A Clinical Lecture

ON

MYASTHENIA GRAVIS.

Delivered at the National Hospital for the Paralysed and Epileptic, Queen Square.

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GENTLEMEN,—I shall first of all show you two cases which are characteristic examples of this disease, and then I shall say a few words about the broad general features which characterize its course, its symptomatology, and, so far as we know, its pathology and morbid anatomy. Unfortunately, there is little to say about its treatment.

TWO TYPICAL CASES.

The first patient is a girl of 25, under Dr. Beevor's care, who until May last was in perfectly good health. She then found that she had some difficulty in speaking, and that after she had talked for a little while her articulation became indistinct, and much more difficult than it usually was. This peculiarity was strikingly illustrated when she tried to read aloud, for after even a few minutes of such reading she became not only inarticulate but actually voiceless. This weakness persisted, and to it was presently added a certain degree of difficulty in using the hands, especially for fine movements, such as picking up a pin, or buttoning her dress. The arms, apparently, at this time were fairly strong, but they also became weak, so that she had difficulty in doing her hair in the morning. The weakness of the hands increased, so that in doing needlework, at which she worked for her livelihood, she constantly found that she was unable to thrust the needle through the piece of cloth which she was sewing, or unable to extract it from the cloth. The lower limbs also began to show a certain weakness, so that she staggered when she walked, and could not walk so far as she used to. She also noticed that she occasionally saw double, and she had a heavy feeling about the eyelids, although it was never noticed that there was any actual drooping of them. Her condition now is one of very considerable weakness in the lower limbs, weakness in the upper limbs, slight difficulty in carrying out extreme movements of the eyes, and marked impairment of articulation, becoming much more obvious after she has spoken for a few minutes. There is no wasting, no visceral disease can be discovered, there is little, if any, difficulty in swallowing, and all the other reflexes are normal.

The second case is that of a patient whom some of you may have seen before; a man who has had, for nearly ten years, a varying degree of weakness in the arms and legs, and also in the ocular movements. Apparently the weakness in this case displayed itself first in the ocular muscles. Then the arms became very easily tired, so that he became quite unable to work with his hands at a higher level than his head, and as he was a house-painter, this soon became a very real and practical inconvenience. He also had very great difficulty with the lower limbs, so that, for example, in going along the street he was only just able to make his way from one lamp-post to another, and when he gained the support of one lamp-post, he had to stop in order that he might recover sufficient muscular force and energy to carry him to the next lamp-post. During the past ten years these different weaknesses have been variable. Sometimes the weakness of the legs was very great, sometimes it was less; and at the present time he is able to get about with a fair amount of comfort. His arms he is still unable to use freely; he has almost complete paralysis of all the ocular movements, and there is very marked double ptosis. He has little if any difficulty in articulating, but he has occasionally suffered from difficulty in swallowing. He has in certain muscles the characteristic myasthenic reaction of which I shall say a little more presently. Otherwise his condition is quite normal; there is no wasting, there is no visceral disease, so far as we can discover, and, as already remarked, the reflexes are quite normal.

These, then, are two characteristic cases of the disease of which I wish to speak to-day.

SYMPTOMS AND CLINICAL HISTORY.

This disease, usually known as myasthenia, although the full name is myasthenia gravis pseudo-paralytica, has only

come into prominence in the last few years. It is characterized, broadly speaking, by great muscular weakness, affecting most strikingly, in the majority of cases, the muscles which are supplied from the medulla oblongata, and are therefore closely related to the maintenance of the vital functions. The muscles, however, of the limbs, both upper and lower, and of the trunk are affected, and in some cases there is reason to suppose that they are affected before the muscles which are supplied from the bulb. So far no definite changes in the nervous structures from which the affected muscles are supplied have been found; and it is interesting to note that so long ago as the Seventies Dr. (now Sir Samuel) Wilks published a case of bulbar paralysis without any anatomical changes, a case which in all probability is to be regarded as the earliest case of myasthenia gravis of which there is any record. A very interesting series of cases apparently of this disease is also to be found at the end of Dr. Beevor's article on bulbar paralysis in Allbutt's *System of Medicine*.

The first sign of weakness in this disease usually occurs in the levatores palpebrarum, giving rise to ptosis. Sometimes this ptosis is equal on the two sides; occasionally it is more marked on one side than on the other. It is frequently associated with weakness of the ocular muscles, and the effort to overcome the ptosis by means of the action of the frontales manifests also some weakness in those muscles. Diplopia, of varying character, is often present, the variation depending on the weakness of different ocular muscles. This weakness varies very much at different times. On some days the patient has no obvious signs of weakness either of the external ocular muscles or of the levatores; on another day there is very marked impairment in the actions of all these muscles. Nystagmoid movements are occasionally present, these also being evidence of weak muscular action. Although the external ocular muscles are so frequently and almost constantly affected, it is extremely rare to have any pupil changes. Difficulty in masticating is also frequently present, the masseter muscles especially becoming easily tired, and the patient not uncommonly during eating supporting his lower jaw with one or other hand. This difficulty in masticating is often more marked in the later part of the day, and it may be said that this is a feature of the muscular weakness generally. The muscles about the mouth are also weak, so that there is difficulty in whistling or in blowing out a candle. Dribbling may occur, swallowing is difficult, fluids being more easily taken than solids, although there may be occasional regurgitation, and the pharyngeal reflex is often absent. Palate weakness is also frequent, giving rise to a nasal voice and inability to blow out the cheeks, frequently associated with the articulatory difficulty which is a marked feature in the first case I referred to. The laryngeal muscles themselves are rarely affected, but aching or stiffness of the tongue is frequently complained of, and it may be impossible for the patient to protrude the tongue, or to move it freely from side to side. One very striking feature related to the weakness of those structures about the mouth or connected with articulation is the character of the speech. When the patient begins to speak, articulation may be clear and the voice good. As he proceeds the weakness becomes marked, the tone becomes lower, a nasal character is imparted to the articulation, and the patient finally becomes both breathless and voiceless.

The respiratory muscles may also be affected, so that there is interference with the amplitude of movements during respiration. There is dyspnoea on the slightest exertion, and, as has already been said, when the patient speaks for a little time there is marked breathlessness associated with the voicelessness already referred to. This dyspnoea constitutes an element of considerable danger, because weakness of the structures which are associated with breathing gives rise to actual crises of dyspnoea, in which the patient may die; and in several of the cases in which death has occurred it has supervened, apparently as the result of an acute crisis of dyspnoea. Besides the trunk muscles, those of the extremities may also be affected. Thus, the arms may become easily tired, and a female patient—as our first patient actually did—frequently complains of an increasing difficulty in carrying out the movements which are necessary in doing her hair in the morning. In the lower extremities the quadriceps and the ilio-psoas group seem to suffer most. Walking far, as a rule, is impossible, and going up more than a few steps of stairs is quite beyond the patient's power. A sudden giving way of the legs, causing somewhat severe falls, is not unusual.

There are various conditions which seem to exercise considerable influence upon this myasthenic weakness. Thus, emotional conditions undoubtedly intensify the weakness in a very marked way. Cold, in some cases, acts similarly, and women affected with the disease are always worst at the menstrual period. Persistence in a movement soon exhausts a muscle, yet even with regard to this point it must be remembered that there are very great variations in muscular weakness, and that a movement which can be repeated only two or three times on one occasion can be repeated as often as twenty or thirty times on another. It is also noteworthy that the patient is frequently very much better and stronger in the early morning, but becomes gradually worse and weaker as the day proceeds, so that movements which can be carried out with ease and facility in the morning are quite impossible in the evening.

The electrical reactions in a case of myasthenia are of very great interest, and the reaction of such cases to faradism is characteristic. It is found that after repeated stimulation of muscles by such a current, the response becomes more and more feeble, so that in time it disappears entirely. With galvanism, however, this phenomenon is not observed. Atrophy of muscles has sometimes been present, but it is by no means the rule. The reflexes are usually very active, but in some cases, probably those in which the weakness has reached an extreme degree, it has been possible after a few taps to completely exhaust the knee-jerk, the muscles thus reacting to mechanical stimuli in the same way as they do to stimulation by faradism.

ETIOLOGY.

Males and females are found to suffer with almost equal frequency, and enough cases have now been published to permit of such statistical evidence being regarded as approximately accurate. The oldest case so far published is 55 years, the youngest 12; but I have at present a patient under my care, apparently suffering from this condition, who is only 8; and it is not improbable that as our knowledge and observation of the condition extend, the limit of age may be increased in both directions. The occupation seems to have no distinct connexion with the disease, although the majority of cases described have occurred in manual workers. In many instances the symptoms have followed some acute illness, such as influenza, scarlet fever, typhoid, or severe diarrhoea; and pregnancy, menstruation, emotional strain, cold baths, and over-exertion have been invoked in different cases as exciting causes. In some instances more than one member of a family has suffered, and occasionally the condition has been superinduced upon some form of weakness already existing, such as lead palsy.

MORBID ANATOMY AND PATHOLOGY.

As regards morbid anatomy, so far the cases examined have shown no definite signs of changes in the nervous structures which supply the affected muscles. Nor have the muscles themselves shown any material alteration, except in rare cases, in which a slight degree of atrophy has been present. In some cases, however, very definite enlargement of the thymus gland has been present, in one a condition of lymphosarcoma, in others lymphoid tissue has been present in the muscles themselves, or multiple tumours have been present distributed throughout different organs of the body in such a way as to give possibly some clue to the real nature of the disease. From all that we can gather in the symptomatology of the disease and the condition of the structures generally, it would seem as if the terminal parts of the lower motor neuron were the parts whose function is interfered with. From the nature of the weakness, its variability, and its distribution, it would seem as if we must invoke the presence of some toxic substance to give rise to this interference with the terminal nervous structures; and the presence, in some cases at all events, of the enlarged thymus gland and of the lymphoid tissue in the muscles and other structures already referred to, perhaps give us a clue to the origin of such toxic substance. It seems possible that this tissue is the source of the poison, and that the discovery of its presence may be the means of throwing much light on the origin of the disease. We cannot help thinking in this relation of myxoedema. We know that myxoedema is a disease which is caused by the absence of a certain glandular secretion from the blood, and that by replacing this secretion artificially the disease can be cured. It is possible that in myasthenia we are dealing with a disease which is, in a certain sense, the converse of myxoedema; that in myasthenia

we are dealing with a diseased condition, the result of the presence of a poison in the blood, this toxic substance being produced by an overgrown or modified thymus, or by the abnormal lymphoid tissue present throughout the body, and even in the muscles themselves. And if this is so, our efforts in regard to treatment will necessarily be directed to the discovery of some substance which will be antagonistic to the poisonous substance secreted from such tissue.

DIAGNOSIS.

The diagnosis of the condition, when one has become familiar with the type of disease, is not very difficult. Undoubtedly the closest analogy which is offered is to those cases of nuclear palsy in which the cells of the nuclei related to the bulbar and the ocular muscles undergo gradual, and in time complete, wasting. In many cases it may be impossible to say to which class of cases a given one belongs. It can only be by careful and repeated examination, by noticing the variation of the conditions, by recognizing the associated weakness and easy exhaustion of the trunk muscles and those of the extremities, that we can be convinced that the condition is one of myasthenia and not one of nuclear disease. In reference to diphtheritic paralysis, as will at once be recognized, the analogy is very close. Similar structures are affected, and they are affected in a similar way; and often in myasthenia the onset of the trouble is almost as rapid as it is in diphtheritic paralysis. In the latter disease, however, there will usually be a history of sore throat, etc., to go upon; there will be an absence of the knee-jerk as contrasted with its activity in myasthenia, and there will be the comparatively early clearing up of the condition under appropriate treatment. Polioencephalitis of a chronic character, which is really the degenerative nuclear palsy to which we have referred already, may also, of course, simulate the condition. An acute polioencephalitis is scarcely likely to be mistaken, the onset being so much more sudden. Hysteria is a name which has frequently been given to cases of myasthenia, and the curious variation in the condition, especially in the earlier stages, when the patient is sometimes apparently quite well, and at other times, even on the same day, profoundly weak and ill, may seem to some extent to justify the mistake. An interesting but tragic example of this error is related in the article in Allbutt's *System*, already alluded to. But careful examination of the weakness of muscles, especially the weakness of ocular muscles, which it is almost impossible for a patient to simulate, will usually convince an observer that the condition is not a functional one.

PROGNOSIS.

The prognosis in this disease is always somewhat grave. It is no doubt true that many cases persist in the same curiously variable condition during many years. The second patient referred to to-day has been in a similar condition to that which he occupies at present for about ten years. I recently saw a man in a similar condition in whom symptoms had been present for at least fourteen years. Yet in other cases there is very little doubt that the disease is a very serious one, is very rapidly progressive, and may lead to sudden and somewhat unexpected death. The danger usually lies in an affection of the respiratory apparatus, and patients have frequently died from what may be described as a respiratory crisis. In one instance the patient was admitted to hospital one afternoon about 3 o'clock; she became suddenly dyspnoeic by 8, tracheotomy was done without affording her any relief, and she died at 2 o'clock next morning. The sudden and tragic changes in a patient apparently well a few hours before stamp the disease as one to be looked upon always as possibly serious. Yet in some cases recovery apparently takes place, and it is possible that this is occasionally permanent.

TREATMENT.

Treatment so far has not resulted definitely in any modification of the diseased condition. Strychnine, no doubt, especially if given hypodermically, seems to have a good influence. Thyroid treatment, and various other forms, treatment by organic extracts, have been tried without any benefit. Yet if the suggestion which the recent pathological findings seem to point to be correct, it is to be hoped that some form of antitoxin may be discovered which will have the effect of antagonizing the poison which is possibly formed by the lymphoid tissue which has been found present in certain cases.