Myasthenia gravis (MG) is a disorder of muscle characterized by antibodies to the acetylcholine receptors (AChRs) at the motor endplate. It is one of the best-studied diseases because it involves a process, neuromuscular transmission, which is well understood physiologically, and because the target protein has been characterized at the molecular level. Moreover, it fulfils established criteria for autoimmune disease, i.e. anti-AChR antibodies can be detected in MG sera, AChR loss at the motor endplate correlates with attached IgG and complement, and immunization against purified AChR leads to an animal model of the disease. In addition, plasma exchange, which depletes circulating immunoglobulins, leads to clinical improvement, and a disorder of neuromuscular transmission can be transferred to experimental animals by injection of MG immunoglobulins. This brief account will focus on the nature and possible origins of the autoimmune response. For more detailed reviews see [1, 2].

**The antigen**
The nicotinic acetylcholine receptor (AChR) of adult striated muscle is an integral membrane protein consisting of five subunits of stoichiometry $\alpha_2\beta_2\delta$. The two $\alpha$-subunits bind $\alpha-$
bungarotoxin (α-BuTx) with high specificity and affinity.

**Immunogenicity of the AChR**

High anti-AChR titres can be detected in many species after immunization with less than microgram amounts of AChR in Freund's complete adjuvant. Antibodies against native AChR bind largely to the extracellular surface of the receptor and some will cross-react with the animal's own muscle AChR causing loss of receptor and a defect in neuromuscular transmission. This condition is known as experimental autoimmune myasthenia gravis (EAMG; see [2]). Antibodies against recombinant or denatured subunits bind mainly to determinants which are cytoplasmic in vivo or are not accessible in the native conformation. These antibodies seldom cause substantial loss of AChR or clinical weakness in the animals.

Antibodies can also be raised in mice by immunization with native AChR without Freund's adjuvant, suggesting that there is no natural immune tolerance towards this autoantigen [4].

**Anti-AChR antibodies in MG patients**

IgG antibodies are detected by binding to detergent-extracted human muscle AChR which has been radioactively labelled with 125I-α-BuTx. Antibody titres are highly variable among patients but are virtually specific for MG. The antibodies have either κ or λ light chain, are of all four IgG subclasses, show variability in their binding to different AChR preparations and to defined regions on the surface of the AChR, and are of high affinity [5].

The fine specificity of the antibody-binding sites has been determined by competition with rat monoclonal antibodies, raised against Torpedo and electric eel AChR, which bind to regions on the AChR surface. A high proportion of the rat monoclonal antibodies (mAbs) were found to compete with each other for binding to the 'main immunogenic region' (MIR) on the α-subunits [6]. These anti-MIR mAbs showed some cross-reactivity between different animal species, and several bound to human AChR. On average, about 60% of the antibodies in any MG or EAMG sera were found to compete with the rat anti-MIR mAbs [7].

With mouse mAbs [8, 9] raised against human AChR, only one in ten of the antibodies bound to the MIR of AChR. Other mouse antibodies bound to four partially overlapping regions, one of which was specific for AChR extracted from embryonic or denervated muscle. Mouse mAbs directed at three regions, including the MIR, competed to a similar extent with antibodies from myasthenia gravis patients for binding to AChR [9].

In spite of knowing the primary sequence of the human AChR α-subunit, it has been difficult to determine the exact amino acid sequences to which the mAbs bind. However, the sequence of α67-76 appears to contribute to the MIR [10, 11], and binding of one other mAb has been mapped to α125-143 [12].

**T cell epitopes in MG**

Most antibody responses to complex antigens are T cell-dependent and experiments in EAMG have shown this to be the case for anti-AChR antibodies (see [2]).

The T cell receptors on T lymphocytes recognize a complex of processed antigen (a T cell epitope) and class II molecule [a product of the major histocompatibility complex (MHC)] presented on the surface of antigen-presenting cells, or on specific B lymphocytes. Recognition leads to proliferation of the T cells which secrete lymphokines that 'help' the B cells to differentiate into plasma cells which synthesize the antibody.

To learn more about the nature of the T cell epitopes, we and others have used recombinant and synthetic AChR sequences to stimulate and clone T cells from MG patients [13, 14]. Several T cell epitopes have been defined but the number and specificity among a larger series of patients and controls needs to be studied. The presentation of T cell epitopes does not appear to be restricted to certain class II molecules.

**Different forms of myasthenia**

Patients can be divided into three groups on the basis of their different age of onset, thymic pathology and MHC antigens (see Table 1). Subtle differences in fine specificity of anti-AChR antibodies have been found in the three main groups [15] (see Table 1).

Penicillamine (Pen)-induced MG occurs in a proportion, probably about 1%, of patients undergoing Pen treatment for rheumatoid arthritis. In most Pen-MG patients, myasthenic symptoms regress and anti-AChR antibodies fall after stopping treatment with the drug. The MHC association, Bw35, DR1, is neither typical of MG nor of rheumatoid arthritis ([16]; Table 1). However, the anti-AChR antibodies in Pen-MG do not appear to differ from those in acquired idiopathic MG with regard to light chain, subclass or affinity. Moreover, Pen-MG anti-AChR binds to several regions on the
Table 1

Clinical and immunological heterogeneity in myasthenia gravis

<table>
<thead>
<tr>
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<th>Myasthenia gravis</th>
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<tbody>
<tr>
<td></td>
<td>Young onset</td>
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<tr>
<td></td>
<td>&lt;40 yrs</td>
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<tr>
<td>Thymic pathology</td>
<td>Hyperplasia</td>
</tr>
<tr>
<td>MHC association</td>
<td>A1, B8, DR3</td>
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<tr>
<td>Anti-AChR antibody</td>
<td>+ + +</td>
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<td>Predominant fine specificity of anti-AChR*</td>
<td>1, 3, 4</td>
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*Greater than 35% competition between mouse mAbs, binding to each of five regions on the surface of the human AChR, and human MG antibodies. Region 4 is equivalent to the MIR. Data taken from [15].

human AChR, probably being most similar to that in young onset patients [15] (see Table 1).

Origin of the autoimmune response in myasthenia gravis

The aetiological importance of T cells in MG is not yet clear. Although specific T cell responses to recombinant AChR can be detected in MG patients, these can also be found in a proportion of healthy individuals. On the other hand, anti-AChR antibodies are found almost exclusively in MG patients, and there is ample evidence that these antibodies cause the loss of AChR which underlies weakness in this disease [1, 2]. Therefore, one must ask what antigenic stimulus switches on the production of specific antibodies.

There are various theoretical possibilities as listed in Table 2. There is circumstantial evidence supporting the hypothesis that MG arises from cross-reactivity with an external antigen [17] or via an idiotypic network [18]. However, there is as yet no direct evidence implicating these reactivities in the onset of the disease, and the existence of abnormal levels of anti-idiotypic antibodies in MG has been disputed [19]. Moreover, the high affinity and specificity of the autoimmune response would tend to argue in favour of a specific antigenic stimulus. AChR can be detected on 'myoid' cells in the thymic medulla [20] and an 'AChR-like' epitope has been identified in thymoma tissue [21]. Removal of the thymus, at least in young onset cases, frequently results in clinical improvement and a fall in anti-AChR levels. Nevertheless, the role of the thymus is far from clear (see [1] for discussion) and it remains a possibility that a low-affinity cross-reaction initiates the disease in susceptible individuals, and that release of complexes of AChR, antibody and complement components from the muscle motor endplates, or from the thymus, leads to production of the sustained, high-affinity antibody response against AChR which can be detected in the patient's serum.

In Pen-MG the response is clearly related to drug treatment. The existence of other Pen-induced autoimmune diseases argues for a general disturbance of immune tolerance with the specificity of the autoantibodies being at least partly dependent on the individual's MHC antigens [22]. No T cell responses have been reported yet in Pen-MG but the relatively rapid fall in anti-AChR following cessation of the drug suggests that Pen may act at the level of the B cell rather than further back in the chain of events that lead to antibody production.

Table 2

Possible origin of autoimmunity in myasthenia gravis

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<table>
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<tbody>
<tr>
<td>Helper T cell defect</td>
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<td>Regulator T cell defect</td>
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<tr>
<td>Idiotypic dysregulation</td>
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<tr>
<td>Cross-reacting epitope</td>
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<tr>
<td>Normal antigen</td>
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<tr>
<td>Abnormal antigen</td>
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<td>Drug-related antigen</td>
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Immune haemolytic anaemia and thrombocytopenia: drugs and autoantibodies

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The study of the mechanisms involved in drug-induced autoimmune cytopenias may provide some information about the events involved in the generation of autoimmune disorders. There is still no definitive answer as to the initial events that trigger drug-induced autoimmune blood cell destruction but the spectrum of clinical conditions undoubtedly has a basis in the molecular interactions of drugs (or their metabolites) with blood cells. These may lead to production of antibodies that in turn may result in the destruction of a particular cellular population. What is clear is that in common with other autoimmune disorders, differences among individuals are important in determining susceptibility to drug-induced autoimmune cytopenia.

Abbreviations used: RBC, red blood cell; DAT, direct antiglobulin test.
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