Remarks

ON

MYASTHENIA AND OPHTHALMOPLÉGIA.*

By SIR WILLIAM R. GOWERS, M.D., F.R.S.,

Consulting Physician to University College Hospital; Physician to the National Hospital for the Paralyzed and Epileptic.

THE mysterious malady commonly called "myasthenia," or "myasthenia gravis," is a rare disease, the special characters of which have only been discerned during recent years. Indeed, it is still not known, even by name, to many members of the profession. It is met with chiefly in the first half of adult life, and is characterized by general feebleness of the muscles, and also by their quick exhaustion on use, and the quick renewal by rest of what power they possess. The same feature is often, but is not always, conspicuous when the muscles are stimulated by electricity, the effect of a tetanizing faradic current of given strength soon, as a rule, ceases, but returns after a brief rest. This weakness is not attended by definite wasting, or loss of electrical excitability. Although general, it is especially marked in the lips, palate, pharynx, and often in the muscles of mastication, and in those of the eyeball. The "bulbar" weakness, indeed, first attracted notice, and the condition has hence been termed also "myasthenia bulbaris."

The course of the disease presents curious variations, but is seldom definitely progressive, nor has great improvement been often seen, except as a transient event. Death has been the result of intercurrent disease, and has yielded no clear indication of the nature or even the seat of the malady. In the absence of fact theories have abounded. Treatment has seldom had marked effect.

The symptoms vary in different cases, and in some there has been considerable loss of power in the eye muscles. The object of this paper is to describe three cases in which this feature was very marked, and also to call attention to another symptom which each presented, a peculiar alteration in the smile, due to the absence of the normal action of the zygomatic and risorius muscles.

The general features of the disease will be perceived from the account of the cases; the special symptoms can be afterwards described and an attempt made to discern what indications they suggest regarding the nature of the disease.

CASE I.—This patient came under my observation long before myasthenia became a clinical conception. Indeed, had it been published at the time, it would have been one of the earliest recorded cases. But the combination of ocular, facial, and bulbar symptoms chiefly attracted my attention, and I waited until I met with another like it, and I had to wait long. She was a girl of 23, and was seen first in 1874, and from time to time during the following four years. Soon after this she died from some intercurrent disease. My notes are incomplete, but they record the chief features of the case.

No family history of neuroses could be ascertained, no preceding disease, nor any exciting cause for the affection. Beyond a tendency to headache she had been well until the age of 21, when her symptoms were first noticed; they commenced gradually, and slowly increased until she came under treatment at the National Hospital for the Paralyzed and Epileptic two years later. During the next six months they increased slightly, but afterwards were almost stationary, some indeed diminishing. The aspect of the patient at once attracted notice by the stiff look of the eyes, and the unnatural expression of the lower part of the face. On closer observation, it was seen that the latter depended on the absence of any natural smile. Instead of a movement outward of the angle of the mouth, when she smiled or laughed, there was only an elevation of the upper lip. There was no action of the zygomatics or risorius, but the levators raised the upper lip, causing a furrow above it beside the nose, and even wrinkling the skin there. Thus there was only an unpleasant snarl as the expression of a pleasant

emotion. There was slight drooping of the eyelids, greater in the left. Movement of the eyes was much lessened. That of the left eye, outwards and inwards, was reduced to one-eighth of an inch. The right could be moved inwards to the full extent, but not outwards beyond the mid-position, to which it was brought back. Hence an attempt to converge caused an excessive movement of the right eye. Both moved downwards freely; upwards there was a very slight movement of the right eye above the mid-position, none in the left. The fundi were normal, and so was vision. The pupils acted to light. She complained of difficulty with the lips, but could articulate fairly. She could not narrow the mouth to whistle as she formerly could. The voice was nasal. The arms were weak, the grasp with the dynamometer being only 10 kg. each. Extension of the fingers was the only movement distinctly deficient. They could not be straightened if the wrist was over-extended. Her legs were readily tired; but she could walk a mile.

Eighteen months later the movement of the eyes was the same, except that she had become able to move the left eye halfway to the outer canthus, and upwards $\frac{1}{2}$ in. But the left eye moved outwards only when tested separately; on looking to the left with both eyes the right moved freely, while the left remained in the mid-position. The same feebleness of the hands continued, but there was no muscular wasting or defect of faradic excitability. She was seen subsequently at long intervals. Four years after she first came under observation, although her general state was the same, her grasp had improved to right 22 kg., left 14 kg. But the difficulty in extending the fingers continued the same, neither more nor less. She could walk further, but not much, and her knee-jerks were found normal. (The knee phenomenon had then (1878) just risen above the medical horizon.) The facial movements presented the same peculiarity. The movement of the eyes was almost the same. Each was moved up $\frac{1}{2}$ in. Neither moved to the right. To the left the right eye still moved well; the left eye only $\frac{1}{2}$ in. Movement downwards was good, in each eye it was attended by a rotation proving the superior obliques to be unaffected. Soon afterwards, as already mentioned, she died, away from observation.

CASE II.—A girl, aged 29, was sent to me on account of general muscular feebleness, which was first noticed three years before, at 26. The feebleness had come on gradually, in arms and legs, without change in sensation or affection of the sphincters. Her aspect at once attracted notice. There was double ptosis, so that the lids concealed a third of the cornea, but the lids were sometimes fully raised. The eyes could not be moved upwards, and very little downwards, the right eye could only be moved outwards to half the normal distance, the left eye still less. Convergence was lessened, and there was slight nystagmus on looking to the left. The pupils acted to light, and slightly on convergence, but accommodation was normal. The eyelids could be closed, but only feebly. The smile consisted only in elevation of the upper lip, the zygomatic muscles being apparently inactive, but a slight furrow occurred on the left side, perhaps from the risorius. The lips were weak, and she had lost her old ability of whistling. The voice was somewhat nasal, and the palate was but little raised on phonation. When the patient was tired, swallowing was difficult, and liquids occasionally regurgitated through the nose. The muscles of mastication were so readily fatigued that the patient had often to rest two or three times during a meal. The muscles of the neck were weak, and the head was kept upright with difficulty, tending to fall backwards or forwards. The arms were feeble, and if used quickly, became still more so. The legs were also weak, and she could only walk two or three hundred yards. A movement requiring force, such as flexion of the hip, could not be sustained for more than a few seconds. The knee-jerks were normal, and there was no foot clonus. There was no wasting. The electrical irritability of the muscles was normal and so was sensation.

Besides nourishing food, she was treated with gentle massage, tonics, and the hypodermic injection of strychnine. The result has been a slight but distinct improvement during the three years up to the present time. I have seen her at intervals of about six months, and without giving

*An English version of a contribution to the special issue of the *Deutsche med. Wochenschrift* in honour of the 70th birthday of Professor v. Leyden. With the exception of the description of the cases it has, however, been entirely rewritten, and only one of the illustrations has before appeared.

the details of her variations, I may describe her present state as observed in March, 1902.

The patient's general condition was the same, but the improvement in many symptoms was conspicuous. The smile, levator only, was little changed except that on the left side in laughing, there was the same slight outward movement of the angle of the mouth. The naso-labial furrow, on smiling, still extended from the nose to just above the corner of the mouth (see Fig. 1). The lips were distinctly stronger; although she could not whistle even a year ago, she had done so on several occasions, loudly enough to call a dog. The tongue was protruded well, and the palate was raised a little better than nine months before. Fluids had ceased to regurgitate through the nose, the voice had lost its nasal character, and choking on swallowing had quite ceased. The masseters contracted strongly, but were soon tired, and the patient had still to rest from eating several times in the course of a meal. The ptosis continued and the eyelids could not be raised higher by the will, although still when she was interested, they were raised excessively, enough to show the sclerotic above the cornea. This was not attended by any overaction of the frontales, but the patient could contract these slightly by an effort of the will. The orbicularis could close the eyelids, but still with little force; the contraction could be easily overcome. The movements of the eyes were as follows (in their observation Mr. Marcus Gunn kindly took part): Upward movement was absent in each; the downward movement was only a little less than normal (eighteen months before it was very slight). The right eye moved outwards (external rectus) about three-quarters of the normal distance, and the associated movement of the left eye (internal rectus) was about half the normal. The two eyes were moved to the left only about one-sixth of the normal, the same degree in each. The lateral movement of each eye separately was the same as when tested together. The lateral movements were attended with a curious disposition of the eyes to move downwards, greater when tested separately than together. No nystagmus could now be observed, but on looking to the left, the left upper eyelid presented up and down nystagmoid movements. (I first noted this two years before in the same degree.) Convergence was weak; for an object 6 in. away the movement was only half the normal; it did not increase when the object was brought nearer, and soon diminished, the right eyeball first moving outwards. The pupils acted well to light and on convergence. Accommodation was fair, but seemed to be sooner exhausted in the right eye than in the left; there was slight hypermetropia. No weakness in the neck could now be observed, conspicuous as it was at first. The fingers could be completely extended, but the grasp was weak, although only slight evidence of exhaustion could be ascertained, successive efforts with the dynamometer resulting in a pressure of 15, 16, 17, 21, 14, 12, 13, and 14 kg. She had become able to write a long letter without fatigue, which was impossible two years before. In the legs, flexion of the hip was difficult; when sitting, the patient could only keep the foot a few inches from the ground for two or three seconds. The flexors of the knee had fair power, although less than the extensors. The knee-jerks were active, and six repetitions caused no diminution. It was not practicable to test thoroughly the "myasthenic reaction," but the application of a tetanizing current to the extensors of the fingers for about a minute caused little indication of diminished irritability. In the zygomatic muscles, no contraction could be obtained on the left side, but only a slight trace on the right, and this may possibly have been due to stimulation of the risorius. The patient presented nowhere any local muscular atrophy, either in the trunk or limbs. She was thin, her weight being 98 lb. and height 5 ft. 6 in.—about two-thirds of the average weight for her height.

These two cases present a striking resemblance, being of the same sex, not far apart in age, and alike in general and local symptoms, and in the course of these. Muscular exhaustibility was not noted in the first case, probably because it was not looked for.

The last case differs from the others in the later age of the patient, and the fact that the defective power in the limbs was much less prominent. Nevertheless, the resemblance in the slight bulbar symptoms, in the condition of the face, and the

defective movement of the eyes was so close as to make it certainly of the same nature.

CASE III.—The patient, a woman, had married at 23, and had one healthy child. But when 29 the cervix uteri was removed by Sir John Williams for carcinoma. She subsequently had two miscarriages in the sixth month of pregnancy, which is, I am told, very common after this operation. I saw her first in June, 1895, when she was 39 years of age. The symptoms had been observed for two years, commencing gradually without apparent cause. Her expression at once attracted notice from the fixed aspect of the eyes and the apparent absence of the power of smiling; these were recognized as the same as presented by the first case. The smile was confined to the region beside the nose; there was the furrow above the lip, and some wrinkling of the skin beside the nose; but even a laugh caused no furrow outside the corner of the mouth. Her lips had become weak so that she was unable to whistle as she could previously. The tongue was well protruded but the voice was nasal, and the palate was raised very little in phonation. The vocal cords moved well. Slight occasional difficulty in swallowing was complained of, and the contraction of the masseters was not strong—the right distinctly the weaker. There was marked double ptosis, equal, the lid covering the upper part of the iris. The left eye was used in fixing, and there was slight divergence of the globes, which increased on looking upwards. The upward movement was about one-half the normal, a little better in the right eye. In lateral movements, that of each external rectus was about one-half the normal, of each internal rectus only one-fourth, and the defect on convergence was in the same proportion. I have no note of the downward movement, but my recollection is clear that it was good. Injections of strychnine were ordered. Six weeks later the right ptosis had increased, so as to conceal half the pupil. The left external rectus could now move the eye out to almost the full extent, but the right external rectus had lost most of its power. The other movements remained the same. After another month (as I afterwards learned) the patient felt so much better that the injections were discontinued, but she came to me again six months later, being weaker. The right eye moved in and out fairly well, the left much as before, and still diverged outwards. The upward movement of the left was only half that of the right, which was about two-thirds the normal. Convergence was still defective, the effort only brought the divergent left eye to the mid-position. The injections were resumed and two months later the ptosis was a little less; movements of the right eye the same, of the left eye to three-quarters of the normal both in and out, but no better upwards. Her smile had improved a little, and her laugh was much more natural, with distinct movement outwards at the angle of the mouth. But in the laugh there was still excess of the elevation of the upper lip and this was much greater on the right side. The voice was scarcely nasal and the palate well raised. A year later (after very irregular injections) the voice was again nasal, scarcely any movement of the palate could be produced, and closure of the eyes was more difficult. Both internal recti were almost powerless. The smile had again become purely levator. Otherwise there was little change. But at the end of another three months she was not so well, and came to me for the last time. She had suffered from profuse menorrhagia and had become very pale. The blood corpuscles and haemoglobin were reduced to one-half the normal. I do not know the state of the uterus; I had then no knowledge of the previous operations for cancer. She was weaker and complained of pains in the limbs after exertion. She died soon after, I am told, from influenza and bronchitis, and inability of her weak thoracic muscles to expel the mucus. All through, the opportunities for observation were rare and not favourable.

REMARKS.

The *nasal smile* is, perhaps, the most convenient designation for the peculiar character of the smile presented by each of these patients, although it might also be called the "levator smile." Its feature is the absence of the normal movement at the corner of the mouth, which either carries the furrow from the nose around the corner of the mouth or produces a separate depression there. In these patients the furrow of the smile was entirely above the upper lip, ceasing

outwards above the angle of the mouth. It is less marked in Case II than in either of the others, although I am only able to give an illustration of this case (Fig. 1). Its abnormal

Fig. 1.—From a photograph by Dr. Batterbury, of Berkhamsted, of the patient Case II, showing the limitation of the smile to elevation of the upper lip and the absence of movement outwards of the angle of the mouth.

Fig. 2.—From a photograph by Dr. Farquhar Buzzard, showing the similar furrow caused by isolated stimulation of the levator labii superioris.

character may not be so conspicuous at first as when it is observed more closely, and especially when it is compared with the normal smile in a person of the same general aspect. Fig. 2 is from a photograph, which has been kindly taken for me by Dr. Farquhar Buzzard, of the effect of gentle faradic stimulation of the levator labii superioris in a patient whose face was anaesthetic in consequence of the removal of the Gasserian ganglion by Krause's operation. The slight contraction of the orbicularis palpebrarum is due to the fact that some of the branches to this muscle cannot be avoided. It will be seen that the furrow produced corresponds in position to that of the patient's smile. In Cases I and III the limitation of the contraction to the muscles raising the upper lip was even more marked, and their contraction was greater in degree, as if by an over-action consequent on the absence of the normal effect of the zygomatic and risorius muscles.

In the case figured, on an energetic laugh, there was a slight movement on the left side of the mouth, probably by the risorius, which only made more conspicuous the absence of the normal movement. The fact that this nasal smile was so conspicuous in each of the cases raises the question whether it may not be a common feature of the disease. It does not seem to have attracted attention, but it might easily escape notice. In several recorded cases "weakness of the lower facial muscles" is mentioned without being definitely specified.*

The Ophthalmoplegia.—Loss of power in the eyeball muscles has been mentioned as among the symptoms of many cases of myasthenia, but unfortunately has seldom been carefully described. In these three cases it was a most conspicuous and enduring symptom. It presents, at first sight, a strong resemblance to the ophthalmoplegia from nuclear degeneration. Yet there are some noteworthy differences, possibly of much significance. One of these is the greater escape of the muscles moving the eyes downwards, and the implication in various degree of those moving the eyeballs upwards. Not less striking is the constant and irregular affection of the lateral muscles, the fact that this was different in degree in associated muscles, and that in some muscles it presented extraordinary variations at different periods. In order to present

better these features, I have brought together the conditions in the three cases in a diagrammatic form which will be readily understood. Each outer circle represents the normal extent of movement of the eye, and the length of the lines indicated the proportion which the actual movement bore to the normal. Where two or three lines are together they represent the variations of power at different times.

In all cases the light-reflex of the iris was perfect, and I believe that this has been the case of all recorded cases. The condition of accommodation was not easy to ascertain, on account of the presence of hypermetropia, but in two it seemed impaired, and the action of the pupil on accommodation seemed impaired with it, but the hindrance to convergence made the observations on this point uncertain.

Fig. 3.—Diagrams to indicate the amount of movement of the eyes, R and L, by the recti, in Cases I, II, and III. The outer circle represents roughly the normal extent of movement in each direction. The lines of different length placed together indicate the variations in the degree of the same movement at different periods of the case.

Ptosis was a marked feature, as in most cases, but there was no correspondence between its degree and the impairment of the upward movement of the eyes. Equally common was the weakness of the orbicularis palpebrarum, which was so marked in the second and third cases, while in the second case the weakness of the frontales was also conspicuous.

My chief object is to call attention to the peculiar effect of the facial weakness, in altering the smile, and to the peculiar characters of the ophthalmoplegia, in the hope that future observers may ascertain how far these are common. I do not propose to discuss the pathology of the disease generally, but I may point out the possible bearing of the facts on the nature of the malady, a subject which remains altogether mysterious.

The pathological problem is whether the symptoms depend upon a change in the muscles or in the nervous system, or both. The "nasal smile" is only one feature of the distribution of the weakness of the facial muscles, and the significant

* This nasal smile, or nasal snarl as it might be called in its extreme form, bears a curious resemblance to the movement of the face by which most monkeys express pleasure. This is well seen in the figures in Darwin's *Expression of the Emotions*. It raised the question whether animals possess zygomatic muscles. By the kindness of Mr. Beddard, of the Zoological Gardens, Dr. Finny has made some dissections for me, which show that the zygomatic muscles are present in the animals, although they have not quite the same form as in man. How far their inaction in expression is the result of a difference in their direction, consequent on the different shape of the face, is a question still to be decided.

fact regarding this is that it corresponds more closely to that met with in idiopathic muscular atrophy (muscular dystrophy) than to known affections of the nervous system. This correspondence (which has been insisted on by Toby Cohn) is seen in the weakness of the frontales, the orbiculares palpebrarum and of the zygomatic muscles. The resemblance is strikingly shown by a comparison of the facial symptoms of myasthenia with the condition of the face in the case figured in my *Manual*, 3rd edition, vol. i, p. 589, which is certainly a case of muscular dystrophy of the facial type (the type called that of Landouzy-Déjerine). It is equally striking in the remarkable case of this type which was described by Duchenne in 1872, and also by Landouzy and Déjerine in 1886, and of which the pathological condition has only recently been described by Spiller.¹ The frontales and orbiculares were entirely degenerated, and the zygomatic muscles almost entirely. Complete as was the degeneration of a large number of the muscles, the motor nerves were absolutely normal. This fact is of great importance, because it shows that idiopathic muscular atrophy, however long its duration, does not involve of necessity any secondary changes in the motor nerves. Slight changes might, indeed, have been expected from the absence of function, but they are apparently not such as to be recognizable by any method of investigation. It is important to call attention to this fact, and the absolute weight of evidence of it presented by Spiller's case (among others), because it is very rare for a case to be so carefully observed during so long a period, and to become the subject of such careful pathological research. The facts also show how much caution is needed before assuming a simultaneous failure of vitality on the part both of the muscles and the motor nerves.

A degeneration of the nerves involves also that of the muscles, and the coincidence of the two should only suggest that the former is primary, when there is conclusive proof of simultaneous affection, which is not easily obtained.

The distribution of the symptoms in the muscles supplied from the medulla oblongata also corresponds to that in muscular dystrophy rather than in known central affections. A striking feature of this is the escape of the tongue and larynx, and the moderate degree of weakness of the lips and palate. In the cases I have here described the variation in the degree of this weakness at different periods was as marked as that of some of the eyeball muscles. The absence of perfect bilateral symmetry was as marked in the masseters in one case as in the eyeball muscles. In maladies which present such a marked difference as exists between myasthenia and myodystrophy (if I may be allowed to yield to the suggestion of analogy, and use a word which may be new), it is not to be expected that any close correspondence should be observed.

But the ophthalmoplegia, from its resemblance to the nuclear form, may be regarded as suggestive of central disease. It is important, therefore, to note the special features to which I have called attention. Future careful observations may increase or diminish their significance. In its irregular distribution and variations, it presents some correspondence to the features of the weakness in the muscles supplied from the medulla in myasthenia compared with that in central disease. It is, moreover, important to remember that we know no reason why the eyeball muscles should not suffer in a widespread muscular malady.

The information afforded by the microscope regarding the nature of the disease is purely negative. The latest methods of research disclose no structural change. This can surprise no one who has considered carefully the features of the malady. Where there is the capacity for normal action, although in diminished degree, normal structure would be anticipated, and an undue quickness of exhaustion would not be expected to be accompanied by visible alterations. The ability for sustained exertion depends on the capacity for immediate renewal of the elements lost in function, a quick renewal by vital metabolism. The exhaustibility in myasthenia must depend upon defective capacity for this prompt vital nutrition, on a too tardy renewal of the molecules to permit exertion to be sustained. When we remember how far below discernment, or any promise of future discernment, the molecules of living tissue are, it will be realized how vast may be the imperfection of their nutrition, which can only be revealed by its functional effects. Hence we are only likely to obtain any pathological facts regarding the seat of

the disease when local changes proceed far beyond the characteristic functional impairment and involve atrophic degeneration. Atrophy of a few muscles has been noted in rare cases, irregular in distribution, but as yet they have afforded no reasons for regarding the malady as other than muscular.

If present facts only enable us to regard myasthenia as a nutritional disorder, impairing the vital processes in the muscle, we should remember that this is hardly more than a statement of the obvious symptoms in pathological terms. It is only more by its implied negation of other morbid processes. The cause of this nutritional incapacity is, so far as we can yet see, the great problem of the disease, and it is the same, whether the malady is regarded as muscular or neural.

The theory has been put forward and advocated that the impairment of function and vital nutrition can be best explained by ascribing it to a toxic agent. The theory is indefinite, but is apparently based on the mysterious selective action of toxins, on the symmetry of their influence, and on the theory that the effects of fatigue are due to the production in the muscles of a toxic material. But when full weight is given to all these facts, its amount is very small. The argument is purely one of analogy, a proverbial pitfall in reasoning. All that it amounts to is that toxic influences may cause symptoms resembling those of myasthenia in some superficial characters. No one has yet suggested that muscular dystrophy has this origin, although it resembles myasthenia in some important features, among them in the symmetry on which so much weight is laid. The symmetry of the action of toxic agents depends on nutritional susceptibility and proves no more than this. It is very difficult for any one who has watched cases of myasthenia during years to conceive that the condition is due to a toxic agent, in the absence of any conceivable source for such an influence. The persistence of the symptoms, their slight inexplicable variations in detail and degree, make it difficult, at present, to go beyond the obvious fact of an imperfection in the vital nutritional power, which seems to be a defect of life, with little tendency to progress. We know, indeed, that many morbid states which have like manifestations may be brought about by divers causes, but where facts are few the need is all the greater for careful scrutiny of the evidence on which theories are ostensibly based.

In recorded cases little benefit has seemed to result from any method of treatment. But in Cases II and III here described the effect of the hypodermic injection of strychnine seemed distinct. Especially in Case II its influence has been marked and sustained, and, in the opinion of the patient, her friends, and her immediate medical adviser, admits of no doubt.

NOTE.—If myasthenia is regarded as due to an impairment of the lower motor neuron, we must look for the origin of the feebleness and quick exhaustion of the motor impulses to the source of these. Since the nerve fibrillae traverse the motor cells without interruption, that source must be in the extremity of the dendrites (the cell having only a nutritional influence). But this fails to explain the "myasthenic electrical reaction," for which a neural cause can only be conceived as impairment of the nerve endings on the muscular fibres. But these depend for the integrity of their nutrition on the cells, and their pathology is still an unknown subject so far as any primary changes are concerned. It is by the muscles that the symptoms must be directly produced, and reasons for looking beyond them are as yet wanting.

REFERENCE.

¹ Contrib. Pepper Laboratory, Philadelphia, 1900.

PHYSICAL CULTURE IN AMERICA.—A Bill has recently been introduced into the United States Senate which provides for the creation of a department of physical culture, whose head is to be a member of the Cabinet. For each State a Commissioner of Physical Culture, at a salary of £800, is to prepare plans for playgrounds, gymnasia, parks, public baths, and other facilities for physical culture compatible with public health, and to have general charge of such matters within the State limits.