THE MIRACLE AT ST. ALFEGE'S

THIRTY years after the event, no one now doubts that a miracle took place in April of 1934 at St. Alfege's Hospital in Greenwich. A middle-aged woman, 'unable to hold her shopping bag' and whose 'head used to fall forwards when she knelt to do the hearth', became bedridden a few weeks later, showing almost all the classical symptoms of severe myasthenia gravis.

In St. Alfege's Hospital an alert Senior Hospital Medical officer, Mary B. Walker, who was not to obtain her M.D. degree from Edinburgh University until a year later, noting the abnormal fatiguability of her patient's muscles, sensed that the cause might be a curare-like poison acting on the motor nerve-endings and thought 'it would be worth while to try the effect of physostigmine, a partial antagonist to curare'. She wrote in her modest letter, reporting the case to *The Lancet*, that 'hypodermic injections of physostigmine salicylate did have a striking though temporary effect', which she felt was an observation of some importance to medicine.[1]

Just how important her discovery was no one in 1934, with possibly one exception, seems to have the slightest premonition, perhaps least of all the quiet, self-effacing Mary Walker. Even her visiting neurological consultant expressed scepticism regarding the value of physostigmine in the treatment of myasthenia gravis. The disease was so rarely seen that neurologists had few opportunities to test Dr. Walker's report. Frequently, moreover, when a dosage large enough to overcome the muscular weakness was used, the untoward 'sympathetic explosion' was so great that the good effects were smothered by the secondary reaction. But Mary Walker was not to be thwarted.

In an attempt to eliminate the parasympathetic stimulation she injected, on 16 June 1934, a new analogue of physostigmine, neostigmine methylsulfate ('Prostigmin'), a drug undoubtedly suggested to her by Philip Hamill, M.D., lecturer in pharmacology and therapeutics at St. Bartholomew's Hospital Medical School, who served as a consultant to St. Alfege's Hospital, and whose interest and advice she had sought during the previous few months, with so much profit.

But Mary Walker's demonstration almost died aborning. No letters appeared in the correspondence columns of *The Lancet* in 1934 and myasthenia gravis did not receive comment of any kind in the volume for the last half of the year. It was her counsellor, Philip Hamill, who seems to have kept the flame burning. In discussing Dr. Walker's presentation of her second case before the clinical section of the Royal Society of Medicine on 8 February 1935, he stated: 'Whatever may be the mechanism of the weakness and fatiguability of the muscles in myasthenia gravis, physostigmine, and its ally, prostigmin, overcome it.' This forthright statement was the turning-point in directional guidance and myasthenia gravis was moved up from its obscure position, buried in the end-pages of the textbooks of the time, to a place of prominence. Research on neuromuscular transmission, already forshadowed by Loewi's discovery[2] of the 'vagusstoff' and the work of Dale and Gaddum[3] on acetylcholine as a mediator at the myoneural junction, was greatly accelerated; the testing of physostigmine analogues soon became expanded; money for patient care was found and clinics established; neurology, a little slow to recognize that Mary Walker's letter had set off a vast chain reaction, the end of which is not in sight even thirty years later, momentarily faltered but soon righted itself and gave her sound endorsement and an appropriate accolade.

But even before the spring of 1934 there had been misses and near-misses. When Aeschlimann and Reinert[4] synthesized and analysed forty-five analogues of physostigmine, the search had been directed towards a substance effective as a parasympathetic

https://doi.org/10.1017/S0025727300030465 Published online by Cambridge University Press

stimulant to overcome postoperative intestinal atony or urinary retention. No thought of the value of any one of the analogues in the treatment of myasthenia gravis was in the mind of either investigator and little did they realize that product number 32 would end up as neostigmine methylsulfate and revolutionize the treatment of an almost unknown disease.

In 1932, some months after neostigmine became available for injection, an account was published of its use in a patient with myasthenia gravis by Lazar Remen,[5] then attached to Kehrer's clinic at the University of Münster in Westphalia. His patient, with ptosis, characteristic weakness of the extended hands and fingers and dysphagia had come under Kehrer's care in December 1931, having had intermittent symptoms, punctuated by relapses and remission, for three years. The diagnosis was unmistakable.

Given an injection of neostigmine, the response was clearly evident in an hour, with lessened ptosis, increased ability to extend the hands and fingers and improvement in swallowing. The dosage of the neostigmine used was not recorded or the exact day that the test was given. It was, however, before 1 March 1932, for on that day, disregarding the favourable test, treatment was begun with glycine. Remen left the observation loosely attached to his paper, for the main concern of his chief was glycine therapy. There the matter rested until Mary Walker, unaware of Remen's work, evoked the same response with physostigmine in June 1934 and with neostigmine a few weeks later. Remen unquestionably had the key in the lock and turned it, but he failed to open the door fully and see what a vast prospect lay beyond. He no doubt followed his chief in pushing his research in an unprofitable direction, but he should be given credit for recording his observation, although not grasping its significance. There may well have been other circumstances, besides his chief's interest in glycine, that hindered this talented young man. His career suddenly was radically changed in 1933 through conditions not of his own choosing. All his scientific reports in the literature ceased after 1932 and he too was 'lost' to the world of medical progress. [Only in early 1964 was it learned that Lazar Remen, trained at the Hufeland Hospital in Berlin and later in Münster, was still living and in general practice in Petach-Tikwa, Israel. Hearing of my interest in his work in 1932, he kindly visited me in Boston in September 1964.]

But if Remen's observation in Münster in 1932 was not followed up by others, this was far from the case in London. To be sure all was silent from June 1934 to 8 February 1935, when Mary Walker[6] reported her second case, this time before the Royal Society of Medicine, ably supported by her mentor, Philip Hamill. This opened the floodgates, and confirmatory observations filled the medical literature for months to come. First was Blake Pritchard,[7] at the Hospital for Epilepsy and Paralysis, Maida Vale, with seven cases and L. P. E. Laurent,[8] who matched Pritchard at the University College Hospital and brought the total cases up to sixteen, without a single failure. Success could no longer be denied and the 'miracle of St. Alfege's' became an integral part of medicine.

Before the end of 1935 the drug had reached America and was used at the Massachusetts General Hospital on 4 April 1935, and a diagnostic test devised by Viets and Schwab.[9] A Myasthenia Gravis Clinic was started the same year. Soon attached to it came a research unit, devoted as years passed to clinical investigations, pathology and thymic surgery. But no matter how far the investigations extended, they all stemmed back to the spring of 1934, when Mary Walker, like so many others of her ilk, o'ertook the flighty purpose and made the deed go with it.

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https://doi.org/10.1017/S0025727300030465 Published online by Cambridge University Press

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ROBERT PERREAU: APOTHECARY HANGED FOR COINING

DR. T. D. WHITTET has sent us the following interesting item which may be regarded as a footnote to Professor Trease and Mr. J. H. Hodson's article 'The Inventory of John Hexam, a fifteenth-century apothecary', *Medical History*, 1965, **9**, 76–81:

I read with interest the article by Professor Trease and Mr. Hodson, on the apothecary who was hanged for coining, as it had a sequel 351 years later.

Among the notes collected by the late Dr. Cecil Wall at the Apothecaries' Hall is the following extract from a letter in the *Sunday Times* of 27 July 1930 by E. V. Lucas:

'Robert Perreau, an apothecary of Golden Square was with his twin brother Daniel hanged for forgery in 1776. Such was their fraternal love that they stood hand in hand while the ropes were adjusted and remained in that position for half a minute after the drop.'

A Robert Perreau is in the Yeomanry list of 1757 in Oxenden Street and in the Livery list of 1769 in St. Albans' Street. He is reported to have died on 17 January 1776, so this is presumably the person.

https://doi.org/10.1017/S0025727300030465 Published online by Cambridge University Press