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Medical History

Some Discoveries on Myasthenia Gravis: The Background

MARY B. WALKER

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The experiments on two very severe cases of myasthenia gravis, showing that a curarizing substance is formed in the muscles themselves and enters the circulation, have not been published in full though they have been demonstrated before medical meetings many times and have been confirmed, though not by all observers. I think the difficulty is that the less severe the myasthenia the less the increase of weakness (sometimes only ptosis) and the longer it takes to come on—20 minutes or more. If the patients are fully under the influence of Prostigmin (neostigmine) or some such drug it does not come on at all.

The experiments show that increased destruction, defective production, or release of acetylcholine cannot be the immediate cause of myasthenia gravis but that something produced in the muscles themselves enters the circulation, causing the abnormal fatigability. Anything which delays the destruction or facilitates the release of acetylcholine would be antagonistic to this curarizing substance.

This experiment on two patients with approximately equally severe generalized myasthenia gravis was performed many times before it was shown at the clinical meeting of the Royal Society of Medicine, section of neurology, at the National Hospital, Queen Square, London, on 17 February 1938. Later in that year it was shown at the meetings of two other medical societies. It has been frequently repeated to show the effect to various doctors. The result was always the same (see Appendix).

Without Prostigmin neither patient could get out of bed or dress and neither could supinate the forearms except for a few feeble movements. Both had an injection of Prostigmin 2·5 or 3 mg with atropine ½ grain (32 mg) and ephedrine ½ grain at 8 a.m. each day. When the effect of Prostigmin was just beginning to wear off, though they were still strong, the circulation was cut off in both arms by sphygmomanometer armlets at a pressure of 200 mm Hg and the patients briskly pronated and supinated their forearms till they tired, which took about a minute.

While the circulation was cut off no weakness was noted in the rest of the body, not even in the eyelids, but a minute and a half after the pressure was released the eyelids began to droop, and by two minutes the weakness was very great, so that the patients were about as weak as they had been before their morning injection of Prostigmin and had to have another injection of 2·5 or 3 mg, which restored their strength in the usual way. As a rule the pressure was released immediately after the pronation and supination had stopped, but it has been maintained for periods up to four minutes. The weakness always came on a minute and a half after the pressure was released and appeared always to be equally severe.

When one arm only was fatigued by pronation and supination with the circulation cut off, and when both arms were exercised in the same way but short of fatigue with the circulation cut off, the ensuing weakness was much less. Cutting off the circulation with the armlets in position for several minutes without exercise caused some weakness but very much less than with exercise, and it passed off with rest for a short time without Prostigmin.

All these experiments were done when the effect of Prostigmin was just beginning to wear off. When the patients were fully under its influence pronation and supination of both forearms for about a minute with the circulation cut off produced no obvious effect, though the patients thought that they felt a little weaker. In a normal subject no weakness was apparent after brisk pronation and supination for a minute with the circulation cut off. Performing the exercise with the venous but not the arterial circulation cut off was too distressing to continue till the muscles were fatigued but some weakness did come on.

Dr. F. Parkes Weber mentioned a man aged 31, an inpatient in the German Hospital in February 1938, with "myasthenia" symptoms of a few months' duration in neck muscles. "Prostigmin seems to act wonderfully but there is considerable wasting of some muscles. Diagnosis rests between myasthenia gravis, progressive spinal muscular atrophy with misleading symptoms, and atypical dystrophica myotonica (though no definite myotonia). We tried your arm constricting method this morning as you showed us but got no result whatsoever. Can this be regarded as a negative diagnostic test for myasthenia gravis? . . . It is noteworthy that the patient tells us that his sister died with similar symptoms to his, and we have heard from a hospital that the diagnosis on her case was progressive muscular atrophy with some wasting of one half of the tongue."

Comment

Dr. J. PURDON MARTIN, honorary consultant at the National Hospital for Nervous Diseases, London, writes: Dr. Mary Walker's article relating to some of her work 35 years ago perhaps requires a short introductory note.

In days when clinical physiology was still a new subject and almost unknown outside the medical schools and special hospitals Mary

Wigtown
MARY B. WALKER, M.D., M.R.C.P., Late Senior Hospital Medical Officer at St. Benedict's Hospital, London

Walker, as a medical officer in an L.C.C. hospital, made two important contributions to the knowledge and treatment of myasthenia gravis. In 1934 she discovered the beneficial effects of Prostigmin on the symptoms of myasthenia and so established the first effective treatment of the disease (and the one which is still in use.) Four years later[2] she showed that the paralysis in myasthenia gravis was not due, as had been thought, to deficiency of a chemical transmitter at the neuromuscular junction but must be due to a positive toxic substance produced in the course of muscular activity, and it is this discovery that she describes here. As an appendix she adds the description of an experiment, the outcome of which was that the injection of the serum from 10 ml of "myasthenie" blood into a rabbit did not cause any apparent symptoms.

The design of the main experiment should be noticed, because the effect which Dr. Walker wished to observe required that the patient's condition should be capable either of aggravation or of improvement, and so would not have been seen if the patient had already been at her worst or at her best.

Dr. Walker twice uses the term "curarizing substance." At the time of which she is writing curare was a topical subject because Dr. Ranyard West had applied this dangerous alkaloid to the treatment of severe cases of tetanus and many people had seen its clinical effects, but it was Mary Walker who had the intelligence to look up the antidote to curare and try its effect on the similar symptoms occurring in disease.

For her first observation (1934) Dr. Walker gained her M.D. at Edinburgh and was awarded a gold medal. More recently (1963) she was the first recipient of the Jean Hunter prize awarded by the Royal College of Physicians for work on nervous exhaustion.

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Appendix: The Experiment

The experiment was performed on one of the two patients to show the effect of myasthenia serum on a rabbit on 12 May 1938 at the request of E. C. Hoff, who was present.

10.15 a.m. Patient lying "flat" (last Prostigmin given at 1 p.m. on 11 May). Ptosis, unable to sit up, and unable to move arms more than a little. Mask-like facies. Right arm occluded with blood-pressure cuff inflated to 140 mm Hg (systolic pressure about 140 mm Hg).
10.21 a.m. Blood-pressure cuff 190 mm Hg. Patient making weak movements of fingers and hands.
10.22 a.m. Blood sample (10 ml) taken from right basilic vein (cuff at 190 mm Hg).
10.23 a.m. Cuff deflated (pulse 90/min).
10.24 a.m. Ptosis, left arm feels heavier than before the experiment.
10.31 a.m. Prostigmin 7·5 mg + 1/100 grain (0·65 mg) atropine subcutaneously.
10.35 a.m. Still lying as before (pulse 66/min).
10.37 a.m. Made some small movements.
10.38 a.m. Slight movements of head, slight elevation, slight twitching in neck.
10.40 a.m. Moves mouth, fingers clench and unclench, moves hands, supinates arm, speaks, voice stronger.
10.41 a.m. Eyelids open. Patient sits up, talks, feels fairly strong.
10.42 a.m. Patient gets out of bed, walks up and down the ward quite steadily.

The rabbit was unaffected by the myasthenic serum. The timing of the effects on the patient is interesting. She recovered her strength 11 minutes after the injection of 7 mg of Prostigmin.

A New Look at Infectious Diseases

Q Fever

G. LAING BROWN

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Q. fever is an infectious disease caused by an organism which, because of its size and cultural characteristics, is intermediate between the bacteria and viruses. Though it resembles the rickettsia organisms—which are responsible for diseases such as epidemic typhus fever, tick typhus, and Rocky Mountain spotted fever—because it is resistant to both drying and many chemical agents which destroy most rickettsiae it has been put into the special classification of *Coxiella*.

The disease was first described in 1937,[1] when it was observed in abattoir workers in Queensland, in Australia. It appeared to be a new disease of yet unexplained origin and so it derived the name "Q"—standing for "query fever." In 1939 Burnet and Freeman[2] showed that the infection was due to a rickettsia-like organism and for this reason it was first named *Rickettsia burneti*, changed subsequently to *Coxiella burneti*.

During the second world war Q fever caused widespread sickness among members of the allied Forces in Italy and the Balkans. Since then the disease has been shown to be world wide in its distribution. In Great Britain it is associated mainly with rural rather than urban communities and in particular it is prevalent where sheep farming and dairy farming are carried on. The organism infects both sheep and cattle but does not appear to cause any clinical disease in these animals, though they do act as carriers of the disease. The organism is excreted in the milk as well as in the urine and faeces of infected animals and is also present in the placenta and uterine discharges at parturition. Characteristically it is very resistant to drying so that the dust in sheep pens and cattle sheds becomes heavily contaminated. Inhalation of infected dust is thought to be the main method of spread of the infection within the flocks and herds, and, of

Bucknall Hospital, Stoke on Trent, ST2 8LD
G. LAING BROWN, M.D., D.P.H., Physician Superintendent