Antisemitism and the History of Myasthenia Gravis

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The recognition, naming and elucidation of the neuromuscular disease myasthenia gravis is bound up with and affected by antisemitism. There is consensus that the first published case report, now recognizable as MG, was written by Thomas Willis in 1672 [1], although this was only realized after Guthrie drew attention to it in 1903 [2]. Interestingly, the late Prof. John Newsom Davis maintained that the first reported patient was the biblical figure Samson, who exhibited varying muscle strength and alopecia that could have been autoimmune mediated [3].

Although the clinical aspects of MG were well recognized and described by the end of the 19th century, it took a further 80 years for the full pathology to be understood [4]. The course of events was influenced by political antisemitism through the lives of four people who made major contributions to the discovery and elucidation of the disease. The people concerned were Samuel Goldflam, Herman Oppenheim, Lazar Remen and Walter Feldberg.

SAMUEL WOLFOWITSCH GOLDFLAM (1852-1932)

Samuel Goldflam was a Polish neurologist who in 1893 published what has been called "in many ways the most important paper written in the history of the disease" [5]. Goldflam described three patients with MG and reviewed previous case reports that he believed represented this new condition.

Born in Warsaw in 1852, Samuel Goldflam began his medical studies at Warsaw University in 1869 and qualified in 1875. He worked for several years as an assistant to Prof. Vilem Lambl in the internal medicine department at the Sw. Ducha ('Holy Ghost') hospital in Warsaw and in 1882 left to study neurology abroad. He worked in the clinic of German psychiatrist and neurologist Karl Westphal at the Charité Hospital in Berlin and then with Jean-Martin Charcot at the Hôpital de la Salpêtrière in Paris – leading neurological institutions of the day [6]. On his return to Warsaw he took up his previous post in Lambl's clinic, but it became apparent that "Because of special conditions in this country at that time, he had not his own service, and therefore treated only out-patients or consulted patients in the wards of his colleagues" [Hausmanova I. Personal communication, 1993]. The "special" circumstances were that he was a Jew. Historian Raphael Mahler [7] wrote:

> Discrimination against Jewish physicians passed through two stages, concomitant with the growth of anti-semitism in Poland. Prior to 1935, Jewish physicians suffered the following disabilities. In university clinics and municipal hospitals it was difficult for a Jew to obtain a position as ordinarius, or even as assistant […] Discrimination was especially rife in university professorships. Distinguished Jewish physicians like the neurologists Samuel Goldflam and Henryk Flatau were not deemed worthy of spreading knowledge in seats of Polish learning. The medical faculty at Warsaw contained no Jew; while of several outstanding Jewish scientists who struggled somehow to the minor position of dozent*, none was ever promoted to the rank even of an associate professor.

Goldflam continued to teach and work at the hospital but, wisely, he also set himself up in private practice like most of his Jewish colleagues [7]. In addition, he established a special clinic, in Warsaw's Granicza Street, for poor Jewish patients and which he himself funded [6]. It was at this clinic, in 1891 and 1892, that he saw the three patients who he recognized as having "an apparently curable bulbar paralytic symptom-complex with involvement of the extremities" [8]. This condition was MG, but the name had yet to be coined (see below). Goldflam reviewed the literature and found several similar cases reported by authors who did not realize that they were dealing with a hitherto undescribed condition. He concluded that what he and others were seeing was a distinct disease entity, and he described its characteristics. It was, he wrote, a form of bulbar palsy, different from that described by Duchenne, often occurring in young people, with frequent involvement of the ocular muscles and the masseter, breathing difficulties, and associated weakness of limb muscles but without any wasting or fibrillation and with normal tendon

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MG = myasthenia gravis

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reflexes. It was variable in severity, not only from day to day but in the course of a day, and there were no abnormal morbid anatomic findings. For many years, MG was known as Erb-Goldflam disease, after the two neurologists who made the first penetrating case analyses. (Wilhelm Erb had presented a paper in 1879 in which he described three patients, who according to his descriptions most likely had MG, which he called "a new, probably bulbar symptom complex.")

Throughout his life Goldflam was involved in Jewish affairs, both parochially and nationally. He was an energetic philanthropist and was involved in the foundation of several charities, including a children's hospital. He was also active politically. In 1916, when Poland was largely under German and Austrian control, he helped to convene a meeting at his home, which he chaired, of all the various political factions of Polish Jewry in an attempt to forge a common response to the political changes at the time [9].

HERMANN OPPENHEIM (1858-1919)

Hermann Oppenheim was acknowledged as the leading clinical neurologist in Germany in the last decade of the 19th century. He was born in Warburg, Westphalia in 1858 and after graduating from the gymnasium in 1876 went on to study medicine at the universities of Gottingen, Berlin and Bonn. He qualified as a physician in 1882 and worked as an assistant at the Maison de Santé in Berlin, but in 1883 moved to the neurological and psychiatric clinics of the Charité, a hospital attached to the University of Berlin [10]. Here, he became the favorite assistant of the aforementioned head of the clinic, Prof. Karl Friedrich Otto Westphal, whose support enabled him to become a *Privatdozent* in 1886. *Privatdozenten* were recognized university lecturers, with the title of professor but unsalaried and who usually supported themselves by working as private practitioners or relied on the support of their families [11].

The history of the discovery and elucidation of myasthenia gravis is bound up with and affected by antisemitism

He wrote extensively on numerous neurological disorders, publishing in 1894 a textbook of neurology, *Lehrbuch der Nervenkrankheiten für Ärzte und Studierende*. Considered a seminal work, it was translated into several languages. The list of Oppenheim's pupils reads like a roll call of eminent early 20th century neurologists. Given the breadth of his interests, it was almost inevitable that Oppenheim would contribute to the emerging concept of MG as a disease entity. In March 1887, he gave a lecture to the Society for Psychiatry and Neurology in Berlin on "a case of chronic progressive bulbar paralysis without anatomical findings" [12]. The patient, a woman of 29 who had been under his care for 18 months, first developed weakness of her arms and legs, followed by difficulties in speech and swallowing and weakness of the facial muscles. She had no ocular symptoms but showed a marked fluctuation in the severity of the muscular weakness and died of respiratory insufficiency. Oppenheim, convinced of a nervous system pathology, was clearly surprised that there were no detectable abnormalities at postmortem. He reported a further patient in 1899, who was found at autopsy to have a mediastinal tumor, which turned out to be a lymphosarcoma and which Oppenheim regarded as irrelevant to the myasthenic symptoms. In 1901 he published a monograph [13] in which he summarized the clinical findings of all the 58 hitherto known and reported cases.

When Westphal became ill at the end of the 1880s Oppenheim was in charge of the clinic. By the time Westphal died in 1890 Oppenheim was regarded as the leading clinical neurologist in Germany and had an international reputation. He was the unanimous choice of the medical faculty at the University of Berlin to succeed Westphal in the chair of neurology, but his nomination was rejected by the Prussian Ministry of Education because he was Jewish. He was advised that this decision might be reversed if he accepted baptism, but he refused [14]. Oppenheim's rejection and his failure to be nominated to a chair affected his work, attitudes and opinions profoundly. He was described thus, a year before his death: "…this most accomplished man, who had been the teacher of many neurologists, and who had swallowed hard the fact that he had never received an official chair …." [15].

Friedrich Jolly was appointed to the chair in his place. Jolly conducted the first electrophysiologic studies in a patient with MG, demonstrating fatigue of the muscles with repeated electrical stimulation, and he is also credited with the first use of the term "myasthenia gravis." In December 1894, shortly after his appointment as Westphal's successor, Jolly gave a lecture to the Berlin Medical Society that was later published under the title: "Uber Myasthenia gravis pseudoparalytica" [16].

LAZAR REMEN (1907-1974)

Lazar Remen was the first to describe the use of an anticholinesterase compound to treat MG. These compounds are effective and until the 1980s were the only therapeutic alternative to surgical removal of the thymus gland. However, in 1932 when Remen made his report, acetylcholine was not known to be involved in neuromuscular transmission. Rather, anticholinesterase compounds were recognized for their role as antagonists of the poison curare and in postoperative patients as stimulants of the muscle of the bowel and bladder. A natural anticholinesterase, eserine, derived originally from the Calabar bean, had been isolated in 1863 but was found to have a short duration of action and numerous and unpredictable unwanted effects. In the search for more therapeutically

useful compounds, Aeschlimann and Reinert in 1931 [17] synthesised 45 compounds analogous to eserine. The 32nd in this series, which they named neostigmine methylsulphate (also known as prostigmine), was the most promising of these. It was this drug that Remen used.

Lazar Remen was attached to the clinic of Professor Kehrer at the University of Munster in Westphalia. He had trained at Hufeland hospital in Berlin and later in Munster. He described the experimental treatment of three patients. The first, a 49 year old man, was the only one of the three with definite MG and the only one to receive a neostigmine injection; the others had indeterminate neurologic disease with myasthenic features. The first patient showed marked and immediate improvement in his strength. Soon after the injection he was able to open his eyes, swallow and extend his arms, none of which he could do previously. The effect lasted for an hour. Curiously, this treatment was not repeated, and the main thrust of Remen's paper was the effects of glycine on creatine metabolism in the three patients – an effect that was slight. Glycine was one of the two known effective therapeutic interventions for MG at the time, the other being ephedrine [18]. The real discovery of anticholinesterases as an effective and safe treatment for myasthenia was left to Mary Walker. In her now famous letter to *The Lancet* in 1934 [19], she reported using physostigmine in one patient to great effect, inspired by the observation of her visiting consultant that MG shared several similarities with curare poisoning. As Viets [5] commented, Remen unlocked the door, but it was left to Mary Walker to open it fully.

The lives of four major contributors – Goldflam, Oppenheim, Remen and Feldberg – were negatively affected by overt, institutionalized antisemitism Paradoxically, this had a beneficial effect on the course of the discovery of MG

Lazar Remen's career was radically affected in 1933 by events outside his control – the accession of Hitler to power in Germany. His name disappears from the medical literature after 1932, and only in 1964 was it discovered that he was alive and well and working as a general practitioner in Petah Tikva, a town in central Israel.

He fled Germany in fear of his life and arrived in what was then Palestine in 1933, and set himself up as a practitioner of obstetrics and gynecology. He built a maternity hospital and directed it for 11 years. From 1945 until his death in 1974 he was in private practice in Petah Tikva. He was extremely well respected in Israel and held chairmanships of local and national medical bodies.

His earlier research with neostigmine was drawn to wider attention by Dr. Stanley Fahn, a relative who was a practising neurologist in the United States. In 1964, Lazar Remen visited Dr. Henry Viets, an eminent American neurologist who had founded the first MG clinic in the U.S. at Massachusetts General Hospital in 1935. Dr. Viets subsequently wrote about Lazar Remen [20]:

> Only in 1964 was this pioneer investigator discovered, a personable and successful practitioner of medicine in Israel. Surprised at my interest in his plight, for no one had sought him out in the interest of myasthenia in over thirty years, he flew to Boston to visit me. He had been virtually lost to the world of medical progress since 1932, for he published no scientific contributions after that date. For his sudden change in status he bears no malice against a world of rough handling, and I am glad to honor him for his fine medical standards and moral uprightness.

WALTER FELDBERG (1900-1993)

Walter Feldberg was a pioneer in the discovery of acetylcholine as a factor in neuromuscular transmission. Born in Hamburg, Feldberg studied medicine in Berlin where he qualified in 1925. Soon after he went to England, first to Cambridge where he worked on nerve physiology, later moving to London where he worked with pharmacologist Sir Henry Dale [21]. On his return to Berlin in 1928 he worked at the Institute of Physiology where he developed the eserinized leech muscle preparation, which was to prove important in later studies.

While in Berlin he had already started his work on acetylcholine. Acetylcholine was known to be the transmitter for autonomic parasympathetic responses, and previous researchers had tried unsuccessfully to show that it was also involved in neuromuscular transmission. Feldberg and Minz in 1931 [22] observed that they could elicit quick contractions or fibrillation of normal mammalian muscles when acetylcholine was injected directly into the arteries supplying them, and that the reaction was unaffected by atropine.

After Hitler's rise to power in Germany in 1933, Feldberg was ordered to leave the Institute in Berlin, but fortunately for him Dale had anticipated this development and obtained a temporary post for him at the Medical Research Council laboratories in Hampstead, London [21]. Here, they carried out their research which was to prove unequivocally that acetylcholine was the neuromuscular transmitter. Their work was first reported at a meeting of the Physiological Society in 1934, and published in 1936 in collaboration with another German refugee, Marthe Vogt [23].

Using the eserinized leech muscle preparation as a bioassay for acetylcholine, they showed first that stimulation of the motor nerve fibers to perfused voluntary muscle caused the appearance of acetylcholine in the venous fluid. Secondly, that direct stimulation of a normal muscle, or of one deprived of its autonomic nerve supply, had a similar result, but that

when the muscle was completely denervated no aceytylcholine appeared in response to effective stimulation. Thirdly, they showed that when the muscle was paralyzed by tubocurarine, stimulation of the motor nerve fibers still caused the release of acetylcholine; and fourthly, that when conduction from motor nerve fibers to the perfused muscle failed from exhaustion after repeated stimulation, acetylcholine was no longer released by stimulation of either muscle or nerve.

They thus established the basic physiology of neuromuscular transmission, which finally enabled work on MG to proceed from anecdotal observation of clinical and pharmacological phenomena to a real understanding of what was happening, and why.

Feldberg went to Australia in 1936 and returned to England in 1940 to take up, for the first time in his career, at nearly 40 years old, a permanent position. He continued to work on neurotransmission – in the brain and in muscles – for the rest of his distinguished career.

CONCLUSIONS

Overt, institutionalized antisemitism profoundly affected the lives of these four pioneers in the field of myasthenia gravis. Paradoxically, it can be said to have hastened the progress of discovery. Goldflam, denied a permanent position at the university hospital, established his own clinic where he encountered the three patients in whom he recognized a complex of signs and symptoms that led him to assert that this was a previously unrecognized disease. Oppenheim was cruelly treated, not by his colleagues but by the authorities; yet it could be argued that Jolly, who was appointed to the chair of neurology that should have been Oppenheim's, made the greater contribution with his electrical studies and by coining the name by which we now know this disease. The expulsion of Feldberg from his post in Berlin led to his intensely fruitful collaboration with Dale and to a real understanding of the pathophysiology of MG. Only in the case of Remen did antisemitism have an entirely negative effect on the course of the elucidation of MG. Remen did no further work in this field, but the discovery of anticholinesterases as an effective therapy was delayed only by a further 2 years.

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