

A History of Treatments for Myasthenia Gravis

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ABSTRACT

Much of the improvement in the treatment of myasthenia gravis (MG) over the past 125 years can be attributed to the effectiveness of general medical measures such as advances in respiratory care and the discovery of antibiotics. Although MG became the model of an antibody-mediated autoimmune disease in the 1970s (the most documented antigen being the muscle acetylcholine receptor at the neuromuscular junction), the pathogenesis of MG has not been the rationale for most treatments found to be useful for this disease. The serendipitous benefit of anticholinesterases for MG in the 1930s subsequently focused attention on the neuromuscular junction. The beginnings of the controversy over thymectomy for MG in the 1940s and 1950s preceded the discovery in 1960 of the function of the thymus. Before the autoimmune pathogenesis of MG was known, adrenocorticotrophic hormone (ACTH) and steroids for MG were tried for reasons that turned out to be incorrect. Further immunosuppressive treatments for MG were largely empirical, following their use in organ transplantation and other autoimmune diseases. More specific treatments, based on our knowledge of pathogenesis, are still experimental but hopefully will be the history of the future.

KEYWORDS: History, myasthenia, treatment

Objectives: On completion of this article, the reader will have a thorough knowledge and appreciation of the history of treatments for myasthenia gravis.

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Although it didn't attract much attention at the time, Wilhelm Erb, Professor Extraordinarius of Internal Medicine at the University of Heidelberg, was the first person to suggest in 1878 that there might be a unique form of bulbar palsy that did not follow the inexorable downhill course of typical progressive bulbar palsy, described in 1860 by Guillaume Duchenne de Boulogne.¹ He was also the first person to attempt to

treat this condition, which eventually became known as myasthenia gravis (MG). One of the three patients whom Erb described with this form of "bulbar palsy" recovered after over 60 galvanic treatments to his mastoid bone and neck muscles, a form of electrical therapy pioneered by Erb.² A second patient got worse during such electrical treatments. These two patients were also given potassium iodide and iron, while Erb's

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third patient was treated successfully with quinine, now known to make MG worse.

In 1893 Samuel Goldflam, a physician in Warsaw, Poland, wrote a description of MG that has been called "in many ways the most important ever written in the history of the disease."³ Goldflam called it "an apparently curable bulbar paralytic symptom-complex"⁴ because all three of his patients improved with similar galvanic stimulation, iron, and quinine. Nineteen years later, however, he reported that all three of his patients had subsequently died.⁵

By 1900 such electrical stimulation for MG was no longer in favor. Hermann Oppenheim of Berlin stated in his excellent monograph of 1901 on *Die Myasthenische Paralyse*⁶ that stimulating electrical treatments for MG were to be avoided. Instead, the patient should rest in bed, speak little, and avoid muscle fatigue, especially during meals. Likewise, in their 1900 "Critical Digest" of MG in the journal *Brain*,⁷ Harry Campbell, from West End Hospital for Nervous Diseases in London, and Edwin Bramwell, Scottish physician and son of Sir Byrom Bramwell, stressed rest and avoidance of muscle fatigue, excitement, and cold. "As to drugs," they admitted, "little can be said." Tonics of potassium iodide, iron, mercury, arsenic, and especially large doses of the stimulant strychnine had been tried but were considered ineffective by most physicians. For the next decade MG was also treated with "organotherapy" (organic extracts of the suprarenals, thyroid, pituitary, and ovarian glands) on the supposition that MG might be an endocrine disorder and that these glands, especially the thyroid and the thymus, counteracted each other.⁸ This latter approach had been stimulated by the autopsy findings in myasthenic patients of tumors of the thymus gland by Oppenheim⁹ in 1899 and Carl Weigert in 1901.¹⁰ In Zurich in 1911 the German surgeon Ernst Sauerbruch partially removed the thymus gland in a young woman with MG to treat her hyperthyroidism. Her physicians were surprised that her MG improved but not her thyroid disease.¹¹ This soon led to the use for MG patients of radioactive thorium and roentgenotherapy in the region of the thymus for the treatment of MG, with variable results.¹²

Despite, or because of, these various attempts, until the 1930s the treatment of MG was described as "a source of discouragement to the patient and a cause of nightmare for the physician."¹³

ARTIFICIAL RESPIRATION

The first mention of "artificial respiration" as treatment for MG is in 1890 in an article in the journal *Brain* by Lauriston Shaw, in which "artificial respiration" was initially performed repeatedly with good results in a man with "sudden and urgent" dyspnea but was "at last ineffectual" and the patient died.¹⁴ The actual procedure is

not described, but at that time it could have been by mouth-to-mouth resuscitation, bellows, or chest compression. "Forced respiration" using nasotracheal tubes or tracheostomy was familiar by then but had been discredited by the well-known French physiologist Leroy as producing emphysema and pneumothorax.¹⁵ It was later condemned by none other than the influential Sauerbruch, who went to great extremes to build cumbersome negative pressure chambers in which to perform his thoracic surgery.¹⁵ Various devices providing intermittent negative pressure ventilation were developed, including one by Alexander Graham Bell in 1882, but the most popular was the "iron lung" invented in 1929 by Philip Drinker (an engineer), Charles McKhann (a pediatrician), and Louis Shaw (a physiologist) at Harvard Medical School, who announced their work in 1929.¹⁶

Tank-type respirators, which avoided a tracheostomy, continued to be used in the United States into the 1960s. Positive pressure ventilators made a comeback in Europe following the poliomyelitis epidemic in Copenhagen in 1952, which proved that intermittent positive pressure breathing (IPPB) was more effective and lifesaving than the cuirass or tank ventilators. Initially during the Copenhagen polio epidemic, IPPB took the form of 450 medical and dental students squeezing bags connected to tracheostomies of polio patients in 4-hour shifts.¹⁷ This emergency eventually led to the Engstrom volume ventilator (1954), the Bennett pressure-cycled ventilator (1957), and the Bird ventilator (1957), as well as to the establishment, in Copenhagen, of the first intensive care unit in 1954.¹⁷

Besides the availability of effective artificial ventilation, patients with MG also benefited from the clinical advent of sulfonamides in 1936 and penicillin in 1947 to treat the pneumonias that often precipitated their need for respiratory support.

EFFECTIVE DRUGS FOUND FOR MYASTHENIA GRAVIS

As knowledge of skeletal muscle chemistry increased, interest turned to creatine metabolism. The simplest amino acid glycine (aminoacetic acid or glycocholl), was found to produce the greatest increase in creatinuria in muscle diseases, including MG, and this was presumed to be beneficial. In 1932 Lazar Remen at the University of Münster, Westphalia, published some encouraging results of treatment of two MG patients with glycine¹⁸ (plus one successful but overlooked result with neostigmine). Walter Boothby of the Mayo Clinic in Rochester, Minnesota, also produced a series of articles between 1932 and 1936 on the beneficial effects of glycine for MG symptoms (usually in combination with ephedrine). In one of these¹⁹ Harriet Edgeworth described her own personal battle with MG as a medical student and the

improvement she experienced in her own MG symptoms when she began using ephedrine (the active ingredient of ma huang¹) for menstrual cramps. Ephedrine is still used as a secondary medication for MG.

The real therapeutic breakthrough for MG, however, came in 1934 when Mary Walker, an assistant house officer at a hospital for the poor in suburban London, gave her patient with MG an injection of physostigmine, an antagonist to curare, with dramatic positive results. She postulated in her letter to the *Lancet*²⁰ describing her findings that "It may be significant that physostigmine inhibits the action of the esterase that destroys acetylcholine." Soon after, she also demonstrated that parenteral Prostigmin (neostigmine), another cholinesterase inhibitor, was also very effective in temporarily alleviating symptoms of MG, and without the central adverse effects of physostigmine. One contemporary neurological consultant exclaimed, "Within three weeks every myasthenic in London was given Prostigmin!"²¹ and in less than 2 months it was being used parenterally by Henry Viets at Massachusetts General Hospital (MGH) in Boston.²¹ Oral Prostigmin was tried successfully in New York 6 months later.²²

Enthusiasm for Prostigmin (neostigmine) became so rampant in the 1940s that Viets claimed in 1945 that "Neostigmine should be considered a deficiency drug" for MG.²³ Another prominent neurologist, Lee Eaton, at the Mayo Clinic stated in 1947, "Theoretically at least, it may be possible to give the patient with MG too much neostigmine. However, this is an error that is less likely to be made than the error of not giving enough."²⁴ As a result, massive amounts—up to 336 mg intramuscularly over 24 hours—were given for "crisis."²⁵ (Mary Walker, by the way, seems to have been the first person to use that term in her first letter, suggesting that physostigmine "might tide a patient over a respiratory crisis."²⁰) Mary Walker made an additional contribution to MG therapy in 1935 by confirming in another letter to the *Lancet* that large amounts (10 to 12 g) of oral potassium chloride also improved myasthenic weakness.²⁶

THE THYMECTOMY CONTROVERSY

In 1939 Samuel Riven, as senior author, reported with colleagues from Vanderbilt University in Nashville, Tennessee, that the drug guanidine was not only well tolerated by five MG patients but also produced favorable results, presumably because it increased the sensitivity of muscles to acetylcholine.²⁷ In the same year, Riven with the surgeon Alfred Blalock and others from Vanderbilt reported the successful removal using tracheal intubation and a midline upper sternal approach of the cystic remains of a necrotic thymic tumor (but no thymus tissue was identified) in a young MG patient.²⁸ Shortly after he assumed the Chair of Surgery in 1941 at

Johns Hopkins University, Blalock performed the first transsternal thymectomy on an MG patient without a thymic tumor. He went on to perform six such operations successfully on nonthymomatous MG patients during the next 6 weeks, claiming improvement resulted in half the cases.²⁹ By 1944 he had performed 20 thymectomies for MG of which 13 improved, but by 1947 he had apparently lost interest in thymectomy, commenting after a surgical paper from the Mayo Clinic, "I thought we had an answer to this problem of the relationship to the thymus and MG, but such does not appear to be the case."³⁰ Blalock went on to fame and glory as a pioneer of cardiac surgery.³¹

The thyroid surgeon Geoffrey Keynes in London was stimulated by Blalock's initial report and performed the first thymectomy for MG in England in 1942. By 1949 Keynes had operated on 120 MG patients who did not have tumors, with 65% of them showing complete or almost complete remission of symptoms.³² He did not operate on thymomas. At first the Mayo Clinic agreed that thymectomy was "of value"³⁰ then disagreed³³ because its doctors—Eaton as neurologist and Theron Clagett as surgeon—initially combined the thymectomy results of MG patients with and without thymomas.¹ When they analyzed them separately, however, they found that the outcome of thymectomy was favorable for females less than 50 years of age without thymoma.³⁴

MG patients who received thymectomy at Boston's MGH did less well than Keynes' MG patients because Viets admitted that he was conservative in patient selection and operated only on patients with long-standing disease.³⁵ Later, in 1953 thymectomy was recommended in Boston for MG females under the age of 40, most of whom received thymic irradiation before surgery, but not for males over the age of 30.³⁶ Physicians at Johns Hopkins Hospital, where Blalock's original series was part of the follow-up, concluded in 1958 that there was no evidence of enhanced improvement in the thymectomized cases, but once again, patients with and without thymomas were not analyzed separately.³⁷

A favorable 1961 report on thymectomy from the combined experience of MGH in Boston and the Mount Sinai Hospital in New York speculated that perhaps Johns Hopkins' lack of enthusiasm for thymectomy was also because milder cases of MG had been used as controls at Johns Hopkins.³⁸ Such problems of nonrandomization and unmatched or no controls have plagued the MG thymectomy literature for 50 years, with prospective randomized studies being recommended for over 25 years.³⁹ Meanwhile, thoracic surgeons have continued to promote various techniques, such as the revival of cervical thymectomy (1965) and the introduction of transcervical thymectomy (1969), extended transcervical thymectomy (1988), and thorascopic thymectomy (1992) to decrease morbidity and of extended transsternal thymectomy (1972) and "maximal" thymectomy

(1988) to remove more thymus.⁴⁰ Almost all results of numerous uncontrolled, retrospective reports of such thymectomies from Europe, Asia, and America claim that thymectomy is effective as a treatment for MG, but skeptics still call for evidence-based results.

NEW "ANTICHOLINESTERASES"

Following its introduction in 1935, neostigmine (Prostigmin) became "the undisputed drug of choice"⁴¹ in the treatment of MG. However, because of the short duration of its action, the possibility of tolerance, and its pronounced cholinergic adverse effects, the search continued for other cholinergic drugs that might be effective, long-lasting, and nontoxic. The long-acting alkyl phosphates turned out to be too long-lasting, their effects lasting weeks in some cases. Diisopropyl fluorophosphate, tried in 1946, proved too toxic for MG patients.⁴² In 1948 Martha Westerberg of the University of Michigan reported on hexaethyltetraphosphate for MG,⁴³ and Burgen and colleagues on tetraethylpyrophosphate.⁴⁴ Octamethylpyrophosphoramidate was introduced by Rider and associates in 1951.⁴⁵ One by one these drugs were eventually discarded in the treatment of MG because the severe toxic effects were more pronounced and longer-lasting than those with neostigmine.⁴¹

Numerous alterations of the neostigmine molecule were also tried by chemists at Hoffman-La Roche, including Ro 2-3198, or 3-hydroxy phenyl dimethyl ethyl ammonium bromide, which in 1950 had an anticholinergic effect in anesthetized man⁴⁶ and when given intravenously to an 11-year-old girl with MG produced an "immediate" alleviation of her symptoms.⁴⁷ In 1951 Westerberg proposed that the chloride of this drug, Tensilon, be used as a treatment for MG.⁴⁸ She even administered up to 250 mg of Tensilon orally in a 5% solution to an MG patient and claimed that it increased strength for several hours, but it was discontinued by the patient because of headaches.⁴⁹ Perhaps it is unfortunate that Tensilon, because of its very brief action parenterally, was abandoned as a therapy for MG. The pharmacology of Tensilon, or edrophonium chloride, at the time stressed its direct stimulation at the neuromuscular junction and its minimal anticholinesterase activity.^{46,47} A severely dysarthric MG patient of mine who was barely understandable on Mestinon (see below), during Tensilon tests spoke (and swore) so clearly, with a New York accent, that it was heartbreaking to hear the effect wear off after only a few minutes.

Mestinon, or pyridostigmine bromide, is a pyridine analogue of neostigmine that was first synthesized by Urban and Schneider in the Hoffmann-La Roche Laboratories at Basle, Switzerland in 1945. It was tried unsuccessfully in 1948 at the same milligram dosage as neostigmine.⁵⁰ However, seven clinical reports in Eur-

ope in 1952 and 1953⁴¹ and four reports in the United States in 1954 established that four-times-higher doses of pyridostigmine, although weaker than neostigmine and not longer-acting, produced a more even response with less toxicity and was subjectively better tolerated by most MG patients.^{41,50-52}

At about the same time, Winthrop-Stearns Inc. introduced WIN 8077, which was reviewed by Robert Schwab⁵³ of MGH at the first MG symposium in 1954, and later by Westerberg in 1956, by which time the drug was called ambenonium chloride or "Mysuran."⁵⁴ (later "Mytelase"). Although of greater potency and duration than either neostigmine or pyridostigmine, ambenonium had more adverse effects than pyridostigmine and, according to Westerberg, even stimulated the central nervous system.

Double molecules of neostigmine (BC40, BC47, and BC48) or of pyridostigmine (BC51), linked by 4 to 10 methylene groups, were found to be more active and have a much longer duration of action than neostigmine.⁵⁵ In the hope that such drugs would be useful for moderately severe but stable MG patients, they were tried clinically first in Vienna⁵⁶ and then New York.⁵⁷ However, the therapeutic actions took days for their full development and adverse effects subsided over a correspondingly longer period. Urecholine, as a choline ester substituting for presumably deficient acetylcholine in MG, was advocated by Herbert Schwarz⁵⁸ in 1955, and aldosterone antagonists spironolactone⁵⁹ and triamterene⁶⁰ to boost potassium were tried, apparently successfully, in the early 1960s. At about the same time, lycoramine derivatives of galanthamine, a potent cholinesterase inhibitor used for MG in Russia, were assessed positively at the National Institutes of Health in Bethesda, Maryland,⁶¹ without apparent follow-up. Another long-acting anticholinesterase, echothiophate, was tried for MG in Pittsburgh⁶² in 1966, with problems similar to those of the alkyl phosphates 15 years earlier. Veratrum alkaloids, which stimulate muscle (and nerve) directly, have been used to treat MG⁶³ since 1933, but even when purified as germine diacetate to eliminate the severe hypotensive and gastrointestinal adverse effects, abnormal sensations prevented this approach from being widely accepted.⁶⁴ From all these attempts pyridostigmine emerged as the new drug of choice for the short-term treatment of the symptoms of MG.

FROM ADRENAL EXTRACTS TO PREDNISONE

Extracts from the adrenal glands had been used successfully to treat three possible cases of MG in Paris at the end of the 19th century,⁶⁵ but results, including worsening, were so unpredictable that this treatment for MG eventually died out. Thirty years later anterior pituitary extract, or "Antuitrin," from Park Davis & Co. was given

by daily subcutaneous injections to two MG patients and the "surprisingly good" results were reported by Harold Simon of Birmingham, Alabama, in *JAMA* on June 8, 1935.⁶⁶ Simon mentioned Boothby's contemporary reports about glycine for MG but not Walker's neostigmine results, nor did he note the stimulating effect of anterior pituitary extracts upon the adrenal cortex published by several investigators in 1933. This new therapeutic approach to MG was discouraged by Nathan Schlezinger at Montefiore Hospital in New York, who reported in 1940 that seven MG patients given Antuitrin showed no improvement.⁶⁷

Adrenocorticotrophic hormone (ACTH) was isolated from the anterior lobe of the pituitary in 1943, and ACTH as "corticotropin" became commercially available from Armour Laboratories in 1948. On the basis of animal work in which ACTH increased the synthesis of acetylcholine by minced brain, reported in 1944, Clara Torda and Harold Wolff were the first to administer ACTH (500 mg over 5 days) to 15 MG patients at New York Hospital, reported in 1949.⁶⁸ Initially patients deteriorated, and one of them died during this period, but a "significant partial remission" began a few days later and continued for "a few weeks" in 10 of the remaining patients.

Cortisone became available in limited supplies from Merck and Co. in 1948, and was immediately tried by Philip Hench and associates at the Mayo Clinic on 14 patients with severe rheumatoid arthritis, with remarkable if temporary clinical improvement. Hench was awarded the Nobel Prize in Medicine in 1950 jointly with the two chemists who had isolated and crystallized biologically active steroid compounds from the adrenal cortex, Edward Kendall of the Mayo Foundation and Tadeus Reichstein of the University of Basel in Switzerland. They were cited for their "discoveries concerning the hormones of the bark of the suprarenal capsule."

Reports appeared during the 1950s of successes and failures with ACTH or cortisone in small series of MG patients. All got very much weaker initially, one with a thymoma dying during the exacerbation caused by cortisone. One year after the 1950 Nobel Prize was awarded to their Mayo Clinic colleagues, Clark Millikan and Lee Eaton concluded, on the basis of two MG patients who received ACTH and three who received cortisone, that "ACTH or cortisone is not the ultimate answer to the problem of MG."⁶⁹

Likewise, none of 10 MG patients given only 100 mg of ACTH daily for up to 6 days and none of three MG patients given 150 to 200 mg of cortisone daily for up to 11 days benefited from these treatments at Johns Hopkins Hospital; David Grob and McGehee Harvey thus stated that, "These hormones would appear to have no role in the management of MG."⁷⁰ This report was considered "especially influential in casting doubt on the usefulness" of ACTH and cortisone for

MG, according to a physician with MG who had responded favorably to ACTH treatments by Torda and Wolff on two occasions in 1949 and 1950.⁷¹ Leo Freyberg, MD, a physician in Troy, New York, subsequently had nine further beneficial ACTH courses during exacerbations over the next 10 years, and in 1960 described his positive personal experience with ACTH, as well as that of five other MG patients, four of whom "definitely improved."⁷¹

Nathan Schlezinger, now at Jefferson Medical College in Philadelphia, Pennsylvania, also described in 1952 his favorable experience with three MG patients (plus seven more in an addendum) treated with ACTH who initially worsened but soon showed "decided improvement," although one treated with cortisone didn't improve.⁷² In 1940 Schlezinger had been unable to confirm Simon's favorable results with anterior pituitary lobe extract.⁶⁷

Although Osserman's 1958 monograph on MG warned that "ACTH is too dangerous to be used in the treatment of MG,"⁷³ Georg Matell and his colleagues, Gösta von Reis and Åke Liljestrand, in Sweden persevered, beginning in 1959, in using 28 (6 to 12 days) courses of 1000 IU ACTH for 12 severe MG cases with marked bulbar symptoms and respiratory difficulties.⁷⁴ Despite profound weakness initially, 11 of the 12 patients improved significantly, with two patients experiencing complete remissions lasting several months. They advocated ACTH as the treatment of choice in severe cases of MG. They were the first to invoke (quite tentatively), as a possible explanation for the benefits of ACTH in MG, John Simpson's 1960 seminal hypothesis⁷⁵ that MG might be an autoimmune disease. The Swedish group presented their results at the Third International Symposium on Myasthenia Gravis in New York City in February, 1965, and by November 1966 both Osserman and Grob of New York independently confirmed the "gratifying" effects of short intensive courses of corticotropin for hospitalized patients with severe MG.^{76,77}

On the rationale that bilateral carotid sinus denervation produced hypertrophy of the adrenal cortex in dogs, over 50 MG patients in Europe had this procedure performed between 1943 and 1960.⁷⁸ Results were unconvincing, although 45% of Thevénard's MG patients were said to have benefited from the surgery and three young males with early onset disease went into complete remission after it.

Synthetic glucocorticoids that could be taken orally, such as prednisone (1-dehydro-cortisone) and prednisolone (a similar analog of hydrocortisone), were prepared microbiologically by Schering Corporation in 1955 and chemically from the acetates by Ciba in 1956. They have approximately four times the anti-inflammatory potency of naturally occurring cortisone with less salt- and water-retaining effects. Mogens Kjaer

in Arhus, Denmark, was the first, in 1971, to report his experience with prednisone treatment for MG, begun in 1965. Repeated 7-day courses of 45 mg of oral prednisone, followed by a tapering of 5 mg daily (or weekly), produced a complete or almost complete remission in six of seven older MG patients, aged 50 to 74 years, with only "rare" initial worsening.⁷⁹

John Warmolts and King Engel at the National Institutes of Health, spurred by two successes using prednisone for pediatric MG in 1968, gave five adults with MG "long-term, high-single dosage" prednisone (100 mg) every other day. They reported in January 1972 that improvement, and in one case complete remission, had been maintained for 6 to 17 months.⁸⁰ They attributed the lack of initial worsening in their patients to discontinuation of anticholinesterase medications.

Ramon Jenkins at the Washington Hospital Center in Washington, D.C., also reported benefit from prednisone for MG in April 1972.⁸¹ He maintained nine MG patients on their previous anticholinesterase drugs, and two experienced decreased strength during the early phase of prednisone treatment. All experienced some eventual improvement from daily or alternate-day prednisone, with five recovering completely or almost completely for 1 or 2 years.

Since then many reports of larger series of MG patients have appeared, documenting the benefits and risks of long-term high-dose oral prednisone for MG. The advantages and disadvantages of various treatment regimens, including starting with low doses to try to avoid (not always successfully) the unpredictable initial worsening, converting from daily to alternate-day dosing after several months, very high dose intravenous methylprednisone for refractory cases, and even the "overuse" of steroids for MG, are still presently debated.

IMMUNOSUPPRESSION BY CHEMOTHERAPY

When Torda and Wolfe first tried ACTH as a therapy for MG in 1949, they did so because ACTH decreased thymic tissue and increased acetylcholine synthesis, which was thought to be defective in MG.⁶⁸ The effect of cortisone on the creatine:creatinine ratio was also considered to be important,⁸² but little if any consideration was given to possible immunological aspects of these therapies until 1960, when Arthur Strauss and colleagues in New York demonstrated the presence of muscle antibodies in the sera of patients with MG⁸³ and John Simpson in Edinburgh, Scotland, presented his hypothesis that MG might be an autoimmune disease.⁷⁵

These considerations, as well as the discovery of the immunological function of the thymus in 1960 by Jacques Miller in London, England,⁸⁴ provided a rationale for trying drugs that had been developed initially for

their cytotoxic effects on lymphomas and leukemias but had then been found useful to suppress lymphocytes and immune reactions following renal transplantation. Their use in treatment of MG got off to a bad start in the United States when one of four MG patients treated with 6-mercaptopurine at the Neurological Institute at Columbia-Presbyterian Medical Center in New York developed a catastrophic depression of the bone marrow on 5 mg/kg 6-mercaptopurine, went into myasthenic crisis, and died.⁸⁵ This tragic event at an influential medical center probably deterred the subsequent use of immunosuppressive therapy in the United States for many years.⁸⁶

The story of immunosuppression for MG was more positive in Europe. By 1967 azathioprine, which is metabolized in the liver to 6-mercaptopurine, was tried at a dose of 100 mg daily for several months on five MG patients in Belgium, with "improvement of varying intensity" after a latency of several weeks.⁸⁷ Azathioprine also proved beneficial for five MG patients in France, reported in 1968.⁸⁸ The largest series of immunosuppressive therapy began in 1963 in Würzburg, Germany, and was reported in 1969 by H. G. Mertens, F. Balzereit, and M. Leipert.⁸⁹ It involved 38 MG patients treated mostly with 6-mercaptopurine (50 to 75 mg/d) or azathioprine (100 mg/d), but also with methotrexate 50 to 100 mg intravenously once a week, actinomycin C (200 µg daily), and/or steroids. Favorable results were obtained in 32 of the 38 cases after periods ranging from weeks to months, and were maintained for a maximum of 4 years. By 1978 azathioprine had been used effectively at a dose of 150 to 200 mg for 110 MG patients in seven clinics in Germany.⁹⁰ Azathioprine treatment for MG was also started in Sweden in 1966 and that series was reported in English in 1976 by Georg Matell and colleagues from Stockholm for 26 MG patients followed for up to 7 years.⁹¹ Improvement at a dose of 2 to 4 mg/kg body weight took 6 to 12 weeks to begin and was maximal after 6 to 15 months, with 80% responding favorably. In 1970 an immunosuppressive agent called "mesoerythrite" was advocated by Albert Szobor and Gyula Petrányi of Budapest, Hungary, on the basis of results with 25 refractory MG patients.⁹²

Cyclophosphamide is another antineoplastic drug that has been used to treat MG. It is an alkylating agent, a nitrogen mustard related to sulfur mustard gas used in chemical warfare during World War I and found to cause bone marrow depression and dissolution of lymphoid tissue. Cyclophosphamide was first used clinically against lymphomas in the 1940s, as an immunosuppressant for bone marrow transplants in the 1960s, and for organ transplants and refractory immunological diseases in the 1970s. K. Nouza and V. Šmat from Charles University in Prague, Czechoslovakia, gave as many as three 20- to 30-day courses of 200 mg intravenous cyclophosphamide to two MG patients with

thymus tumors, one of which was invasive, and reported in 1968 that it significantly improved the patients' functioning.⁹³

Martesio Perez and colleagues from Manila in the Philippines reported in 1981 their remarkable success using oral or intravenous cyclophosphamide, usually with prednisone, for 42 MG patients. Of these, a large percentage were in drug-free remission 2 years later, although serious adverse effects such as leucopenia and subsequent malignancies were encountered.⁹⁴ Different means of administration of cyclophosphamide to avoid these adverse effects, including monthly "pulses" or brief high-dose courses, are presently advocated for MG refractory to other therapeutic modalities.

BIOLOGIC AGENTS FOR IMMUNOSUPPRESSION

Cyclosporin, a small cyclic peptide of 11 amino acids obtained by fermentation from a soil fungus discovered by Jean Borel in 1972, is marketed as cyclosporine by Sandoz Ltd. in Basel, Switzerland, and blocks production of cytokines by T lymphocytes. The first clinical trials for organ transplantation occurred in 1978, and the drug was approved for this use in the United States in 1983.

At the Seventh International Conference on Myasthenia Gravis in New York in 1986, Maurice Goulon and colleagues from three hospitals in France reported definite clinical improvement of severe MG within 4 months in nine patients given cyclosporine 2 to 10 mg/kg for 8 to 12 months, but stressed the significant nephrotoxicity.⁹⁵ At the same meeting Richard Tindall and associates in Dallas, Texas, described a first for MG, their double-blind randomized placebo-controlled trial of cyclosporine at 6 mg/kg for recent-onset MG in 10 treated patients (plus 10 placebo controls). In 1987 Tindall and colleagues reported favorable results for six of the 10 treated patients.⁹⁶ The average age of Tindall's MG patients was 65 years, and four discontinued the trial because of nephrotoxicity or persistent nausea. Rolf Nybert-Hansen and L. Gjerstad in Oslo, Norway, reported in 1986 on an open study of cyclosporin for MG, which they had begun in 1984, stating that 5 to 10 mg/kg improved the symptoms of MG in five of six patients with "tolerable" side effects.⁹⁷

Tindall organized a similarly controlled multicenter trial in the United States in 1988 of cyclosporine at a slightly lower dose of 5 mg/kg for steroid-dependent MG patients, which unfortunately was terminated in 1990 by Sandoz, not for safety reasons but "because of multiple reasons, including limited resources and prioritization of clinical programs." However, subsequent reports from some of the centers involved confirm that cyclosporine, taken for over a year, helps MG

patients discontinue corticosteroids, but many discontinue the drug because of toxic side effects, including malignancy.

The most recent biologic immunosuppressive agent to be used to treat a series of MG patients is mycophenolate mofetil or "Cellcept." Mycophenolic acid was originally isolated in 1896 from a penicillium culture, and in the 1940s through the 1970s it was found to have antineoplastic, antibacterial, antifungal, and antiviral properties. Its immunosuppressive action, inhibiting proliferative responses of T and B lymphocytes, was only discovered in the 1980s. To improve the oral bioavailability of the parent compound, mycophenolate mofetil was developed in 1990, and in 1992 it was first tried in human kidney transplant trials with little toxicity. The first case report of successful treatment of severe refractory MG using mycophenolate mofetil appeared in 1998,⁹⁸ and two open-label series of MG patients treated successfully with mycophenolate mofetil were reported in 2001.^{99,100}

IRRADIATION

Thymic irradiation is usually omitted from current reviews of MG therapies, although it has had its advocates throughout the 20th century. Roentgenotherapy in the region of the thymus was mentioned as early as 1927,¹² and five courses of X-ray irradiation for a tumor of the thymus were administered between 1933 and 1936 to the Vanderbilt MG patient¹⁰¹ before Blalock successfully removed the necrotic remains in 1936.²⁸ Charles Aring reported in 1943 on remissions obtained for three MG patients, two of whom had mediastinal masses, by "deep" roentgen ray treatments begun in 1938.¹⁰² Keynes found improved results of surgery for thymomas when he gave those MG patients preoperative irradiation to the thymus region.¹⁰³

Thymic irradiation was more controversial for MG patients without thymoma. Grob concluded in 1953 that it didn't help,¹⁰⁴ and Henson and colleagues advised against it preoperatively in 1965.¹⁰⁵ However, preoperative radiation therapy for nontymomatous MG was advocated by Schwab in 1961¹⁰⁶ (and again in 1971¹⁰⁷) and by Theodore Phillips and Franz Buschke from the University of California in San Francisco in 1967.¹⁰⁸ An interesting two-decade follow-up of 16 MG patients without tumors who underwent thymic irradiation alone, without thymectomy or steroids, was reported by Anupam Routh and colleagues from University Hospital in Jackson, Mississippi in 1983, with improvement "if he or she survived the post-treatment lag period of several months."¹⁰⁹

Once antilymphocyte chemotherapy had been shown to be helpful, general irradiation therapy of lymphocytes was also tried. Splenic radiation of five MG patients was reported in 1981 by W. King Engel

and colleagues at the National Institutes of Health to improve functioning for 1 to 4 months.¹¹⁰ Total lymphoid irradiation was also tried by Engel et al, with improvement lasting 6 months for one MG patient but not for another.¹¹⁰ In 1993 Luca Durelli and associates from Torino, Italy, summarized several years' follow-up of 12 thymectomized MG patients who underwent presumably safer low-dose total body irradiation with objective clinical improvement in 50%.¹¹¹

BLOODLETTING

A curarelike factor circulating in the blood of myasthenics has been postulated since the early descriptions of MG.⁶ In 1960 Ernst Stricker and colleagues in Basel, Switzerland, reported that hemodialysis of eight MG patients resulted in undoubted improvement lasting 2 to 3 weeks in five patients with severe MG.¹¹² As possible explanations they discounted removal of anticholinesterase drugs, spontaneous remissions, psychological responses, or shifts of ions such as K^+ , Mg^{2+} , or Ca^{2+} . They suggested that dialysis removed a neuromuscular blocking substance of low molecular weight. In 1971 Todd Ing and colleagues from Chicago, Illinois, provided a case report of repeated improvement of MG by hemodialysis in a patient with chronic renal failure,¹¹³ again without explanations other than those provided by Stricker et al.¹¹² Lactic acid in myasthenic muscles with precarious neuromuscular function was Bernard Patten's explanation for the "Mary Walker effect," in which exercise of forearm muscles produced increased ptosis in some MG patients.¹¹⁴

In 1964 daily lymph drainage of the thoracic duct, which after 2 weeks reduces lymphocytes and immunoglobulins from peripheral blood, produced at the same time an immunosuppressive effect in kidney transplantations that lasted as long as the drainage continued. Between 1970 and 1977 the originators of this technique, the surgeon Curt Franksson and his colleague Kurt Bergström, collaborated with neurologists Georg Matell and Gösta von Reis in Stockholm, Sweden, to produce rapid and pronounced temporary improvement of myasthenic symptoms in all but one of 30 MG patients after 2 weeks of thoracic duct lymph drainage.¹¹⁵ They found it of great value in the acute treatment of myasthenic crisis. In contrast to a single case report from Galveston, Texas, of 82 days of thoracic duct drainage of an MG patient in which the cell-free lymph was returned each day without apparent change,¹¹⁶ retransfusion of the patient's own cell-free lymph (or later of immunoglobulin G preparations from the patient's lymph) caused a rapid worsening of myasthenic symptoms in the Swedish patients, evidence for a soluble myasthenic factor in the circulation.¹¹⁷

By 1977 the antibody-mediated autoimmune pathogenesis of MG at the neuromuscular junction

had been clearly established.¹ One of the criteria, that reduction of antibodies ameliorates the disease, had been hinted at by lymph drainage but was also provided by a technique called "plasma exchange" or "plasmapheresis" (the drawing off of plasma). This had been done by cumbersome manual techniques on animals as early as 1914. It was applied to humans in the early 1950s to obtain blood components and in 1960 to treat macroglobulinemia. With the development in the late 1960s of cell-separator machines that could safely remove several liters of plasma in about 2 hours, plasma exchange therapy was performed in the 1970s for several potentially antibody-mediated autoimmune diseases.

MG was one of the most likely of these to benefit from plasmapheresis because human acetylcholine receptor antibodies had been reported in the sera of 87% of MG patients by John Lindstrom and Vanda Lennon from the Salk Institute, La Jolla, California, in 1976 with clinical colleagues.¹¹⁸ A. J. Pinching and D. K. Peters from Hammersmith Hospital in London, England, together with John Newsom-Davis from the National Hospital for Nervous Diseases in London, also reported in 1976 documented clinical improvement after a course of daily plasma exchange for two MG patients with severe acquired disease.¹¹⁹ A patient with congenital myasthenia did not improve. Plasmapheresis for MG was pioneered in the United States by Peter Dau at Children's Hospital in San Francisco, who published his favorable results on his first five MG patients in 1977.¹²⁰ Dau added azathioprine to his plasmapheresis regimen, because results from plasmapheresis were temporary, and he may also be credited with introducing azathioprine therapy for MG into American practice.

GLOBULINS

Antilymphocyte globulin (ALG), prepared from the serum of an animal that has been immunized with lymphoid tissue from another species, proved in 1971 to be highly immunosuppressive of cell-mediated immunity, especially in renal transplantation. Antithymocyte globulin (ATG) was similarly prepared by immunizing goats with human thymocytes and was given intramuscularly over 28 to 73 days to 10 MG patients by immunologist Bernard Pirofsky and colleagues at the University of Oregon in Portland, Oregon, beginning in 1971. They chose MG because it was "the best model" to compare five patients with thymectomy and five without thymectomy.¹²¹ During 5 years of follow-up, those who had had thymectomies had the best clinical response to ATG, which lasted about 2 years.¹²² Albert Szobor and colleagues in Budapest, Hungary, used ALG and ATG for 10 seriously ill MG patients, with improvement in seven.¹²³

Beginning in 1970, Gabriel Genkins from Mt. Sinai Medical Center, New York, treated 57 patients

with periodic intramuscular injections of 10 cc pooled gamma globulin, for over 8 years in some patients, as "an effective and non-toxic adjuvant."¹²⁴ Intravenous administration at that time was risky because of allergic reactions, but in 1979 it was discovered that gamma globulins purified by enzyme digestion under special conditions of acidity were tolerated when given intravenously. Given for primary immune deficiencies in 1980 and for autoimmune idiopathic thrombocytopenia in 1981, high-dose intravenous gamma globulin (IVIg) was first reported to improve MG by Philippe Gajdos and 8 colleagues from Garches and Paris, France, in February 1984.¹²⁵ Edward Arsura and associates from Maimonides Medical Center in Brooklyn, New York, were the first to report on IVIg in the United States, describing rapid and temporary improvement in 12 MG patients.¹²⁶ Numerous similar studies were soon to follow, often comparing IVIg with plasmapheresis, both effective temporary treatments for MG.

FUTURE HISTORY

When the chair of my department was told that I was interested in the history of MG, he responded, "Keesey, I'm more interested in MG history for the *next* 100 years!" Indeed, many experimental approaches are presently being considered toward therapies for MG based upon the remarkable advances in knowledge of the immunology and pathogenesis of MG that have accrued over the past 25 years. The most remarkable aspect of the history of past and present therapies for MG reviewed here is the major roles that empiricism and serendipity have so far played, with all the uncertainty that accompanies such approaches. We still await the perfect cure.

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