female-to-male ratio is 2:1 in the young adults, but in older adults there is a male predominance.

Pathogenesis. About 85% of patients have autoantibodies against postsynaptic acetylcholine receptors, while most of the remaining patients have antibodies against the sarcolemmal protein *muscle-specific receptor tyrosine kinase*. These autoantibodies appear to be pathogenic, as the disease can be passively transferred to animals with serum from affected individuals, and therapeutic maneuvers that decrease autoantibody levels are associated with a reduction in symptoms.

The mechanism of action of the various autoantibodies appears to differ. Anti-acetylcholine receptor antibodies are thought to lead to the aggregation and degradation of the receptors, and also to damage of the postsynaptic membrane through complement fixation. As a result, postsynaptic membranes show alterations in morphology and are depleted of acetylcholine receptors. This limits the ability of myofibers to respond to acetylcholine. Autoantibodies directed against muscle-specific receptor tyrosine kinase do not fix complement. Instead, these antibodies seem to interfere with the trafficking and clustering of acetylcholine receptor within the sarcolemmal membrane, the net effect again being decreased acetylcholine receptor function.

There is a strong association between pathogenic anti-acetylcholine receptor autoantibodies and thymic abnormalities. Approximately 10% of patients with myasthenia gravis have a *thymoma*, a tumor of thymic epithelial cells (Chapter 13). An additional 30% of patients (and particularly those who are young) have a different thymic abnormality called *thymic hyperplasia*. This peculiar condition is marked by the appearance of B-cell follicles in the thymus. The thymus normally contains small numbers of myoid cells, stromal cells that express skeletal muscle antigens. It is hypothesized that both thymoma and thymic hyperplasia disrupt normal thymic function in a manner that promotes autoimmunity against acetylcholine receptors expressed on thymic myoid cells. In contrast, thymic abnormalities are usually absent in cases of myasthenia gravis that occur in older patients or that are not associated with anti-acetylcholine receptor autoantibodies; the basis for the development of autoantibodies in such cases is unknown.

Clinical Features. Patients with anti-acetylcholine receptor antibodies typically present with fluctuating weakness that worsens with exertion and often over the course of the day. *Diplopia* and *ptosis* due to involvement of extraocular muscles are common and distinguish myasthenia gravis from myopathies, in which involvement of extraocular muscles is unusual. In some patients, symptoms are confined to ocular muscles, while others develop generalized weakness that can be so severe as to require mechanical ventilation. Cases with antibodies against muscle-specific receptor tyrosine kinase differ from typical cases by exhibiting more focal muscle involvement (neck, shoulder, facial, respiratory, and bulbar muscles).

Diagnosis is based on clinical history, physical findings, the identification of autoantibodies, and electrophysiologic studies. The latter reveal a decrement in muscle response with repeated stimulation, a characteristic of this disorder. Overall mortality has dropped from over 30% in the 1950s to less than 5% with current therapies. Acetylcholinesterase inhibitors that increase the half-life of acetylcholine are the first line of treatment. Other treatments, such as plasmapheresis and immunosuppressive drugs (e.g., glucocorticoids, cyclosporine, rituximab), can bring symptoms under control by decreasing autoantibody titers. Thymectomy is often effective in patients with thymoma, but is of uncertain benefit in those with thymic hyperplasia or lacking thymic abnormalities.

Lambert-Eaton Myasthenic Syndrome

Lambert-Eaton myasthenic syndrome is an autoimmune disorder caused by antibodies that block acetylcholine release by inhibiting a presynaptic calcium channel. In contrast to myasthenia gravis, rapid repetitive stimulation increases muscle response. Muscle strength is augmented after a few seconds of muscle activity. Patients typically present with weakness of their extremities. In about half of cases there is an underlying malignancy, most often neuroendocrine carcinoma of the lung. Symptoms may precede the diagnosis of cancer, sometimes by years. It is thought that the stimulus for autoantibody formation in paraneoplastic cases may be the expression of the same calcium channel in the neoplastic cells. Patients without cancer often have other autoimmune diseases, such as vitiligo or thyroid disease. Treatment consists of drugs that increase acetylcholine release by depolarizing synaptic membranes and immunosuppressive agents, such as those used to treat myasthenia gravis.

Congenital Myasthenic Syndromes

Rare disorders falling into this group most commonly have an autosomal recessive mode of inheritance and are marked by varying degrees of muscle weakness. Causative mutations have been identified in genes encoding several different presynaptic, synaptic, or postsynaptic proteins. The most common of these are loss-of-function mutations in the gene encoding the ε-subunit of the acetylcholine receptor. Another group of mutations affect proteins that are important in normal clustering of acetylcholine receptors on postsynaptic membranes. Many patients with congenital myasthenic syndromes present in the perinatal period with poor muscle tone, external eye muscle weakness, and breathing difficulties, but others have milder forms of the disease and may not come to clinical attention until adolescence or adulthood. The clinical presentation, response to drugs such as acetylcholinesterase inhibitors, and prognosis depend largely on the underlying mutation.

Disorders Caused by Toxins

Botulism is caused by exposure to a neurotoxin (popularly known as *Botox*) that is produced by the anaerobic Gram-positive organism *Clostridium botulinum*. Botox acts by blocking the release of acetylcholine from presynaptic neurons (Chapter 8). *Curare* is a common name for related muscle relaxants that block acetylcholine receptors, resulting in flaccid paralysis. It was initially discovered and used as poison on arrow tips by indigenous people in the Amazon rain forest. At one time it was used as a muscle relaxant during certain forms of surgery, but has now been