Myasthenia gravis from Thomas Willis to the present

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ABSTRACT

The history of the development of knowledge of myasthenia gravis is reviewed. Clinical profiles of the immune and non-immune mediated forms of myasthenia are discussed. The current theory of pathogenesis is reviewed. Tests used to diagnose myasthenia gravis, and their comparative diagnostic yields are presented. Past and current modalities of treatment are reviewed. Future therapeutic strategies are introduced. The roles of the thymus and thymectomy in the genesis and treatment of myasthenia gravis are discussed.

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The term "myasthenia gravis (MG)" is a mixed marriage of Greek and Latin. It is derived from the Greek word "myasthenia," muscle weakness; and the Latin word "gravis," severe. Myasthenia gravis is a disorder of neuromuscular junction (motor endplate). Other disorders of motor endplate include the Eaton-Lambert myasthenic syndrome, infantile botulism, and tick paralysis.

Neuromuscular junction in myasthenia. That MG was a disorder of the neuromuscular junction was known as early as 1895 when Friedrich Jolly, the German neurologist, using faradic stimulation, detected the early onset of fatigability, upon repetitive stimulation, in muscles of MG patients, suggestive of abnormal neuromuscular transmission.[1] The elucidation of what was wrong in the neuromuscular junction in MG had to await the resolution of 2 controversies: The first was whether transmission at the neuromuscular junction is chemical or electrical (the "soups" versus the "sparks" controversy). The controversy was finally resolved in favor of the "soups". The "soup" was found to be the transmitter acetylcholine. The second controversy dealt with whether the abnormality in the neuromuscular junction in myasthenia is pre-synaptic, as proposed by Desmedt,[2] or post-synaptic, as proposed by Grob et al.[3] This controversy was resolved in 1973[4] in favor of the post-synaptic locus of pathology. Two gifts of nature[5] helped focus attention on the post-synaptic region as the main locus of pathology in MG: the first was the discovery of the electric organ of electric eel and torpedo fish, an almost pure acetylcholine receptor glycoprotein.[6,7] The second was snake venom of cobras and kraits (alpha bungarotoxins), with high binding affinity to acetylcholine receptor glycoprotein.[8] It was not until the 1990s that the structure of the acetylcholine receptor was defined.[9] The receptor is a pentameric transmembrane protein concentrated on the crests of the post-synaptic junctional folds. Each receptor is a glycoprotein of molecular weight 250,000 comprised of the following glycopeptide subunit chains: alpha$_2$, beta, gamma, and delta.[10,11] The subunits are arranged around a central ion channel. The ion channel is closed in the resting state and open when acetylcholine binds to the receptor. Acetylcholine receptor antibodies bind to all the subunits with a high proportion binding to the alpha subunit. The alpha subunit is thus, the site of antibody attack in MG, hence called the main immunogenic region. Receptors undergo a continuous turnover, with a half life in the

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Table 1 - Myasthenia gravis acetylcholine receptor subtypes.

Features	Mature (Adult)	Embryonic (Fetal)
Synonyms	Junctional	Extrajunctional
Turn-Over Rate	Slow (10 days)	Fast (<24 hours)
Dominance	Normal adult NMJ	Denervation and fetal NMJ
Receptor Channel		
Conductance	High	Lower
Mean open time	Shorter	Longer
Subunit	ε (epsilon)	γ (gamma)
Antibody titers in neonatal myasthenia	High	Higher

NMJ - neuromuscular junction

range of approximately 5-7 days.[12,13] Two acetylcholine receptor subtypes have been described, mature (adult), and embryonic (fetal).[14,15] The characteristics of each of the subtypes are listed in **Table 1**.

Pathogenesis. Having resolved the nature of neurotransmission (electrical or chemical), and the locus of pathology (pre- or post-synaptic), attention was directed to the nature of the abnormality in the post-synaptic region, namely, autoimmunity. The autoimmune story of MG began with the clinical observations of D.W. Smithers and John Simpson. Smithers is credited with the first suggestion, in 1958, that MG may be due to an autoimmune process.[16] Two years later, in 1960, John Simpson,[17] a Scottish physician at the National Hospital, Queen Square in London, in a review of 404 myasthenic patients seen at the National Hospital, confirmed Smithers'observation. Simpson noted an association of MG with hyperthyroidism, rheumatoid arthritis, lupus erythematosus and sarcoidosis. He concluded that these associations, as well as the presence of thymic abnormalities in MG supported an immune process.[16,17] Smithers' and Simpson's clinical observations were followed by the identification, in 1973, of acetylcholine receptor as the autoantigen.[18] This conclusion was arrived at by the purification and biochemical analysis of the acetylcholine receptor using the electric organ of electric eel and torpedo fish as a source of pure acetylcholine receptor, and snake venom of cobras and kraits (alpha Bungarotoxin) with high affinity binding to acetylcholine receptor. Three years later, in 1976, the search for, and identification of acetylcholine receptor antibodies was successful by the serendipitous production of experimental autoimmune MG (EAMG) in rabbits who unexpectedly developed MG-like disease after being immunized with purified acetylcholine receptor for the purpose of obtaining antibodies.[19] These and other studies helped identify the role of the acetylcholine receptor and sequence of events in MG. The binding of the receptor antibody to the acetylcholine receptor on the post-synaptic membrane of the neuromuscular junction leads to lyses of post-synaptic membrane, degradation of receptor, and pharmacologic blockade of intact receptors. These events result in reduction in the amount of functionally active receptors in the post-synaptic membrane and subsequent reduction in safety factor for neuromuscular transmission. The era from 1895 to 1976 was thus characterized by (1) The identification, by Jolly, of an abnormality in neuromuscular transmission in MG, (2) the observation, by Smithers and Simpson, of MG as an autoimmune disease, (3) the identification, by Patrick and Lindstrom, of acetylcholine receptor as the autoantigen in MG, and (4) the serendipitous production of experimental autoimmune myasthenia and the identification of receptor antibodies by Lindstrom et al. The 1980 and the 1990s were characterized by the identification of the roles of T and B cells in MG. These studies showed that acetylcholine receptor-specific T helper cells induce proliferation and differentiation of B cells which secrete anti-acetylcholine receptor antibodies.[20,21] Through a series of tedious experiments, a schema for the pathogenesis of MG, though incomplete, has been developed (**Figure 1**).[20] There is overwhelming evidence to support the concept that the predominant immune effector response in MG is humorally mediated. Evidence in favor of a cell-mediated immune response includes focal collections of mononuclear cells (lymphorrhages) in muscle from MG patients, clusters of mononuclear cells near the motor endplate, and the occurrence of antibody- as well as complement-dependent cell-mediated cytotoxicity in some experimental models of MG.[22]

Early clinical descriptions. Thomas Willis, the English physician (of Circle of Willis fame), is usually credited with the first description of MG.[23] In 1672, 3 years before he died, he published a book De anima Brutorum (the soul of Brutes) which included a report of a woman with long-standing paralysis of her limbs and tongue: "There is another kind of this disease depending on the scarcity and fewness of the spirits, in which the motion fails wholly in no part or member, yet it is performed weakly only, or depravedly by any; those who be in trouble with a scarcity of spirits, are able at first rising in the morning to walk, move their arms this way and that, or to lift up a weight with strength; but before noon, the stores of spirits which influenced the muscles being almost spent, they are scarce able to move hand or foot. I have now a prudent and honest woman in cure, who for many years has been obnoxious to this kind of bastard palsey not only in the limbs, but likewise in her tongue; this person for some time speaks freely and readily enough, but after long, hasty, or laborious speaking, she becomes mute as a fish and cannot bring forth a word, nay, and does not recover the use of her voice till after an hour or two". This case is considered by many to be the first written description of MG. Critics of the authenticity of Willis' description being that of a myasthenic patient point specifically to the following 2 unusual

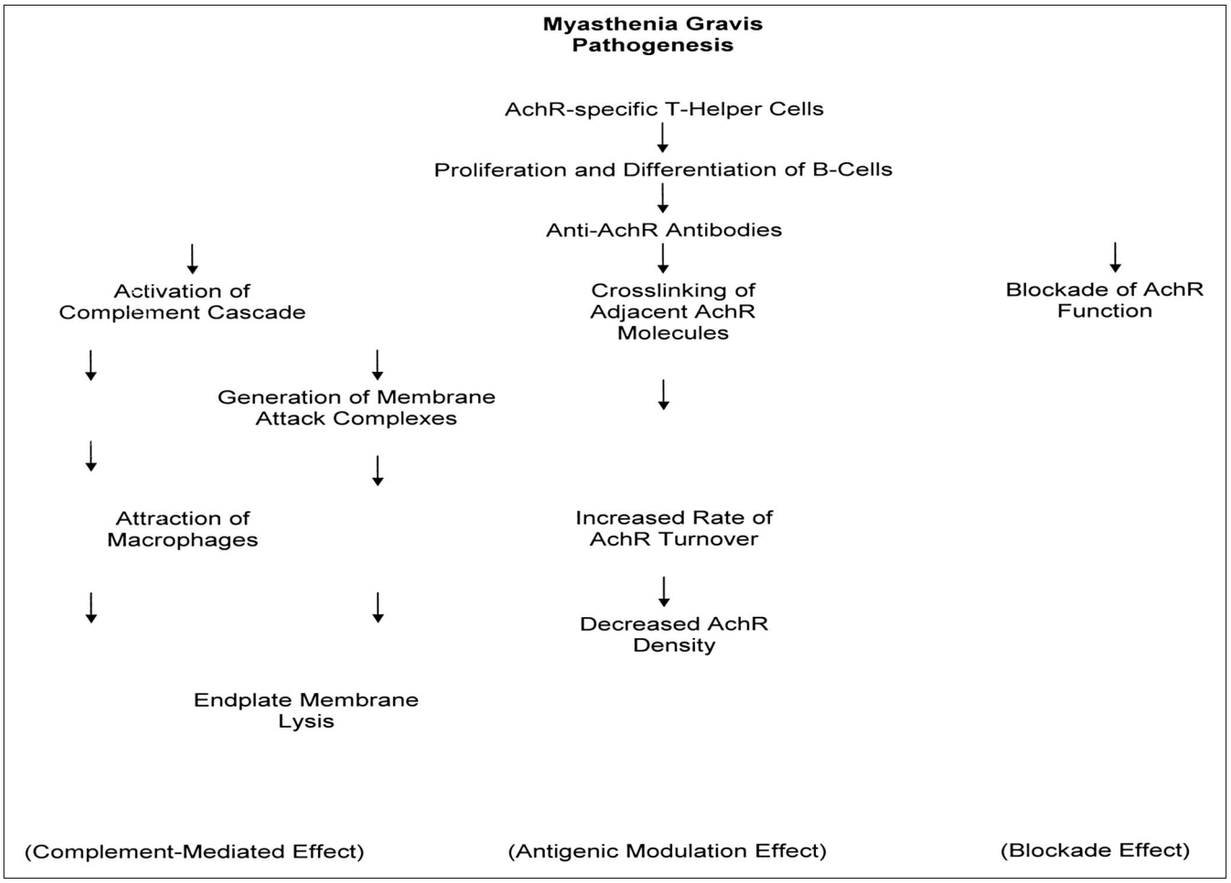

Figure 1 - Schematic diagram of the immunopathogenesis of myasthenia gravis. AchR - acetylcholine receptor

Table 2 - Myasthenic syndromes site of pathology.

Myasthenic syndrome	Presynapse	Postsynapse	Synaptic cleft
A. Acquired			
Myasthenia gravis (MG)		+	
Lambert-Eaton myasthenic syndrome (LEMS)	+		
B. Congenital			
Familial infantile myasthenia (FIM)	+		
Congenital paucity of synaptic vesicles	+		
Congenital paucity of secondary clefts (CPSC) syndrome		+	
Slow channel syndrome		+	
Fast channel syndrome		+	
Congenital endplate AchE deficiency			+
Deficiency and short open time of AchR		+	
Abnormal interaction of Ach with AchR		+	
Congenital AchR deficiency		+	
Congenital AchR and AchE deficiency		+	+

AchE - acetylcholine esterase, AchR - acetylcholine receptor

features in his patient: the presence of severe extremity weakness with normal ability to speak, and the muteness "as a fish" for 2 hours. Those who doubt that Willis described the first case of MG, credit Herard with describing the first convincing case of MG in 1868.[24] The first American case of MG was described in 1644[25] in Chief Opechancanough, an American Indian warrior chief portrayed leading his troops to battle from a litter on which he was carried by his troops. Thus, the first description of MG may have been from North America. The first case in childhood was by Samuel Wilks, an English physician, in 1877.[26] The first case of neonatal transient myasthenia was reported in 1942[27] and the term juvenile MG, to describe the immune mediated disease in children and adolescents, was coined by Osserman, in 1956. Congenital myasthenia was first described by Paul Levin in 1949[28] in 2 siblings at birth, and subsequently established and described in detail by Engel.[29] Eponyms to describe MG include Erb-Goldflam-Oppenheim disease, and Hoppe-Goldflam symptom complex. These refer to descriptions of MG by Wilhelm Heinrich Erb, German neurologist, in 1878;[30] Johann Ignaz Hoppe, Swiss physiologist, in 1892; Samuel V. Goldflam, Polish neurologist, in 1893,[31] and Herman Oppenheim, German neurologist and psychiatrist, in 1901.[32] Wilhelm Heinrich Erb was the first to suggest that some features of MG (bilateral ptosis, severe neck weakness, difficulty chewing, and recovery) differentiated it from progressive bulbar palsy.[16] Samuel Goldflam confirmed Erb's observation.[16] Henry Viets considers Goldflam's paper to be the most important ever written in the history of the disease.[16,33] The reports by Erb and Goldflam carefully describe the fatigue, fluctuating weakness and tendency for relapses and remissions.[9]

Clinical picture. Myasthenia gravis should be viewed as a multisystem disorder affecting the motor system (weakness), the thymus gland (thymic hyperplasia, thymoma), and the peripheral immune system (increased incidence of other autoimmune syndromes, significant increase in circulating autoantibodies, immune attack on acetylcholine receptor). Myasthenia gravis affects all age groups. It is divided into 2 major groups: immune-mediated and non-immune-mediated. The immune-mediated group comprises most myasthenic patients and includes adult onset MG, juvenile MG, and transient neonatal myasthenia. The non-immune-mediated group is represented by congenital myasthenia. Myasthenia gravis is considered congenital when symptoms occur within the first year of life, in the absence of circulating antibodies to the acetylcholine receptor. The abnormality in all immune-mediated cases is post-synaptic. The abnormality in the non-immune-mediated cases may be pre-synaptic, synaptic, or post-synaptic. In most, however, the abnormality is post-synaptic (**Table 2**). The clinical picture in the immune-mediated adult onset and juvenile MG is identical. It is characterized by fluctuating muscle weakness and fatigability manifest with use of muscle and recovery with rest. Bulbar and ocular muscles are characteristically involved. The disorder is more common in females. Weakness may be limited to ocular and bulbar muscles or may be generalized from onset. Some ocular-bulbar cases do progress to a state of generalized weakness. A severe, acute fulminating type is more common among young women. Most of the juvenile cases occur in patients younger than 5 years or older than 10 years.[34] Female preponderance in juvenile myasthenia increases with age of onset. The low frequency of juvenile myasthenia in postpubertal males is attributed to the suppressive effect of androgens on some aspects of humoral and cell-mediated immunity.[35] Transient neonatal myasthenia occurs in 21-45% of babies born to myasthenic mothers. The clinical picture is characterized by feeble cry, feeding difficulty, facial and generalized weakness. The onset of symptoms is usually in the first 3 days of life with spontaneous remission within 5-47 days. A familial form of immune-mediated MG was first reported by Henry Hart in 1927.[36] Approximately 4% of myasthenic patients have a family history of the disease. Human leukocyte antigen (HLA) is implicated as a genetic factor predisposing to MG. There is increased frequency of HLA A_1, B_8, DR_{W3} in female myasthenics with early onset and thymic hyperplasia. There is also increased frequency of HLA A_3, B_7, and DR_2 in male myasthenics with late onset and thymoma.[37] Several categories of drugs have been reported to have adverse effects on myasthenic patients. They include analgesics, general and local anesthetics, antibiotics (aminoglycosides and ciprofloxacin), anticonvulsants, cardiovascular drugs (beta blockers, calcium channel blockers, quinidine, procainamide), corticosteroids, hormones, neuromuscular blocking agents (succinylcholine, vancuronium), ophthalmic drugs, and psychotropic drugs.[38,39] Some drugs, such as beta blockers and chloroquine have pre-synaptic effects; others, such as polymyxins, tetracyclines, and procainamide, have post-synaptic, receptor-blocking effects; others, such as phenytoin, chlorpromazine, aminoglycoside antibiotics, and verapamil, have combined pre- and post-synaptic effects. A small subset of drugs, notably the antirheumatic agent, D-penicillamine, have been implicated in the pathogenesis of a variant of the disease. They act by production of anti-acetylcholine receptor antibodies.[40] The natural history of myasthenia comprises 3 stages: 1) an active stage, lasting 5-10 years, of progressive weakness and labile course; 2) an inactive stage, with less fluctuations and lability; 3) burned out stage, 14-20 years post symptom onset, with minimal fluctuations and relatively static weakness. The most severely affected muscles become atrophic.[41] The clinical picture of the congenital (non-immune-mediated) MG is characterized by ptosis, ophthalmoplegia, proximal muscle weakness and

fatigability, unresponsive, usually, to anticholinesterase agents. Twelve types of congenital MG have been described based on the nature of the abnormality at the neuromuscular junction.[29] The degree of severity in individual cases is measured by a grading scale originally described by Osserman[42] in which group I refers to ocular disease only; group IIA refers to mild generalized weakness and good response to treatment with anticholinesterases; group IIB refers to moderate generalized weakness and not as good response to treatment; group III refers to acute fulminant onset and respiratory involvement; and group IV refers to late severe myasthenia developing at least 2 years after onset of groups I or II symptoms. Another scale proposed by Jaretzki[43] for clinical research standards consists of 5 classes I-V with classes II, III, and IV further subdivided into a and b categories.

Laboratory diagnosis. In most myasthenic patients, diagnosis is based on the distinctive clinical picture. Confirmatory diagnostic tests are pharmacologic, serologic, and electrophysiologic. Prostigmin and Tensilon (edrophonium) are the 2 agents used in pharmacologic testing. A prompt and marked improvement in muscle weakness occurs in myasthenic patients following injection of these agents. Serologic tests include measurement of the level of acetylcholine receptor binding, blocking, and modulating antibodies. Other antibodies associated with MG include antibodies against muscular cytosolic proteins such as actin, myosin, alpha actinin, titin, rapsyn, ryanodine receptor and muscle-specific receptor tyrosine kinase (MuSK). Titin is associated with paraneoplastic MG and thymoma; MuSK with seronegative immune-mediated myasthenia.[11] Antistriational muscle antibodies are prevalent in patients with thymoma. Electrophysiologic tests include repetitive nerve stimulation (proximal and distal nerves), electromyography, nerve conduction velocity, and single fiber electromyography. Less frequently used tests to confirm the diagnosis of MG include the use of high impedance audiometry to test the stapedial reflex, and the Lancaster red-green test of ocular motility to test for double vision. Based on the effect of temperature on myasthenic weakness, a cold (ice-pack) test for myasthenia has been used.[44-46] Application of an ice pack to the ptotic lid results in elevation of the lid. The yield of pharmacologic, serologic, and electrophysiologic tests increases with generalization of the weakness. The overall yield of pharmacologic tests is between 88-92%, of serologic tests between 53-90%, of electrophysiologic tests between 31-89%,[34] and of stapedial reflex test between 71-93%.[47] There is no difference in the yield of serologic tests between males and females.[19,34,48] Positive (high) acetylcholine receptor antibody titers have been reported in other conditions than MG. These include penicillamine induced myasthenia-like syndrome, amyotrophic lateral sclerosis treated with snake venom, elderly patients with autoimmune diseases, and first-degree relatives of myasthenic patients.[49-52] Serologic status does not seem to influence outcome.[34] A higher yield of serologic test has been reported in myasthenic patients with thymic hyperplasia as compared to those with normal thymus.[34,53] Between 10-20% percent of autoimmune myasthenic patients are seronegative. Approximately 40-70% of such patients have antibodies to the muscle-specific receptor MuSK.[11,54,55] Including proximal muscles (facial, biceps, triceps, deltoid) in the repetitive nerve stimulation test doubles the yield of this test when compared with testing only distal muscles (hand muscles).[34,56-60] A comparative evaluation of the overall yield of all confirmatory tests suggests that after single fiber electromyography, which is the most sensitive clinical test for neuromuscular transmission, the overall yield is highest with pharmacologic tests, followed in decreasing order of yield by combined proximal-distal repetitive nerve stimulation, serology, and distal repetitive nerve stimulation.[34,58] An important part of the workup of myasthenic patients is CT of the mediastinum in search of a thymoma. Ten percent of myasthenic patients have a thymic tumor and 70% have thymic hyperplasia. Patients with thymoma usually have more severe disease, higher level of acetylcholine receptor antibodies, and more severe electromyographic abnormalities.

The thymus and myasthenia gravis. In the search for the locus of pathology in MG, early investigations focused on the central nervous system because of the clinical similarity between MG and progressive bulbar palsy. These early studies revealed absence of pathology in the central nervous system and occasional abnormalities in the thymus gland. The first description of a thymic tumor in myasthenia was reported by Oppenheim in 1899[16] as an incidental autopsy finding. Two years later, in 1901, Karl Weigert[61] reported the presence of an invasive tumor of thymus origin in the anterior mediastinum in the autopsy of a myasthenic patient. The term "thymoma" to refer to tumors of thymic origin was proposed, in 1916, by James Ewing.[16] Elexious T. Bell, in 1917, reported the presence of thymoma in 10 patients and thymus enlargement in 17 patients out of 56 autopsies on patients with myasthenia.[62] Edgar Hughes Norris, in a review of the pathology of MG published almost 20 years after Bell's report[63] confirmed the presence of pathological changes in the thymus and further defined these changes as comprised of various degrees of epithelial hyperplasia, and considered the thymoma as a marked degree of hyperplasia. The presence of lymphoid follicles with germinal centers in the thymus of myasthenic patients, but not in normal thymus, was described by Herbert Sloan in a review of 350 thymus glands obtained at autopsy.[16] The presence of myoid cells (cells with striations resembling myofibrils) in the thymus were first noted by Sigmund Mayer in 1888.[16]

The term myoid cells was coined by J. A. Hammer in 1910.[16] These cells were believed to disappear from the thymus with maturation. In 1970, however, Robert Van del Velde and Nathan Friedman reported their presence in the thymus of adult patients with MG.[64] Their role in the genesis of MG has not been determined with certainty, as they have also been reported in the thymuses of patients without myasthenia.[16] The first thymectomy in a patient with MG was carried out in 1911 by Ferdinand Sauerbruch to treat the patient's concomitant hyperthyroidism. At that time, thymic reduction was a treatment for hyperthyroidism.[16] Unexpectedly, post-operatively, the patient's myasthenic symptoms (but not hyperthyroid symptoms) improved. Subsequently, in 1936 (reported in 1939) and 1941, Alfred Blalock performed thymectomy for treatment of MG with and without thymoma, respectively.[65,66] Available data on thymic histology in MG suggests that 25% of such thymuses are normal and 75% are abnormal. The abnormal thymuses show hyperplasia in 85% and a thymoma in 15%.[13]

Treatment modalities. There are 4 modalities of treatment for MG: a) supportive; b) symptomatic, the use of acetylcholine esterase (AchE) inhibitor preparations (prostigmin and Mestinon) to allow maximum binding of acetylcholine to the functionally intact receptors; c) direct approach to reduce the autoimmune attack through thymectomy, corticosteroids, cytotoxic immunosuppressive drugs (azathioprine, cyclophosphamide, cyclosporine), plasma exchange and immunoglobulins; and d) experimental therapies such as antithymocyte serum, whole body and splenic irradiation, and splenectomy.[67] Prior to 1930, bed rest was the main mode of treatment, supplemented with diet high in calcium and albumin; tonics (arsenic, phosphorus, quinine, iron, strychnine); suprarenal, thymic, ovarian and testicular extracts; radioactive thorium injections; and thymic and thyroid irradiation.[68] In 1929, Harriet Isabel Edgeworth, a young American biochemist at Rush medical school in Chicago with myasthenia, took ephedrine with amidopyrine to relieve menstrual cramps. Her strength improved. By further tests, she established that the ephedrine was the effective agent. She published her findings in 1930.[69,70] Between 1932 and 1936, Walter Boothby at the Mayo clinic, in a series of publications, described the beneficial effect of the amino acid glycine in MG.[71] Of the currently used modalities for treatment of MG, the acetylcholine esterase inhibitors were the first to be introduced and the ones often used as the initial therapy. Physostigmine was introduced in 1934. In that year, Mary Broadfoot Walker, a young Scottish physician on the house staff of St. Alfege's hospital near London, was caring for a woman with MG. The visiting consultant in neurology, Dr. Derek Denny-Brown, pointed out to Dr. Walker the similarities between curare poisoning and MG and mentioned that physostigmine was the antidote for curare.[70] Walker injected her myasthenic patient with physostigmine with striking improvements in eyelid, jaw, arm strength and swallowing, which she reported in a letter to the journal Lancet in 1934.[72] To avoid the side effects of physostigmine, Dr. Walker began to search for another drug. At the suggestion of Dr. Phillip Hamill, she tried the recently synthesized Prostigmin (Neostigmine) with equally good results. Her findings were published in the Proceedings of the Royal Society in 1935.[73] Walker's demonstration of the beneficial effects of Neostigmine was greeted with skepticism because of the rapidity of response. Her results, however, were soon confirmed by several reports. Credit for the introduction of Neostigmine could have gone to Lazar Remen, were it not for his professor. Remen reported the use of Neostigmine in the German literature in 1932, 3 years earlier than Walker.[74] His professor was interested in the effects of glycine on myasthenia and relegated the success of Neostigmine to a small print text in the case summary.[70] Subsequent to physostigmine and prostigmin (Neostigmine), Tensilon was introduced in 1950 by MacFarlane and colleagues,[75] pyridostigmine (Mestinon) in 1954 by Kermit Osserman,[76] and Mytelase in 1955 by Robert Schwab.[77] The first immunosuppressant agents used in the treatment of MG were corticosteroids. Corticosteroid therapy for MG was introduced in the 1950s but soon abandoned because of exacerbation of weakness leading to respiratory crises and death. Corticosteroid therapy was re-introduced in 1965 when it was shown that the exacerbation of weakness was transitory, and that following the initial (within 7-10 days) deterioration noted in approximately one third of patients, there was marked improvement in the weakness. The use of corticosteroids was popularized in the 1970s. The exacerbation of weakness following the initiation of corticosteroid therapy is not well understood. The following mechanisms may be operative: a) defect in excitation-contraction coupling exacerbated by corticosteroids, b) direct effect of corticosteroids on the acetylcholine receptor such as a blocking action upon ion channels of the acetylcholine receptor. The response to corticosteroids is age related. Older patients respond more favorably. There is no effect on the response of gender, disease severity, disease duration, or the presence of thymoma. Controversy exists regarding the best way to administer corticosteroids, daily high dose, alternate day high dose, or alternate day low dose with a gradual increase in dose.[78] Daily high dose is claimed to lead to more rapid improvement, whereas with alternate day low dose, the early exacerbation of weakness is presumably less likely.[79] In designing long-term therapy with corticosteroids, consideration should be given to the needs of the individual patient and the stage of the disease. A physician or a lawyer may tolerate the cushingoid appearance from chronic use of corticosteroids. However, a fashion model with mild to

moderate disease will not tolerate this side effect. The introduction of other immunosuppressive agents followed that of corticosteroids. Thus, azathioprine (Imuran) was introduced in 1967, cyclophosphamide (Cytoxan) in 1980, and cyclosporine A in 1987. Azathioprine, a purine antimetabolite is a relatively weak immunosuppressive drug with delayed onset of effect (improvement in strength begins after 2-8 months). It may be used alone, in patients in whom corticosteroids are contraindicated or not sufficiently effective, or in combination with corticosteroids, which allow marked improvement in weakness with a lower dose of corticosteroids.[13,67,79] Azathioprine action is predominantly on T-cells. It reduces T-cell-dependent acetylcholine receptor antibodies.[13] Cyclophosphamide is a potent immunosuppressant used to treat patients refractory to other forms of therapy.[67,79] Cyclosporine is a potent immunosuppressive and immunomodulating agent that inhibits amplification of T-lymphocyte immune response. It is used to treat patients refractory to other forms of therapy.[13,67,79] Improvement begins in one to 2 months and maximum improvement is achieved 6 months or longer after initiation of treatment. Plasma exchange and intravenous immunoglobulins are short-term immunotherapeutic agents. Plasma exchange, introduced in 1976, is indicated as the treatment modality in a) acute, severe, or rapidly progressive MG with impending myasthenic crisis, b) stable, but significantly symptomatic MG prior to thymectomy, c) chronic, moderate to severe MG in a patient who has responded inadequately to other forms of therapy. It presumably acts by removal of circulating acetylcholine receptor antibodies and immune complexes. Improvement is rapid (usually after the third exchange), lasts approximately 6-8 weeks and occurs in 75% of patients.[67,79-81] Intravenous immunoglobulins yield positive results in a few days in 70-100% of patients. Improvement lasts for between one and 3 months. Transient exacerbation of weakness has been reported in some patients after initiation of immunoglobulin treatment.[82,83] Favorable aspects of immunoglobulins therapy include a high rate of response, rapid onset of improvement, absence of recognized toxicity, and reproducibility of response. Negative aspects of immunoglobulin therapy include the temporary nature of the response (30-60 days, high cost, and the risks associated with injection of human blood).[67,84] Intravenous immunoglobulins are especially useful in myasthenic children in whom plasma exchange is not as readily administered as in adults. The mechanism of action of this form of therapy is poorly understood. Possible mechanisms include down-regulation of antibodies directed against acetylcholine receptor and the introduction of anti-idiotypic antibodies.[85] One recent randomized controlled trial did not show a significant difference between intravenous immunoglobulins and plasma exchange for treatment of severe exacerbations of MG.[86]

The use of thymectomy in MG was introduced by Alfred Blalock, a surgeon at Vanderbilt University at the time, in 1936 and published in 1939.[65] It was first used in myasthenic patients with thymoma, and was then extended 2 years later, in 1941, to patients without thymoma.[66] Previous to that, an association between the thymus and MG was first noted by Karl Weigert, a German pathologist, in 1901,[61] and thymectomy was carried out in a myasthenic patient with hyperthyroidism by H. Sauerbruch, a German surgeon, in 1911.[87] A controversy raged from 1950 to 1954 between the experience at Mayo Clinic, which claimed that thymectomy is of no value,[88] and the experience at the National Hospital, Queen Square, which promoted thymectomy as the best hope for young myasthenics.[89] Critical analysis of data from both centers later revealed that most patients in the Mayo Clinic had thymomas, whereas those in the National Hospital had thymic hyperplasia. The controversy was thus resolved by the conclusion that thymectomy is useful in properly selected patients.[90-92] Thymectomy is now well established as a treatment modality for MG in adults.[93] A recent retrospective review of controlled, non-randomized studies reveal that thymectomy confers only moderate benefit.[94] Definitive data on the usefulness and safety of thymectomy in childhood myasthenia is not yet available. Preliminary reports suggest that it is an effective and safe mode of treatment in children.[95,96] The mechanisms of action of thymectomy include a) elimination of a source of continued antigenic stimulation (the thymic myoid cells), b) elimination of a reservoir of B cells secreting acetylcholine receptor antibodies, and c) helps correct a disturbance of immune regulation.[13] Following thymectomy, antibody titers drop, seronegativity is higher, and the rate of neonatal transient myasthenia in newborns is lower.[97] The open transsternal route to thymectomy is the optimal surgical approach (compared to the transcervical route) for complete thymic removal.[98] Mean remission rate of myasthenia following the transsternal approach is 30% with a range of 25-60% compared to a mean rate of 20% with a range of 6-24% for the transcervical approach.[99] A video-assisted thoracoscopic approach has been recently introduced and is claimed to be as effective as the transsternal route.[96,100,101]

Associated disorders. Several diseases have been reported in association with MG. Among the immune-mediated disorders, the most commonly reported associations are with hyperthyroidism and rheumatoid arthritis. Less commonly reported associations include systemic lupus erythematosus, pernicious anemia, glomerulonephritis, Sjögren disease, primary ovarian failure, Lambert Eaton syndrome, hemolytic anemia, ulcerative colitis, Crohn's disease, pemphigus,

Table 3 - Chronological sequence of development of knowledge of myasthenia gravis.

Date	Event
1644	First American case of myasthenia gravis. ?Earliest clinical description[25]
1672	First case of myasthenia gravis (Thomas Willis)[23]
1868	First ? confirmed case of myasthenia gravis (Herard)[24]
1877	First childhood case of myasthenia gravis (Wilks)[26]
1878	Erb cases[30]
1888	Myoid cells described in thymus (Mayer)[16]
1892	Hoppe cases[31]
1893	Goldflam cases[31]
1895	Abnormal NMJ transmission in myasthenia gravis (Jolly)[2]
1899	Thymic tumor in myasthenia gravis (Oppenheim)[16]
1901	Oppenheim cases[32]
1910	Term "myoid cells" coined (Hammer)[16]
1911	First thymectomy in myasthenia gravis and hyperthyroidism (Sauebruch)[16]
1916	Term "thymoma" coined (Ewing)[16]
1927	First familial myasthenia gravis case (Hart)[36]
1930	Use of ephedrine in treatment (Edgeworth)[69,70]
1932	Use of glycine in treatment (Boothby)[71]
1932	Use of Neostigmine in treatment (Remen)[74]
1934	Use of physostigmine in treatment (Walker)[72]
1935	Use of Neostigmine is treatment (Walker)[73]
1936	First thymectomy for myasthenia gravis and thymoma (Blalock)[65]
1936	Thymic hyperplasia in myasthenia gravis described (Norris)[63]
1941	First thymectomy for myasthenia gravis without thymoma (Blalock)[66]
1942	First transient neonatal myasthenia case (Strickroot et al)[27]
1949	First congenital myasthenia gravis case (Levin)[28]
1950s	Introduction of corticosteroid treatment[78]
1950	Introduction of Tensilon (McFarlane)[75]
1954	Introduction of pyridostigmine (Mestinon) (Osserman)[76]
1955	Introduction of Mytelase (Schwab)[77]
1956	Pathology is post-synaptic (Grob & Johns)[3]
1956	Term "juvenile myasthenia" coined (Osserman)[42]
1957	Pathology is presynaptic (Oesmedt)[2]
1958	Myasthenia gravis is autoimmune disorder, clinical observation (Smithers)[16]
1960	Myasthenia gravis is autoimmune disorder, clinical observation (Simpson)[17]
1966	Steroids re-introduced for treatment[78]
1967	Azathioprine used for treatment[15,67,79]
1970	Myoid cells in thymus of myasthenic patient (Van de Velde & Friedman)[64]
1973	Post-synaptic locus of pathology confirmed (Patrick)[4]
1973	Acetylcholine receptor is autoantigen (Patrick)[18]
1976	Identification of acetylcholine receptor antibody (Lindstrom)[19]
1976	Plasma exchange used in treatment[79]
1980	Cyclophosphamide used in treatment[79]
1980s	Role of T and B cells defined[20,21]
1984	IVIG used in treatment[82,83]
1987	Cyclosporine used in treatment[13,29]
1990s	Structure of acetylcholine receptor defined[9]

scleroderma, sarcoidosis, adrenalitis, thrombopenia, polymyositis, and pancytopenia. Association with multiple sclerosis has been rarely reported. Other reported associations include dystonia with diurnal variation, familial limb-girdle myopathy, myotonic dystrophy, hypothyroidism, and Satoyoshi syndrome. Although there is a considerable body of evidence concerning the heart in MG, a definite relationship between the heart and MG remains elusive.[102,103] Reported cardiac disorders in MG include cardiac arrhythmias (predominantly with thymoma and myocarditis), left ventricular dysfunction reversed by Neostigmine, reduced diastolic peak-filling rate improved by pyridostigmine, and focal hemorrhagic infiltrates or true myocarditis.[77]

Future trends in therapy. Future trends in therapy are multifaceted and include 1) specific immunotherapies, such as agents that will inhibit or powerfully suppress the acetylcholine receptor antibody, as well as T-cell directed therapy;[11,13] 2) non-specific immune modulation, such as splenectomy to eliminate the reservoir for antibody-producing lymphocytes,[104] total lymphocyte irradiation,[105] and the use of monoclonal antibodies against T-helper cell antigen to block the immunoproliferative cascade and subsequent antibody production;[79,106] 3) specific immune modulation, such as the use of B-cell toxins (to reduce antibody production by B-cells),[107] and anti-idiotype "therapeutic" antibodies to block binding of antibodies to the acetylcholine receptor;[108] and 4) non-immunologic strategies, such as post-synaptic membrane modulation to decrease the rate of degradation of the acetylcholine receptor.[105]

Myasthenia gravis then and now. The preceding historical perspective shows that since Thomas Willis's description of MG, several significant

developments in knowledge about the disorder have occurred. From a disorder solely acquired, immune-mediated, non-familial, due to a post-synaptic acetylcholine receptor pathology, responsive to acetylcholinesterase inhibitors, to a disorder which is both acquired and congenital, immune- and non-immune-mediated, non-familial and familial, due to pre-synaptic, synaptic and post-synaptic pathology, in which anticholinesterase inhibitors may or may not be effective. In addition, the structure of the acetylcholine receptor is much better known, and there is a basic understanding of the pathological mechanisms by which antibodies to acetylcholine receptor impair transmission at the motor end plate. The chronological sequence of events in the development of knowledge of MG from 1644 to the present is summarized in **Table 3**.

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