CLINICAL OBSERVATIONS ON THE USE OF PROSTIGMIN IN THE TREATMENT OF MYASTHENIA GRAVIS

BY

L. P. E. LAURENT, M.D., M.R.C.P.

MEDICAL REGISTRAR TO UNIVERSITY COLLEGE HOSPITAL

In June, 1934, Dr. Mary Walker of St. Alfege's Hospital, Greenwich, in a brief letter to the Editor of the *Lancet*[1] made a communication which did not receive the attention it deserved from the medical profession. She explained the rationale which had led her to try the influence of physostigmine on a case of myasthenia gravis. Owing to the antagonistic effect of this drug to the action of curare, and in view of the resemblance between myasthenia gravis and curare poisoning, she decided to see whether physostigmine "would counteract the effect of the unknown substance which might be exerting a curare-like effect on the myoneural junctions." She obtained definite improvement in her case of myasthenia, but was checked in her attempt to give larger doses by the toxic influence of the drug on the alimentary tract. Later, using prostigmin,* she was able to produce an even more striking improvement in a severe case of myasthenia, and she demonstrated her results at a meeting of the Clinical Section of the Royal Society of Medicine on February 8th, 1935.

The pharmacological action of this drug has already been extensively studied by Aeschlimann and Reinert,[2] and its influence on the alimentary tract in man has been particularly observed by Carmichael, Fraser, McKelvey, and Wilkie.[3] These papers give a complete account of what we know at present of the pharmacological effects of drugs of this group; no details are therefore given here.

At University College Hospital Dr. E. A. Blake Pritchard and myself approached the problem of confirming Dr. Walker's work, using different methods, and we both came to the same favourable conclusion. His paper giving objective proof has already been published.[4] The following observations on seven other cases of myasthenia gravis thus bring the total number of successes in the treatment of that disorder with drugs of the physostigmine group to sixteen. Not a single failure has been experienced by either of us up to the present.

Case I

A single woman, aged 28, in May, 1925, suffered from occasional attacks of diplopia, for which she consulted an ophthalmologist. She was very slow in recovering from a typical attack of German measles in December of that year, complaining of general fatigue, and in the following February she was frequently noticed to have a sleepy appearance; this latter was due to ptosis, from which she suffered towards the evening only. In April, 1926, she was still continuing her work as an art student, but was experiencing difficulty in raising her brush to the canvas in the afternoon, and her head showed a tendency to droop towards evening. The following month she had to give up her work, as she could no longer walk more than 400 yards without a rest, and was experiencing difficulty in entering tramcars. She became progressively worse until the end of 1927, when her symptoms reached their maximum; they have since remained substantially of the same nature and degree, with the important exceptions set forth below. During the whole of this period from 1925 she has been under my personal observation.

Since the onset of the disease the menses, which had previously been regular, have become irregular, and there has been a marked relapse in the myasthenia during the ten days preceding the period. From the beginning of menstruation the symptoms improve, and the patient is at her best during the intermenstrual period. She then walks well for about twenty yards, when she tires, develops a waddling gait, and has to rest. She can chew an ordinary meal, but pauses unduly between mouthfuls, and usually holds her closed fist to support her chin while she chews. Diplopia occurs at frequent intervals daily, and ptosis, practically absent in the morning, is slight, bilateral, and intermittent towards evening. During the premenstrual phase she is unable to walk more than a few yards, and sometimes is unable to stand. The severity of the ptosis makes reading impossible, speech weakens at the end of a long sentence, and mastication is extremely difficult. At night she experiences great difficulty in turning over in bed, and cannot sit up from the supine position. These severe relapses have been checked by the administration of oestrin during the past two years, and a communication upon that aspect of the case will be published later. She has received thyroid extract, suprarenal whole gland, suprarenal cortical extract, glycine, and ephedrine. No beneficial result was noticed with any of these, except that the patient claims to have noticed some subjective improvement on ephedrine.

RESULTS ACHIEVED WITH PROSTIGMIN

On February 14th, 1935, I gave her a subcutaneous injection of prostigmin 2 c.cm. with atropine sulphate 1/200 grain. I did not discuss the possible result with the patient, remarking only that it would do her no harm. For ten minutes there was no change, then quite suddenly she complained that her eyes felt very queer, and I noticed that the eyelids were now strongly retracted, giving an appearance of exophthalmos. The external ocular movements, which had been limited to a very small range on attempting lateral deviation, and had been impossible on looking upwards, were now of full range, and did not diminish on repetition. About twenty minutes after the injection I asked the patient to raise her arms above her head. She did this with a sudden jerk, having innervated the muscles too strongly. For many years past she had been unable to raise her arms above the horizontal level and keep them in that position. For the next few minutes every movement she carried out was exaggerated in the same way, but she quickly readjusted herself to the new state of affairs.

She then proposed to test herself by attempting certain movements which had been impossible for many years. From the erect posture she sat down on her heels and got up again without the slightest difficulty. Abduction of the hip, usually impossible when standing, was now carried out freely and repeatedly. Finally, she decided to dance to the wireless, and was able to do this for several minutes. The effect of the drug lasted five hours, after which she gradually relapsed to her previous state. Next day, after 2 c.cm. of prostigmin, she was able to go to the theatre, to reach her seat without difficulty, to walk in the lounge during the interval, and to reach home still stronger than she usually was at her best.

Before treatment the patient's grasp on a recording dynamometer was: right, 15 lb., and left, 10 lb. Ten minutes after 2 c.cm. of prostigmin it was: right, 30 lb., and left, 30 lb. Twenty minutes after the injection it was: right, 37 lb., and left, 35 lb. I have related this case with some detail, as it was the one which enabled me to give Dr. Walker the first confirmation of her work.

Case II

A single woman, aged 26, while attending a gymnasium class in October, 1929, noticed that "week by week she was able to do less and less." The weakness affected all four limbs equally, and the swinging of Indian clubs above her head was one of the first difficulties. For the next few months she was normal in strength on some days, but on others she would suddenly feel weak "when least expecting it." In February, 1930, while out to post a letter, her legs gave way suddenly and she fell down; she was able, however, to pick herself up at once, and to continue her errand. This sudden "giving way" of the legs is an important early symptom of myasthenia, which misleads experienced neurologists into a diagnosis of hysteria, owing to the history of recovery without rest. I saw the patient for the first time in October, 1930, and her state was then as follows. She had a slight permanent ptosis on the left side and a typical "sneering" smile. She chewed

* Prostigmin = dimethyl-carbamic ester of 3-oxyphenyl-trimethyl-ammonium-methyl sulphate. Supplied by Hoffmann-La Roche, Ltd. (1 c.cm. of the solution contains 0.5 mg.)

with difficulty. The speech was monotonous and had a slight nasal quality. The muscles of the shoulder girdle were particularly weak, and the arms could not be raised above the horizontal; the legs were apparently unaffected. Eleven months later she began to get worse, and was hardly able to walk at times. In March, 1932, she was having nasal regurgitation of fluids and attacks of dyspnoea lasting up to two hours, and in the following month she was bed-ridden, unable to raise her head off the pillow or her arms off the bed. She was having frequent attacks of dyspnoea, and when I saw her she had swallowed nothing for forty-eight hours. I advised against the use of a stomach tube, which always increases the dyspnoea in such cases, and on the next day, after a night's sleep, she was able to take two cups of milk with little difficulty. Since that date she has gradually improved. When I visited her on February 14th, 1935, I found that her doctor, Dr. Donald Ross, had independently given her 1 c.cm. of prostigmin on the previous day with good results.

On February 18th she was admitted to University College Hospital, and the following morning I found that she had a well-marked ptosis on the left side, and weakness of both external and superior recti limiting ocular movements to a considerable degree. Her mouth could not be kept shut without support. Her facies showed the typical "sneering" smile, and she was unable to close her lips. Her arms could not be raised to the horizontal, and her grasp was very weak. She was able to walk a few yards before collapsing. I gave her subcutaneously 3 c.cm. of prostigmin with atropine 1/100 grain; ten minutes later she stated that she felt somewhat better, and the ptosis had certainly improved. Twenty minutes after the first injection I gave her a further 2 c.cm. of prostigmin. An hour after the first injection the patient was able to close her lips, to keep her teeth in contact without support, to whistle, and to smile pleasantly. Ptosis was now extremely doubtful. She could raise her arms above the horizontal, walk fifty yards, and grasp the observer's hand so as to produce pain.

Case III

The patient, a married woman aged 47, first experienced diplopia in 1924 when she saw two balls while playing golf. Soon after she developed ptosis on the left side, the symptoms being always worse towards evening. In 1925 her speech had a nasal quality after prolonged talking, and sometimes she became mute and required several minutes' rest before she could resume conversation.

She has had some dysphagia with nasal regurgitation, especially of fluids, almost continuously. Chewing is always difficult, and she lives entirely on slops. Her limbs have been affected to a much lesser degree, her arms being sometimes weak, especially during the cold weather, but never strong enough to enable her to play the piano. Her legs have remained comparatively unaffected. In 1927 she lived in South Africa for eight months, where she sun-bathed a good deal, and improved considerably without any other treatment. She has been treated for long periods by thyroid extract, injections of gold salts, and ephedrine by mouth. Some slight improvement followed the gold injections, but no method of treatment has so far given any objective results.

At examination on February 20th, 1935, she had a nasal voice, which tired quickly; her soft palate moved very little, even after rest. There was a well-marked ptosis on the left side, but the external ocular movements were full at rest and on repetition, although she experienced diplopia on looking upwards. The left side of the face was definitely weaker than the right, an unusual feature. Whistling was impossible.

Prostigmin 2 c.cm. and atropine 1/200 grain was given subcutaneously. The patient knew that benefit was expected from this treatment, but she was given no indication of the time required for the drug to act. Seven minutes after the injection she declared that her speech felt easier, and it was clear that her voice was improving. Eleven minutes after it she was able to whistle for the first time in ten years, and twenty minutes after the injection the right eyelid became retracted, the left ptosis was improving, and the face was quite symmetrical on smiling. She drank her tea without any suggestion of nasal regurgitation, and declared that it was "nice to be able to swallow straight." She also expressed her delight at being able to talk with her mouth full! An hour after the injection there was no sign or symptom which would have led to a suspicion of myasthenia.

Case IV

A married woman, aged 52, was treated at the London Hospital in 1902 for difficulty in speaking, dysphagia with nasal regurgitation of food, and weakness of her arms and legs. Since the onset of the illness she has gone through seven pregnancies, and that aspect of the case has already been reported.[5] On February 21st, 1935, her condition was as follows. She was seen in the evening, and she then had a slight ptosis. External ocular movements, full at first, rapidly tired, and squint and diplopia developed; the closure of the eyes was very weak. She could raise her arms above her head, but could not keep them there for more than a few seconds. Whistling was impossible. There was great tiredness on walking after 200 yards.

Prostigmin 2 c.cm. and atropine 1/200 grain was given subcutaneously. After eight minutes a little belching occurred and tears came profusely. The patient complained of feeling somewhat giddy and of excessive salivation. Twenty minutes after the injection she held her arms above her head for five minutes without difficulty, diplopia could not be induced, and she was able to whistle with ease. An hour after the injection she felt better and stronger than she had done for years. Duration of the improvement was three hours.

Case V

A single woman, aged 34, had some diplopia in 1924 when she worked as a cinema attendant. She changed her occupation and the symptoms cleared up. In 1929 there was weakness of the hands; she had difficulty in getting on buses, and dropped objects frequently. There was apparent recovery until a year ago, when intermittent ptosis, worse in the evening, developed. The patient's arms tired readily, but her legs only after walking a mile or so. Since taking ephedrine there has been some improvement.

Before the injection of prostigmin there was marked right ptosis, with the typical "sneering" smile, and great weakness of the orbicularis oculi. The grasp of the right hand was 27 lb. and of the left 26 lb. Prostigmin 2 c.cm. with atropine 1/200 grain was given subcutaneously; ten minutes later the patient experienced a "feeling of tightness around the eyes." Within fifteen minutes of the injection the ptosis had disappeared and could not be induced by looking upwards repeatedly, closure of the eyes was of normal strength, and the smile was very much improved. The patient's right grasp was 32 lb., and the left 31 lb.

Case VI

A market gardener, aged 50, has been treated with insulin for diabetes mellitus since 1930. In 1926, while in New Zealand, where he was born, he suffered from drooping of the right eyelid, which was better after rest and worse after exertion and in the evening. This symptom lasted a few months and cleared up following "electrical treatment." This unilateral ptosis recurred in August, 1934, and has persisted, with the same variations as before. Weakness of closure of both eyes was the only other physical sign. On February 22nd, 1935, there was a well-marked ptosis on the right side with some lid retraction on the left. Prostigmin 2 c.cm. with atropine 1/200 grain was given subcutaneously; ten minutes later the ptosis was very slight, and in thirty minutes it was absent. Closure of the eyes was then of normal strength.

Case VII

The patient in this case was an unemployed man, aged 28, who eight years ago began as a typical case of myasthenia gravis. His first symptom was ptosis, which was always worse in the evening than in the morning. He experienced occasional diplopia, difficulty in mastication, and nasal regurgitation of fluids. Two years after the onset his arms became heavy and weak. Since then his condition has been stationary, with no spontaneous remissions. He has had an extensive course of ephedrine, without showing any signs of improvement, subjective or objective.

On February 19th, 1935, I examined him and had the advantage of Dr. J. Purdon Martin's opinion on the case. The patient was a thin man, with marked ptosis and bilateral facial weakness. The external ocular movements were practically absent. On attempting to smile the corners of his mouth were raised slightly, but there was no lateral move-

ment of his lips. The muscles of his shoulder girdle showed definite wasting, particularly the spinati. There was a general diminution in size of all the limb musculature, and the tendon reflexes were all unobtainable, in spite of the fact that the power of the limbs was good and could not be tired by ordinary exertion. We were thus dealing with a case of muscular dystrophy, which had shown myasthenic features in the past.

The only hope was to see whether there were still some myasthenia which might be removed with prostigmin. He was given 2 c.cm. with atropine 1/100 grain. Twenty minutes later, as there was no response, a further 2 c.cm. of prostigmin was given. The only result obtained was that half an hour later the patient was able to whistle, a feat of which he had not been capable for many years. The ptosis on the left side was relieved sufficiently to enable him to clear his line of vision without tilting his head backwards. The experience with this case suggests the obvious help which prostigmin may give in the diagnosis of early and slight cases of myasthenia gravis.

Discussion

The patients in the cases described have all received some previous treatment, and any apparent improvement noted before was slow, subjective, and never beyond doubt. Those in Cases I, II, III, IV, and VII had received injections in the past, and all declared their disappointment with them as a method of treatment. The element of suggestion with prostigmin injections can therefore be discounted. The patients in Cases I, II, III, V, VI, and VII have been taking ephedrine for long periods, and they derived only slight and doubtful benefit, while those in Cases I and II have been treated with deep *x*-ray therapy to the thymus with no unequivocal result. Thyroid extract intermittently was given in Cases I, II, III, and IV, but there was no improvement of any kind. In Cases I and III injections of gold salts were given, and some subjective improvement resulted after a few weeks. Finally, the patients in Cases I and II have taken glycine in doses of 30 grams daily for a month without the slightest benefit.

An injection of saline was given later in Case II when the patient expected prostigmin. Her annoyance at the apparent failure led me to give up this method of control, which was also open to the criticism that lack of the subjective sensations induced by prostigmin might influence the patient. The evidence for the action of the drug was better provided by my observations that in any particular patient grading of the size of the dose of prostigmin, without the patient being aware of the change, caused in strict proportion a shortening of the time before improvement began and a longer duration of the improvement when it was established.

The combination of prostigmin and atropine caused the following mild and transient symptoms: belching, vertigo, lachrymation, twitching of the eyelids, sensation of stiffness about the eyes, photophobia, and perspiration. They occurred between twenty and thirty minutes after the injection, and never lasted more than a few minutes. The patients were all satisfied that the ultimate result overshadowed any initial unpleasantness. Owing to the belching I have avoided giving the injections either just before or just after meals.

I have had an opportunity of testing another drug of the prostigmin group—namely, methyl-phenyl-carbamic ester of 3-oxyphenyl-trimethyl-ammonium-methyl sulphate, supplied by Hoffman-La Roche, Ltd. I was surprised to find that although Aeschlimann and Reinert[2] have shown that it has no anti-curare action, the " anti-myasthenic " effect was little short of that of prostigmin. In Case II 5 c.cm. was given without atropine. The action was slower in its onset, and the duration of the improvement was only three hours. The photographs (Figs. 1 and 2) show the effect of this drug. To a case, not described above, 5 c.cm. has also been given, and the effect was similar, with slower onset and shorter duration.

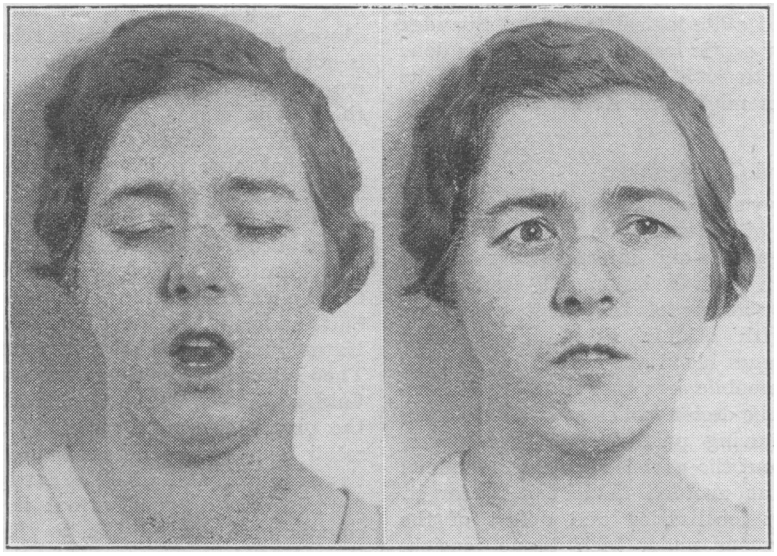

FIG. 1.

Case II.—Before treatment. Maximum effort to shut mouth and open eyes.

FIG. 2.

Case II.—One hour after 5 c.cm. of the methyl-phenyl-carbamic ester of the prostigmin group.

The experience gained indicates that prostigmin will be of the greatest value in the treatment of myasthenia. Its use is obviously indicated in severe cases with dyspnoea. When dysphagia is present the general condition of the patient will be much improved if the drug is used so as to make one good meal a day possible. Finally, administered in small doses of 1 or 2 c.cm. in the milder cases it will enable the patients to lead a more pleasant life. The possibility of continuous relief of symptoms by repeated injections or by oral administration is under consideration, but caution is needed until the mechanism involved is understood more fully.

Summary

1. The action of prostigmin on seven cases of myasthenia gravis is described. All of these had previously been for some time under the writer's care.

2. The beneficial results in every case, though lasting for only a few hours, have far surpassed anything experienced by the patients with other methods of treatment.

3. Unpleasant symptoms have been of a very mild nature.

4. Another drug of the same group, which has no anti-curare action, has been found to have definite anti-myasthenic properties.

I am indebted to many colleagues for valuable help: to Dr. Mary Walker, who discussed with me freely and generously all her previous experience; to Dr. F. M. R. Walshe, Dr. E. A. Blake Pritchard, Dr. Charles D. Hatrick, and Dr. Donald Ross for access to their cases; and to Messrs. Hoffmann-La Roche, Ltd., for supplies of the drug.

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