THE MARY WALKER EFFECT: MARY BROADFOOT WALKER

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On February 17, 1938, Mary Broadfoot Walker, MD presented a patient with myasthenia gravis at a clinical meeting of the Royal Society of Medicine. The meeting was held at the National Hospital, Queen Square, London. In the former workplace of William Gowers and John Hughlings Jackson, she described what came to be known as the Mary Walker effect:

> "The left eyelid, when not under the influence of prostigmin, droops so that the whole of the iris is covered. At a time when the effect of prostigmin is wearing off, the circulation is cut off in both arms by inflating sphygmomanometer cuffs to 200 mm. Hg. The forearms are then pronated and supinated until they are tired; this usually takes over a minute. No increase in the droop of the eyelid takes place at this stage. The pressure in the cuffs is then released. After a latent period of a minute and a half increased droop develops. In two minutes there is a very great increase in weakness of the muscles generally. The pressure has been maintained for varying periods after the pronation and supination have ceased, with the same results."

Wilson and Stoner found increased ptosis in 12/14 patients using this maneuver. Walker said one might not see the effect if the patient was under the influence of an acetylcholinesterase inhibitor, or if the myasthenia gravis was mild. Walker felt that this proved that myasthenic weakness was not due to a deficiency of acetylcholine at the neuromuscular junction. She thought that myasthenic muscles released a curarizing agent during activity, which passed into the bloodstream and blocked neuromuscular transmission elsewhere. In her MD thesis of 1935, she hypothesized that "perhaps a virus acts on some substance formed temporarily during muscle contraction to form a curarising quaternary ammonium base, substance x, which acts on the muscle in which it is formed, and is carried by the blood stream to the rest of the muscles." Walker's speculation was incorrect, but it resulted in the search for a circulating factor causative of the disease.

Concerning priority, Samuel Goldflam (1893) and Friedrich Jolly (1895) noted that exercise of one muscle group could provoke weakness of non-related muscles in myasthenia gravis. Keynes wrote in 1961 that this finding was "named rather late in the day the Walker-effect, the phenomenon having been again described by Dr. Mary Walker in 1938." Mary Walker stated in her 1938 paper that "it is well known that in myasthenia gravis, weakness throughout the body develops if one group of muscles is exercised." The Mary Walker effect was much more than the phenomenon previously described by Goldflam and Jolly, and was demonstrated by her before many physicians in order to support her hypothesis about the pathogenesis of the disease.

1. Walker MB. Myasthenia gravis: a case in which fatigue of the forearm muscles could induce paralysis of extra-ocular muscles. Proc R Soc Med 1938;31:722.
2. Wilson A. Stoner HB. Myasthenia gravis: a consideration of its causation in a study of fourteen cases. QJM 1944;13;1-18.
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4. Walker MB. Some discoveries on myasthenia gravis: the background. Br Med J 1973;2:42–43.
5. Lanska DJ. Mary Broadfoot Walker. In: Aminoff MJ, Daroff RB, editors. Encyclopedia of the Neurological Sciences, 2nd edition, vol. 4. Oxford: Academic Press;2014:742-743.
6. Keynes G. The history of myasthenia gravis. Med Hist 1961;5:313-326.

Mary Broadfoot Walker was born in Wigtown, Scotland in 1888. She received her Bachelor of Medicine and Bachelor of Surgery degrees in 1913 from the Glasgow and Edinburgh Medical College for Women. From 1913-1916 she was resident medical officer of the Hackney Union Infirmary, Homerton, outdoor house surgeon at the

West End Branch of the Glasgow Royal Maternity and Women's Hospital, and medical officer of the Birmingham General Dispensary. From 1916-1919 Walker was a ward physician in the Royal Army Medical Corps attached to the 63rd General Hospital in Malta and Salonica (Greece). She subsequently worked as a salaried "Poor Law Service" medical assistant at the Greenwich Union Infirmary/St. Alfege's Hospital (1920-1936). St. Alfege's was not a teaching hospital where research was fully supported, which made her subsequent contributions to the area of neuromuscular disease in the 1930s all the more impressive. Walker became a member of the Royal College of Physicians in 1932, and received the MD Thesis Gold Medal from the University of Edinburgh on Dec. 20, 1935. Her thesis was entitled "A Contribution to the Study of Myasthenia Gravis." In 1936 she moved to St. Leonard's in Shoreditch. Dr. Walker declined an invitation in 1938 to join the staff of the Elizabeth Garrett Anderson Hospital as a consultant, because of her lack of personal finance and dependence on a salary. In 1939, heavy bombing required her transfer to St. Francis Hospital, Dulwich (South London). Walker next moved to St. Benedict's Hospital, Tooting, where she rose to the rank of senior medical assistant/senior hospital medical officer. In 1954 she retired and moved back to her family home (Croft-an-righ) in Wigtown, Scotland. Although Dr. Walker was never named a fellow of the Royal College of Physicians, she was awarded their Jean Hunter Prize in 1963 for the advancement of research into the treatment of nervous exhaustion. Mary Broadfoot Walker died September 13, 1974, and was buried in the Wigtown cemetery.

1. K.S.M. Mary Broadfoot Walker M.D.Edin, M.R.C.P. Lancet 1974;2:1401-1402.
2. P.W.R. Dr. Mary Walker. Lancet 1974;2:1582.
3. Keeney AH, Keeney VT. Mary B. Walker, M.D. and the pioneering use of prostigmin to treat myasthenia gravis. Doc Ophthalmol 1997;93:125–34.
4. Keesey JC. Contemporary opinions about Mary Walker: a shy pioneer of therapeutic neurology. Neurology 1998;51:1433–1439.
5. Lanska DJ. Mary Broadfoot Walker. In: Aminoff MJ, Daroff RB, editors. Encyclopedia of the Neurological Sciences, 2nd edition, vol. 4. Oxford: Academic Press;2014:742-743.
6. Johnston JD. The contribution of Dr. Mary Walker towards myasthenia gravis and periodic paralysis whilst working in poor law hospitals in London. J Hist Neurosci 2005;14:121-37.

Walker was the first to clearly demonstrate that strength temporarily improved in patients with myasthenia gravis when they were given physostigmine or Prostigmin (neostigmine). In a June 2, 1934 Lancet article, she noted:

> "The abnormal fatiguability in myasthenia gravis has been thought to be due to curare-like poisoning of the motor nerve-endings or of the 'myoneural junctions' in the affected muscles. It occurred to me recently that it would be worth while to try the effect of physostigmine, a partial antagonist to curare, on a case of myasthenia gravis at present in St. Alfege's Hospital, in the hope that it would counteract the effect of the unknown substance which might be exerting a curare-like effect on the myoneural junctions. I found that hypodermic injections of physostigmine salicylate did have a striking though temporary effect."

Photographs showed the improvement in ptosis after treatment with physostigmine in "Mrs. M." No improvement occurred with control injections of water, pilocarpine, strychnine, adrenaline, ephedrine, or acetylcholine. Walker commented:

> "I think that this effect of physostigmine on myasthenia gravis is important, though it is only temporary, for it improves swallowing and might tide a patient over a respiratory crisis. It supports the opinion that the fatiguability is due to a poisoning of the motor end-organs, or 'myoneural junctions,' rather than to an affection of the muscle itself. It may be significant that physostigmine inhibits the action of the esterase which destroys acetylcholine."

Jolly (1895) suggested that physostigmine might be used in myasthenia gravis, and Murri (1896) tried physostigmine without success, as the patient did not tolerate the medicine. Remen (1932) observed temporary improvement with neostigmine (Prostigmin), but was mostly focused on the treatment of myasthenia with glycine.

In a 1979 letter, Derek Denny-Brown relayed how this treatment of Mrs. M with physostigmine came about. Denny-Brown visited St. Alfege's every two weeks. He diagnosed Walker's patient with myasthenia, and asserted that Walker had never heard of the disorder. Walker asked the cause, and Denny-Brown commented that it was

unknown, but that it resembled curare poisoning. Denny-Brown stated that Walker did not know what that was. Denny-Brown recommended a strychnine-like medication and moved on to the next patient. Walker approached him while he was examining the next patient, and asked if she could try physostigmine. Denny-Brown stated that Walker had looked up the antidote to curare in a Burroughs Wellcome annual doctor's book. He agreed with the medication trial, even though he thought that it was unlikely to work. Denny-Brown noted:

> "It was 2 weeks before I visited the hospital again, and this time she was waiting for me at the front entrance, in a great state of excitement. 'You must come and see my patient with myasthenia-she is cured.' Sure enough, there was no more weakness. . . . I am not very proud of my part in the discovery of the effect of prostigmine [sic] for if anything I attempted to discourage its trial!"

The letter was written 45 years after the event, and was told from the point of view of only one of the two protagonists.

1. Walker MB. Treatment of myasthenia gravis with physostigmine. Lancet 1934;1:1200–1201.
2. Keeney AH, Keeney VT. Mary B. Walker, M.D. and the pioneering use of prostigmin to treat myasthenia gravis. Doc Ophthalmol 1997;93:125–34.
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5. Johnston JD. The contribution of Dr. Mary Walker towards myasthenia gravis and periodic paralysis whilst working in poor law hospitals in London. J Hist Neurosci 2005;14:121-37.

Walker presented another patient with myasthenia ("D.C" or "Miss C") at a meeting of the Royal Society of Medicine on Feb. 8, 1935. Miss C responded nicely to Prostigmin, another acetylcholinesterase inhibitor. Physostigmine also improved the patient's ptosis but caused nausea, vomiting, and a faint feeling so it was abandoned. Prostigmin was much better tolerated, but more expensive than physostigmine. Walker later estimated that Prostigmin injections would cost a patient with myasthenia gravis £50 per year. The response was so dramatic and quick that some in the audience questioned if the patient was functional. London neurologist Douglas McAlpine clarified in a letter to The Lancet that the patient presented by Mary Walker clearly had myasthenia. He had cared for the patient previously, and saw her again after Dr. Walker's presentation to verify the response to Prostigmin. Pritchard, Laurent, and Denny-Brown also published papers or letters confirming the response to Prostigmin in patients with myasthenia gravis. Walker's observation was published in the Proceedings of the Royal Society of Medicine in April 1935.

1. Walker MB. Case showing the effect of prostigmin on myasthenia gravis. Proc R Soc Med 1935;28:759–761.
2. McAlpine D. Treatment of myasthenia gravis with "Prostigmin." Lancet 1935;1:516.
3. Keesey JC. Contemporary opinions about Mary Walker: a shy pioneer of therapeutic neurology. Neurology 1998;51:1433–1439.

Mary Walker's MD thesis on myasthenia was likely written in September 1935. In the 139-page document, three patients were described in detail: Mrs. M, D.C./Miss C, and Miss W (a new patient). Walker's first patient, Mrs. M, went into remission ~5 months after onset. Concerning Miss W's first symptoms of myasthenia, Walker wrote that "at a Christmas party in 1916 the guests remarked that the patient could not smile properly, and that she looked 'peculiar, as if she were crying.'" Like Miss C, Miss W did not tolerate physostigmine, but responded well to Prostigmin. Walker observed that in Miss C and Miss W:

> "Full strength returns for several hours; they can hold their own in a pillow fight with the nurses, and sometimes 'terrorise' them by trying to lift them up, to show how strong they are. In the case of the lighter nurses they succeed."

Dr. Walker clearly knew her patients well. She also knew that myasthenia was a remitting disease, and commented that "the remissions characteristic of the disease make it difficult to appraise the value of remedies."

Her MD thesis conclusions included the following:

- Prostigmin was best at temporarily removing symptoms
- Long continued daily administration of large doses did not diminish the response or cause untoward results
- Muscles weak from disease may regain strength
- Atropine helped for the side effects of Prostigmin
- Adjuvants such as ephedrine, KCl, or veratrine helped
- The treatment was not curative, but it enabled even a patient with severe myasthenia gravis to lead a normal life
- "No case of myasthenia gravis should now die of the disease."

1. Walker MB. Thesis for the degree of M.D. in the University of Edinburgh: a contribution to the study of myasthenia gravis. University of Edinburgh;1935.
2. Johnston JD. The contribution of Dr. Mary Walker towards myasthenia gravis and periodic paralysis whilst working in poor law hospitals in London. J Hist Neurosci 2005;14:121-37.

Laurent and Walker published a paper in The Lancet in 1936 which clarified that Prostigmin could be used orally in patients with myasthenia, and that prolonged treatment was tolerated. They noted no increase in myasthenic symptoms from this treatment. Altogether, Walker published eight papers and one thesis on myasthenia gravis.

1. Walker MB. Treatment of myasthenia gravis with physostigmine. Lancet 1934;1:1200–1201.
2. Walker MB. Case showing the effect of prostigmin on myasthenia gravis. Proc R Soc Med 1935;28:759–761.
3. Pritchard EAB, Walker MB. The effect of prostigmin on the symptoms and on the myogram in myasthenia gravis. J Physiol 1935;84(Suppl):35P–36P.
4. Hamill P, Walker MB. The action of "prostigmin" (Roche) in neuro-muscular disorders. J Physiol 1935;84(Suppl):36P–37P.
5. Walker MB. Potassium chloride in myasthenia gravis. Lancet 1935;2:47.
6. Laurent LPE, Walker MB. Oral and parenteral administration of prostigmin and its analogues in myasthenia gravis. Lancet 1936;1:1457–1459.
7. Walker MB. Myasthenia gravis: a case in which fatigue of the forearm muscles could induce paralysis of extra-ocular muscles. Proc R Soc Med 1938;31:722.
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9. Walker MB. Thesis for the degree of M.D. in the University of Edinburgh: a contribution to the study of myasthenia gravis. University of Edinburgh;1935.

Mary Walker also contributed to the understanding of familial periodic paralysis. In a letter to The Lancet on July 6, 1935, she was the first to appreciate the significance of hypokalemia in attacks of periodic paralysis. Biemond and Daniels had reported hypokalemia in a patient with the disorder in 1934, but they did not comment on it. Walker subsequently was senior author on a paper on familial periodic paralysis, in which she highlighted hypokalemia triggered by a glucose meal, and treatment of the attacks with potassium chloride.

1. Walker MB. Potassium chloride in myasthenia gravis. Lancet 1935;2:47.
2. Biemond A, Daniels AP. Familial periodic paralysis and its transition into spinal muscular atrophy. Brain 1934;57:91-108.
3. Aitken RS, Allott EN, Castleden LIM, Walker M. Observations on a case of familial periodic paralysis. Clin Sci 1937;3:47–57.

There is a rumor that Sir Charles Dodds described Dr. Walker's contribution to myasthenia gravis as "an old hen scratching in a dung heap came up with a pearl." This statement is not compatible with the intelligence and diligence evident in her papers and MD thesis. Mary Walker's discovery of three therapeutic pearls

(physostigmine and Prostigmin in myasthenia; KCl in periodic paralysis), is far more than most physicians of her era can claim, and she did it while practicing in a non-academic setting. Even if Dodds said it, we should classify the statement as clearly false. No history of myasthenia gravis is complete without discussing the contributions of Dr. Mary Broadfoot Walker.

References:

1. Keesey JC. Contemporary opinions about Mary Walker: a shy pioneer of therapeutic neurology. Neurology 1998;51:1433–1439.