenia

Table 2 *Serological abnormalities*

Thyroglobulin antibodies
Antinuclear antibodies
Striated muscle antibodies
Rheumatoid factor
Erythrocyte antibodies
Gastric parietal cell antibodies
Heterophile antibodies
Neuronal antibodies
Pituitary antibodies
Pancreatic-islet cell antibodies
Epithelial cell antibodies
Basement membrane antibodies
Cold lymphocytotoxins
Fasle positive Wassermann reaction
Adrenal antibodies
Smooth muscle antibodies
Mitochondrial antibodies
Acetylcholine receptor antibodies

gravis, serum complement has been implicated. Early investigators found some evidence of an inverse correlation between serum complement concentration and disease state[4] and their second study of serial complement estimations in a large group of patients revealed a close correlation between a fall in serum complement concentrations and disease activity.[3]

Recent experimental work has substantiated the importance of complement in the disease process with the demonstration that experimental allergic myasthenia gravis (EAMG) cannot be induced in rats depleted of complement.[36] The elegant demonstration of immune complexes containing immunoglobulin G (IgG) and complement factor 3 (C3) on the postsynaptic membrane in myasthenic patients,[37] also adds support to the theory that complement may be necessary to allow anti-acetylcholine receptor antibodies to exert pathogenicity.

Electronmicroscopic observation of the neuromuscular synapses has revealed that immune complexes are much more sparse and difficult to find in the worst affected subjects, suggesting that severe damage to this area occurs. This had been predicted by previous workers; for instance, Keynes[38] noted that thymectomy was most useful in early myasthenia gravis and least helpful in longstanding cases, and he speculated that in the chronic cases irreversible damage had taken place.

Nastuk *et al*[3] also noted in their study that the serum complement was normal in those with longstanding disease, suggesting a burnt-out process. Their work was extended and confirmed in a later study of complement metabolism in 75 myasthenic patients.[39] Here it was demonstrated that the greatest abnormalities of serum complement metabolism were found in patients with mild disease. These results are repeated in EAMG where decreased amounts of deposited immune complexes are found in animals with severe chronic illness.[40] The findings can all be explained by the fact that in severe myasthenia gravis, or in severe chronic EAMG, a smaller quantity of acetylcholine remains on the damaged endplate.

Behan and Behan[40] in their study of complement metabolism in myasthenia gravis found that it was the plasma C4 concentrations which were most often abnormal and they suggested therefore that utilization of complement is via the classical pathway with the early components being involved. This work helped to confirm the hypothesis of Toyka *et al*[41] who postulated that complement was implicated in the pathogenesis of the disease after studying the myasthenic weakness induced in mice by passive transfer of human myasthenic serum.

Immune complexes have not only been demonstrated on the muscle endplates, but Behan and Behan[39] also reported evidence of circulating serum immune complexes. Their first study was done using the anticomplementary assay but the results have now been confirmed with the use of two different techniques.[42] The identity of the antigen in these complexes is unknown but in view of the fact that acetylcholine is lost from the postsynaptic membrane and that antibody coated segments of receptor are shed into the postsynaptic space in both the human and experimental disease, these complexes may represent antibody-bound receptor.

In myasthenia gravis therefore, a vast array of immunological abnormalities can be demonstrated. They are all thought to reflect a disorder of immunoregulatory equilibrium but how the imbalance between the various T and B cell subpopulations first occurs is unknown.

Genetics

It has been known for a long time that genetic factors are involved in autoimmune diseases. In myasthenia gravis familial cases have been reported since 1900 when Oppenheim stated "I observed the disease once in a woman whose sister died of the same disease".[44] He gave no further clinical details and it was Marinesco[45] who first suggested a hereditary influence in the disorder. Within the last decade, an overrepresentation of certain histocompatibility (HLA) antigens has been reported,[46-49] providing good evidence for a genetic predisposition.

It is convenient to discuss the familial cases under the headings of neonatal, juvenile (including congenital) myasthenia gravis, and twin

studies.

Neonatal myasthenia gravis This disorder occurs only in infants born to mothers with myasthenia gravis and the condition usually lasts from two to six weeks after birth and then disappears. About one in seven affected mothers give birth to a baby with neonatal myasthenia gravis. It has been suggested that this short-lived disorder is caused by the transplacental passage of acetylcholine receptor antibody.[50] Antibody has, however, been demonstrated also in infants without disease who have been born to myasthenic mothers,[51 52] which suggests that other factors may be involved.

Neonatal myasthenia gravis progressing to the permanent illness has been recorded on only one occasion.[53]

Juvenile myasthenia gravis This term is applied to any case of the disease arising between birth and puberty, excluding the neonatal type. It tends to be more benign but more often permanent than the adult form. Some authorities have subdivided this group in order to classify children under the age of two as having congenital disease.[54]

There have been 19 reports in the literature of congenital myasthenia gravis occurring in families (table 3). An important characteristic of these cases is the preponderance of males.[74] An X-linked form of inheritance seems, however, most unlikely. The possibility of autosomal recessive transmission was suggested by Bundey[74] in a study of several families but since first cousins of the siblings involved also had myasthenia gravis dominant inheritance would appear more probable.

Table 3 *Familial myasthenia gravis occurring before the age of two*

Sibs affected	*Sibs unaffected (no)*	*Age at onset*	*Reference*
4 brothers	2	< 2 years	55
2 brothers	?	< 2 years	56
brother, sister	0	< 1 year	57
3 brothers, 1 sister	1	< 3 months	58, 59
1 brother, 1 sister	4	< 1 year	60
male twins (dizygous)	?	< 2 years	61
brother, sister	?	birth	62
4 brothers	2	< 2 years	63
brother, sister	?	birth + ?	64
2 brothers	0	< 2 years	65
2 sisters	0	< 2 years	66
brother, sister	2	1 + 3 years	67
brother, sister	1	8 + 12 months	68
brother, sister	?	birth	69
2 brothers	0	6 + 18 months	70
2 brothers	10	6 months	71
brother, sister	3	birth	71
female twins (monozygous) + brother	?	< 1 month	72
2 brothers	1	6 months	73

There have been instances in families of two siblings having juvenile myasthenia gravis, with the disorder arising in one of the children before the age of two and thus being classified as the congenital form.[75] This subdivision appears too restrictive and seems to have little to recommend it: it is perhaps more useful to call all the cases juvenile myasthenia gravis and to remember Bundey's dictum that "those who are most genetically prone to develop myasthenia do so in early life".[74]

There are several reports of the juvenile type occurring in siblings,[70 75-79] occasionally, one parent and the offspring are affected[62 67 70 80 81] or first cousins have the same disease.[62 64 82 83] In Bundey's series the prevalence of myasthenia gravis in first degree relatives of patients with the juvenile form was about 2%. The prevalence of the disease in relatives of adult index patients is considerably less than this[84] the fact which originally made Bundey suggest that those "who are most genetically prone to develop myasthenia do so in early life".[70]

Juvenile myasthenia gravis is associated with other autoimmune illnesses in the same way as is the adult form.[85] An increased incidence of autoantibodies to various tissue antigens is detectable in these patients also and the presence of thyroid disease with thyroid autoantibodies is unexpectedly increased in their relatives, although the figures do not reach statistical significance.[74] Antibodies to skeletal muscle are also detectable in the first degree relatives of these patients.[86]

The family studies cited here do not point to any obvious mode of inheritance: recessive transmission is unlikely because parents, second and third degree relatives may have the disorder and dominant inheritance is militated against because of the skipping of generations.

Twin studies The study of twins offers a unique method of evaluating the role of genetic and environmental factors in any disease as observed originally by Sir Francis Galton in his classical study. Myasthenia gravis has been reported in 15 pairs of monozygotic twins (table 4) with concordance of the disease in five of the female pairs and one of the male pairs. In the remaining nine sets of twins, only one had the disease. These reports are in contrast to the studies in fraternal twins, where of the nine cases studied, concordance was not present in any. Four of those affected were girls, two with unaffected brothers and two with unaffected sisters. One of the twin sisters with myasthenia gravis whose brother did not have the disease, did in fact have

Table 4 *Pairs of twins where one or both had myasthenia gravis*

Both twins affected	*Sex*	*Reference*
Monozygotic	M, M	61
,,	F, F	87
,,	F, F	88
,,	F, F	89
,,	F, F	54
,,	F, F	90
One affected	*Sex*	*Reference*
Monozygotic	M (M)	50
,,	F (F)	91
,,	F (F)	6, 66
,,	F (F)	81
,,	M (M)	92
,,	F (F)	93
,,	M (M)	94
,,	F (F)	71
,,	F (F)	70
Dizygotic	F (F)	95
,,	F (M)	96
,,	F (M)	62
,,	— (—)	97
,,	— (—)	97
,,	— (—)	97
,,	M (M)	94
,,	F (F)	71
,,	M (F)	70

a non-twin brother and a maternal cousin who suffered from the same illness.[62] Thus these reports of twins suggest that although genetic factors are involved they cannot be the only important influence.

Histocompatibility antigens Our understanding of several chronic diseases has recently been increased by the discovery that there is a genetic component to their development. This has been shown by demonstrating that certain histocompatibility antigens have an association with particular diseases. Histocompatibility (HLA) antigens are cell-surface components present in the membrane of most, but not all, cells in varying amounts. For practical purposes in humans, leucocytes are used to identify these antigens: indeed they were the source of the first tissue antigens recognized and gave their name to the system: HLA system—*h*uman *l*eucocyte *a*ntigen system.

The expression of the HLA antigens is controlled by the major histocompatibility complex (MHC) which in man is present on chromosome 6. At least four loci are now known: A, B, C and D at each of which a large number of alleles may occur. The tissue antigens are the expressions of the genes at these loci; A, B, C and DR (D-related) antigens are recognised by serological methods while D antigens are identified by a more complex and more difficult to interpret technique called the mixed leucocyte reaction. Classical mendelian laws of inheritance apply to the HLA system.

The interest of this subject to immunologists lies in the fact that studies of the similar system in the mouse (the H2 system) have revealed that there is a relationship between the alleles in this area, relative resistance to viral infection[98] and specific immune responses.[99] Only weak associations between HLA type of disease were originally found in man but with more extensive study definite relationships have been established (see table 5).

In myasthenia gravis an overrepresentation of histocompatibility antigens A1 and B8 has been well documented.[46-49] The early reports suggested that this increased frequency was only present in female patients.[46 48 100] Large numbers of male patients have not yet been studied but two recent studies[101 102] do show that HLA-B8 is increased in males who develop myasthenia gravis before the age of 35. Thus the HLA relationship shown may be with the age of onset of disease, rather than with the patient's sex.

Further confirmation of the striking relationship between HLA-B8 and myasthenia gravis was obtained by an analysis of 56 cases which included seven Negro and Indian patients.[47] In these two races HLA-B8 is quite uncommon yet the three young females were all HLA-B8 positive. Patients in the group were also subdivided on the basis of their thymic pathology. Although the number of cases was small it appeared that it was females with thymic hyperplasia in whom the association with HLA-B8 was expressed (nine of 16 cases), not those with a thymoma.

This work was confirmed in the 1977 histocompatibility workshop[103] where HLA antigens and thymic pathology were compared in 106

Table 5 *HLA and disease associations*

Disease	*HLA antigen*
Acute anterior uveitis	B27
Ankylosing spondylitis	B27
Reiter's disease	B27
Acute lymphatic leukaemia	A2
Behcet's syndrome	B5
Ragweed hay-fever	B7
Multiple sclerosis	A3, B7, DW2
Addisonian adrenalitis	B8
Dermatomyositis	B8
Chronic active hepatitis	B8
Coeliac disease	B8
Dermatitis herpetiformis	B8
Graves' disease	B8
Hodgkin's disease	B8
Juvenile diabetes	B8
Myasthenia gravis	A1, B8, DW3
Psoriasis	B7
Systemic lupus erythematosus	BW15

patients with myasthenia gravis: no association between HLA-B8 and thymoma was detected. Feltkamp *et al*[86] identified a significant increase in a different antigen, HLA A2, in patients over 40 years old who had a thymoma but Fritze[47] could not confirm this finding and indeed thought he had observed an association with HLA A3 in elderly males with a thymoma.

Family studies of the HLA system and myasthenia gravis are of great importance. Dick *et al*[49] studied 17 families involving 31 patients with myasthenia gravis. Six of these were families where the parent had the disease and there were children of the marriage. In seven families, the patients were studied as offspring. Two patients were sisters and the last three families were ones in which three generations were involved. It was clear from these family studies that while there was a definite association between myasthenia gravis and HLA B8 antigen, the relationship was not a direct one. It was demonstrated unequivocally that the inheritance of HLA B8 was not an essential prerequisite for the development of the disease. Nor did homozygosity for HLA B8 increase the chance of developing myasthenia gravis. In the case of two identical sisters, homozygous for HLA B8, only one had the disease; their two brothers with HLA B8 were both healthy.

This family study more than any other genetic examination shows that other factors, including environmental, are involved in induction of the disease. The possession of HLA B8 clearly increases one's susceptibility to myasthenia gravis but other influences must also play a part.

Some data on HLA antigens in the congenital disease is available, but it is conflicting. In one family in which there were two siblings with congenital illness,[49] both had inherited HLA B8 from their mother. The mother was homozygous for HLA B8 so that it was impossible to determine which B8 allele each had inherited. In the other study[73] two brothers with congenital myasthenia were found to have different HLA profiles, the first having HLA A1/A2, B17/B12 (with absence of DW3) and the other HLA A3/A1, B7/BW22 (and again absence of DW3).

Early reports of HLA typing in disease did not include study of the D locus or DR (D-related) locus antigens. In disorders where an association with HLA B8 had been demonstrated, such as coeliac disease or Sjogren's syndrome, an even more obvious relationship to the D locus antigen DRW3 has now been shown.

Two studies of D locus antigens in myasthenia gravis have been made[104 105]: in both, the association of HLA-DW3 with the disease was less than the association with HLA-B8. In an attempt to resolve the question 130 cases of the disorder were recently analysed for B8 and DRW3 antigen frequencies: it was shown that while DRW3 was overrepresented, B8 showed an even greater frequency of association.[103] Finally, Safwenberg *et al*[102] examined the HLA antigens in 54 male myasthenic patients and detected an increased representation of B8 in those whose disease developed before the age of 35: no significant relationship with D antigens was present.

Thus it appears that susceptibility to myasthenia gravis is more closely linked to the HLA B locus than to the other HLA loci.

Although this association of HLA B8 and myasthenia gravis has now been demonstrated conclusively, no correlation was found between the possession of HLA B8 and the titre of anti-acetylcholine receptor antibody in 40 myasthenic patients examined by Smith *et al.*[106] Naeim *et al*,[107] in another study did suggest that there was such a relationship between antibody titre and the possession of B8 antigen but their data was weakened by the small number of patients and the conflicting data in some of their tables.

The increased incidence of HLA B8 antigen in myasthenia gravis may hold true for Caucasians but not for all other races. It does not seem to be the case in Japan where a study of Japanese myasthenics revealed an increased association of HLA B12 especially in young females with early disease and thymic hyperplasia.[108] These workers also found HLA B5 was increased in patients with thymoma.

Experimental allergic myasthenia gravis (EAMG) The animal model for myasthenia gravis has been studied in various species including the mouse,[109] rat,[40] monkey,[111] rabbit[112] and guinea-pig[110] but there have been few studies of the genetic factors involved. The tentative conclusions reached, therefore, do not allow us to determine the exact role of the histocompatibility complex in the experimental disease. One group of workers[109] has shown that the susceptibility of inbred mouse strains to the disease correlates with the H-2 haplotype possessed by the strain, but it could be argued that their inoculation procedure was not the best available. The definitive experiments, are those in which congenic strains of mice (i.e. those differing genetically *only* at the H-2 locus) are used, since these will help to define the importance of histocompatibility types in the course of the disease. These studies are described by Lennon in this

Festschrift.

The results of experiments being carried out at present in our own laboratory suggest that EAMG in the rat, as evaluated electrophysiologically by the measurement of miniature endplate potentials in isolated rat diaphragms *in vitro*, is related to the major histocompatibility antigen. Our preliminary studies in this species have revealed an association between the titre of acetylcholine receptor antibody and certain histocompatibility loci. The genetic data reported thus help to confirm the resemblance between EAMG and human myasthenia gravis.

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