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The Mary Walker effect: Mary Broadfoot Walker

Stuart J McCarter[1], David B Burkholder[2], James P Klaas[3], Jennifer M Martinez-Thompson[4], Christopher J Boes[5]

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Abstract

Mary Broadfoot Walker (1888–1974) was the first to demonstrate the 'Mary Walker effect' describing the weakness of other muscle groups following release of the arteriovenous occlusion of an unrelated exercising muscle group in patients with myasthenia gravis, which led to the search for a circulating causative agent for myasthenia gravis. She was the first to clearly demonstrate that strength temporarily improved in patients with myasthenia gravis with physostigmine or Prostigmin (neostigmine). This dramatic treatment response has been erroneously termed the 'Mary Walker effect'. Further, she noted hypokalaemia during attacks of weakness in familial periodic paralysis, pioneering treatment with potassium chloride. Although Mary Walker practiced in a nonacademic setting and trained at a time when women were not allowed to train alongside men, she was the first to convincingly demonstrate three life-changing treatments in the field of neuromuscular medicine, a feat that few physicians of any era can claim.

Correspondence to:
Stuart J McCarter
Department of Neurology
Mayo Clinic
200 First Street Southwest
Rochester, Minnesota
55905
USA

Email:
mccarter.stuart@mayo.edu

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Background

Mary Broadfoot Walker (Figure 1) 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.[1–3] From 1913–16 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.[4] From 1916–19 Walker was a ward physician in the Royal Army Medical Corps attached to the 63rd General Hospital in Malta and Salonica (Greece).[1] She subsequently worked as a salaried 'Poor Law Service' medical assistant at the Greenwich Union Infirmary/St Alfege's Hospital (1920–36). 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 20 December 1935[5] for her thesis 'A Contribution to the Study of Myasthenia Gravis'.[6] In 1936 she moved to St Leonard's in Shoreditch.[5,7] Walker declined an invitation in 1938 to join the staff of the more prestigious Elizabeth Garrett Anderson Hospital, London, as a consultant because of her lack of personal finances and dependence on a salary.[5] In 1939, heavy bombing required her transfer to St Francis Hospital, Dulwich (South London).[5] Walker next moved to St Benedict's Hospital, Tooting, where she rose to the rank of senior medical assistant/senior hospital medical officer.[5] In 1954 she retired and moved back to her family home (Croft-an-righ) in Wigtown, Scotland. Although Walker was never named a fellow of the Royal College of Physicians, she was awarded the first Jean Hunter Prize from that organisation in 1963 for the advancement of research into the treatment of nervous exhaustion. Mary Broadfoot Walker died on 13 September 1974 at the age of 86 years, and was buried in the Wigtown cemetery.[2,5]

The Mary Walker effect

Samuel Goldflam (1893) and Friedrich Jolly (1895) noted that exercise of one muscle group could provoke weakness of nonrelated muscles in myasthenia gravis, with Goldflam being the first, although Jolly has historically erroneously been given priority for this discovery.[8,9] In 1929, Bourgeois reported a patient who developed eyelid drooping after repetitive finger flexion.[10] This phenomenon remained unexplained for decades. On 17 February 1938, Walker presented a patient with myasthenia gravis at a clinical meeting of the Royal Society of Medicine and described what ultimately became known as the 'Mary Walker effect':[8]

> 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

[1]Neurology Resident, [2–4]Assistant Professor of Neurology, [5]Professor of Neurology, Department of Neurology, Mayo Clinic, Rochester, MN, USA

Figure 1 Mary Broadfoot Walker (1888–1974). Wellcome Collection, Creative Commons Attribution (CC BY 4.0) terms and conditions https://creativecommons.org/licenses/by/4.0

> 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.[11]

Walker herself noted in her 1938 description that 'it is well known that in myasthenia gravis, weakness throughout the body develops if one group of muscles is exercised'.[11] Further, she 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. However, Walker's findings differed from prior reports. She described muscle weakness in unrelated muscles that did not occur until the release of arteriovenous occlusion caused by sphygmomanometer deflation, leading Walker to hypothesise that myasthenic muscles released a curarising agent during activity, which entered the systemic circulation and blocked neuromuscular transmission at skeletal muscle motor endplates elsewhere. This was in contrast to a competing theory that a neuromuscular junction deficiency of acetylcholine was the cause of myasthenia gravis.[6,11] In her MD thesis of 1935, she hypothesised 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'.[6] Her finding was replicated by Andrew Wilson and H Berrington Stoner, who found increased ptosis in 12 out of 14 patients when using this maneuver.[12] While the 'Mary Walker effect' was known prior to Walker's manoeuvre and her hypothesis was ultimately incorrect, her manoeuvre carries more weight than prior descriptions of this effect as it led to the search for a circulating factor causative of myasthenia.[7,8,13] As a matter of clarification, it is also important to note that the 'Mary Walker effect' has erroneously been attributed to her reports of the dramatic influence of physostigmine and Prostigmin (neostigmine) on the symptoms of myasthenia gravis; however, it actually refers to the weakness that develops in other muscle groups following release of arteriovenous occlusion of an unrelated exercising muscle group that Walker elegantly demonstrated.[14]

Pioneering treatment for myasthenia gravis

Prior to 1934, a variety of treatments for myasthenia gravis had been proposed, with glycine and ephedrine initially showing promise. Harriet Edgeworth, an American chemist with myasthenia gravis, wrote about the use of ephedrine in myasthenia gravis in 1930 after coincidentally noticing improvement in her symptoms once started on ephedrine for menstrual cramps.[15] Walter Boothby, occasionally collaborating with Edgeworth, reported several experiments from 1932–36 noting the effects of glycine (typically in combination with ephedrine) on myasthenia gravis, although these were not substantiated by other investigators.[16–18] Prior to Boothby's published work on glycine, German physician Lazar Remen published his work in 1932 on the effects of glycine on the symptoms of myasthenia gravis.[19] Jolly suggested that physostigmine might be used in myasthenia gravis based on its pharmacologically opposite effects of the myasthenic reaction, but Murri (1896) tried physostigmine without success as the patient did not tolerate the medicine.[20,21] In his 1932 manuscript, Remen briefly reported a patient with myasthenia gravis who could open his hands, open his eyes and eat 1 hour after an injection of Prostigmin with improvement lasting for 30 min to 1 hour; however, the patient could not tolerate the injection owing to dizziness and vomiting.[19] Despite the improvement, Remen did not mention this finding in his conclusions and instead continued his focus on glycine for the treatment of myasthenia gravis.[16,17,19]

Walker was the first to clearly demonstrate that strength temporarily improved in patients with myasthenia gravis when they were given physostigmine or Prostigmin.[2,5,16,17] Unlike Murri and Remen, Walker administered atropine in conjunction with physostigmine to mitigate the nausea and vomiting induced by physostigmine without reducing the drug's effectiveness.[22] In a 2 June 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.[23]

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.[23] In particular, Walker thought that physostigmine may be useful in preventing myasthenic respiratory crisis:

> 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.

In a 1979 letter, Dr Derek Denny-Brown relayed how this treatment of Mrs M with physostigmine came about.[3] Denny-Brown, who described Mary Walker as a recluse, visited St Alfege's every 2 weeks and diagnosed Mrs M with myasthenia gravis, a disorder that Mary Walker had never heard of before.[3] Walker asked the cause, and Denny-Brown commented that it was unknown, but that it resembled curare poisoning. 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 after looking 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, stating that physostigmine had previously been tried without benefit in the disease.[3] Denny-Brown noted in a 1979 letter:

> 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![3]

Denny-Brown's account, written 45 years after the event, provides an interesting view of the circumstances surrounding this significant moment in the treatment of myasthenia gravis, as the only other description of the situation comes from Walker's 2 June 1934 *Lancet* letter.[23] In this June letter, she thanked Dr Philip Hamill (lecturer in pharmacology and therapeutics at St Bartholomew's Hospital Medical School and consultant to St Alfege's) and Dr WD Wiggins (medical superintendent of the hospital), but did not mention Denny-Brown. Walker made no mention of her decision process or Denny-Brown in her 1935 MD thesis.[6]

Walker presented another patient with myasthenia ('DC' or 'Miss C') at a meeting of the Royal Society of Medicine on 8 February 1935.[22] Physostigmine improved the patient's ptosis but caused nausea, vomiting and a faint feeling so it was abandoned (although atropine was able to reduce these side effects without impairing muscle strength).[22] Miss C also responded nicely to Prostigmin. Prostigmin was much better tolerated as it was less cardioinhibitory than physostigmine, but it was more expensive. Walker later estimated that Prostigmin injections would cost a patient with myasthenia gravis £50 per year (ninepence). Eventually, she and Laurent reported that oral Prostigmin could be given in large doses without untoward effects.[24] Miss C's response to Prostigmin was so dramatic and rapid that some in the audience questioned if the patient had a functional disorder. London neurologist Dr Douglas McAlpine later clarified in a letter to the *Lancet* that the patient presented by Mary Walker clearly had myasthenia, as he had previously cared for the patient and her disease had in fact progressed despite treatment with ephedrine.[25] He saw Miss C again after 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. Based on McAlpine's congratulatory remarks to Walker in his *Lancet* letter that Walker 'must be heartily congratulated on her discovery which will enable the unfortunate sufferers from this disease to enjoy many of the pleasures of life of which they have formerly been deprived', it is clear that she was well respected by those she had directly worked with.[6,16,25] Walker's observation was published in the *Proceedings of the Royal Society of Medicine* in April 1935.[22]

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, DC/Miss C and Miss W (a new patient).[6] Walker's first patient, Mrs M, went into remission approximately 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.[6]

Walker clearly knew her patients well and was able to take a relatively rigorous scientific approach to understanding the pathophysiology of disease despite working in a hospital system in which research was not well supported. 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'.[6] Ultimately, many of the conclusions from her MD thesis remain largely unchanged today including: 1) that Prostigmin is best at temporarily improving myasthenic symptoms; 2) long continued daily administration of large doses did not diminish the response or cause untoward results; 3) muscles that are weak from myasthenia gravis may regain strength; 4) ephedrine (as well as potassium chloride and veratrine, neither of which is studied today) may be a beneficial adjuvant therapy for refractory myasthenia; and, 5) treatment is not curative, but it enabled even a patient with severe myasthenia gravis to lead a normal life.[6] While her statement of 'no case of myasthenia gravis should now die of the disease' may not entirely hold true, her discovery drastically reduced the morbidity and mortality of an otherwise commonly fatal disease.[6] Altogether, Walker published eight papers and one thesis on myasthenia gravis.

Understanding familial periodic paralysis

The utility of potassium salts in the treatment of periodic paralysis was noted in the early 1900s, but was not routinely employed as the pathophysiology was unclear.[26] Mary Walker's ability to associate clinical observations with potential causal aetiologies contributed to the understanding of familial periodic paralysis. Similar to how Remen reported the effect of Prostigmin on myasthenic symptoms without significant commentary on the subject, Dr Arie Biemond and Dr A Polak Daniels reported a difference in potassium levels during an attack of periodic paralysis and during the interval between attacks in one out of 14 patients in 1934.[27] However, these authors dismissed the significance of this finding stating: 'a chemical analysis of the blood in this disease has been reported several times and the results have always differed … Therefore, we think that only an autonomic imbalance exists'.[27] The authors commented that these patients likely had an 'alteration of the chemistry of some of their striated muscles'.[27] In a 1935 letter to the *Lancet* on the effect of potassium chloride for the treatment of myasthenia gravis, Walker reported a patient with familial periodic paralysis. She demonstrated that the patient had low serum potassium levels during two separate paralytic attacks that then normalised in the intervals between attacks, providing the first acknowledged association between hypokalaemia and weakness during attacks.[28] She further clarified these findings in a 1937 paper in which she showed that carbohydrate-rich meals and oral glucose loads could reliably precipitate attacks of weakness in a patient with hypokalaemia-associated periodic paralysis. While demonstrating hypokalaemia, she also showed that other serum electrolytes were normal during attacks. Further, she demonstrated that the administration of oral potassium chloride reliably began reversing symptoms within 10 min of administration with complete resolution after 1 hour, providing additional evidence for hypokalaemia as the causal aetiology for weakness in periodic paralysis.[29] Much like her ability to recognise the importance of Prostigmin for the treatment of myasthenia gravis unlike those before her, her ability to acknowledge the association between hypokalaemia and weakness in periodic paralysis led to yet another important discovery in the field of neuromuscular disease.

Scientific contributions from humble origins

Regarded as a shy and unobtrusive yet intense and thoughtful physician, Walker's scientific contributions are even more impressive considering the circumstances surrounding her career.[2] Walker practiced during an era in which women were not admitted to the University of Edinburgh as women were required to train separately from men 'to preserve public order',[2,30] so she had to attend the Glasgow and Edinburgh Medical College for Women for her medical education. Despite choosing to work in a Poor Law hospital where research was not well supported, she provided one of the most important neurologic contributions of her time in demonstrating effective treatment for myasthenia gravis.

She received little recognition for the magnitude of her discovery at the time despite how well known the treatment became in the London medical schools in the 1930s following her report. In fact, her post in the Poor Law system made contemporaries believe that there was another Mary Walker at a different hospital who was responsible for her discovery, with one commenting: 'It puzzled me that a great medical discoverer should be relegated to such a lowly post at St. Francis Hospital … where I first met her, so that for some days I thought she must be another doctor of the same name'.[31] Moreover, perhaps given her status as a female physician and work in the Poor Law system, contemporary physicians attempted to take credit, albeit unsuccessfully, for her discovery. Dr Leonard Sinclair relates a story from physiology professor Samson Wright on the day Mary Walker's report of physostigmine was published:

> That evening he was due to chair a Section meeting at the Royal Society of Medicine. To his surprise, he was telephoned that morning by a fashionable and prominent consultant neurologist who asked his permission to present 'his discovery' of the new treatment for myasthenia gravis at the meeting. Samson Wright welcomed him to attend, but mischievously then telephoned Mary Walker and invited her to attend as well. That evening he opened the meeting by referring to the new treatment for myasthenia, and then pointedly called the diffident discoverer Dr Mary Walker to say a few words about it. The eminent neurologist was put in his place and remained there.[32]

Interestingly, despite her accomplishments, she was never elected a fellow in the Royal College of Physicians. In time, she would come to be admired by her medical peers even though she spent her entire career in the 'academic wilderness of the Poor Law system, which, though it had of course its outstanding doctors, was not such as to stimulate or nourish the questing spirit'.[1] In 1963, 9 years after retiring from medicine, she was awarded the first Jean Hunter Prize for the advancement of research into the treatment of nervous exhaustion by the Royal College of

Physicians of London 'for her original contribution to the fundamental knowledge of the nature of myasthenia gravis, made while carrying out the routine duties of a medical officer at a large metropolitan hospital'.[5] In its description, the Royal College acknowledged not only her scientific accomplishments, but also the significant barriers that she faced while performing them.

Conclusions

There is a rumour that Sir Charles Dodds described Walker's contribution to myasthenia gravis as 'an old hen scratching in a dung heap came up with a pearl'.[3] This statement (paraphrasing Johannes Kepler) is not compatible with the intelligence and diligence evident in her papers and MD thesis, and is clearly a false and misleading statement. Mary Walker's discovery of three therapeutic pearls for devastating neurologic disease, including: 1) physostigmine; 2) Prostigmin (neostigmine) in myasthenia gravis; and, 3) potassium chloride in periodic paralysis, are far more than most physicians of her, or any, era can claim. As noted by Dr J Purdon Martin, the scientifically rigorous approach she applied to identify an appropriate treatment for myasthenia gravis while attempting to understand the underlying pathophysiologic process, all while practicing in a nonacademic setting without clear mentorship, makes her contributions even more impressive.[33] Further, the demonstration of the 'Mary Walker effect' led to the search for a circulating causal agent for myasthenia gravis and postulation of an autoimmune-mediated process until antibodies to acetylcholine receptors were discovered in 1973.[34,35] While it is clear from McAlpine's letter that those who worked directly with Walker respected her scientific mind, the greater contemporary medical community initially did not share this admiration. The Royal College of Physicians helped correct this oversight when they awarded her the Jean Hunter Prize in 1963. No history of neuromuscular disease is complete without discussing the contributions of Dr Mary Broadfoot Walker.

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