

THE HISTORY OF MYASTHENIA GRAVIS*

by

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I AM greatly honoured by having been invited by the University of Durham to deliver the fourth Grey Turner Memorial Lecture. The name of Grey Turner, that great surgeon and surgical historian (who himself never missed an opportunity of commemorating his predecessors and giving them their due) carries my mind back to 1922, when I was a chief assistant to Professor George Gask on the first Surgical Professorial Unit at St. Bartholomew's Hospital. Every year Gask would take his team to visit another surgical school and one of our earliest expeditions was to visit Grey Turner's clinic here in Newcastle. It was a valuable experience for us young men, whose main surgical training had been during four years of war in the field hospitals in France and Flanders. Later, as I came to know Grey Turner better, I admired him more and more, and enjoyed his companionship when, in the fullness of time, we served together on the Council of the Royal College of Surgeons of England. I was naturally pleased when he asked me to contribute a section on 'The thyroid, parathyroid and thymus glands' for the fourth edition of his *Modern Operative Surgery* published in 1956. I like to think that he would have been interested in tonight's lecture on a theme not unconnected with that contribution.

The history of some diseases, such as those of the skeleton, can be traced even for millennia owing to the relative durability of the morbid material. Of others, affecting soft parts only, there can be no trace except in the literature of the subject, and even then it is rare to find the earlier writers providing a clear clinical description of anything except the more obvious morbid conditions. It very rarely happens that one of them should describe convincingly an obscure neuro-muscular disorder such as the subject of today's discourse, now known as *Myasthenia Gravis*.

I have recently come across an unpublished Latin letter written in 1658 by Dr. John Maplet, a physician working in Bath, to Dr. Thomas Browne of Norwich, the celebrated author of *Religio Medici*. Maplet reports that he is in charge of

a little boy of seven who cannot speak; his limbs also and all his joints are so wanting in strength that he can neither stand nor walk.

It had been suggested that the loss of speech was due to a short *frænum linguæ*, or that his weakness was due to rickets, or all his symptoms to a 'native folly'; but Maplet rejects all these and says,

* The Grey Turner Memorial Lecture, University of Durham, delivered at the Royal Infirmary, Newcastle-upon-Tyne, 22 February 1961.

I see sparks of intelligence and a glow of sense flickering, and at times shining, in the gestures and signs of the patient. He speaks after his fashion, though dumb, more clearly than some who have unspoiled means of vocal communication.

He therefore thought

that the defect is of a nervous kind and that the Nerves are either obstructed or nourished by a vicious humour. If, therefore, this humour were purged and rectified and the nerves lightened of their burden, might not new vigour flow into the habit and structure of the body?

Among his suggested remedies was 'a decoction made of sinews', for the tendons were long confused with the nerve trunks as conductors of nervous impulses. It is, of course, not possible to assert that this was an example of juvenile myasthenia. It might equally well, perhaps, have been an *amyotonia congenita*, such as is sometimes even today confused with myasthenia.

There was, however, a more eminent contemporary of Maplet who soon afterwards gave an extraordinarily precise and well-observed description of patients suffering from myasthenia gravis. This was Dr. Thomas Willis of Christ Church, Oxford. Willis is certainly, I think, one of the most important medical writers of the seventeenth century. He did not make any single forward step in science to compare with Harvey's demonstration of the circulation, but he covered a very wide field of observation in physiology, anatomy, and neurology, including mental disorders. He was distinguished even among the early fellows of the Royal Society. Everyone knows the implications of 'the circle of Willis', an eponym which I trust will never be done away with by any modern improver of nomenclature. It is less well known that he first distinguished true diabetes mellitus, and showed that the polyuria was not due to any disease of the kidney. He even anticipated the recognition of hormones in the circulation by his suggestion that the phenomena of puberty were due to a ferment distributed through the body from the genitals. Unfortunately all his writings were composed and published in Latin. An English translation was published in three folio volumes in 1683, but these books are hard to come by and are insufficiently well known. They are packed with shrewd observations—along with much nonsense, it must be admitted. For my present purpose I want to draw attention to his book *De Anima Brutorum*, published in Oxford in 1672. This dealt mainly with nervous and mental diseases. In the English version of 1683, where Willis is discussing what he calls 'the habitual and spurious palsies', he describes persons who

are distempered with Members very much loosened from their due vigour and strength, and with a languishing of their Limbs; so that though they are well in their stomach, and have a good and laudable pulse and urine, yet they are as if they were enervated, and cannot stand upright, and dare scarce enter upon local motions, or if they do, cannot perform them long: yea, some without any notable sickness, are for a long time fixed in their Bed, as if they were every day about to dye; whilst they lie undisturbed, talk with their Friends, and are chearful, but they will not, nor dare not move or walk; yea, they shun all motion as a most horrid thing . . . wherefore the sick are scarce brought by any persuasion to try whether they can go or not. Nevertheless, those labouring with a want of spirits, who will exercise local motions as well as

The History of Myasthenia Gravis

they can, in the morning are able to walk firmly, to fling about their Arms hither and thither, or to take up any heavy thing, before noon the stock of Spirits being spent, which had flowed into the Muscles, they are scarce able to move Hand or Foot.

It seems, therefore, that Willis was familiar with generalized myasthenia and had observed the phenomenon of fatiguability with recovery after rest so characteristic of the disease. He then goes on to describe a particular patient with another common symptom:

At this time I have under my charge a prudent and honest Woman, who for many years hath been obnoxious to this sort of spurious Palsie, not only in the Members, but also in her tongue; she for some time can speak freely and readily enough, but after she has spoke long, or hastily, or eagerly, she is not able to speak a word, but becomes mute as a Fish, nor can she recover the use of her voice under an hour or two.

In another part of the book dealing with sight and its defects Willis describes typical diplopia in 'a young man obnoxious to the palsie', another example, probably, of myasthenia gravis. When he comes to discussing the theory of the condition Willis is quite startlingly modern.

In this kind of spurious palsie [he says] arising from the defect, or rather, the weakness of the Animal Spirits, than their obstruction, it may be suspected, that not only the Spirits themselves are in fault, but besides, that sometimes the imbecillity and impotency of local motion doth in some measure also depend upon the fault of the explosive Copula suffused everywhere from the blood into the moving Fibres.

This looks like an inspired anticipation of the modern theory of the action of acetylcholine, the chemically explosive link between nerve and muscle, and so completes Willis's claim to be regarded as the first describer of the syndrome now called myasthenia gravis, though he did not give it a specific name.

Although Willis had given so definite an indication of his knowledge of the syndrome, two centuries were to pass before we get a suggestive description of another myasthenic patient. This is in a paper published in 1877 by Sir Samuel Wilks, physician to Guy's Hospital. Wilks's house physician was at first inclined to believe that the patient, a girl of unstated age, was hysterical, but she had an unexplained squint with general weakness and great difficulty in speaking. After a month in hospital she became much worse with very indistinct speech, dysphagia, and inability to cough. Shortly afterwards she died with respiratory paralysis. No pathological changes in the medulla were discovered post-mortem. Wilks included this case under his account of the bulbar palsies, though he was naturally puzzled by not finding any disease of the central nervous system.

Two years later a fuller description was given by a German physician, Erb, working in Friedreich's clinic in Heidelberg. Eleven years before he published his report he had seen a man of fifty-five, who presented over a period of four months several symptoms of myasthenia, namely, bilateral ptosis, weakness of the neck muscles, and dysphagia. Erb treated the patient with the galvanic current, believing he had found a diminished response in the masseters, trapezius

and other neck muscles. A remission occurred and this was not unnaturally attributed to the treatment, though we should now regard it as having been spontaneous. Erb's second patient was a woman of thirty seen in 1870. She exhibited ptosis and diplopia, dysphagia, and generalized weakness. The condition fluctuated in severity, and at one time she became nearly normal. Later the general weakness increased and her speech became nasal. She died suddenly eighteen months after she was first seen. The third patient was a merchant aged forty-seven, seen in 1871, who for a year had complained of weakness of his neck muscles. Later he had bilateral ptosis, weakness of the facial muscles, and generalized weakness. Electrical treatment gave no improvement.

Erb may thus be credited with having established several features of the disease, namely, the frequency of ptosis with diplopia, dysphagia, weakness of the neck, and the course of remissions and relapses, but there was no post-mortem examination of the second patient, who died, so that there was no evidence from morbid anatomy. Erb admits that he did not with certainty distinguish the condition from other forms of bulbar palsy, and so did not presume to give it a name—although his own name was used as an eponym at a later date.

Several more isolated descriptions of patients with symptoms of myasthenia followed during the next fifteen years.

In 1886 Eisenlohr of Hamburg attended a girl of eighteen, and emphasized, like Willis, the variations in the condition seen in the course of a single day, and noted external ophthalmoplegia. The patient soon died with diaphragmatic respiratory paralysis, and no abnormality was found at the post-mortem examination.

In 1887 Oppenheim, working in Westphal's clinic in Berlin, observed a maidservant of twenty-nine for over a year. Her condition fluctuated in severity, and Oppenheim was much interested in differentiating her disease from a hysterical condition, noting that Wilks's house physician had also had his doubts on this point. Eventually she died in respiratory paralysis, and again no abnormality was found in the central nervous system. Oppenheim's mention of hysteria is of importance even at the present time. Of several hundred myasthenic patients with whom I have had contact few have escaped the accusation of hysteria at some stage in their history. In very many patients treatment has been delayed because they could not convince their doctors that they really had something the matter with them.

In 1890 Shaw described myasthenia in a baker aged thirty-seven, showing the typical dysarthria, diplopia, weakness of the masseters, and copious expectoration. The man died six months later with respiratory paralysis, and for the first time his physician reported the use of artificial respiration. This prolonged his life, but ultimately failed.

Other examples were added to the literature during the next three years, including one reported by Dreschfeld of Manchester in 1893. This was the first really adequate description given by an English physician since the time of Wilks, and it is, indeed, far better and more full than his. The patient was a

The History of Myasthenia Gravis

woman of thirty-six with a history covering fifteen years. The first symptom had been bilateral ptosis. This passed off and recurred five years later with diplopia, difficulty in talking, dysphagia, and weakness of the arms. When she was admitted to the Manchester Royal Infirmary she was much worse, and died three days later with respiratory paralysis. Dreschfeld, like many others before him, was much puzzled by not being able to find any lesion to account for the disease. It was even suggested that it should be distinguished by the name 'Bulbar paralysis without anatomical findings', but this did not find favour. In 1895 a German physician, Strümpel, had suggested the name 'Asthenic bulbar palsy', but this also was not adopted.

In 1893 came a critical event in the story of myasthenia, when Goldflam published a paper described by Dr. Viets as being 'in many ways the most important ever written in the history of the disease'. Goldflam added descriptions of three more examples and analysed the symptom-complex in detail, so that a full clinical picture could be formed. As we well know, no myasthenic patient is exactly like any other, but Goldflam synthesized all the observations made up to that point and strove to differentiate the picture from that of a true bulbar palsy, pointing out the absence of atrophy in the muscles affected (though this is not invariably true), the absence of fibrillation, the normal responses to electrical stimulation, the presence of sphincter control, the normal reflexes with exhaustion after repeated stimulation, and the normal palatal reflex. As a matter of particular importance he noted the weakness of the muscles supplied by the fifth cranial nerve, these being seldom, if ever, affected in bulbar palsy. Goldflam was familiar with all the preceding literature of the subject, so that, although his three patients did not suffer from a severe type of the disease, he appreciated practically all the main clinical features which we recognize today, and fully realized the patients' liability to suffer sudden death in spite of previous temporary remissions.

At last a name was given to the disease, honouring Erb as the first physician to give a fairly full account of it—the Erb-Goldflam symptom-complex, as it is sometimes known even today, though it might even more suitably have been called the Willis-Goldflam disease. Goldflam did not, in fact, cite Willis as a witness, almost his only omission. Willis's priority does not seem to have been noticed until 1903, when L. G. Guthrie drew attention to it in a letter to the *Lancet*.

It is of interest to note in passing that one of the most famous text-books ever written, Osler's *Principles and Practice of Medicine*, published in 1892, the year before Goldflam's paper, contains no mention of any disease resembling myasthenia other than the bulbar palsies—unless we are to suspect that it may be hidden under the term 'hysterical ptosis, which is double and occurs with other hysterical symptoms' (p. 791).

In 1895 a new event was the first use of the name *myasthenia gravis pseudo-paralytica* for the disease. This was suggested in a paper published by a German physician, F. Jolly, who described the condition in two boys aged fifteen and fourteen. The first one suffered from severe dysphagia and died suddenly while

eating. The second one had generalized weakness and great difficulty in chewing food, but no dysphagia. Jolly made the important observation in this boy that exhaustion of one group of voluntary muscles induced weakness in other groups that had not been stimulated, thus suggesting the presence of some neuro-muscular inhibiting factor in the circulation. This has been named rather late in the day the Walker-effect, the phenomenon having been again described by Dr. Mary Walker in 1938.

The name *myasthenia gravis* suggested by Jolly was accepted at a meeting of the Berlin Society of Psychiatry and Neurology in November 1899, and it has been generally adopted, though without the appendage *pseudoparalytica*, added by Jolly to indicate the absence of any structural changes. The name *myasthenia gravis* is, of course, an unfortunate mongrel, being derived from Greek words *μῦς*, a muscle, and *ἀσθένεια* weakness, while *gravis* is Latin for heavy or severe. It is additionally unsatisfactory since it is now obvious that the disease is frequently not severe at all, but may be present for years in a very mild form. There should, therefore, be a distinction between 'myasthenia' and 'myasthenia gravis' from a clinical point of view.

Up to 1895 *myasthenia* had been recognized only in England, Germany, and Austria, observation having been stimulated by the papers of Erb, Goldflam, and Jolly. From 1895 onwards reports began to multiply from sources in other countries, including France and Italy. The first, reported from America, came in 1897 when J. Collins described *myasthenia* in a young woman whose symptoms appeared during pregnancy. The first description of the disease in a young child was made in 1898, also by an American, Mailhouse, whose patient was a boy aged two years and nine months. As is so often now found in children, the disease was in an acute form, the boy dying suddenly after a month's illness. He had most of the classical symptoms in a severe form with occasional brief, but complete, remissions. He had no difficulty in breathing, but died while attempting to swallow some coffee. Mailhouse was probably the first to describe clearly how the boy was unable to smile, a feature which greatly troubled his mother. Two authors, who added one more example in 1901, reviewed all the literature up to 1900, and concluded that their patient was the ninety-first on the list. It seems odd to us in 1961 that in twenty-one years, 1879–1900, less than 100 *myasthenic* patients had been observed and described. Dissemination of clinical news certainly took place very much more slowly in the nineteenth century than in our super-documented world today.

From the year 1900 onwards reports of *myasthenic* patients multiplied rapidly, and in 1901 an important event was the first description of finding a thymic tumour in a *myasthenic* patient. No connexion between the thymus gland and *myasthenia* had previously been suggested, but Laquer and Weigert in Frankfurt strongly indicated its presence in their reports. Bulbar palsy was excluded by their finding no changes in the central nervous system. For some time the observation of the association with a thymic tumour remained an observation and nothing more. No explanation was forthcoming, and experimental removal of the tumour was not surgically feasible. In fact the whole

The History of Myasthenia Gravis

subject of treatment of diagnosed myasthenia has hardly been mentioned because, of course, there was no treatment. The physiology of muscular contraction was not understood, and the cause of myasthenia as a pathological condition was totally unexplained. No abnormality had ever been found at examination after death, and very occasional atrophy of a particular muscle group was the only physical change detected during life. But in 1904 T. R. Elliott, writing in the *Journal of Physiology*, offered the suggestion that possibly there might be a chemical substance liberated at the nerve endings to initiate the contraction in the muscle fibres. Yet twenty-eight years were to pass before any such substance was identified. Then in 1932–3 Loewi of the University of Graz reported that the compound acetylcholine was probably responsible for the transmission of the nerve impulse in the heart, though he did not believe that a humoral mechanism existed in striated muscle. But in 1936 Sir Henry Dale reported further work to show that acetylcholine was liberated at motor nerve endings to produce the same effect in ordinary muscles and that its action was limited by the ferment, cholinesterase. At last after a lapse of nearly three centuries Dr. Maplet's humoral mechanism had been vindicated and the 'explosive copula' suggested by Willis had been identified. The path had now been laid open for fruitful investigation of the cause of the apparent failure of normal neuro-muscular transmission in myasthenia gravis. During the next ten years physiologists investigated the nature of myasthenia by means of myography and electromyography, while pharmacologists tried to isolate an inhibiting factor from the serum of myasthenic patients. In 1944 the demonstration of this substance was claimed by Andrew Wilson and H. B. Stoner working at University College Hospital.

Meanwhile there had at last been some progress in the treatment of myasthenic patients. Their lot had hitherto indeed been pitiable. In the milder forms of the disease the patients might suffer merely from a variable diplopia, often with some degree of ptosis, but large numbers of sufferers from myasthenia, which could really be called 'gravis', were grievously incapacitated, a misery to themselves and a tax on their families. Most of those who deteriorated inexorably towards respiratory paralysis and death could only be accounted fortunate. Others in a chronic state of partial or intermittent incapacity carried on for a few years and then succumbed to some ordinary respiratory infection.

In 1929 Dr. Harriet Edgeworth of Tucson, Arizona, had herself been a chronic myasthenic for twelve years. Being also herself a research worker, she was subjected on many occasions to being a research patient or guinea-pig. Thus in 1928 she was made to take suprarenal gland in five different forms, including one made from the interrenal body of the dogfish and another in the form of raw beef suprarenal in large quantities. None had any appreciable effect. In 1929 she was taking ephedrine and amidopyrine for menstrual cramps and chronic sinusitis, and found to her surprise that it gave her considerable increase in strength. She proved by experiment that this was due to the ephedrine, and she reported this in 1930 and again in 1933. Then in 1934 came the most important event in the whole of this historical narrative. Dr. Mary

Walker, working as a house officer in St. Alfege's Hospital in a London suburb near Greenwich, had a myasthenic woman of fifty-six under her care. One day she questioned the visiting neurologist, Dr. Denny-Brown, about the mysteries of myasthenia. We may figure the scene as a hospital corridor with an eager and importunate junior pattering after the busy consultant. He is in a hurry and throws over his shoulder the remark, 'Yes, it's like curare poisoning'. Dr. Walker, knowing from her text-book that the antidote to curare is physostigmin, thinks, 'Then why not try it on the patient?' The injection was given and there was striking temporary improvement. She described this startling event very quietly in a brief letter in the *Lancet* published on 2 June 1934 with photographs of the patient 'before and after'. She acknowledged the interest and advice of Dr. Philip Hamill, late lecturer on pharmacology at St. Bartholomew's and consultant to St. Alfege's, for it was he who suggested a trial of a more recently synthesized drug, prostigmine. This was therefore tried by injection on 16 June 1934, and there then took place what Dr. Henry Viets of Boston is calling in a forthcoming paper, 'The Miracle at St. Alfege's'. Dr. Walker made a further report to a meeting at the Royal Society of Medicine in December 1934, and from that time the lives of hundreds of myasthenics throughout the world has been transformed. Not only were their symptoms alleviated or even abolished for several hours after an injection of prostigmine, but also their expectation of life was greatly improved and many could return to an almost normal existence. Further, it was found that ephedrine, already for three years in use by itself, would increase the effect of prostigmine by about 15 per cent, though its influence is variable.

Encouraged by this striking advance in therapy, Dr. Henry Viets started at the Massachusetts General Hospital in Boston the first special clinic for myasthenics in the world, and here the disease has been intensively studied ever since. Papers written by Dr. Viets have stimulated interest in myasthenia in all countries, and he can truly be regarded as one of the pioneers in the proper exploitation of this great therapeutic advance.

It had long been supposed that myasthenia gravis was a rare disease, and, indeed, many doctors in this country have declared that through a life-time's practice they have never seen an example. It seems certain, however, that this idea of rarity is a delusion. It is difficult to get an accurate estimate of the incidence of so variable a disease in any given population, but the best opinion in the United States believes that there are not less than 6,000 to 12,000 clinically identifiable myasthenics in that country, that is, one in every 18,000 of the population. There may be a further large number of undetected potential patients with mild symptoms not needing specific treatment. It is estimated that in England and Wales there are at least 1,100 diagnosed myasthenics, again with many more undiagnosed. There is a natural reluctance to consider making a diagnosis of a supposedly very uncommon disease, leading to a delay in starting the appropriate treatment, so that the rarity delusion must be dispelled.

But to return to the historical sequence of events—effective medical treatment having been established in 1935, an entirely new move was made in an even

more positive direction. The use of prostigmine was an immense advance, but it was still only palliative treatment. Patients became much happier and their lives were prolonged, but their disease was not being cured. It has already been mentioned that an association between a thymic tumour and myasthenia was established in 1901. During the next thirty-five years more than sixty reports had accumulated of pathological changes in the thymus glands of myasthenic patients. In 1911 Sauerbruch in Zurich had carried out a thymectomy in a patient suffering from both myasthenia and hyperthyroidism, with a view to improving the thyroid condition. This it failed to do and later a thyroidectomy was done with more effect, but incidentally the myasthenia was improved also, suggesting a possible connexion between thyroid and thymic disease. Nevertheless it was many years before another attempt was made to treat myasthenia by removal of a thymic tumour. This was first done successfully by Ballock in Baltimore on 26 May 1936. The patient was a girl of nineteen with severe generalized myasthenia. The disease had run a course of four years with repeated partial remissions and relapses, but the attacks were becoming progressively worse. X-ray examination showed a dense shadow in the mediastinum and the presumed thymic tumour was treated by radiotherapy. There were a series of myasthenic crises and Ballock watched the patient carefully so as to operate during a mild remission. His cautious procedure underlines the fact that thymectomy is never an emergency operation, but must be carefully timed to coincide with an optimum phase of the disorder. A midline transternal approach was made, prostigmine being given both before and after the operation. The patient made a good recovery and twenty-one years later was in good health except for occasional slight relapses when she had respiratory infections or other accidents. She was seldom taking any drug. Sauerbruch twice attempted to repeat this experience in 1937, but both patients died from mediastinitis. His first operation was done at the instigation of Herbert Adler, who was advanced in his ideas. He claimed to have produced muscular weakness in dogs by injection of an extract of thymic tumours and by implantation of thymus glands. He postulated that the thymus was producing in myasthenic patients a substance capable of interfering with the action of acetylcholine, and had thus promoted the gland to a position among the endocrine organs, though not, perhaps, to a front seat in the orchestra.

Ballock reported the result of his operation in 1939, and two years later took a second critical step when he removed the entire thymus from six myasthenic people, though none had any gross pathological changes. The microscope revealed only numerous so-called 'germinal centres', which are now recognized as characteristic of the disease. All the patients recovered and three of them within a month of their operations no longer needed any medication. Ballock made a preliminary report soon afterwards, and three years later, in 1944, was able to report favourably on the results of operation on twenty patients, only two of whom had thymic tumours.

At this point I fear I cannot avoid becoming somewhat personal, because in February 1942 I was invited to perform the first thymectomy done in this

country, the patient being a girl of nineteen with severe generalized and progressive myasthenia. She was under the care of Dr. Arnold Carmichael at the National Hospital for Nervous Diseases, Queen Square. The operation was done with the help of J. E. Piercy at the New End Thyroid Clinic, Hampstead—now the New End Endocrine Clinic. This first operation was a success and the patient during the latter part of the World War worked ten hours a day as a land-girl. Myasthenic patients gravitated naturally to Queen Square, so that more patients were soon forthcoming and as the results became known they began to arrive at New End Hospital from all parts of the world. By the time I retired from active surgery in 1956 I had operated on 281 myasthenic patients, and was able to draw conclusions from much the largest series so far recorded. But it was not without considerable criticism and opposition that thymectomy was finally established as the best hope for most of the younger myasthenics. The story is of interest not only as history, but also as an object lesson and a warning of the harm that can be done by a misuse of statistics and by the exaggerated importance sometimes given to an opinion because it happens to emanate from a well-known medical centre.

While our experience was building up in London, another series of operations was being done by Drs. Eaton and Clagett in the Mayo Clinic, and in 1950 they reported on the results obtained in seventy-two patients, with 142 non-operation cases as a control. To our surprise and dismay they concluded that thymectomy was of no value in influencing the course of myasthenia gravis and they recommended the removal of tumours, only because they regarded these as being potentially malignant. This opinion was so completely at variance with ours formed by observation of a much larger series that we naturally looked closely at the Mayo Clinic figures in order to discover the source of the discrepancy, fortified as we were by the thought that we had tried to avoid all surgical bias by working in close collaboration with our medical colleagues, who had been primarily responsible for a careful follow-up of nearly all the patients. I was never on the staff of the National Hospital, but for many years I regularly attended the clinics held there by Dr. Carmichael and his assistants and even operated on some of the patients in the hospital theatre. It was soon plain to me that the Mayo Clinic and the New End Clinic were reporting on quite different categories of patient, so that statistical comparison of our results was really without meaning. Fairly early in the investigation we had found that 12–15 per cent of the myasthenics coming to us had thymic tumours, and had seen that not only were these patients on the average more seriously ill, but that also the results of operation were very much worse. Consequently we separated our series strictly into the tumour and non-tumour cases, and reported our conclusions chiefly on the second category. The Mayo Clinic, on the other hand, had not made this separation, had done most of their operations on the tumours, and had naturally, as it seemed to us, formed quite erroneous opinions of the results to be obtained in the non-tumour majority. They even added a rider to the effect that the thymus gland had no connexion with the disease. We therefore ignored their report and proceeded on the course we had already set,

closing our ears to the murmurs uttered on all sides that of course the Mayo Clinic had proved the operation to be useless and why did we go on doing it.

For three years our position was difficult and subject to widespread criticism although our results continued to be good. Then in 1954 I was invited to give the Annual Oration at the Medical Society of London, and chose for my subject: 'Surgery of the thymus gland; second (and third) thoughts.' There was a large audience nearly the whole of which was sympathetically expecting a surgical climb-down and admission of misplaced enthusiasm and failure. I carefully reviewed the position in the light of our extensive experience and proceeded to re-affirm our favourable opinion, reserving until the end an announcement that the Mayo Clinic had a short time before performed a complete *volte-face*. They had revised their statistics on the plan that we had suggested and now agreed that thymectomy was successful in properly selected patients, and was indeed fully justified as the best hope for cure that could be offered. In fact, 'the man recovered of the bite; it was the dog that died'. My kind audience, having come to sympathize, was agreeably surprised to find that no sympathy was needed after all, and the meeting ended in quite a different atmosphere from that with which it had begun.

But the harm was done. So definite a statement emanating from so authoritative a source and published in a journal with so wide a circulation as the *Journal of the American Medical Association* had reverberated round the world. The recantation, on the other hand, was first published in a neurological journal with a relatively small circulation, so that the revised opinion was uttered hardly above a whisper, and it took a long time for the news to permeate the general consciousness. Sometimes I think it has hardly done so even now.

I last visited the Mayo Clinic in 1956 and found that my friends there were largely in agreement with our views, though they were still sceptical as to whether thymectomy was effective in males. We have no doubts on this point, but it is more difficult to get satisfactory statistics for males because there are fewer of them than of females and they tend to get the disease at a later age. We have found that the operation is equally effective in comparable patients of either sex. It is sometimes better to look at individuals rather than at statistics.

Last July I had a long conversation with Dr. Kermit Osserman of the Mount Sinai Hospital, New York. With Dr. Henry Viets he is now one of the two leading authorities on myasthenia in the United States, and he told me that he is sure that insufficient use had been made of thymectomy in his country.

I think it can now be said that thymectomy is established as the most hopeful form of treatment for the severer forms of myasthenia, that is, for myasthenia *gravis*, provided the patient is under fifty years of age. Beyond this age the operation is ineffectual and has no place. The best results are obtained in patients under thirty. The combined efforts of modern medicine and surgery have in the last twenty-six years completely transformed the lives and prospects of sufferers from what in its worst forms is a truly terrible disease.

I have arrived at this point in the historical narrative keeping its main outlines clear and simple, but there are many contributory factors in the

continually advancing front of clinical and scientific research. The electron microscope has made clearer our conception of the structure of the neuromuscular junction and how it works. The sites of production of acetylcholine in the end-plates can be seen, and a credible theory of propagation of the nervous impulse by changes in electrical potentials can be formulated. Control of the acetylcholine reaction, the explosive copula, is effected by the action of another protein, cholinesterase, which inactivates acetylcholine by hydrolyzing it into its components, acetate and choline. In the myasthenic patient partial nerve-block is produced by some substance in the circulation which interferes with the production or action of acetylcholine. This is countered by any drug, such as prostigmine, acting as an anticholinesterase factor, and so the myasthenic patient benefits temporarily by its use. The pharmacists have been very busy searching for still more effective compounds of this kind. A variety of drugs have been synthesized and their clinical effects tried, but so far only one, mestinon (pyridostigmine bromide), has rivalled prostigmine. Mestinon acts for longer periods and in some patients gives greater relief but it does not act equally well in everyone. Some patients benefit by using both drugs.

Clinicians have become increasingly aware that overdosage with anticholinesterase drugs can produce a cholinergic state closely resembling a myasthenic crisis and dangerous to life. So another anticholinesterase drug, tensilon, has come into prominence as a diagnostic test for myasthenia. Its action is brief but very rapid, and it can be used to differentiate the cholinergic from the acute myasthenic state. If it has no effect, it may be inferred that the patient is in a cholinergic crisis, and relief can be obtained by the immediate exhibition of atropin. Full understanding of the potentialities of the various drugs is an essential need for the successful management of the myasthenic patient, by both physician and surgeon. Thymectomy can admittedly be a dangerous operation, but mortality is low in those clinics where the management is properly understood. The greatest danger is to those patients whose condition has been allowed to deteriorate too far by a hesitant or waiting policy. Lives are now being saved in this critical state of affairs by a post-operative tracheostomy with a pulsating respirator to carry the patient through the phase of respiratory failure, and to allow for removal of bronchial secretions, which, if they accumulate, lead to panic and crisis.

Radiotherapy has been found to have a definite place in the treatment of myasthenia, but only for the thymic tumours. This form of treatment has been highly developed by I. G. Williams and Arthur Jones at St. Bartholomew's, in conjunction, of course, with very accurate radio-diagnosis. So successful has this been for thymic tumours that the operation has become relatively safe, some of the patients being rendered for the time being non-myasthenic. In fact Professor E. F. Scowen has accumulated at St. Bartholomew's an impressive series of tumour patients treated only by radiotherapy, and this cannot fail to affect the surgical approach when it comes to publication.

I have already said that in 1944 Professor Andrew Wilson demonstrated the presence of a curare-like substance in the serum of myasthenics. He also made

extracts of the thymus glands removed at operation with the same results, the potency being related to the effectiveness of the thymectomy. Later, working at Liverpool University, he found that the foetal thymus is equally active, and sought to extend his research by obtaining large quantities of suitable material from the thymus glands of foetal whales. From this source he has succeeded in preparing an almost pure substance which will produce in small animals a muscular weakness resembling human myasthenia; but the last stage, the isolation of a quite pure substance which might yield knowledge of molecular structure, has so far eluded him.

Recently an entirely novel hypothesis for the explanation of myasthenia has been advanced by J. A. Simpson of Edinburgh, who was responsible for an extensive and detailed survey of the results of thymectomy in my patients. This hypothesis is based on the possible occurrence of an auto-immune response of muscle in which an antibody to end-plate protein may be formed. This substance would then be in competition with acetylcholine, partially blocking it from performing its function at the end-plates. It is further suggested that the reticulo-endothelial system, specifically the thymus gland, might then react to the end-plate protein as if it were a 'foreign' substance, the thymus being under the influence of a growth hormone from the pituitary. Myasthenia gravis would then be an allergic condition, producing a restricted myositis, which would be likely to be benefited by thymectomy. But all this holds much speculation.

One may also speculate on the possible function of the always large thymus of the foetus *in utero*. Might it conceivably be helping to control foetal movements? It is well known that the general muscle tone of all new-born infants is very low, though an exaggeration of this state amounting to clinical myasthenia is seen only in babies born of myasthenic mothers and is a transient condition. On the other hand, in connexion with the problem of safe anaesthesia for surgical operations, A. L. Stead (1955) has drawn attention to the fact that, in a sense, all new-born infants are myasthenic. Their hypersensitivity to *d*-tubocurarine exactly resembles that of myasthenic adults, one of the first signs being its effect on the muscles of respiration, whereas they are resistant to a depolarizing agent such as suxamethonium. If the foetal thymus is normally producing a competitive neuromuscular blocking agent, then myasthenia might be regarded as a pathological reversion to a foetal state, but there would still be no explanation of why this should happen. There is surely something still to be learnt of the physiology of the thymus in infants and its relation to the work, already mentioned, of Andrew Wilson.

So the thymus gland as a member of the endocrine complex still guards its secret. Myasthenia is one of the oddest and most unaccountable diseases that afflict the human body. Its variability was recognized by Thomas Willis in 1672. It looks as though at least the full three centuries will have passed before we find the full answer to all the enigmas that it raises.

REFERENCES

- ADLER, H. (1937), *Arch. klin. Chir.*, CLXXXIX, 529-32.
BLALOCK, A. (1939), *Ann. Surg.*, CX, 544.
BLALOCK, A. (1941), *J. Amer. med. Ass.*, CXXVII, 1529.
BLALOCK, A. (1944), *J. thorac. Surg.*, XIII, 316.
DALE, H. H. (1936), *Harvey Lect.*, XXXII, 229.
DRESCHFELD, J. (1893), *Brit. med. J.*, II, 176.
EATON, L. M., and CLAGETT, O. (1950), *J. Amer. med. Ass.*, CXLII, 963-7.
EATON, L. M., and CLAGETT, O. (1953), *Proc. Ass. Res. nerv. Dis.*, XXXII, 107-24.
EDGEWORTH, H. (1930), *J. Amer. med. Ass.*, XCIV, 1136.
EDGEWORTH, H. (1933), *J. Amer. med. Ass.*, C, 1401.
EISENLOHR, C. (1887), *Neurol. Centralbl.*, VI, 337, 361, 389.
ELLIOTT, T. R. (1907), *J. Physiol.*, XXXV, 367.
ERB, W. (1879), *Arch. Psychiat. Nervenkr.*, IX, 336-50.
GOLDFLAM, S. (1893), *Dtsch. Z. Nervenheilk.*, IV, 312-52.
GUTHRIE, L. G. (1903), *Lancet*, I, 330.
JOLLY, F. (1895), *Berl. klin. Wschr.*, XXXII, 1-7.
KEYNES, G. L. (1954), *Lancet*, I, 1197-202.
LAQUER, L., and WEIGERT, C. (1901), *Neurol. Centralbl.*, XX, 594.
LOEWI, O. (1932-3), *Harvey Lect.*, XXVIII, 218.
MAILHOUSE, M. (1898), *Boston med. surg. J.*, CXXXVIII, 439-41.
(SAUERBRUCH) SCHUMACHER & ROTH (1913), *Mitt. Grenzgeb. Med. Chir.*, XXV, 746-65.
SHAW, L. E. (1890), *Brain*, XIII, 96-9.
SIMPSON, J. A. (1960), *Scottish med. J.*, V, 419-36.
STEAD, A. L. (1955), *Brit. J. Anaesth.*, XXVII, 124.
WALKER, M. (1938), *Proc. roy. Soc. Med.*, XXXI, 722.
WALKER, M. (1934), *Lancet*, I, 1200.
WALKER, M. (1935), *Proc. roy. Soc. Med.*, XXVIII, 759.
WILKS, S. (1877), *Guy's Hosp. Rep.*, XXII, 7-55.
WILLIAMS, I. G. (1952), *J. Fac. Radiol.*, III, 176-85.
WILLIS, T. (1672), *De Anima Brutorum*, Oxford, 404-6.
WILLIS, T. (1683), *Two Discourses concerning the Soul of Brutes*, trans. by S. Pordage, London, 81, 164-7.