MYASTHENIA GRAVIS.

VOLUME I.

by

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"MYASTHENIA GRAVIS".

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Contents.

INTRODUCTION.

The young research worker in a clinical field is commonly advised to make a close study of a small number of cases of the disease in which he is interested. This advice is sound if the small sample is representative of all cases of the disease or if a particular aspect is being studied for which the cases have been specially selected. In the work described here the mechanism of myasthenic weakness has been studied in this way on a representative sample of the clinical material. Even this limited sample is enough to show that the current idea of myasthenia gravis as a disorder of function of the neuromuscular junction of skeletal muscle is only part of the truth.

On the other hand I am convinced that there is still much to be learned about disease by a study of a large population. It is only in this way that it is possible to recognise the less common manifestations, especially where the occurrence of these is 'not statistically significant'. The use of statistics in biological research is to show whether the association between phenomena might have occurred by chance. The ability to recognise when this is unlikely is of obvious value. There is a common but mistaken impression that the conclusion that two phenomena could have been associated by chance necessarily implies that they must have done so. An alternative method used in other branches of natural science is to associate certain phenomena within a hypothesis and then to extrapolate the hypothesis into fields where it can be tested. This method has also been used in the present work.

The concept grew out of a study of a large series of patients/

patients with myasthenia gravis made, at the invitation of Dr. E. Arnold Carmichael at the National Hospital for Nervous Diseases, Queen Square, London, with the main purpose of evaluating the role of thymectomy in the treatment of the disease which was at that time controversial. In the previous years I had studied the effect of corticosteroids on myasthenia gravis in the Gardiner Institute of Medicine, Western Infirmary, Glasgow and had begun to work on electromyography through the kindness of Professor Sir John McNee. The response to cortisone was not such as to commend itself for therapeutic purposes, but it was clear that this drug was able to influence the course of a disease which was at that time considered to be a 'biochemical lesion' of the neuromuscular junction. The only rationale for its use appeared to be the thymolytic action of the steroid yet the nature of the relationship between the thymus gland and the muscular disease was obscure and even the normal function of the thymus was unknown.

Since there were so many unknowns I decided to ignore the current concepts of myasthenia gravis, including the assumptions that there were no sensory symptoms and no wasting of muscle, and to investigate the patients seen at the National Hospital as though they were suffering from a new and undescribed disease.

The case records of the National Hospital were scrutinised from the year 1934 and the fate of every case diagnosed as myasthenia gravis by the staff of that hospital was ascertained by correspondence with the patient, his doctor, other hospitals or the Registrar General. Sir Geoffrey Keynes kindly permitted me to include all the cases seen by him at St. Bartholomew's Hospital and New End Hospital, London. In this/

this way a total of 404 cases was available for study. Where death was not known to have occurred the patients were invited to attend the National Hospital for examination. Thirty patients could not be traced, 129 were dead and 245 were known to be alive. They were invited to attend the National Hospital for examination. I was able to examine 181 of these patients and the other 64 who were unable to attend the hospital (mainly due to residence abroad) were asked to complete a detailed questionnaire with the assistance of their family doctor.

Full case histories were taken from the 245 known survivors and the entire nervous system was examined in the patients who attended for examination. The information was recorded on a pro forma and was supplemented by details recorded in the case records. The information recorded was designed to show the sex and age of onset, duration, order of muscle involvement, state of reflexes, muscle atrophy, response to neostigmine, and response to thymectomy if this was done. In addition, a record was made of factors which aggravated or improved symptoms, factors which precipitated the original attack and relapses, the effect of menstruation and different periods of pregnancy, and the nature of any associated disease.

The data provided the material for the evaluation of the role of thymectomy (Appendix C) but while this work was being prepared for publication I realised that certain features recurred in the histories. On my return to Glasgow in 1955 I conceived the idea that instead of rejecting the data as 'irrelevant' it would be worth considering whether there was some correlation between them. It immediately seemed appropriate to regard the pathological features from the same point of view. Histological changes in muscle and other organs/

organs had been described for many years but were always dismissed as 'non-specific' on the grounds that similar changes occurred in other diseases. In the same way the recent description of myasthenic syndromes in some muscular diseases had given rise to the opinion in the 1950's that myasthenia was a type of muscular reaction not confined to one disease and so myasthenia gravis might not be a clinical entity. As soon as the concept of a disease which could occasionally be generalised and which had pathological features in common with the connective tissue diseases was considered, the hypothesis of an immunological disorder resembling systemic lupus erythematosus suggested itself. The lymphoid nature of the thymus then seemed more important than any possible function as a ductless gland. For the first time the way seemed open to a theory of myasthenia gravis which would comprehend all the known facts.

On my return to Glasgow in 1955 I obtained the co-operation of Dr. John Anderson in an attempt to produce an 'autoimmune myasthenia' in mice by inoculating them with an emulsion of homologous muscle with Freund's adjuvant. The results, which were unsuccessful, were not reported in my Honyman-Gillespie Lecture (Appendix D) because the lecturer is forbidden to discuss experiments on animals. Dr. Anderson also collaborated in a search for antibodies against muscle in 1956 and 1957 but we discontinued the experiments because of negative results.

When I moved to the Northern General Hospital, Edinburgh in 1956 I continued with the clinical and electromyographic studies but when Nastuk et al (1959) reported the presence of a cytolytic effect of myasthenic serum the search for antibodies against muscle was resumed with the help of Dr./

Dr. W.R.M. Alexander of the Rheumatic Unit in the Northern General Hospital. Our results were again negative but by this time I was sufficiently impressed by the clinical and pathological data to formulate the 'autoimmune hypothesis' in a Honyman-Gillespie Lecture delivered in the University of Edinburgh in April, 1960. Coinciding with its appearance in print (Appendix D) Strauss et al (1960) announced the discovery of antibodies against muscle in the serum of myasthenic patients. Though he has used the same techniques as these authors, Alexander is still unable to confirm their results. A possible reason for the discrepancy will be given in a later chapter.

The publication of my hypothesis was justified by a quotation from Hughlings Jackson (Simpson, 1960a).

> 'The use of hypotheses is the method of science. To suppose we can make discoveries by the Baconian method is a delusion. A hypothesis or supposition is not a conclusion; it is only a starting point for methodical observation and experiment, the endeavour being not only to prove it, but to disprove it.'

If the hypothesis is valid, one would expect to find previously unsuspected correlations between myasthenia gravis and other diseases associated with abnormal immunological tolerance. The thymus should have an important role in immunology and antibodies against various organs might be found in the blood of myasthenic patients.

In the following year Miller (1961) published his preliminary account on the function of the thymus as an immunological organ, thus confirming the theoretical basis which had been speculative in my hypothesis. In this Thesis are described the further investigations which I have made in Edinburgh/

Edinburgh showing unsuspected correlations between myasthenia gravis and rheumatoid arthritis, pernicious anaemia, and Hashimoto's disease and confirming the presence of various organ-specific antibodies in the blood of many myasthenic patients. Now for the first time a rational basis is provided for the operation of thymectomy and some obscure points are clarified such as the necessity to operate within a certain period and the latency of the improvement which may result. Light is thrown on the nature of neonatal myasthenia. A possible genetic and hormonal control of the immunological mechanism is suggested.

In the second part of the Thesis the mechanism of transmission failure is re-examined in the light of my own work and a new concept is outlined which reconciles the electrophysiological, pharmacological and, for the first time, the histological abnormalities of myasthenic muscle. This leads to some personal studies on the drug treatment of the disease and the nature of neostigmine-resistance and death in myasthenic patients. These have not been published in extenso but are necessary for a proper understanding of the nature of the disease.

The whole Thesis is, then, a monograph on all aspects of myasthenia gravis. I have contributed to them all except the pathological, but the reason for presenting the work as a whole instead of a selected part is that it is exactly this sectarian approach to myasthenia gravis which has obscured the fact that, far from being a unique 'biochemical' disorder, it is part of a widespread immunological disorder and so its true position is in the mainstream of modern medicine.

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The clinical and electromyographic work is my own but

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I am indebted to Dr. E.A. Carmichael and the Medical staff of the National Hospital, Sir Geoffrey Keynes of St. Bartholomew's Hospital, London, Professor Sir John McNee and Professor E.J. Wayne of the Department of Medicine, Glasgow University, Dr. J.B. Gaylor, Dr. J.B. Stanton, Dr. J.K. Slater and other colleagues for permission to examine their cases. Miss Joyce Mayo was invaluable in helping to trace the London cases. All thymectomies in the series of 90 cases seen in Edinburgh have been carried out by Mr. Andrew Logan to whom I am most grateful for enabling me to continue my researches into the operating theatre itself.

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CHAPTER I.

HISTORICAL REVIEW.

Myasthenia gravis was not recognised as a clinical entity until late in the 19th century, but it is now accepted, since Guthrie (1903) drew attention to it, that this was the probable disorder in a patient described in great detail by Thomas Willis (1672). The next recorded observation was also in England by the London physician Samuel Wilks (1877) and he was the first to notice the striking absence of gross pathology in the nervous system.

The disease then became better known in the German schools with the magnificent contributions of Erb (1879) and Goldflam (1893). Though it seems certain that cases were observed by Byrom Bramwell and others (Simpson, 1960 a Fig.1,1) the disease was not clearly recognised until the review by Campbell and Bramwell (1900) of the cases reported up to that date.

The main contribution made by Erb was the establishment of the clinical picture. Though he was an early exponent of electrodiagnosis he apparently failed to notice the typical myasthenic reaction to faradic current applied to a motor nerve. Some of the symptoms he noted (such as hyperacusis in his first two cases)have been forgotten until the present writer drew attention to sensory phenomena. (Simpson, 1960a).

Goldflam (1893) particularly emphasised the rapid exhaustion of affected muscles and the short term variability, which is so striking, as well as longer term remissions and exacerbations. He also drew attention to the normal or lively/

lively reflexes which will be commented on in a later chapter, but noted that the knee jerk could be exhausted by repeated stimulation. The clinical picture was now so completely described as to more than justify the eponym 'Erb-Goldflam disease' still used in European literature.

The name 'myasthenia gravis pseudoparalytica' was first given by Jolly (1895). He noted that when the muscles were stimulated repeatedly by faradism, a reaction of asthenia was promptly demonstrated yet when the muscle no longer responded to this type of stimulus it would respond immediately to galvanism. This fundamental observation is still the basis of all electrodiagnostic tests (Chapter 15). Jolly termed it 'the myasthenic reaction'. He also suggested the use of physostigmine as a form of treatment but there is no record that he ever used it.

In the next five years cases were reported from all over Europe including Britain and from the United States and these have been well reviewed by Viets (1953). It was, however, the comprehensive review of Campbell and Bramwell (1900) that made 'myasthenia gravis' a well-recognised diagnostic entity to British and American neurologists.

Campbell and Bramwell (1900) described all the features which are now well recognised and many which were 'rediscovered' by my own survey, including the age and sex incidence, the variability, the distribution and the occasional occurrence of retraction of the upper eyelids (Page 275). One symptom (also described by Buzzard, 1900) which I have not encountered is spontaneous clonic movements of limbs or jaw. They state quite firmly that no sensory disorders are present but in their review give an account/

account of cases described by several authors which had transient loss of sensation in one or other part of the body. After reviewing the essentially negative pathological findings they reach a conclusion which is worth quoting in full since it is so similar to the conclusion which will be reached in this thesis.

> "The view we ourselves put forward is that the disease is due to a poison probably of microbic origin acting upon the lower motor neurons and interfering with their functional activity without necessarily producing discoverable change in structure. We suggest that the poison acts upon the motor fibre (= axon) or end-plates; as to whether it also acts upon the cell-body (in bulbar nuclei or anterior horns), we can form no opinion ..... The poison may conceivably act upon the motor nervous system, or upon the muscles themselves".

Though some of the analogies with which they illustrate their argument would no longer be acceptable their general conclusion in favour of 'an attenuated toxin' associated with infection is essentially similar to my own conclusions. The science of immunology had yet to come.

The concept of a 'myasthenic toxin' remained in the literature from that date. In 1901 Laquer and Weigert reported a case of myasthenia gravis associated with a thymic tumour. Weigert (1901), reporting the presence of round cell infiltration in the muscles, thought that they were metastases from a thymic tumour but Dussard (1905) soon disproved this and termed them 'lymphorrhages' because they appeared to leak from blood vessels. He found them in the adrenal and other organs including a posterior root ganglion and concluded that 'it is necessary to assume that the toxic agent is capable of exerting an influence on the/

the function of other tissues besides muscle in order to account for the sensory, mental, vasomotor and secretory disorders occasionally met with in the disease'. He advocated more attention being directed to the condition of the blood, the marrow, the lymphatic system and the fatty and connective tissues as the best hope of solving the pathogenesis of myasthenia gravis.

Keschner and Strauss (1927) give an admirable review of the disease before the introduction of anticholinesterase treatment. In their opinion 'the symptoms of the disease are best explained by assuming the presence of some toxic, possibly autotoxic, agent which has a special influence on the protoplasmic constituent of voluntary muscle and a less specialised influence on the function of other tissues'. 'It would seem', they comment later, 'that in all probability the thymus is of significance in the physiologic and pathologic processes merely by virtue of its lymphoid character', and 'the peripheral site of origin of the myasthenic reaction is most likely the perifibrinal network'.

The concept of an autotoxin has gone out of favour until replaced by the modern theory of autoantibodies. If these three conclusions were restated in modern terms they would admirably sum up my own point of view.

It has been repeatedly confirmed that thymic tumours occur in 15-20% of cases of myasthenia gravis and that in the others the thymus is abnormal in that it contains 'germinal centres'. Sporadic attempts to treat myasthenia gravis by irradiation of the thymus or by thymectomy followed but the beneficial results claimed by some surgeons (Keynes, 1949, et seq.) were hotly disputed by others/

others. An analysis by the writer (Simpson, 1958) confirmed the value of thymectomy in certain types of case and resolved the apparent discrepancies of other workers. This is described in Chapter 10 and in Appendix C. There can now be no doubt that the thymus is in some way important in the pathogenesis of myasthenia gravis.

Early workers including Oppenheim (1887) and Jolly (1895) recognised a resemblance between myasthenia gravis and curare-poisoning and suggested using physostigmine, the antidote to curare, in the treatment of myasthenia. Apparently it was used but abandoned as ineffective. Mary Walker's demonstration of the dramatic relief afforded by physostigmine, and later of its analogue neostigmine, (Walker 1934 a,b.) coinciding with Dale and Feldberg's (1934) confirmation of the role of acetylcholine in neuromuscular transmission turned all thinking towards the concept of a biochemical lesion causing a block of transmission at the neuromuscular junction. In the next 25 years, the rapid advance of neurophysiology and of pharmacology suggested several mechanisms for such a block, leading to many arguments. With few exceptions all of these ignored the fact that the thymus was invariably abnormal and that its removal would effect improvement in the myasthenic state. The trend of thought of Campbell and Bramwell (1900), Buzzard (1905), and Keschner and Strauss (1927) was forgotten while all interest centred on a presumed 'biochemical lesion' at the neuromuscular junction.

The way out of this impasse was first suggested by the writer in a Honyman-Gillespie Lecture on 28th April, 1960 at the University of Edinburgh (Simpson, 1960a). It was suggested/

suggested that the thymus was not an endocrine gland (as had been previously assumed) except in so far as it regulated the formation of blood cells and, indirectly, of plasma proteins. It was suggested that myasthenia was the result of an abnormal immunological reaction in which an antibody was formed against the protein of the end-plates of muscle. This concept arose out of a review of the largest series of cases seen by any single author which suggested that the muscular lesions could occasionally be associated with disorders of other tissues in a manner closely resembling systemic lupus erythematosus. Quite independently Strauss et al (1960) reported that antibodies against muscle could occasionally be found in the blood of myasthenic patients. I have suggested a possible mechanism by which such an antibody could account for the physiological and pharmacological changes in myasthenia gravis (Simpson 1960a. Appendix D), but this is not an essential part of the hypothesis and other possible mechanisms will be described in Chapter 16. This conclusion confirms, in a more sophisticated way, the suggestions of Campbell and Bramwell (1900) and of Buzzard (1905). In the following year the outstanding work of Miller (1961) confirmed the major importance of the thymus as an immunological organ.

This thesis provides a fuller account of the reasons for reaching this conclusion and reports extended observations which now suggest that there is sometimes a clinical and serological overlap between myasthenia gravis and other disorders of the type described at the time of writing as 'autoimmune diseases'. The closing chapters give an account of personal studies on the nature of the failure of neuromuscular transmission and on the treatment of/

of the myasthenic patient. The thesis ends with a survey of evidence which suggests that many of the deaths are due to unrecognised overdosage with anticholinesterase drugs.

CHAPTER 2.

NATURAL HISTORY OF THE DISEASE.

Race:

The majority of the patients in this series are Caucasian, including patients from Ireland in the West (Case MN5766) to Greece and Turkey in the Middle East (Cases NH26385, NH59889). One Asiatic (Case MN7550) was studied closely. Other Indian cases and African negroes known to me have not been included because of insufficient data but there is no doubt that myasthenia gravis affects all races (Harvey, 1948; Kennedy and Moersch, 1937).

Prevalence:

The population from which the present series is drawn does not permit an estimate of prevalence. Estimates which have been made in this country and in Norway are of the order of 1 in 40,000 (Ferguson et al, 1955; Garland and Clark, 1956; Pennington and Wilson, 1961; Storm-Mathisen, 1961). Kurland and Alter (1961) assessed the incidence in the United States of America as 1 in 10-20,000 of the population.

Sex and Age:

Myasthenia gravis is more common in women especially in the first half of life, but when the first manifestation of the disease is in later life, men are more frequently affected. In earlier reviews of part of this material it was found that females were affected twice as often as males (Simpson 1956a, 1958). In the first decade of life the number of girls affected was 4.5 times the number of boys but the disproportion decreased in later years and was reversed in later life. The expanded/

expanded series now reported confirms the main trends previously reported but in the age group over 50 the disease is equally common in both sexes. Figure 2,1 shows the age and sex distribution of cases with and without a known thymic tumour. These are shown separately because, as will appear later, the natural history of myasthenia is different in the presence of a thymoma.

Figure 2,1 and Table 2,1 show that thymic tumours occur with equal frequency in each sex. The modal ages at the time of onset (as judged by the earliest recognisable symptoms of myasthenia) are shown in Table 2,1. These figures show that the modal age at the onset of symptoms is virtually the same for both sexes although the predominance of females in the younger group makes the mean ages different for each sex. A thymoma is equally common in either sex but the modal age is 25 years older. In earlier reviews of part of this material the modal age for male patients and the proportion of males in the older age groups were both higher. With the larger series it is now apparent that the only difference between the sexes is the higher incidence of cases in women under 40 years of age.

It will be seen from Figure 2,1 and Table 2,1 that when the first symptoms of myasthenia gravis appear after the age of 40 there is a 30% chance that the patient has a thymic tumour. Keynes (1955) has remarked on the absence of cases of myasthenia gravis with a thymoma under 20 years of age and the low incidence under 30 (4 per cent).

The age distribution of the 202 female cases reported by Schwab and Leland (1953) is similar to the present series but they had many fewer young males so that the/

the modal age of their 167 male patients was 61 years. The much smaller series of Grob and Harvey (1953) and of Storm-Mathisen (1961) show a similar trend to my cases. The latter author records similar results from earlier writers (his Table 2) but it must be remembered that none of these authors have given separate figures for patients with and without thymic tumours. The statement by Garland and Clark (1956) that the disease occurs with equal frequency in each sex below the age of 30 can only be based on the small size of their series. (Exact comparison is impossible as other authors have used mean age as a measure of central tendency. This is unfortunate because of the skewed distribution and the relatively small numbers of many series).

The significance of the sex and age distribution will be discussed in Chapter 14. At this point it is desirable to point out that the age distribution curves for each sex are regular and monomodal though skewed. The distribution is certainly not random nor is there any suggestion of a multiplicity of diseases related by a common symptom complex (Simpson, 1960a).

A benign type of myasthenia gravis which is virtually confined to the extraocular muscles is more common in males (Grob, 1953). In my series the incidence was 1.6% of female cases and 9% of males. None of these patients had a thymoma (Simpson, 1958). Despite this Grob (1953) states that the prognosis is worse in males than in females. Storm-Mathisen (1961) agrees with Grob but only when he is analysing the cases treated with anticholinesterase drugs. Untreated male cases appeared to have a much better prognosis and he was unable to account for this discrepancy. My own findings, which are detailed in Chapter 10, are the converse/

converse (Simpson, 1958) and Hoefer et al (1953) found no difference in the course of the disease between the sexes.

Mode of onset:

The onset of symptoms may be insidious so that the patient is only occasionally aware of disability. This may cause difficulty in establishing the time of onset. Some patients insist that they have always been weak but I have not been able to confirm this from independent sources.

Case MN5625 had weakness of one side of the face at the age of 3. During the next 18 years she had four more attacks of facial palsy on one or other side, each lasting for about six months. With some of these episodes her tongue felt 'numb' but there was no loss of taste sensation. She knew that she had a 'lazy eye' on the left but denied diplopia or ptosis and had not noticed any other weakness.

When she was 14, there was a brief spell when she could not hold things in her left hand. When she was 21 she attended the Northern General Hospital, Edinburgh, with a complaint of bilateral facial weakness which had started four months previously (Fig. 2.2). Almost complete facial palsy was noted but in addition she was found to have weakness of the tongue, the left side of the palate, and the flexor muscles of the neck. Trunk and limb muscles were powerful until exercised against resistance when the right triceps, left finger flexors, flexors of both hips and the left hamstring muscles were found to 'fatigue' rapidly. All tendon reflexes were brisk and the plantar reflexes were flexor. Sensation was normal. To further questioning she stated that she had/

had noticed a slight goitre one week earlier.

Investigation confirmed that she had myasthenia gravis. There was an excellent response to pyridostigmine in all muscles except the facial and these have remained as in Fig. 2,2.

Case NH50769 had double vision for the first time at her wedding when she was aged 20. She later developed generalised myasthenia gravis. She stated that she had been 'a frail child' until the age of 14.

Case MN3054 (Fig. 2,3b) fell while skating at the age of 24. For the following month both legs were weak when running. She then remained well until weakness of the legs returned in the last trimester of her fourth pregnancy fourteen years later. This was followed by difficulty holding her arms up to dress her hair. A diagnosis of muscular dystrophy was made elsewhere. I saw her in Edinburgh at the age of 44. She had typical myasthenia gravis at that time and subsequently developed mild thyrotoxic goitre. She has remained well for six years on pyridostigmine medication.

It is possible that some cases of this type have had mild myasthenic weakness since early childhood but in view of the fallibility of memory and the natural tendency to extrapolate backwards, only the earliest known date of definite 'fatiguable' weakness has been used in establishing the age of onset (Fig. 2,1). With this type of onset the patient is aware of weakness on physical exercise (Cases NH715, MN1939). The onset is more often sudden. In this type it is rare for physical exercise to be the precipitating factor though this was noted by some patients. Cases NH3329 and NH12345 were hurrying for a train. Case NH61508 was harvesting, Case NH42782 playing football and Case GK/DB and

MN7345/

MN7345 were playing tennis when they noticed weakness for the first time.

In my experience an emotional upset has been a more common precipitating factor. The latent period may be remarkably short but I have not been able to obtain independent confirmation of the intervals described by patients. Emotional disturbances preceding the onset of the first symptom were noted in 4 cases by Wilson and Stoner (1944) and this was well known to earlier writers (Campbell and Bramwell, 1900). Three patients in the present series attributed the sudden onset (or a relapse) to 'shock' during the bombardment of London (Cases NH1786, NH6352 and NH42883). Case NH42883 was thrown to the ground by blast and was unable to rise again. The initial diagnosis of hysterical paralysis was later changed to myasthenia gravis. Other causes have been the sudden death of a near relative (Cases NH4384, NH62047, MN887, MN3539, MN5503) or anxiety about illness of a child or spouse (Cases NH23458, NH44923, NH62031), a discovery of a husband's infidelity (Case NH43986) or a divorce (Case NH61465). One patient (Case NH61502) was certain that he was about to be killed in an accident involving the crane which he was driving. He was unhurt, but his first symptoms of myasthenia started in the next few days.

The emotional reaction may also account for onset of myasthenia on the day following dental extraction (Case NH15565) and for the ocular myasthenia which started two weeks after a blow on the eye in a patient with a family history of thyroid disease (Case NH61500). Case NH33170 developed generalised myasthenia gravis six months after a crush injury of the chest and later noted that relapses were/

were usually caused by worry or anxiety. Ptosis first developed at a party, (Cases NH9174 and 61513) or during the wedding ceremony (Cases GK/SE and NH50769). Case NH61425 had difficulty in swallowing for the first time during an examination.

On the other hand, Case NH/EC/IH had a remission when she was blown up by a 'doodle bomb' during the war and Case NH25196 had an immediate remission when weakness of her hands caused her to drop a hot water bottle. She had a severe burn and no myasthenic symptoms were present for the next two weeks despite withdrawal of neostigmine. Case NH26672 had a remission when her husband was injured by falling from a roof.

Only a little less common as a precipitating factor is a febrile disease, usually an upper respiratory infection. (Cases NH/D-B/MT, NH3274, NH4648, NH7195, NH8191, NH13612, NH17235, NH17834, NH23870, NH26385, NH26546, NH33710, NH41288, NH50891, NH61427, NH61434, NH62032, MN2986, MN4977 and MN6933). The preceding infection was herpes zoster in Cases NH/MC/GS and NH/MC/AW.

Symptoms may first appear during pregnancy (Cases GK/DJ, GK/ET, NH33942, NH61127, MN3054, MN3912, MN7587), in the puerperium or in the next six months (Cases GK/SR, NH19400, NH62039, MN3451, MN5683 and MN7779). The onset after pregnancy was more likely if the child was unwanted. Other cases began after a miscarriage (Case NH9175).

The diagnosis was made in some cases after they had shown an abnormal response to a relaxant drug used during anaesthesia, as described in Chapter 17. Unfortunately the reason for inducing anaesthesia was sometimes to permit otolaryngological investigation for dysphonia (Case GK/JB) or dysphagia (Cases GK/SE and NH62039) when the true cause of /

of these symptoms had not been recognised.

In some cases there was no obvious precipitating factor and the nature of the disease remained unrecognised because of the unusual site of the affected muscles. Thus eight cases presented as unilateral or bilateral facial palsy (Cases NH/EC/KW, NH34298, NH34399, NH43312, NH61465, MN3539, MN3609, MN7776).

It will be pointed out in a later section that the muscles of respiration are usually spared until the disease is widespread throughout the musculature. Nevertheless one patient presented with acute dyspnoea without obvious cause.

> Case MN382. A man aged 47 suddenly became extremely short of breath while at his work. He collapsed but soon recovered. Six weeks later he developed double vision and in another four weeks he again collapsed suddenly with inability to inflate his lungs. The initial diagnosis at a casualty department was 'hysteria or disseminated sclerosis'. He now has typical myasthenia gravis and Raynaud's syndrome.

There is a graphic account of a similar case in a report by Strümpell (1896). Such a dramatic onset of serious symptoms without obvious cause commonly leads to a diagnosis of psychoneurosis. This diagnosis is particularly likely where the onset of symptoms follows an emotional disturbance. The apparent absence of signs if the patient enters the consulting room after a period of rest in the doctor's waiting room is in striking contrast to the dramatic symptoms described by the patient. If the latter are related to an unhappy love affair (Case NH9174, MN4536), quarrels with wife, relatives or neighbours (Cases MN1906, MN3546, MN4084 and MN4186/

MN4186) or to similar emotional trauma, a psychopathological explanation may seem inescapable. These factors, added to a lack of alertness to the possibility of myasthenia gravis, account for the fact that most patients with that disease are treated as 'hysterics' for many months or years before the true diagnosis is established.

Case NH5343 had double vision in 1931 and this returned at intervals with ptosis and facial weakness, always precipitated by emotional upset. The diagnosis of myasthenia gravis was not established until 1946.

Case MN6792. In January 1959 this 19 year old girl was unable to speak after a long ride on a motor scooter. Her jaw was 'stiff'. This was attributed to cold but it persisted and she began to complain of severe physical tiredness. Her eyelids closed though she was not sleepy. She could open them for a few moments only. In two months she was unable to support her head or to stand without assistance. She had difficulty in chewing, swallowing and speaking and was unable to cough.

In the following 10 months she was in three psychiatric hospitals and one large teaching hospital in London. She was put in 'solitary confinement' and eventually she attempted suicide. Finally she was seen by a psychiatrist who had previously worked in New End Hospital, London, and who recognised the true nature of the disorder. There was immediate improvement after thymectomy in 1960 though she still requires to take pyridostigmine.

Further course:

The further course of the illness is equally variable. Many cases have a rapid, if not simultaneous, involvement/

involvement of most of the skeletal musculature. The prognosis is less favourable in these cases. Storm-Mathisen (1961) found that 60% of males (but only 30% of females) who develop generalised signs in the course of a month die within seven years. In other cases the spread occurs gradually or sporadically over a period of months or years.

Less often the initial symptoms subside and no further weakness is noted for a long period. The longest remission of this type in the present series was 14 years (Case MN3054, described on page 236). Case NH/PS/LB had one remission of 10 years and a second of 8-9 years but this was exceptional. According to the descriptions in current textbooks, remissions of this type are characteristic of the disease but those authors with wide personal experience report that significant remission occurs in only 20-40% of all cases (Kennedy and Moersch, 1937; Ferguson et al, 1956; Grob, 1958; Osserman, 1958). The higher figures are from those authors who include remissions of one month's duration. If a period of three months complete freedom from symptoms is specified the incidence of remissions is about 20% of cases (Storm-Mathisen, 1961).

In the present series 'valuable' though not necessarily complete remissions of more than a month occurred in fewer than half of the patients and usually only in the early years of the illness unless the natural history was altered by removal of the thymus gland (Chapter 10). Remissions became less frequent and less prolonged as time went on. More than one long remission was uncommon and the present series suggests that if myasthenic symptoms return after an absence of a year or more/

more they usually become progressive.

Relapses are precipitated by the same factors as the first attacks, principally by emotional strain or by infections (Hyland, 1936). The emotional strain need not be severe. For instance, many patients with myasthenia gravis are troubled with ptosis or dysarthria only when they enter a crowded room or are otherwise embarrassed (Cases NH3962, NH9174, NH61504). This was recognised by T. Buzzard (1900) but has been neglected. It is stressed here because of its importance in assessing the Walker effect (Chapter 16) and because of its practical importance in the management of a case of myasthenia gravis.

Other causes of temporary aggravation of symptoms are menstruation and pregnancy (Chapter 8) and extremes of cold or heat. A stuffy atmosphere or a hot bath are particularly disturbing to some patients (Cases NH108, NH4388, NH5554, NH52972, NH44941, NH61493 and NH62049.) This intolerance of climatic extremes has been reported by Edgeworth (1933) and Wilson and Stoner (1944).

Relapses appeared to be induced by inoculation against typhoid (Case NH62050). Case NH4636 had a relapse after Jennerian vaccination and Cases NH/PS/LB and NH37065 had attacks precipitated by eating shellfish to which they also showed skin allergy. Thévenard et al (1949) described the onset of myasthenia gravis in association with serum sickness due to injection of antitetanus serum six weeks previously. On the other hand Storm (1948) reported two cases which appeared to improve after anaphylactic shock. He attributed the improvement to diminution of permeability of the muscle membrane.

Many patients were weaker after sleepless nights or after/

after taking alcohol (Cases GK/EF, NH29870, NH31922, NH62042, NH62050, NH2914). It has not been possible to decide whether these and the other factors just described are genuine first order effects or due to a psychological response to the circumstances, but it should be noted that transitory deterioration is sometimes caused by the same factors in disseminated sclerosis in which the pathogenesis may be related to that postulated for myasthenia gravis in this thesis.

The role of bright sunlight is equally puzzling. This often causes ptosis and blurring of vision. It might be that normal people have an overactivity of the levatores palpebrarum muscles to counteract a reflex eye-closure in these circumstances and that this response 'fatigues' in the myasthenic, but it is difficult to account for the statement of some patients (e.g. Case NH44923) that bright sunlight made them feel generally weaker even when it was not accompanied by excessive warmth. This has been noted previously by Wilson and Stoner (1944).

The factors listed here have nothing in common except that they represent the extremes of the normal environment. It would be a fair summary of the opinion expressed by many patients that any departure from the normal routine, be it temperature, light, excitement or worry, may cause increased weakness.

The 'active' and 'burned out' stages:

I have formed a strong impression that the clinical state is most labile during the first 5-7 years after which there is less fluctuation. Major remissions are most common within 1-3 years of the onset and it is much rarer for a long remission to occur after the disease has been established/

established for more than 5 years if the thymus is not removed (Simpson, 1958). As the presence of a thymic tumour may adversely affect the course of the disease, cases without a thymoma will be considered separately in Chapter 3 and in all statistics.

Table 2,2 shows the duration of illness before death due to myasthenia gravis (excluding deaths directly attributable to surgery or to incidental disease). It will be seen that most of the deaths occur in the first year. This experience is in agreement with that of Grob and Harvey (1953), Rowland et al (1956) and Storm-Mathisen, (1961). Death usually occurred 4-7 years after the onset of the disease whether thymectomy was carried out or not. Deaths from myasthenia gravis per se rarely occurred more than ten years after the onset of symptoms. There may be persistent weakness of the muscles of expiration constituting a constant hazard of death from asphyxiation by inhalation of foreign-bodies. This may cause sudden death in a patient who does not show signs of 'active' disease. Rowland et al (1956) report a similar experience of the 'brittle' nature of the expiratory reserve in some late cases.

Case NH3533. This young woman had ptosis and diplopia when she was aged 21. Later she developed generalised myasthenia but it was not unduly severe and there were several remissions of up to 18 months duration. For many years she led a full life on 7-8 tablets of neostigmine daily. Eighteen years after the onset she choked while eating an orange and she was unable to cough up a segment which was impacted in her glottis. Death rapidly occurred from asphyxiation.

Case/

Case NH31378, a boy aged 18, was very well and without symptoms while taking 7 tablets of neostigmine daily eighteen months after thymectomy. One day he stepped out of a bath, gave a sigh and died immediately.

Undoubtedly some cases continue to advance for many years, but in the average case the 'active' stage of the disease is limited to a period of 4-7 years and the subsequent course depends on the extent of the damage sustained during that period. In Chapter 10 it will be shown that if thymectomy is to be beneficial the operation must as a rule be carried out during this period (Simpson, 1958, 1960a).

The course of the illness may be benign and the affection may remain limited to a few muscles. Grob (1953) stated that 20-30% of cases show only extraocular muscle involvement. He considered that the further prognosis is good if there is no wider spread in the next two years. Ferguson et al (1955) agreed with this conclusion in general but reported that 16% of such cases did show extension to other muscles after 3-13 years. Only 36% of the ocular cases in the series described by Osserman (1958) and none of the series of Storm-Mathisen (1961) failed to spread.

Case GK/CG had myasthenic diplopia and ptosis from 1923. He did not develop generalised symptoms until 1943. These were not affected by thymectomy in that year and he died three months later.

In my experience restriction to the ocular muscles has been found in 9 % of male patients and in only 1-2% of females. This difference in incidence from the other series quoted above was at first believed to be due to the fact that the first 407 cases were seen at the National Hospital/

Hospital for Nervous Diseases and so may have been a selected group as there are two large Departments of Ophthalmology nearby which might collect the purely ocular cases (Simpson, 1958). I now think that this could not account for the apparent difference in experience since, during the last eight years, I have seen 90 cases of myasthenia gravis in Edinburgh including all those referred to the Department of Ophthalmology at the Royal Infirmary. In no cases have I failed to detect involvement of neck or limb muscles. I believe that this is due to certain techniques of examination which will be described in the next chapter.

The much lower incidence of 'ocular myasthenia' in women, who constitute the greater part of this series, may account for disagreements regarding prognosis. Grob (1958) considers that men have a worse prognosis than women whereas in my experience women have had a poorer prognosis than men unless treated by thymectomy (Simpson, 1958). The basis for this conclusion is set out in Chapter 10.

The prognosis is, on the whole, poorer if myasthenia gravis is associated with a thymic tumour. Muscular weakness is usually severe and difficult to control with neostigmine. Nevertheless, although these generalisations are some guide to prognosis, it is impossible to predict the course of any individual case. A patient with rapidly advancing myasthenia requiring high dosage of anticholinesterase drugs during the first year may nevertheless have surprisingly little disability when the illness enters the 'burned out' phase (Cases NH2325, NH2648, NH2927, NH26672, NH33833, NH40112, NH44941). On the other hand a patient who has had many years of remission may nevertheless enter a rapidly advancing phase with danger to life (Case NH47889).

CHAPTER 3.

SYMPTOMS AND SIGNS.

A feature of myasthenia gravis is the variability in muscular strength from day to day or even from hour to hour. These changes in muscular strength may be due to physical exertion but, as in the long term relapses, the emotional state is an important factor. The cheerful patient who is determined to get well often has a smooth course and is able to reduce his medication progressively. Emotional disturbance will cause increased weakness with diminished response to anticholinesterase medication and this deterioration may occur within hours of the traumatic event. Very occasionally sudden stress may initiate a remission (Cases NH25196, NH26672 and NH/EC/IH, cited in Chapter 2).

Myasthenic weakness:

The symptom which differentiates the myasthenic diseases from all other causes of muscular weakness - and to which the term myasthenia is now restricted in the English-speaking countries - is rapidly progressive loss of power of a skeletal muscle if it is contracted repeatedly without rest or if a contraction is maintained. The contracting muscle may lengthen gradually if it is supporting a load, or a coarse tremor develops. This is interrupted by brief rest periods which become more and more frequent until the attempt to sustain the contraction ceases (Fig. 3,1). This is often described as 'muscular fatigue'. It is entirely different in nature from normal fatigue but the term will suffice for descriptive purposes since there is no convenient English term. Gradual 'fatigue' is not always seen and failure of contraction may be sudden.

Because/

Because of the undoubted effect of physical exercise most myasthenic patients become weaker as the day progresses. This is 'a textbook symptom', yet some patients are at their weakest soon after waking in the morning (Cases NH/EC/HS, NH4749, NH9174, NH42883, MN5766). This cannot be accounted for by lack of nocturnal treatment since it has been noted by several patients before the diagnosis was made and indeed this was reported before the introduction of anticholinesterase treatment (Auerbach, 1902; Boothby, 1934). With drug treatment some patients are very weak in the morning, rapidly improve towards the middle of the day and deteriorate again towards the evening (Turner, 1953).

Muscular atrophy:

Recovery with rest or full medication is often incomplete - a point which is apparently unknown to some authors who have tried to account for myasthenia gravis entirely on the basis of a disorder of transmission at the neuromuscular junction. The practical importance of this is that full restoration of power should not always be expected from anticholinesterase medication or from thymectomy. A patient may pass from myasthenic to 'cholinergic' weakness without an intervening stage of normal muscular power (Chapter 19).

Campbell and Bramwell (1900) emphasised the absence of muscular atrophy in myasthenia gravis though it was mentioned in 10 of the 60 cases reviewed by them and this statement is repeated by most authors who have written about the disease since then. Permanent weakness with wasting of muscles ('myasthenic myopathy') is probably more common than generally believed, particularly in the extraocular/

extraocular muscles, triceps brachii, iliopsoas, quadriceps femoris and tongue (in that order). In this series atrophy was present in 10% of female and 20% of male cases (Simpson, 1958). Wasting of the tongue occurred in 12 patients in the characteristic distribution which causes three parallel longitudinal furrows (Fig. 3,2). (Cases NH/EC/DH, NH48570, NH61494, MN269, MN294, MN1906, MN2327, MN3231, MN4588, MN6481, MN6998, MN7788). The triple-furrowed tongue is sometimes named after Kinnier Wilson (1954) but was previously described by Erb (1879) and F. Buzzard (1905), and other writers of that era (Campbell and Bramwell, 1900). The reason for this selective wasting is unknown.

I have previously described a woman who had a benign myopathy with myasthenic features (Walton et al., 1956). As its nosological position is uncertain consideration of this case will be deferred until Chapter 8 which deals with congenital myasthenic syndromes.

Some patients with persistent weakness but without the 'fatigue' phenomenon and without further response to neostigmine in the 'burned out' stage of the disease, show a paradoxical improvement with moderate exercise and are at their weakest after a period of physical rest. Most of these patients have been males. (Cases GK/HA, NH/EC/SP, NH/EC/KW, NH7195, NH8162, NH11102, NH61430, NH61503, NH62041). This paradoxical phenomenon has been referred to by the writer (Simpson, 1964b) but has not been described by other workers.

Effect of thymoma:

There is no distinctive clinical sign of the presence of a thymoma. It is often accompanied by a particularly severe and progressive type of myasthenia with/

with poor response to neostigmine. I have never found a thymoma in patients who have had myasthenic weakness restricted to the ocular muscles nor has such a case been reported by others (Simpson, 1958). Neostigmine requirements averaged 50% more than that of non-tumour cases and the incidence of 'myopathy' was much higher (10% in women and 22% in men, Simpson, 1958). Thyroid disease occurred with similar frequency in both groups and there was no special tendency for the complications described in later chapters to be associated with a thymoma with the exception of aplastic anaemia (Chapter 7) and the presence of a circulating antibody against muscle (Chapter 13). Myocarditis has been reported by other workers only in cases with a thymoma (Mendelow and Genkins, 1954; Chapter 11).

Some patients with a thymic tumour have a benign course and may respond well to thymectomy (Chapter 10) but on the whole the prognosis is much worse when a tumour is present in the gland. For this reason it is advisable to have lateral as well as postero-anterior radiographs. With well exposed plates it is rare to miss a thymoma (Fig. 3,3). Many experienced radiologists (Good, 1947) do not consider that there is any advantage in using tomography (Kemp Harper, 1952). Bétoulières et al,(1954) and Hare and Mackay,(1963) outline the thymus by insufflation of oxygen into the mediastinum. An example of this technique (for which I am indebted to Dr. M. Summerling) is shown in Fig. 3,4. It is of doubtful value as a routine procedure since thymic tumours are usually identifiable without the injection and the size of the non-neoplastic gland is not closely related to the severity of the disease. Calcification may be seen in a thymoma. It is never present/

present in the 'hyperplastic' type of thymic enlargement.

Muscles affected:

Myasthenia gravis affects only striated muscle and never the smooth muscle of the viscera. The possibility of affection of cardiac muscle will be discussed in Chapter 11. In some cases a single muscle may be affected. Rarely extension of a single finger may be weak suggesting that the pathological change may be confined to part of a muscle. Any skeletal muscle may be involved, usually several at a time, but some are more frequently involved than others. Fig. 3,5 from Simpson, (1964c) shows the frequency with which muscles may be affected a) as the initial symptom, and b) at any stage of the disease up to the most recent time I have examined each patient (10-15 years for the majority of cases). Spread to previously unaffected muscles is rare after the 4-7 year 'active' period. It will be seen that the relative incidence of involvement of muscles at some time during the course of a large series of cases follows closely the probability that these muscles will be the first to show myasthenic signs (Simpson, 1960a). The distribution in this series closely resembles those of Kennedy and Moersch (1937) and Osserman (1958).

The extraocular muscles and levatores palpebrarum are most frequently involved being affected at some time in more than 90% of cases. Transient ptosis or diplopia are by far the most frequent presenting symptoms (Fig. 3,6). Unlike neurogenic disease causing these symptoms the paresis of extraocular muscles or of a levator palpebrae is usually associated with weakness of orbicularis oculi on one or both sides.

The/

The next most commonly affected muscles are the flexors and extensors of the neck, the shoulder girdle muscles and hip flexors in that order, closely followed by the muscles for facial expression (Fig. 3,7), mastication, swallowing and speech. There is a strong tendency for the proximal muscles of the limbs to be more severely affected than the distal, a distribution more characteristic of a myopathy than of a neuropathy. The upper limbs are more often involved than the lower and indeed the average patient is unaware of leg weakness until this is elicited by clinical examination. In the upper limbs the extensor muscles are more severely affected than the flexors. In the lower limbs, on the contrary, the flexors are more often affected than the extensors and weakness is often confined to the hip flexors.

The erector spinae group is frequently involved but other trunk muscles usually escape in the milder cases. Respiratory and abdominal muscles are, fortunately, usually only involved in the most severe cases though they may sometimes be among the earliest affected. One example of a case presenting as severe inspiratory dyspnoea of sudden onset is described in Chapter 2 (Case MN382).

Symptoms and signs:

Symptoms are usually confined to the results of weakness of muscles which are 'fatigued' by normal everyday use or by a particular movement required by the patient's work or by a daily activity such as typing or playing the piano (Cases NH33833, NH62026, MN8090). This may lead to a wrong diagnosis of a craft palsy or cramp (Simpson, 1964b). Systematic examination may reveal unsuspected weakness or fatiguability of other muscles, but examination must be thorough/

thorough and must include contraction maintained against resistance for an adequate period. This point is stressed because failure to observe it may account for the discrepancy between this series and others in the literature regarding the proportion of cases with myasthenia confined to the ocular muscles. Many patients referred to me as cases of 'pure ocular myasthenia' were shown to have involvement of othermuscles when tested to fatigue, usually of neck flexion and abduction of the shoulders (Simpson, 1960a). On the other hand, many experienced physicians refuse to diagnose myasthenia gravis in the absence of ocular or bulbar symptoms. Fig. 3,5 confirms that there is statistical justification for this point of view, but there is no doubt that severe myasthenia may spare these muscles and present in unusual ways.

Ptosis may be unilateral or bilateral (Fig. 3,6). It commonly changes from one eyelid to the other without apparent cause. Ptosis may be brought on by bright sunlight or by looking fixedly at an object above eye level. This manoeuvre provides a useful diagnostic test (Fig. 2,4) (Chapter 17). It is equally often precipitated by emotional disturbance such as the entry into a crowded room of a patient lacking self-confidence (Simpson, 1964b).

Double vision may also be induced by embarrassment as well as by directing the gaze as in reading. The two images may separate steadily or, very characteristically, one image may appear to 'slip' suddenly (Simpson, 1960a). The unusual and variable nature of the diplopia may cause diagnostic difficulty since analysis will show that some but not all muscles supplied by one or more of the III, IV or/

or VIth cranial nerve on one or both sides is weak. This very fact should immediately make the ophthalmologist think of myasthenia gravis and suspicion is increased if there is also ptosis and weakness of orbicularis oculi. The separation of the visual images increases if the patient's gaze is fixed on an object at the periphery of the visual field and one or both eyes may be seen to drift back towards the primary position of gaze. Sometimes this is corrected by an extra voluntary effort. This causes a coarse nystagmus which may be monocular or binocular. The most severely affected muscles are the elevators and abductors of the eyeballs, but commonly all extraocular muscles are affected. There may be severe strabismus but more often the eyes are in the primary position with only 5-10° of voluntary movement in each direction.

I have never personally seen convincing evidence of 'fatiguability' of the pupil reflexes but it was recorded in the earlier case records of Cases MH 5232 and has been described previously by Markeloff (1912). Fatigue of visual accomodation may be more common (Fontaine, 1952; Rabinowitch and Vengrjenovsky, 1935). Francois et al (1955) consider that there is no definite evidence of pupillary abnormalities in myasthenia gravis.

Weakness of the muscles of the face may not be noticed at first by the patient but in 10 cases of the present series it was sufficiently severe to be diagnosed as Bell's palsy until the further course revealed its true nature. The correct diagnosis may be suggested by some anomalous features.

Case MN8088. This young woman was referred as a case of Bell's palsy of the right side of the face but remarked/

remarked that soap entered her left eye. The right lower face was weak but the left palpebral fissure was the larger and closure of both eyes was slightly weak. Further examination showed fatiguability of neck flexion and of both deltoid muscles.

The patient may not be aware of facial weakness but friends notice that the smile is distorted into a vertical 'snarl' (Figs. 3, 2 & 3, 7). Whistling may be impossible and women find difficulty in applying lipstick because of failure to pout the lips and to roll them in the customary manner.

Weakness of the masseters is common but may only be noticeable when chewing tough meat. It should always be tested for by asking the patient to hold his jaw open and closed against resistance for at least 30 seconds. Weakness may be so great that the patient may be forced to sit with a hand supporting her jaw, especially if the posterior nuchal muscles are also weak. The posture is so typical as to suggest myasthenia gravis when seen to be habitual (Figs 5, 1 & 9, 2).

Involvement of the striated muscle of the pharynx leads to dysphagia. Swallowing may be normal at the beginning of a meal but becomes impossible after a few mouthfuls. If the tongue is affected there is progressive thickening of speech, and if laryngeal and respiratory muscles are affected there is characteristic fading of the voice after speaking for a short time.

Weakness of the limb muscles may, surprisingly, be ignored by the patient until it becomes clamant. Quite commonly inspection reveals unsuspected weakness, but only if the patient is exhorted to maintain muscular contraction against/

against resistance for a sufficiently lengthy period or if he makes repeated maximal contractions for the same period. For instance women often notice fatiguability of the deltoid muscles as they are forced to stop for a rest when fixing their hair or doing work above shoulder level such as hanging out clothes on a line. If a patient with these symptoms is asked to hold the arms outstretched they gradually sag in less than a minute. A coarse tremor may develop (Fig. 3,1). The arms are dropped for a second then raised again immediately, only to be dropped once more. The cycle becomes shorter and shorter until further arm-raising is impossible. The sudden drop of the arms and the renewed effort has the appearance, to the unaccustomed eye, of a hysterical phenomenon. It is a genuine paresis and the prompt restoration is due to post-tetanic facilitation, (Chapter 15).

Weakness of the triceps may not be evident to a patient unless his work requires its use as in sawing, scrubbing or pushing a load. It is, in fact, one of the commonest muscles to undergo permanent 'myopathic' change yet the patient is often unaware of it (NH980, NH9174, NH9175, NH61431, NH62038). Weakness of the muscles of the forearm and hand cause drop-wrist and weakness of the grip. The patient, having started a task with normal strength, unexpectedly drops whatever he is holding. It will be observed from Fig. 3,5 that the forearm and hand muscles are spared in more than half of the cases. This is an important fact to remember since many conventional ergographic or electromyographic tests utilise these muscles.

The most commonly affected muscles of the lower limbs/

limbs are the ilio-psoas and quadriceps. The patient may only notice difficulty when making a high step as on entering a bus but eventually begins to tire on stairs, being unable to complete the ascent. Some patients complained of sudden dropping due to weakness of the legs without warning fatigue. A useful method of testing flexion and adduction of the thighs is to ask the patient to sit on the edge of a table and then to cross each leg over the other in turn for one minute or until the sequence is terminated by weakness.

In very severe cases with involvement of the pelvic musculature there may be stress incontinence of the bowel or bladder (NH3533, NH61453, MN5401). This is due to weakness of the external sphincters but smooth muscle is never affected.

Reflexes:

Tendon reflexes are usually present despite statements to the contrary in the majority of textbooks. In fact they are usually brisk and may even be clonic (Campbell and Bramwell, 1900; Simpson, 1960a). The observation has been made previously by Shaw (1890) and Goldflam (1893). If a tendon reflex is elicited repetitively the jerk may decrease progressively until it disappears. Absence of a single tendon jerk may be an indication of myopathic change. It may occur quite early in the history of the disease but is usually a late manifestation. Persistent absence of many reflexes should suggest that the weakness is due to carcinomatous myasthenia rather than myasthenia gravis (Chapter 9). The plantar reflexes are usually physiological in uncomplicated myasthenia gravis.

Severely ill patients often produce excessive quantities/

quantities of frothy secretion in their mouth. It's source is uncertain. When it is associated with the use of neostigmine or similar drugs it is often salivary in origin, but thick glairy mucoid secretion was reported many years before the use of anticholinesterase drugs (Shaw, 1890). It is sometimes the cause of death by asphyxiation and at post mortem examination it sometimes appears to have originated from the bronchial mucous glands.

Excessive sweating was also noted by many patients in the present series even before they started treatment. It is possible that some of these patients had unrecognised thyrotoxicosis but I have no evidence on this point (Cases NH5232, NH11102, NH23458, NH33151, NH33710, NH43312, NH59496, NH61437, NH61502). It is interesting to note that 4 of these 9 cases had a thymic tumour.

CHAPTER 4.

ASSOCIATED NEUROLOGICAL DISORDERS.

When this study was commenced I accepted the conventional idea that myasthenia gravis was due to a defect of neuromuscular transmission. Nevertheless, in accordance with the policy of recording without prejudice all symptoms described by the patients examined, the following information was noted.

Pain:

Pain in and around the eyes, the back of the neck and the shoulders was commonly reported. It was aching in type. A few patients mentioned similar pain in other muscles after an attempt to prolong a weakening contraction. This suggests that the pain is associated with the extra effort required to maintain posture. Some patients also described pain in the shoulder girdle at the onset of the illness before weakness was noticeable. From their descriptions it appeared to be similar in type to that which is often found in polymyositis.

Cases GK/MU, NH1671, NH20760, NH47693, NH58369 and MN382 described brief attacks of substernal pain, especially while stooping. The cause of this is unknown. None of them had a thymoma and the pain did not appear to be of myocardial or pericardial origin. It was sometimes associated with palpitations. Pain of this type is mentioned without comment by Hyland (1936) and Russell (1953).

Paraesthesia and anaesthesia:

A sensation of 'stiffness' of affected muscles is more common than pain. This is not uncommon in motor disorders/

disorders owing to the lack of a suitable terminology for the layman to describe the sensations experienced when a limb is weak. In this context 'numbness' quite often implies inability to move the part. Acroparaesthesia due to Raynaud's phenomenon was also found (Chapter 7).

Cases GK/ML, NH/EC/LM, NH/PS/JF, NH40820, MN105, MN382, MN2257, MN3126, MN4275, MN5095, MN5409, MN6792 and MN7720 all mentioned transient paraesthesiae of the hands or thighs. These could be accounted for by traction or pressure on peripheral nerves or by unrelated disorders such as cervical spondylosis. Some may have been of the same nature as the paraesthesia which is sometimes noted by patients with muscular dystrophy who have to lie for long periods in bed without being able to change position. Others may have been associated with hyperventilation. Nevertheless when all these causes of abnormal sensations were excluded there remained a small number of cases with unexplained paraesthesia or actual sensory loss. Before describing these some disorders of hearing will be described. Though not generally recognised, these can be accounted for in terms of a mechanical disorder due to muscular weakness.

Case GK/MV noticed weakness of her arms while dancing in 1943. In the following year myasthenia gravis became generalised. When dysphagia developed she became deaf and this fluctuated in severity.

Case NH33122 became deaf at the same time as she experienced difficulty in chewing when aged 24. This was shown to be due to myasthenia gravis. Tuning fork tests were thought to indicate perceptive deafness but she stated that her hearing also improved with neostigmine.

Case/

Case MN2257 felt that her ears were blocked and that she could blow them out when she was fatigued.
Case MN4301, a schoolmaster, has intermittent deafness when he is tired.
Cases NH/PS/IM, NH3279, MN2016, MN7778, and MN7781 had deafness which was not remittent and cannot be related to the myasthenic state.

The onset of deafness in one or both ears simultaneously with an acute myasthenic relapse and sometimes remitting with treatment may be accounted for by obstruction of the eustachian tubes associated with pharyngeal paresis. Eulenberg (1898) described a myasthenic patient with deafness for low frequency tones only. He attributed this to paresis of the tensor tympani muscles. The following case appears to be similar though the diagnosis of myasthenia gravis has not been fully substantiated.

Case MN4588. This patient was described by Rostowski and McHarg (1953) as a case of Amyotrophic Lateral Sclerosis complicated by progressive lipodystrophy. She had been admitted to the Royal Edinburgh Hospital for Mental and Nervous Disorders on 26/11/48 at the age of 24 years with a complaint of deafness, poor eyesight and weakness of the hands which caused her to drop things. In addition, she described some difficulty with speech, an inability to wrinkle her forehead and a general weakness and tiredness with feelings of discomfort across the chest, in the neck and in the lumbar region. Deafness and 'tiredness' had both started when she was 13. 'Sometimes' according to Rostowski and McHarg, 'she would hear certain/

certain voices - especially high pitched voices - better than others'. Her hearing was changeable, being better at certain times than at others. Sometimes she said she could hear the birds singing. It was also thought that she could hear better against a background of noise.

Because of the fluctuating nature of the deafness and the paucity of objective findings the consultant otologist at first considered that deafness was hysterical but in 1947 audiometry showed an almost complete deafness with retention of only a few of the high notes. (This is the converse of the usual finding in nerve deafness). Deafness, and later blindness, were considered hysterical, but the development of muscle atrophy of limbs and tongue was evidence of organic disease (confirmed by an illustration). Her legs became completely paralysed and loss of body fat was attributed to 'lipodystrophy'. Though plantar reflexes were normal, the wasting associated with brisk reflexes and 'fibrillary twitching' of the forehead, tongue and hand muscles which developed after atrophy was already severe were considered to indicate a diagnosis of 'atypical amyotrophic lateral sclerosis' though the duration of illness (11 years) and the partial recovery before discharge from hospital must throw doubt on that diagnosis.

She remained extremely tired and weighed only 6st. from 1949 to 1951 but gradually regained strength. After influenza in 1958 she again became very weak but recovered again so that when I saw her in March 1960 all muscles were powerful except the wasted hand muscles and the right facial muscles. Reflexes were normal and conduction velocity of the left ulnar nerve was within normal limits. A study of her earlier case record revealed/

revealed that on the day of admission 'she got up in the morning, packed her suitcase, stood in the bus, carried her own cases and discussed details including her sweet ration, but her voice was 'going and going' and she was getting down in spirits by the time she arrived'. The tongue was wasted but not fasciculating and she stated that she had not noticed fasciculation in the 26 years of her illness.

The history is most suggestive of myasthenia gravis. Her condition in 1960 was characteristic of the 'burned out' type ('myasthenic myopathy'). At this stage neostigmine responsiveness is lost (Chapter 18) so the lack of response found in 1960 does not controvert that diagnosis. Unfortunately it does leave an element of doubt regarding the true diagnosis.

The first two cases described by Erb (1879) in his classical paper on myasthenia gravis complained of hyperacusis and he attributed this to paresis of the stapedius muscle of the middle ears. Giddiness and tinnitus are frequently mentioned in early case records (Campbell and Bramwell, 1900) and auditory, visual and other sensory disturbances are referred to by Keschner and Strauss (1927). Harvey (1948) found sensory symptoms in 15% of his cases. In the trigeminal area, tingling of the face, lips and tongue or unilateral sensory loss of the face with diminished corneal reflexes have been described by Harvey (1948), Russell (1953) and Alajouanine et al (1957). Transitory bilateral anosmia followed by parosmia was recorded by Berkeley (1897) and Alajouanine et al (1957). Loss of taste sensation occurred in the cases reported by Kojewnikov (1896) and Symonds (1922).

Case/

Case MN2986 lost her sense of smell and taste completely for three or four weeks. This was the onset of her myasthenic illness and these symptoms could have been due to the respiratory infection which precipitated it. Case MN5625 had transient numbness of the tongue. (It is necessary to appreciate that some patients cannot clearly distinguish between 'numbness' due to loss of sensation and the feeling associated with inability to contract a muscle).

Case MN5095 developed myasthenia gravis in 1948. Radiology revealed a thymoma which was not completely removed at thymectomy because of operative difficulties and so radiotherapy was given. From 1948 to 1960 the myasthenic symptoms were quite well controlled by neostigmine though the dose was raised progressively to 600mg. orally in 24 hours. From 1958 to 1960 speech and swallowing became difficult. During the same period he complained of tingling feelings and numbness in his legs and in the middle, ring and little fingers of both hands, a sensation like water in his left ear, and loss of taste sensation. It was confirmed by examination that he could not taste with any part of his tongue. The tongue was smooth (Fig. 4.2) and he later developed megaloblastic anaemia which is further described in Chapter 7. His death from 'cholinergic crisis' is also recounted in Chapter 19. In view of the possibility that he had pernicious anaemia it is unfortunate that the spinal cord was not examined at autopsy.

Symonds (1922) described two cases of myasthenia gravis in a clinical lecture. One of these also had anosmia and/

and the other had pharyngeal anaesthesia. Even allowing for the possible hysterical nature of the latter sign, it is interesting to note that in 1922, before the neuromuscular theory of myasthenia was established, Symonds wrote: 'I think there are some arguments which favour the theory that the disease is nervous in origin. One is the not uncommon occurence of sensory symptoms in the form of pains or numbness'. Buzzard (1905) had already objected to the summary dismissal of sensory symptoms by Campbell and Bramwell (1900) and it seems clear that it was well recognised that sensory disturbances were occasionally present until the attention of physicians was directed exclusively to the transmission at the neuromuscular junction. One of the cases described by Buzzard (1905) had loss of pain sensation in the legs, ulnar border of the upper limbs, cuirasse region of the chest and round the nose. The history suggests a diagnosis of tabes dorsalis but no evidence of syphilis was found at post mortem examination. There are surprising resemblances between this case and MN5095 described above. Another of Buzzard's cases had a localised area of anaesthesia and after death was found to have 'lymphorrhages' in the appropriate dorsal root ganglion.

Anaesthesia of the pharynx and larynx was reported by Wernicke (1893). Schwab and Viets (1958) report similar symptoms in a case of 'subsiding peripheral neuritis' in whom a diagnosis of myasthenia gravis had been made but later rejected.

Case MN3126, a 32 year old University Lecturer, had a sore throat in December, 1957. It cleared up with an oral antibiotic but headache persisted for 2 weeks.

Three/

Three weeks after pharyngitis he become aware of weakness of both legs. Eventually he had to lecture from a chair. There was, at the same time, considerable tingling paraesthesia of the soles of the feet, finger tips and occasionally the lips. It did not spread. The legs ached with use but not at rest and there was no calf tenderness. His right arm began to fatigue when writing on a blackboard and then substernal pain on effort was noted.

The pupils were unequal but reactive. Pin-prick sensation was diminished at the finger tips. Tendon jerks were decreased but not absent. All muscles of the upper limbs showed 'pathological fatigue' and a Harvey-Masland test was typical of myasthenia (Fig. 4.1). Nevertheless the referring physician's diagnosis of peripheral neuritis was accepted in view of the sensory changes and the finding of decreased conduction velocity of the right ulnar nerve. The conduction time from wrist to abductor digiti minimi (by the method of Simpson, 1956b) was 6.5 msec. It should not be more than 4-5msec.

In 1959 tingling of the finger tips and weakness recurred for a short period and again in 1961. He had always refused to take pyridostigmine until then. It probably improved his condition but he always attributed improvement to some other factor. In 1961 nerve conduction velocity was normal.

The possibility of a myasthenic reaction associated with polyneuritis will be discussed in Chapter 9 . In retrospect it now seems more likely that this is a case of true myasthenia gravis with prominent sensory symptoms.

Case/

Case NH32170 had a transient Brown-Séquard syndrome.
Case NH20468 had a cauda equina syndrome at one stage.

It is most likely that the two latter cases are examples of coincidental disease. Nevertheless it is apparent that sensory disturbances do occur in patients with myasthenia gravis and were frequently reported before the disease was 'explained' as a disorder of neuromuscular transmission. Some of the sensory symptoms can be accounted for on mechanical grounds but it is difficult to explain them all in this way and it is necessary to consider the possibility of occasional involvement of sensory neurones or of sensory end-organs.

'Epilepsy' and psychiatric disorders:

Case NN4636 had a miscarriage in 1953 when aged 45. A few months later she developed thyrotoxicosis which subsided after 3 months treatment with thiouracil. It has not recurred but she still has antithyroid antibodies in her blood (Table13,1)and there are supraorbital pads indicating previous exophthalmos (Fig. 3,2). In 1954 she began to have ptosis and generalised fatigue due to myasthenia gravis. It was well controlled by neostigmine and she had a remission for more than a year in 1957-58. In 1959 there was a slight recurrence which subsided without treatment. In March 1960 she had the first of a series of attacks in which she suddenly lost consciousness without warning, hurting her head in the fall. She was unconscious for 4-5 minutes and was not incontinent. On admission to Maryfield Hospital, Dundee, lumbar puncture yielded xanthochromic cerebrospinal fluid but further investigation in the Department of Neurosurgery, Edinburgh, showed no cause for this and it was attributed to the head/

head injury. On transfer to my care she showed signs of generalised myasthenia in the later part of the day. This was fully controlled by 30mg. of pyridostigmine twice daily.

In February, 1962 vaccination against smallpox was followed by increasing weakness but she continued to take an inadequate dose as she would never accept the diagnosis. In October 1962 while on holiday she suddenly felt herself rotating; her face, hands and feet tingled; she gave a cry and fell to the ground unconscious with rigid muscles. Later the same evening a similar attack occurred while she was in bed. There can be no question of sudden loss of power of her legs, postural syncope, or overdosage with anticholinesterase drugs. Radiology of skull and chest, and EEG records taken during waking and sleeping periods were normal. Her blood did not contain L.E. cells. The 'fits' remain unexplained.

Case MN5401 developed myasthenia gravis when aged 63. The initial symptom was inability to hold up her head, followed in 2-3 weeks by difficulty in chewing, swallowing and 'blurring' of speech, which were rapidly relieved by neostigmine. During the first two months of the illness she had two 'blackouts'. The second of these occurred in hospital and was followed by 'fighting and shouting' for 5 minutes. The greatest dose of pyridostigmine prescribed at that time was 360mg. (6 tablets) in one day and she was also having belladonna. Muscarinic symptoms later developed on a dose of 600-720mg. per day. A single EEG recording was normal and the 'fits' never recurred. She died two years later and no autopsy was obtained.

Case/

Case MN5652. This 29 year old electrician had always been very active. His hobby was long distance cycling. Ten years earlier he was knocked out in a road accident. When aged 16 he had exophthalmic goitre. When first seen in 1960 his eyes were very prominent (Fig. 5,1) but there were no signs of thyrotoxicosis. In March 1960 he fell from a staging, striking his chin. It could not be ascertained whether this was due to a 'blackout' but from that time on he had frequent momentary lapses of consciousness. He had to give up cycling as he was falling so often and felt 'sleepy'. He was certainly unconscious in some of these. He became so forgetful that he had to be removed to a position of less responsibility at his work and his father became concerned at an apparent intellectual deterioration. A suggested diagnosis of post-influenzal depression seemed reasonable.

On admission to the Northern General Hospital in June 1961 he was unable to remember much about the previous year. Brief spells of automatism were witnessed. There was slight weakness of the right thigh muscles, left internal strabismus and nystagmus to both sides but the significance of these findings was not appreciated. Some EEG recordings were normal, others showed occasional bursts of 7c/s theta waves bifrontally or in the left temporal region. Sphenoidal recording and activation with barbiturates did not give further evidence so a recording was made while bemegride 150mg. was slowly injected intravenously. This evoked bilaterally synchronous sharp and slow wave complexes and runs of 4-5c/s waves with fronto-central phase reversal/

reversal. The record was compatible with epilepsy but did not suggest a focal origin for the discharges. In a later (unactivated) recording some sharp waves appeared in leads from the left temporal region, especially during overbreathing, and taking the whole series of recordings into consideration it appeared that there was a discharging focus in that region of the brain.

Fits witnessed in the ward (and recorded by cinematography) were compatible with a temporal lobe origin. He suddenly stopped speaking, stared and sometimes made irregular twitching movements of both hands. Thick glairy mucus streamed from the mouth. He did not fall and was probably never incontinent. The attack lasted for 3 minutes and recovery was sudden.

Air encephalography did not reveal any gross cerebral abnormality and the cerebrospinal fluid was normal so the fits were treated with anticonvulsant drugs. Since 1961 he has had hydantoinates, phenobarbitone and primidone in different combinations but continues to have 2-4 attacks every week.

In May 1962 the attacks became associated with brief 'choking'. A few days later he complained of pain in his back, difficulty in controlling his head, and severe weakness of his legs, especially in the evening. This was followed in another week by upper limb weakness, ptosis of the right eyelid, double vision and loss of voice when speaking. Examination at that time showed typical, very severe, generalised myasthenia gravis, confirmed by electromyography and by/

by an edrophonium test. In retrospect it seems possible that his inability to cycle was an early symptom of myasthenia.

Despite increasing dosage of neostigmine he became extremely weak so thymectomy was carried out by Mr. Andrew Logan on 3/7/62. The thymus was unusually vascular but was otherwise typical of myasthenia gravis. The post-operative course was unusually difficult. He had a myasthenic crisis three days after operation but by the tenth day he was in balance and on following days began to show signs of overdosage. His condition remained grave for many months, swinging from one extreme (myasthenic crisis) to the other (cholinergic crisis) because a severe neostigmine-resistant weakness made it difficult to assess the required dosage. Tracheostomy was carried out on 21/9/62 and he was ventilated by a positive-pressure respirator for most of the following thirteen months. Towards the end of this period he became emaciated and food and mucus were entering the lungs despite constant vigilance in the management of the cuffed-tracheostomy tube. A jejunostomy was made and he was fed with casein hydrolysate, milk and eggs by this route. (Fig. 18,5).

Meanwhile minor attacks had persisted, apparently unrelated to the therapeutic state. In September 1962 he had a grand mal seizure. He was disorientated for many weeks. The muscles barely responded to anticholinesterase drugs (supplemented with ephedrine, potassium, prednisolone, anabolic steroids and spironolactone at different times). It seemed certain that/

that he was going to die.

On 2/10/63 (fifteen months after thymectomy) he became very agitated, pulled out the tracheostomy and jejunostomy tubes and seemed to be in a paranoid state. From that day he began to improve rapidly. A response to neostigmine reappeared, the muscles became more bulky, subcutaneous fat reappeared and his mental state rapidly returned to normal. In one month he was able to spend weekends at home and in two months was discharged home. Now, six months later, he is overweight, powerful but with myasthenic 'fatigue' which is well controlled on 315mg. (21 tablets) of neostigmine daily. He still has minor fits 2-3 times each week.

This case has been described in detail to illustrate some points which will be made in other chapters such as i) the fact that myasthenic weakness may be changed to 'cholinergic' weakness without intervening normal strength (Chapter 19) ii) the post-operative remission may be delayed for 1-3 years but may then be just as satisfactory as the immediate ones (Chapter 10) iii) the onset of mental symptoms and fits appeared to coincide with the first myasthenic symptoms. This, and the frequent opportunity for observation under controlled conditions, made it quite certain that the fits were not due to asphyxia or to overdosage with drugs.

Case NH/PS/AJ had 4 attacks of unconsciousness between 1917 and 1924. He developed myasthenia gravis in 1936.

Case NH/EC/GT had 'blank spells' on several occasions.

Case NH/MC/AW had myasthenia from 1938 to 1955 (when last seen). From 1949 she had occasional brief sensations of being 'far away' during which she was unable to speak.

Case/

Case NH12374 had fits from age 1-11. Myasthenia gravis started when he was 35 and persisted until death at 51 years.

Overdosage of anticholinesterase drugs or severe hypoxia accounted for the fits which occurred in the first few days after operation and which caused the death of three patients (NH18338, MN4603 and MN7788). In the other cases the nature of the seizures remains unexplained. None of them had lupus erythematosus cells in the blood and there is, at present, no evidence of gross cerebral pathology. In two cases there were unexpected findings in the brain at post mortem.

Case MN2257 had severe myasthenia gravis from 1950 until her death in 1957 at the age of 51. In 1951 after a spell of hard work she became acutely dyspnoeic and everything went black. She fell forward in her car and was probably unconscious for 5-10 minutes. She had two similar attacks in 1952 and 1953 but although she hadbeen extremely 'tired' since 1950 it was not until 1955 that myasthenia gravis was diagnosed. Even under treatment she sometimes fell for no apparent reason but it is not certain that she lost consciousness. She often complained of burning pain substernally and in her throat, unrelated to exertion. There was a family history of diabetes.

She died in 1957. On reviewing the case notes it now seems probable that death was due to overdosage with neostigmine. Autopsy revealed a thymoma (which was not visible on radiographs) and abnormality of the thyroid gland resembling lymphadenoid goitre (further described in Chapter 5). The spleen was slightly but definitely enlarged/

enlarged (220gm) and contained two whitish nodules showing lymphoid and reticular hyperplasia. There was no evidence of myocardial disease. The white matter of one convolution of the cerebral cortex which was examined microscopically showed slight microglial hyperplasia (Dr. A.F.J. Maloney).

Case MN3231 died at the age of 48 after having had myasthenia gravis for 15 years. The thymus was removed thirteen years previously. Death was due to cholinergic crisis (further described in Chapter 19). She lost consciousness just before death but had not done so on any other occasion so far as is known. There was occasional retrosternal tightness.

At autopsy the myocardium showed brown atrophy and there was minimal atheroma of the coronary arteries. A few argyrophilic plaques which were morphologically identical to those found in Alzheimer's Disease were found scattered sparsely and irregularly in the cortex of the frontal and temporal lobes of the brain. There was no neuroglial reaction to their presence and apparently no loss of neurones, and no neurofibrillary tangles were identified (Dr. A.F.J. Maloney).

The significance of the latter finding is unknown. In the former case it is possible that the microglial hyperplasia was due to cerebral anoxia. It does not seem likely that this could account for cases such as MN5652 where epileptic fits coincided with or preceded the onset of myasthenia gravis.

Mynsthenic patients tend to be nervous and excitable, the personality resembling that associated with thyrotoxicosis. It is not surprising that fear of choking should cause panic or/

or hysterical reactions (NH62045, MN3231), and depression with fear of dying during sleep (NH33170, NH36773) is fully understandable. In addition to this, true psychotic disorders were recorded in eight cases (NH/EC/JH, NH18338, NH40934, NH57049, NH62045, MN3231, MN5652, MN7776). It is possible that these neuropsychiatric abnormalities are coincidental but it must be recorded that they feature in three large series (Osserman, 1958; Simpson, 1960a; Storm-Mathisen, 1961). These series are compared in Table 7,1 of Chapter 7. The coincidence of myasthenia gravis and 'epilepsy' has been noted before. Fearnsides (1915) and Pages and Passouant (1953) each reported single cases but Hoefer et al (1958) recorded eight patients in a series of 180 cases of myasthenia gravis who had convulsive seizures and one additional patient who had syncopal attacks without convulsive movements. In most of their cases epilepsy had been present for several years before the onset of myasthenic symptoms. All were of the grand mal type associated in one with psychomotor attacks and in another with psychomotor and focal motor seizures. Only one of the eight cases had an EEG pattern permitting a diagnosis of epilepsy. It was recorded from a child aged 9 who was said to have had myasthenia gravis since birth with slow motor development. Grand mal epilepsy first appeared at the age of 4 years. This case appears to be of the congenital type described in Chapter 8 which may differ from true myasthenia gravis. Hoefer and his colleagues are probably justified in their conclusion that the incidence of epilepsy in this small number of myasthenic patients is greater than would be expected in a random sample of the population of New York but it must be stated that one patient had a family history of seizures, a second had a head injury at/

at the age of 3 years with loss of consciousness of uncertain duration, and a third had recovered from apparently uncomplicated measles when the seizures started. Autopsies were performed in three of the patients who died. The brain was not examined in one and no gross abnormality was found in the other two. Roger and Darcourt (1958) report a case of myasthenia with thymic tumour who had repeated epileptic attacks and confusional states.

CHAPTER 5.

ENDOCRINOLOGY.

Thyroid:

A relationship between myasthenia gravis and disorders of the thyroid gland is beyond doubt. The association with thyrotoxicosis was first reported by Rennie (1908) who considered that it was coincidental. The literature is summarised by Millikan and Haines (1953) and by Osserman (1958). Most of this literature has concentrated on the possibility that thyrotoxicosis may be causally related to myasthenia gravis. Cohen and King (1932) drew attention to some similarities existing between the two diseases, notably hypertrophy of lymphatic tissue, occasional lymphocytosis, occasional glycosuria, and the presence of lymphorrhages in muscle tissue.

Thyrotoxicosis:

On the basis of a number of patients (Thorner, 1939; McEachern and Parnell, 1948; Maclean and Wilson, 1954) it has been suggested that there is a 'see-saw relationship' between the two diseases, myasthenia increasing as thyrotoxicosis comes under control and vice versa. No such relationship was found by Bartels and Kingsley (1949) or by Levy et al (1951) and indeed some physicians have taken the opposite point of view, ordering thyroidectomy for their patients in the hope of favourably influencing the myasthenia gravis. The first report on thymectomy performed by Sauerbruch for myasthenia gravis (Schumacher and Roth, 1913) describes marked improvement of myasthenia after thymectomy but an associated exophthalmic goitre was not affected. They made the interesting observation that lymphocytosis present before operation returned to normal after/

after it (see Chapter 12).

Millikan and Haines (1953) described 25 cases of hyperthyroidism and myasthenia gravis seen at the Mayo Clinic. They found that the temporal relationship was quite irregular. In 48 per cent of cases the hyperthyroidism came before or simultaneously with the myasthenia gravis (12% more than five years previously). They occurred virtually simultaneously in 20% and myasthenia gravis preceded thyrotoxicosis in 32%. They were unable to confirm a 'see-saw' relationship of 'physiologic antagonism' between the two diseases and concluded that they were separate diseases which were associated in some unknown manner. My experience has been similar. The following representative cases illustrate thyrotoxicosis preceding myasthenia (MN5652, MN4636), preceding myasthenia then recurring as myasthenia subsides (MN4934), occurring pari passu with myasthenia (MN7543) and following resolution of myasthenia (MN7781).

Case MN5652. Had exophthalmic goitre at the age of 16 from which he made a full recovery. His eyes remained prominent and lid-lag could often be demonstrated. Myasthenia gravis started at the age of 29. A description of this will be found in Chapter 4 (Fig. 5,). At that time his serum contained 6.0ugm. of protein-bound iodine (normal). Complement fixing antibody against thyroid was present in his blood to a titre of 1/16.

Case MN4636 is also described in Chapter 4. She had transient thyrotoxicosis at the age of 45 and did not develop myasthenia gravis until 9 years later. At that time the only clinical evidence of the former disease was slight palpable enlargement of the thyroid gland/

gland and prominent supraorbital pads (Fig. 5,2). Von Graefe's sign was occasionally present. At the time of the photograph her serum level of protein-bound iodine was 5.1ug/100ml. Complement-fixing antibodies against thyroid were present in her blood to a titre of 1/16.

These two cases are representative of many in which thyrotoxicosis preceded myasthenia gravis by a number of years.

Case MN4934. In 1956, when aged 26, she was investigated for thyrotoxicosis on account of loss of weight and tremor but there was no goitre, exophthalmos or perspiration. There was no family history of thyroid disease. Her mother had glycosuria associated with obesity and a maternal uncle died of diabetes mellitus.

Myasthenia gravis began in the early months of 1959 without obvious cause and became quite severe though fully responsive to pyridostigmine (240-360mg. daily). She tended to retract her eyelids when excited and her neck was full but there was no evidence of genuine thyrotoxicosis (Fig. 5,3). Thymectomy was performed in July 1961 with immediate benefit. The dose of pyridostigmine was progressively reduced to 120mg. daily in the first year and 60mg/day in the second year.

In October 1962 her eyes became very prominent. In January 1963 after disappointing news she began to lose weight and developed a fine tremor and moist skin; the goitre increased in size (Fig. 5,3) and tachycardia with frequent extrasystoles was found. The serum level of/

of protein-bound iodine at that time was greater than 14µg/100ml. and antibodies against thyroid and gastric mucosa were present in her blood (see Table 13,). Thyrotoxicosis was controlled by carbimazole which she still requires. She feels very tired at times but there is no myasthenic weakness and she is not helped by taking pyridostigmine. This was discontinued in February 1964.

Case MN7543 noticed occasional palpitations from the age of 33. When she was 36 she had double vision in bright sunlight and noticed tiring of her arms when dressing her hair. There was then progressive spread of myasthenia gravis though this was not diagnosed until 2 years later. When she was 38 she also developed a Raynaud syndrome. She had never had a goitre but a maternal aunt had had myxoedema for 10 years.

In the Northern General Hospital in the fourth year of myasthenia she was thin, deeply suntanned and excitable. There was no goitre or specific evidence of thyrotoxicosis. A high titre of antinuclear factor (A.N.F.) was present in her blood but no antithyroid substances. A radioiodine test of thyroid function gave a 'T' index of 22.5 and Kt ('thyroid clearance') of 16.0, figures well within the hyperthyroid range.

Case MN7781 (G.W.I.- M733/52). In December, 1951 this 30 year old woman started to have myasthenia gravis of the extraocular muscles and face (Fig. 5,4). There was no personal or family history of thyrotoxicosis. Her mother had rheumatoid arthritis.

I treated her with ACTH and cortisone which seemed to improve the myasthenic weakness for a few months but then/

then her legs became weak. At the same time she became deaf in the left ear (conductive type) and she had night sweats. She was excitable and rather aggressive. Myasthenia responded well to neostigmine and I did not see her again as I left Glasgow.

In 1959 the myasthenia relapsed and she was readmitted to Glasgow Western Infirmary under the care of Professor E.J. Wayne. At that time she had slight exophthalmos and moderate iron deficiency anaemia. A radioiodine test showed a gland uptake of 72% in 4 hours, 74% in 48 hours with a TPI of 0.75, results suggesting early thyrotoxicosis. No thyroid antibodies were found in her blood (Dr. J. Anderson). In the next few months symptoms and signs of thyrotoxicosis increased and a goitre became apparent (Fig. 5,4). The basal metabolic rate was now +50% and the serum protein-bound iodine (PBI^{127}) was 7.7µg/100ml. A thyroid suppression test with thyroxine in March 1960 was negative. These findings indicate hyperthyroidism.

Professor Wayne kindly asked me to see her again in January 1960. She still had 'fatiguable' weakness of the proximal muscles of the upper limbs but a Harvey-Masland test showed a recruiting response from abductor digiti minimi.

In my experience a disorder of thyroid function has been present at one time or another in 21 % of women and 9 % of men suffering from myasthenia gravis. These figures are much higher than the incidence of 5% suggested by Millikan and Haines (1953) but their figure refers only to thyrotoxicosis. In my series other types of thyroid disorder were noted clinically or at post mortem examination/

examination (Tables 5,1-3).

i) Thyrotoxicosis.

ii) Transient goitre ± toxic symptoms.

iii) Persistent non-toxic goitre.

vi) Myxoedema.

v) Lymphadenoid goitre.

Not included in this table but probably examples of type 2 without recognised thyrotoxicosis are many patients who had a moderate degree of exophthalmos. This has been noted by previous authors (Walsh, 1957). Other cases had a thick supraorbital pad of fat which closely resembles that seen in recovered thyrotoxicosis (Simpson, 1960a) (Figs 22,32,52) Klar (1930) has previously described oedema of the lids in a similar case of myasthenia.

Case MN3912. One of these patients has a high titre of complement fixing antibody against thyroid (1/128) which would support the concept of previous thyroid disease. She also has a raised titre (1/32) of antibody against gastric mucosa. She has had iron deficiency anaemia but still has gastric acid in response to histamine and a normal level of vitamin B12 in the serum (350µµg).

Another group in whom the diagnosis of non-goitrous thyrotoxicosis must be considered is exemplified by cases NH5232, NH11102, NH23458, NH33157, NH33710, NH43312, NH59496, NH61437, NH61502. All of these patients complained of profuse sweating and weight loss and many were unusually nervous or irritable. These symptoms often preceded the use of anticholinesterase drugs so cannot be attributed to the muscarinic side-effects of treatment. They were elicited retrospectively when I examined

examined the patients at a follow-up clinic. None of them showed clinical signs of goitre at that time and none were noted in the earlier case records. Both of these groups must be suspected of having had subclinical thyrotoxicosis at some time in the past but they are excluded from the calculated incidence.

Non-toxic goitre and lymphadenoid goitre:

Attention must now be directed to the remaining cases, the non-toxic goitres and myxoedema which have been ignored in the recent past. That this is unjustified is shown by a brief review of the literature from pathologists who describe in the main non-toxic goitres, often lymphadenoid (Norris, 1936; Miller, 1940; Giardano and Haymond 1944). These authors usually considered that the changes were involutionary in a previous exophthalmic goitre. Rowland et al (1956), however, found four non-toxic nodular goitres in a post mortem series of 26 myasthenics and Ringertz (1951) found 5 abnormal thyroids in 18 autopsies. One of these was a non-toxic nodular goitre (without lymphoid infiltration), one gland (from a girl of 16) was considered to be of toxic type, and three showed patchy parenchymal atrophy with cellular disintegration associated with dense lymphoid infiltration. Two of these had lymphoid follicles in the thyroid 'giving to the picture a certain resemblance to that of lymphadenoid goitre'. Both of these patients had a thymic tumour.

The following case seems to be closely similar. The thyroid section was shown in my Honyman-Gillespie lecture and the possibility of its being Hashimoto's disease was discussed. The illustration was omitted from the published/

published version on the advice of a specialist in the subject but passing reference was made to the possibility of an association with lymphadenoid goitre (Simpson, 1960a).

Case MN2257. In 1950, at the age of 44 years, she had a series of choking attacks followed by severe tiredness and dyspnoea. In one of these attacks in 1955 she had substernal discomfort and pain in the left flank followed by tingling in the ulnar border of the left hand. Weakness increased and she had further substernal discomfort. She was admitted to Edinburgh Royal Infirmary (Dr. Halliday Groom) in May, 1956. The diagnosis of myasthenia gravis was then established but she remained very weak despite increasing dosage of neostigmine. When she was admitted to the Northern General Hospital in April, 1957 she was taking 105mg. of neostigmine and 2gr. ephedrine daily. She felt more comfortable when the dose was increased but never recovered sufficient strength to be out of bed. She was troubled with colic, diarrhoea and headache but these symptoms were controlled with atropine. At that date this was the accepted management. I would no longer increase the dose as I did then to 425mg. neostigmine and 1700mg. pyridostigmine daily (equivalent to 70 tablets of neostigmine). In retrospect it is certain that death was due to overdosage as facial twitching was noted in addition to muscarinic signs (Chapter 19).

Post mortem examination revealed a thymoma which had not been detected radiologically. The naked-eye appearance of the thyroid gland was normal but microscopy showed severe parenchymatous atrophy, some slight interstitial fibrosis and a very pronounced focal/

focal and diffuse lymphocytic infiltration. There were numerous large lymphoid follicles with active germinal centres, characteristic of 'lymphadenoid goitre' (Fig. 5,8). The spleen contained white nodules which showed lymphoid and reticular hyperplasia (Dr. A.F.J. Maloney).

Case MN2327. I saw this 19 year old girl in Glasgow Western Infirmary in May 1956 with a three month history of myasthenia gravis. Thymectomy was performed in September 1956. The initial response was good but she subsequently relapsed. When admitted to the Northern General Hospital, Edinburgh in April 1957 she was well controlled on 300mg. neostigmine daily. Her tongue showed three longitudinal furrows. There was unsustained ankle clonus. Towards the end of 1957 she relapsed and in February 1958 died suddenly of respiratory failure. Thyroid disease had not been suspected during life.

At autopsy in Law Hospital, Dr. R.I. Shaw Dunn found 24gm. of thymic tissue. The aorta was of small calibre. The thyroid gland was normal in external appearance but on microscopical examination showed a diffuse lymphocytic infiltration described as closely resembling a typical Hashimoto's struma. There was a cystic teratoma of the ovary. The spleen was distinctly enlarged (229gm) and intrapulmonary lymph nodes were slightly more prominent than usual.

Case MN5503. This female patient who had myasthenia gravis and pernicious anaemia with slight hypothyroidism is described in Chapter 7. At post mortem it was found that her thyroid gland showed changes typical of Hashimoto's/

Hashimoto's disease.

In 1963 Dr. W. Lancaster kindly referred to me a case of myasthenia gravis with clinical signs of Hashimoto's disease. A point of special interest is that the latter developed 5-7 years after thymectomy.

Case MN7390. J.McD. (male) was found to have active pulmonary tuberculosis and at the same time he developed ptosis, diplopia, dysphagia and weakness of the arms in 1943 when aged 19. Myasthenia gravis was diagnosed and treated with neostigmine until 1955 when thymectomy was carried out by Mr. Paterson Brown in Edinburgh Royal Infirmary. Neostigmine requirements were reduced from 25 to 10-15 tablets daily.

From 1960 he complained at intervals of abdominal pain, sweating and tiredness which were alleviated by regulation of the dosage of neostigmine and pyridostigmine. During one such episode he was admitted to Inverness Royal Infirmary (Dr. W. Lancaster) where it was noted that he had a diffuse goitre and pigmentation of the face (Fig. 15,1). He was complaining of tiredness and dyspnoea which were not improved by regulation of dosage and were not apparently due to reactivation of tuberculosis. He was overweight and showed no clinical evidence of thyrotoxicosis.

A radioiodine uptake test gave a TPI of 1.6 and the protein-bound iodine was 1.4mg/100ml. Serum cholesterol concentration was 200mg/100ml. Antibody titres against thyroid tissue were T.C.H. 1/2,500,000; C.F.T. 1/256; precipitin test positive within 24 hours. The zinc sulphate turbidity was 14.4 units and thymol turbidity 8.2 units. A diagnosis of Hashimoto's disease was/

was made and treatment started with l-thyroxine (0.1mg. daily) in February 1963.

He was admitted to the Neurological Unit in July 1963. The E.S.R. was 70-85mm. in the first hour (Westergren). No L.E. cells were found in his blood and antinuclear factor was not detected. Antibody titres against thyroid were estimated by Dr. W.J. Irvine as T.C.H. 1/25,000, C.F.T. 1/16. No antibodies active against gastric or liver tissues were found. Serum electrophoresis showed increased gammaglobulin, thymol turbidity was 5 units and the cephalin-cholesterol flocculation was positive. The pulmonary tuberculosis was considered to be inactive. No mediastinal tumour could be detected by radiology. Myasthenia was well controlled by pyridostigmine 60mg. t.d.s. and neostigmine 15mg. t.d.s. (alternating) and ephedrine gr.$\frac{1}{2}$ t.d.s. Persisting tiredness was considered to be caused by Hashimoto's disease.

The occurrence of Hashimoto's disease in a patient without a thymus is believed to be unique. While it was awaiting publication (Simpson, 1964a), Daly and Jackson (1964) reported another patient who had Hashimoto's disease associated with myasthenia gravis. It is possible that the combination is more frequent than hitherto realised. The finding of Ringertz (1951) already quoted that lymphadenoid change was common in the thyroid at post mortem in myasthenics is substantiated by cases in this series. Oosterhuis (1963) lists one case of 'struma lymphomatosa' in a myasthenic woman who had a thymoma and there were two cases in the series of Storm-Mathisen (1961).

Myxoedema/

Myxoedema:

Myasthenia gravis was associated with primary myxoedema in three cases reported from the Mayo Clinic (Feinberg et al, 1957). It is increasingly recognised that so-called primary myxoedema is usually attributable to Hashimoto's disease but this diagnosis was not made in these cases. Only one case of myxoedema occurred in the present series and this was attributed to the effects of radiotherapy applied to the larynx. The patient's blood contained L.E. cells (Case GK/ES, described in Chapter 7). Case 56 of Storm-Mathisen (1961) described in Chapter 7 had arthropathy and a previous history of haemolytic jaundice and may well have had an autoimmune disease.

It is important not to mistake thyrotoxic or myxoedematous myopathy for myasthenia gravis. Both may cause 'fatiguable' weakness but do not respond to anticholinesterase medication (Chapter 17).

The relationships just described invite speculation. It is submitted that chance coincidence must be dismissed. Nevertheless thyroid-function studies do not show any tendency for the majority of myasthenics to have increased thyroid function (Chapter 6). The inconsistent temporal relationships between thyrotoxicosis and myasthenia make it inconceivable that one disease can 'cause' the other. This possibility is finally demolished by the report of an athyroid patient who developed myasthenia gravis (Drachman, 1962). The special case of Hashimoto's disease will be discussed in Chapter 13, but at this point it is necessary to conclude that all types of non-malignant thyroid disease are in some way linked with/

with myasthenia gravis.

The clue to this relationship may be provided by the following observation which is believed to be original (Simpson, 1960a). In 20 cases there was a family history of goitre, toxic or simple, or of myxoedema. The affected relative was usually a sister or a female and could be on either side of the family (Table 5,4). The exact incidence is uncertain since patients have only been questioned systematically since I became aware of it at the end of 1953. Soon after this Macrae (1954) reported a myasthenic child whose mother had hyperthyroidism. Oosterhuis (1963) has recently reported that 9 of 116 patients with myasthenia gravis had a family history of thyroid disease (and 5 of these had personal evidence of thyroid disease). Its importance lies in the fact that a constitutional or genetic defect may predispose to the development of Graves' disease (Bartels, 1941). It is therefore suggested that a gene may have variable expression producing either thyroid disorder, myasthenia gravis or both (Simpson, 1960a). Quite recently it has been shown that there is also a genetic factor in the autoimmune diseases including thyroiditis. Thus the various disorders described in this section may be part of a spectrum of diseases, genetically determined but perhaps requiring an acquired precipitating factor. This genetic defect may alter immunological responses (Simpson 1960a, 1964a).

Further discussion is delayed until the rest of the evidence has been reviewed but at this point it is appropriate to suggest that a genetic control of the thyroid would be likely to act through a hypothalamo-pituitary mechanism (Chapters 13,14).

Pituitary/

Pituitary:

There is scanty evidence of a pituitary factor in myasthenia gravis though it has been claimed that pituitary extracts modify neuromuscular transmission in that disease (Torda and Wolff 1951; Kane, 1955). Personal experiences with the administration of adrenocorticotrophin (Chapter 18) indicate that the effect could be due to the thymolytic action of that hormone. This could not account for the reported improvement of myasthenia and of malignant thyrotoxic exophthalmos after irradiation of the pituitary by Zondek and Ticho (1951) but this result has never been verified.

Cases of myasthenia gravis associated with adenoma of the pituitary are reported by Tilney (1915), Dittler (1952) and Grob (1958). Torda and Wolff (1951) described eosinophilic accumulations in the pituitary. On the other hand Rowland et al (1956) found no abnormality in 22 pituitary glands of patients dying of myasthenia gravis.

In the present series the pathologist reported that the pituitary gland was unusually large at autopsy in three cases.

Case NH/HH/GB also had a large thyroid gland (histology not described).

Case MN7783 (described above) had pernicious anaemia and Hashimoto's disease.

Case MN7784 had a thymoma.

Unfortunately the pituitary glands were not examined microscopically but there is little doubt that abnormalities of the pituitary are not present in the majority/

majority of cases and, in my opnion, are unlikely to be of actiological significance. Nevertheless it must be borne in mind that the widely accepted pituitary factor in exophthalmic goitre is not associated with recognisable histological changes.

The contrary view, that pituitary-adrenal insufficiency may be responsible for myasthenia gravis, is an old idea recently revived by Kimura and Yamomoto (1954). These workers found atrophic degeneration of the anterior pituitary, marked atrophy of the adrenal cortex and hyperplasia of the thymus at autopsy of a severe case of myasthenia gravis. They suggest that an antagonism exists between the thymus and the adrenal cortex. Possible feed-back relationships between the thymus and the pituitary have been described by experimental biologists (Chapter 12). The following case is of interest in this respect.

Lactation:

Case MH61509 had a thymectomy by Mr. Geoffrey Keynes in 1949 for severe myasthenia. She had diplopia and ptosis eight years previously but generalised spread had occurred in 1948. There was a good response to operation with improved response to neostigmine so that two weeks after the operation severe muscarinic signs occurred. At the same time she began to secrete milk from both breasts and this lasted for 3 months.

Lactation associated with exophthalmic goitre (and possible Hashimoto's disease) was described by Brain (1959). He considered that his patients were suffering from an over-production of more than one pituitary hormone.

Post-thymectomy exophthalmos:

Another/

Another observation which might be interpreted as withdrawal of thymic inhibition from the pituitary is the transient eye-lid retraction which often occurs immediately after thymectomy (Chapter 18) but probably the best evidence for a pituitary factor in myasthenia gravis rests on the effects of pregnancy and of menstruation.

Pregnancy and menstruation:

Many women with myasthenia gravis are weaker at some time in the menstrual cycle (Keynes, 1952). This is sometimes the first three or four days of menstruation but in others it is the premenstrual week which is worse and their strength improves when bleeding starts. Psychological factors may be more important than hormonal.

The psychological state must also be considered in assessing changes during and after pregnancy. Two patients described a sudden change in their myasthenic status at a time when they had just become pregnant although they were unaware of this until the next menstrual period was missed.

Case NH4384 suddenly improved before she missed a period. She was convinced that this coincided with the date of conception which she was able to define accurately as it occurred during her husband's return on short leave during the War. Myasthenia recurred just before the first post-partum period three months after the baby was born.

Case NH/PM/IM, on the other hand, relapsed two years after thymectomy and only realised later that she was pregnant. She had previously been without symptoms. Pregnancy was terminated at the fifth month. Myasthenic symptoms/

symptoms disappeared on the same day.

Tilney (1907) also reported the appearance of myasthenia gravis immediately after conception.

The effect of pregnancy on myasthenic weakness is very variable (Viets et al, 1942; Harvey, 1948; Fraser and Turner, 1953; Kennedy and Moersch, 1937). Some patients have a relapse, others a remission. Viets et al, (1942) concluded (from a study of only 8 patients) that there was commonly a moderate relapse in the first trimester and often a remission, sometimes complete, during the last six months. The pattern may be diametrically opposite in different pregnancies in the same patient. The largest series, by Fraser and Turner (1953), reported on 14 pregnant women with myasthenia gravis; one patient was seen in two pregnancies. They agreed with Harvey (1948) that the course was most variable but were unable to confirm the late-pregnancy remission described by Viets et al (1942). They reported that labour was relatively normal but advised that the patient should be admitted to hospital 2-3 weeks before the expected date, to anticipate or avoid premature onset of labour. They gave an increased dose of neostigmine as labour proceeded to combat muscular fatigue. All of the authors quoted above are agreed that a normal labour can be expected, other circumstances being normal, but that there is great danger of a relapse in the post-partum period, especially during the first 3 weeks. According to Fraser and Turner (1953) this occurs in about half the patients.

The series described here is larger than any yet reported but it must be emphasised that most of the data is based on retrospective interviews with patients coupled with/

with a study of contemporary case records. I have only looked after four pregnancies and no relapse occurred during or after pregnancy in any of these. These patients felt fitter than usual (as in many normal pregnancies) but could not be said to show genuine remission from myasthenia.

It is possible that these differences reflect individual variations in the hormonal changes during pregnancy, as suggested by previous authors, but it might be well to consider in the future whether the patient's emotional state is not a more important factor. A wanted pregnancy sometimes seems to be associated with remission and so is a desired termination of pregnancy. On the other hand an illegitimate pregnancy or an accidental miscarriage may precipitate a relapse. The 'curve' shown in Table 5,5 parallels the emotional responses of many normal women to their pregnancy, labour and the exhaustion of the puerperium. It is interesting to note that I have no records of pregnancy occurring in a myasthenic patient who is known to have had a thymic tumour.

Table 5,5 is so arranged that it can be used in the same way as a 'balance'chart used in biochemistry. It does not include patients who were unaffected by pregnancy but this does not affect the concept of a balance. It will be seen that there is no consistent effect of pregnancy on myasthenia but that in general there is a tendency to relapse in the first trimester, to remit in the second and third, and to relapse again after the child is born. The later remission often occurred during or immediately after labour which sometimes required instrumental assistance. In my opinion Fraser and Turner (1953) underestimate the dangers of labour.

Case GK/LB had a baby when she was 23. The child died after four months and two months later the patient began to have myasthenia gravis which became generalised with severe/

severe bulbar involvement. She required 18 tablets (270mg.) neostigmine each day. There was a good response to thymectomy (Mr. Geoffrey Keynes) in March 1951. Soon after this she became pregnant. She improved greatly in the second trimester and was able to discontinue the 6 tablets of neostigmine which she had still required. Labour was uneventful but the child was myasthenic for a few days after birth. On the third day of the puerperium the patient had sudden respiratory failure and died despite attempted resuscitation.

Case GK/MM. This patient developed myasthenia gravis in 1942 when 18 years old. Mr. Keynes performed a thymectomy in 1946 with great benefit. In 1947 she had a baby which was myasthenic for a few days although at that time she was able to discontinue neostigmine. She remained well until February 1955 when she had a miscarriage of a 2 month pregnancy; there was a slight recurrence of myasthenia.

Case NH9175. This patient first showed signs of myasthenia after a miscarriage in 1932 when she was 24 years old. In a second pregnancy she remitted during the second trimester. Labour was normal but there was a severe relapse immediately afterwards.

Despite these cases I would agree with previous authors (reviewed by Osserman, 1958) that a normal labour can usually be expected and that myasthenia gravis does not normally constitute an indication for termination of pregnancy.

Gonadal:

The effects of menstruation and pregnancy just described/

described have been related to changes in pituitary function but other workers have considered the possibility that gonadal hormones may influence the neuromuscular status. The anabolic effect on protein of this group of steroid hormones is well known but seems insufficient to account for the correlations.

Schrire (1959) investigated pregnandiol metabolism in women with myasthenia gravis. He reported that there was an abnormally low excretion of pregnandiol in the urine during the proliferative and the lutcal phases of the menstrual cycle. Schrire is unable to account for a low recovery of pregnandiol from the urine after injection of progesterone into his patients nor for the recovery of very large amounts of pregnandiol after administration of ACTH. His suggested explanations do not carry conviction and Dr. K. Fotherby has been unable to confirm his results in my patients (Simpson 1960a) (see Chapter 5).

The involution of the thymus which commonly occurs in pregnancy has been attributed by some workers to the effect of ovarian hormones (Venning, 1955). Whatever its mechanism this might play a part in myasthenia gravis. Osserman (1958) discusses the possibility that acetylcholine may be formed in the gravid uterus but does not make a convincing case. He quotes various unproductive trials of oestrogens, gonadotrophins, and testosterone, all apparently without effect. I have used anabolic steroids in the treatment of severely emaciated myasthenic patients (Chapter 18) but have not observed any alteration in the myasthenic status.

Adrenal:

The recognition that muscular weakness resulted

from/

from failure of the adrenal cortex led to some uncritical attempts to account for myasthenia gravis in terms of adrenocortical insufficiency. It soon became apparent that myasthenia gravis was entirely different from the adynamia of Addison's disease. Nevertheless there are a few reports of the coincidence of adrenal insufficiency with true myasthenia gravis (Kane and Weed, 1950; Boulet et al, 1956; Boulet et al, 1959; Thiodet et al, 1961). One case occurred in the present series.

Case MM5409. He began to have double vision and Raynaud's syndrome at the age of 16. Diplopia was variable in degree but never absent. Apart from tiring easily he had no further localised symptoms until 1960 when he was 38, when he developed ptosis of the right eyelid during glandular fever. When I saw him four months after the onset there was weakness, increased by effort, of both eyelids, orbicularis oculi and of the proximal muscles of the limbs. Tendon jerks were brisk and plantar reflexes flexor. He then remembered that he had been unable to purse his lips to inflate balloons for the previous 4 years. His blood pressure was 150/105mm.Hg. He felt stronger on pyridostigmine but complained of ache in all muscles and formication under his skin. When the dose was increased to 360mg/day he felt more energetic than he had done for years. Despite this he was emotionally unstable and frequently complained of visual deterioration.

In March 1961 haematology was normal, serum sodium 134mEq/l., serum potassium 4.5mEq/l., serum chlorides (as NaCl) 100mEq/l., total plasma proteins 7.5g/100ml. Tests for A.N.F., rheumatoid factor and L.E. cells were/

were negative.

In the next two years his condition varied from time to time but even at his strongest it was still possible to produce ptosis of one eyelid by fixing his gaze above head level for one minute. He had some bizarre ideas. At one time he tried complete elimination of sugar from his diet. This had no adverse effect. In December 1962 he prepared a strong infusion of liquorice. After taking this he had oedema of the face and ankles for 2 days but otherwise felt well. (The cortisone-like action of liquorice may have been beneficial but its withdrawal might account for the next part of his story).

Fourteen weeks later he drew attention to dark pigmentation of his buttocks and elbows. His face was now bronzed but there was no buccal pigmentation. His blood pressure was now 110/70mmHg. He was readmitted to the ward with a diagnosis of Addison's disease. All tests were confirmatory but as he had an unusual ability to excrete water in the Kepler test the endocrinological consultant requested that it be repeated after giving cortisone. The delay was unfortunate because he had a typical Addisonian crisis which did not respond to large doses of hydrocortisone, DOCA, salt and measures to sustain his blood pressure.

Autopsy (Dr. A. Gordon) showed that adrenal failure was due to bilateral adrenal tuberculosis. He considered that the thymus was normal.

It was considered that the adrenal failure was coincidental since diplopia had been present for 20 years and undoubtedly responded to pyridostigmine.

Goni/

Goñi (1946) has reported cases of myasthenia gravis with adrenal lesions at autopsy and reviewed reports of similar cases. The lesions consisted of lymphocytic infiltrations and similar lesions were found in other organs. These have been reported for many years (Buzzard, 1905; Bell, 1917, Rowland et al, 1956). All authors have considered that they are coincidental. In the present series they were found in cases MN7782 and MN7783.

Simpson (1960a) pointed out that lymphocytic infiltration of various organs might be due to a defect of immunological tolerance and it is interesting to bear in mind the recent evidence that 'idiopathic' Addison's disease may result from an autoimmune process (Anderson et al, 1957).

In some of the patients reviewed here small adenomas have been found in the adrenal cortex (MN3231, MN7783) and Rowland et al (1956) found an adenoma in the adrenal glands in two of 26 autopsies. The possibility that these might be provoked by a pituitary hormone may be considered but I have not been able to investigate this aspect further.

Parathyroid:

Blizzard et al (1962) have supported the autoimmune concept of Addison's disease by the finding of adrenal antibodies in the patients' serum. They discuss clinical and serological relationships with thyroiditis and with idiopathic hypoparathyroidism. Two of three patients with the latter condition (which was associated with moniliasis) had serum antibodies against adrenal tissue.

Parathyroid hyperplasia has been reported at autopsy in/

in three cases of myasthenia gravis (Alter and Osnato, 1930; Castleman and Norris, 1949) but Adams et al (1936) found no disturbance of the blood levels of calcium and phosphorus and my own findings are in agreement (Chapter 6).

Pancreatic islets:

Many authors writing before the introduction of anticholinesterase drugs reported glycosuria and abnormal sugar tolerance in a high proportion of cases of myasthenia gravis (Williams and Dyke, 1922; Hale-White and Payne, 1926-27; Cohen and King, 1932). Brain (1940) stated that there was diminished sugar tolerance, with or without glycosuria, in many myasthenics. This statement is omitted from the latest edition of his textbook. Nevertheless glycosuria has been present in 3% of patients in the present series. Diabetes mellitus was confirmed in cases GK/DQ, NH/PM/WB, NH3962, NH11406, NH59889, NH61423, NH61493 and MN8279. Glycosuria was also present in GK/LB, NH3962, NH44196 and MN4301. Further cases with diminished glucose tolerance are listed in Chapter 6.

The incidence of diabetes mellitus in the general population has been estimated as 1.0-1.5% (Joslin, 1959) but the incidence of latent diabetes might be much higher and so there may be no significance in these figures but the following cases are interesting.

Case NH61493. A 33 year old R.A.F. officer developed ptosis at the end of 1944. Myasthenia was diagnosed when he saw double and had difficulty in chewing in September 1945. Sir Geoffrey Keynes removed his thymus in January 1946. The operation was very successful though he had a temporary relapse in 1951. Two weeks after the operation he suddenly developed severe diabetes/

diabetes mellitus.

Case GK/DQ. This young woman began to have occasional double vision in 1933 (age 27) when she had her first symptoms of diabetes. Her mother and brother had diabetes mellitus. In 1942 her grip became weak and in 1945 she was unable to speak or swallow unless she took neostigmine. She died two days after thymectomy in September 1947. Poorly controlled diabetes was a contributory factor.

Osserman (1958) found diabetes in 3% of 325 cases of myasthenia gravis. Thus, though Bolten (1931) considered that the most common abnormality in myasthenia was increased sugar tolerance, there appears to be a *prima facie* case for considering a possible relationship of myasthenia gravis and diabetes mellitus. I have also noted that many patients who do not have diabetes mellitus have a family history of that disease (Simpson, 1960a) (Cases NH60149 (MN1939), MN1906, MN2257, MN3054, MN4301, MN4603, MN4611, MN4649, MN4934, MN4977, MN6503, MN8092. This possible correlation was not considered at the interviews of the National Hospital cases and so this statement depends only on the recorded cases. The Edinburgh experience suggests that the true incidence may be higher.

Diabetes mellitus is, of course, a common disease. In view of the familial thyroid disorders described above and the possibility of immunological abnormality in the causation of diabetes, it is necessary to reserve judgement. Since this chapter was written Frenkel (1963) has reported on the effect of insulin and potassium in myasthenia gravis. The subject matter of his paper is not relevant in the present context but it is/

is interesting to note that nine of eleven myasthenic patients investigated by that author showed abnormalities in glucose tolerance either on simple carbohydrate loading or after steroid therapy.

Spontaneous hypoglycaemia in myasthenic patients is briefly referred to by Walsh (1957) and Osserman (1958). No details are given.

CHAPTER 6.

BIOCHEMISTRY.

There have been few reports on possible biochemical abnormalities in the muscles or in the blood of myasthenic patients since interest became focussed on the neuromuscular junction.

Muscle:

Nevin (1934) analysed muscle from a single case to see whether there was any abnormality of the bound phosphorus compound such as creatine phosphoric acid and adenosine triphosphoric acid which are known to play a role in the contraction of muscle. He did not find any abnormality.

Cumings (1939) found a high potassium content in a biopsy specimen of muscle. He subsequently conducted potassium balances which appeared to demonstrate that neostigmine caused liberation of potassium into the blood-stream which returned to the muscle as weakness reappeared, though urinary excretion of potassium was not increased (Cumings, 1940, 1941). The work was done at a time when it was not realised that it is important to refer all estimations to the level of non-collagen nitrogen to eliminate discrepancies due to the large amount of connective tissue in pathological muscle.

Adams et al (1936) reviewed previous studies on the metabolism of carbohydrate, nitrogen, creatine, creatinine, calcium and magnesium and showed that they were contradictory. They made personal studies of these items and also of sodium, potassium, phosphorus, sugar, urea, amino acids and uric acid. Their/

Their results were within normal limits. Since no later authors have shown significant evidence to the contrary I do not propose to review the literature further. Creatinuria may be found, especially in women, but the incidence is no greater than in other diseases associated with difficulty in taking food or with muscular wasting. Milhorat and Wolff (1936) showed that creatinuria in myasthenics was increased when the disease was rapidly progressive and this has been my own experience.

Serum and muscle enzymes:

A former theory that the defect of neuromuscular transmission in myasthenia gravis might be due to a pathologically high level of cholinesterase ('true' or 'pseudo') in the blood was abandoned when it was shown that the serum level was low (Stedman and Russell, 1937) or normal (Wilson and Stoner, 1944). Goodman et al, (1939) found normal values in muscle. I have not carried out personal studies since histochemical methods support this conclusion.

I have studied the serum levels of glutamic pyruvic transaminase (GPT), glutamic oxalacetic transaminase (GOT), aldolase, and creatine phosphokinase. The blood levels of these enzymes are often raised in diseases involving damage to the membrane of muscle cells. The results (Table 6,1) have been substantially normal.

I do not believe that current biochemical techniques have anything to contribute with regard to the fundamental nature of myasthenia gravis, but I have made some investigations to determine whether there is any disturbance of protein in the plasma and cerebrospinal fluid such as might be expected in association with abnormal formation of antibodies/

antibodies (Chapter 13) and to determine whether the endocrine disorders which were detected clinically (Chapter 5) were present in subclinical form in other cases of myasthenia gravis.

All biochemical estimations other than radioiodine studies were carried out in the Biochemistry Department of the Northern General Hospital under the direction of Dr. S.L. Tompsett.

Plasma Proteins:

The plasma proteins were estimated in 41 cases and electrophoretic separation was carried out in (Table 6,2). There was no significant abnormality in most cases but definite hypergammaglobulinaemia was found in 11 cases, (including the four previously reported by Simpson, 1960a) and in 5 others the electrophoretic profile showed a prominent peak in the $\alpha 2$ or β globulin bands. For the present purposes the upper limits of normal levels for plasma globulins were taken as:- $\alpha 1$ 0.5, $\alpha 2$ 0.8, β 1.15, γ 1.6 g/100ml. plasma. (These figures exceed the upper limits usually adopted for the electrophoretic method of estimation so that it is safe to assume that higher levels are pathological). Three cases (MN2327, MN7390, MN7550) had 2.0gm/100ml. or more of gammaglobulin. The first two of these cases had Hashimoto's disease. Thévenard and Mende (1955) found decreased gammaglobulin in five cases and raised in one but Lowenthal and van Sande (1956) criticised their work on technical grounds pointing out the necessity to use absolute values rather than percentages. They found raised gammaglobulin and lowered albumen in the serum of myasthenic patients (the albumen change was less constant and should be ignored as it alters secondarily to changes in the/

the globulins). Osserman (1958) and Corridori (1960) found no change in the electrophoretic pattern. Single cases of myasthenia gravis with hyperglobulinaemia are included in the reports of Castaigne et al (1961), Steidl et al (1962) and Oosterhuis (1963). These results are not necessarily contradictory since both hyperglobulinaemia and agammaglobulinaemia may be associated with thymic tumours (Chapter 7).

Abnormal cephalin-cholesterol flocculation and thymol-turbidity tests were found in some of the present cases. Some of these had electrophoretic patterns within normal limits but these tests may indicate the presence of specific but unidentified proteins (Table 6,2). The erythrocyte sedimentation rate was usually normal but shows a tendency to be raised in association with Hashimoto's disease (MN2327, MN5503, MN7390), pernicious anaemia and haemolytic anaemia (MN5095, MN5503, MN7780) but not with uncomplicated thymoma. These correlations suggest that MN4636 may have unrecognised thyroiditis though her protein-bound iodine is still in the normal range (Table 6,4). They are consistent with the hypothesis that immunological mechanisms are active in myasthenia gravis.

Störtebecker (1955) found raised titres of antistaphylolysin in 72% of 25 cases of myasthenia gravis and raised titre of streptolysin in 36% of cases. The coli agglutination titre was raised in 64% of cases. Further personal studies on immune globulins are presented in Chapter 13.

Cerebrospinal fluid proteins:

As lumbar puncture is rarely carried out on patients with/

with myasthenia gravis it is impossible to comment on the frequency with which abnormal findings are made. A high level of protein in the cerebrospinal fluid was present in one of 32 cases of myasthenia reported by Kennedy and Moersch (1937). De Haene and Roussel (1955) described a case with 'albumino-cytological dissociation'.

In the present series few patients had a lumbar puncture but in ten of these the protein content of the C.S.F. was 50mg/100ml. or greater (Table 6,3). In all of these cases a positive neostigmine test justified the diagnosis of myasthenia gravis. The table shows the related conditions which might have been correlated with the biochemical abnormality. A possibility which was unconsidered when the earlier data were obtained is that a raised level of protein in the cerebrospinal fluid may be associated with myxoedema. This possibility can certainly be excluded in the last three cases.

Endocrine function tests:

As shown in Chapter 5 there is a high incidence of clinically recognisable disorders of endocrine function in myasthenic patients. If these are to be considered as separate though related entities it is necessary to demonstrate that there is not a subclinical disorder of endocrine function in all cases. If a biochemical lesion were causative it should be present in every case whereas with the relationship postulated in this thesis the endocrinological abnormalities would only be detected occasionally. In this section are listed the results of a survey carried out in the Northern General Hospital, Edinburgh in 45 cases of myasthenia gravis.

Thyroid/

Thyroid function tests were carried out on 41 cases (Table 6,4). Most of the radioiodine and protein-bound iodine tests were made by the Department of Endocrinology of the Western General Hospital, Edinburgh and the plasma cholesterol and basal metabolic rate estimations by the Department of Biochemistry of the Northern General Hospital, but as some of the radioiodine uptake and clearance tests were made in Edinburgh Royal Infirmary or other hospitals using different techniques, the results are charted according to the interpretation of the laboratory. Normal figures were recorded in 35 cases and there was evidence of hyperthyroidism in 4 cases. Some of the patients who had normal tests of thyroid function had a previous history of goitre or of possible hyper-thyroidism (Chapter 5). Hypothyroidism was found in Case MN5503, shown at later autopsy to have Hashimoto's disease. The other case with subnormal activity (MN6476) had a thymoma. He died later in another hospital and no post mortem examination was made. Case MN7390 is the patient with Hashimoto's disease described and illustrated in Chapter 13.

These results show that there is a high incidence of disorders of thyroid function in patients with myasthenia gravis but as the majority of cases have normal function this cannot be a causative factor.

The same comment may be made on carbohydrate metabolism as measured by the standard glucose tolerance test (Table 6,5). This and the following series of tests were carried out under the direction of Dr. S.L. Tompsett of the Northern General Hospital. The serum calcium and inorganic phosphate concentrations were normal in 34 cases (Table 6,6). Urinary excretion of 17-hydroxycorticosteroids and/

and 17-ketosteroids was normal (Table 6,7) except in Case MN5409 during investigation for the tuberculous adrenocortical failure which terminated his life after many years of myasthenia gravis (Chapter 5). The very low values reported for Case MN6433 were probably due to incomplete collection of urine and the same explanation may account for the unusually low value in another 9 of the 30 cases. There has certainly been no clinical evidence of adrenocortical insufficiency. Two cases (MN7776 and MN7779) showed a normal eosinopenic response to the injection of 0.3ml. of 1/1000 adrenaline solution.

Schrire (1959) has reported an unusually low recovery of pregnanediol from the urine of patients with myasthenia gravis. Dr. K. Fotherby of the Medical Research Council Clinical Endocrinology Unit has kindly carried out some investigations on my cases. He investigated four women during different phases of the menstrual cycle (MN4275, MN4536, MN4586 and MN4611), one pregnant woman (MN3912) and one man (MN4301). In every case Dr. Fotherby considered that the pregnanediol excretion was normal for the appropriate condition. He also tested the response to injections of ACTH and of progesterone, again with normal findings.

From these results it may be concluded:

1. There is no evidence of gross myopathic disease.
2. There is a high incidence of disorders of plasma and cerebrospinal fluid protein fractions, consistent with an immunological disorder (Chapter 13).
3. There is no regular disorder of endocrine function but many cases show evidence of clinical or subclinical disturbance of thyroid function or of carbohydrate metabolism/

metabolism.

4. Low rates of excretion of steroids are reported but the significance is uncertain. The results were obtained from a routine laboratory under the supervision of an expert on the estimation of steroids in the urine but the urine specimens were obtained in a busy unit with insufficient nursing staff for accurate biochemical work.

CHAPTER 7.

CLINICAL EVIDENCE OF DISSEMINATED DISEASE.

When medical opinion is unanimous about the nature of a disease, any observation which conflicts with the concept is rejected as irrelevant or mistaken. This has been the experience of myasthenia gravis. The possible association of the neuromuscular syndrome with other disorders has been overlooked for the twin reasons of seeming irrelevancy, and the current thraldom to the 'statistically significant' with the false corollary that any lesser degree of association must be coincidental.

Aplastic anaemia:

One exception to this rejection has been pure red-cell aplasia which has been associated with thymic tumours, with or without myasthenia gravis. The association of selective erythroblastic aplasia with thymoma was first reported by Matras and Priesel (1928). The aplasia is not always confined to the erythroid elements of the blood but may be pancytopenic (Green, 1958; Barnes and O'Gorman, 1962) and the first case associated with myasthenia gravis and thymic tumour was of this type (Wintrobe, 1946). The neutropenia with thymic tumours may be cyclical and associated with agammaglobulinaemia (Martin et al, 1956; Lambie et al, 1957; Barnes and O'Gorman, 1962) but the latter has not yet been reported in myasthenia gravis.

The thymic tumour may be of any of the variety of histological types which are described and there is no consistent pattern. Parry et al (1959) were unable to demonstrate/

demonstrate a humoral marrow-inhibitory factor in their patient who did not have myasthenia.

Since the early report of Wintrobe (1946), the only patients who have had the syndrome of thymoma with erythroid aplasia associated with myasthenia gravis have been those reported by Chalmers and Boheimer (1954), Bakker (1954), Weinbaum and Thompson (1955) and Grob (1958). The case of Chalmers and Boheimer (1954) was from the National Hospital series included in this survey and is described briefly below.

Case NH22715. Myasthenia gravis was diagnosed at age 46 and there was excellent response to treatment with neostigmine and ephedrine. Eighteen months later he complained of progressive tiredness, dyspnoea and palpitation although myasthenia was well controlled. He was found to have severe normochromic anaemia with little poikilocytosis. The blood picture was:- Hb. 27% (4g), R.B.C. 1,340,000/c.mm., P.C.V. 11.5%, M.C.V. 85cμ., M.C.H.C. 35%, W.B.C. 5200/c.mm. (polymorph neutrophils 49%, lymphocytes 47%, monocytes 4%, eosinophils absent), platelets 325,000/c.mm. No reticulocytes or nucleated red cells could be found on repeated examination.

Sternal marrow showed normal precursors of white cells and platelets but few if any red-cell precursors. A slight increase in plasma and reticulum cells was described (Dr. Chalmers).

The direct Coombs test was negative and the total serum protein level was 6.9g/100ml. (albumin 3.4g/100ml; globulin 3.5g/100ml). Red cell fragility, bleeding-time, clotting time and clot retraction were normal. The blood/

blood Wassermann and Kahn tests were negative.

The serum bilirubin level was less than 0.5mg/100ml; blood urea 21mg/100ml; thymol turbidity 1.2 units, alkaline phosphatase 3.4 K-A units. The first alcohol-histamine test meal showed no free hydrochloric acid in the stomach but free acid was detected in a repeat test.

Radiography (without tomography) did not reveal a thymic tumour but in view of the known relationships and the possibility of helping both the myasthenia gravis and the anaemia (Humphreys and Southworth, 1945) the chest was explored and a thymoma found. It was successfully removed.

Chalmers and Boheimer had previously administered adrenocorticotrophin and various haematinics without success. An initial haematological remission followed the operation (Fig. 7,1) but was not sustained, but further temporary improvement seemed to follow a later splenectomy. The next relapse responded well to ACTH and the bone marrow then showed active normoblastic erythropoiesis. This was maintained for a short time but then the patient required further blood transfusions. Haemosiderosis resulted which caused his death on 3/2/55.

It seems unlikely that thymic tumour 'causes' the anaemia since thymectomy is not always beneficial and indeed aplastic anaemia has developed in a patient two years after resection of a thymoma (Clarkson and Prockop, 1958). The Coombs test for human globulin has been negative in the reported cases but Eisemann and Dameshek (1954) have reported autoimmune haemolytic disease associated with pure red-cell hypoplastic anaemia and a possible association with/

with immunological disorders is provided by the recent finding by Holborrow et al (1963) of antinuclear factor in the blood of a patient with the syndrome of thymoma and red-cell aplasia (without myasthenia gravis). The favourable response to ACTH (Chalmers and Boheimer, 1954) and to prednisone (Parry et al, 1959) would be in keeping with a possible immunological mechanism.

Pernicious anaemia:

No other association between myasthenia gravis and disorders of the blood was reported until my papers of 1960a and 1964 apart from passing references to single cases of pernicious anaemia in the series of myasthenic patients reported by Schlezinger (1940), Rowland et al, (1956), Walsh (1957) and in a case record from the Massachusetts General Hospital, New Eng. J. Med. (1956). When I saw the first four of my series of ten cases of pernicious anaemia I assumed that this was a wrong initial diagnosis made to account for the patients' weakness. In these earlier cases it was not possible to confirm the diagnosis by rigid haematological criteria so they were simply described as cases of macrocytic anaemia (Simpson, 1960a). In later cases the diagnosis is completely authenticated. Since this association has been considered coincidental by other authors but is an important factor in the argument developed in this thesis the cases will be described more fully than others cited.

Case NH3279. When aged 16, she rapidly developed a goitre. It lasted for 2 years then subsided. When seen at the age of 53 she could not describe thyrotoxic symptoms but the B.M.R. was known to have been +55% of normal/

normal. A sister had goitre and died at operation. At the age of 50 she developed pernicious anaemia which responded to injection of liver extract. At that time she was complaining of increasing lassitude, fatigue, pallor, loss of weight and breathlessness on exertion. Although the diagnosis could not be reviewed in retrospect, the history is entirely compatible with it. At 53 years she noticed ptosis and weakness of the proximal muscles of all limbs, with aching of the neck, arms and legs but no paraesthesia. There was severe deafness in the left ear. A diagnosis of myasthenia gravis was made one month later by Dr. George Riddoch. There was an excellent response to neostigmine but 40 tablets daily (600mg.) were required for control of myasthenic symptoms. Thymectomy six months later showed that the gland contained a cystic cavity but it was otherwise involuted. The response to thymectomy was very good, the neostigmine dosage being reduced to 16 tablets (240mg.) but eight months after operation she developed pneumonia and died.

Case MN4650. This patient complained of tiredness, breathlessness and a sore tongue at the age of 29. A diagnosis of pernicious anaemia was made and she received injections of liver extract for the next 16 years though the diagnosis was never confirmed in a hospital. When she was 45 she developed arthritis of hands and feet and at that time liver injections were discontinued. When she was 43 both eyelids started to droop and she had occasional diplopia.

Dr./

Dr. J.B. Gaylor saw her in Glasgow Eye Infirmary and made a diagnosis of myasthenia gravis. There was a satisfactory response to neostigmine. There was a family history of myasthenia-like illness and of thyrotoxicosis which is described in Chapter 8.

Unfortunately my case notes (made before the possible significance was realised) do not record whether liver therapy was resumed so the diagnosis is rather uncertain. For the same reason, the notes on the following three cases, also kindly referred by Dr. J.B. Gaylor, are not as well documented as one would wish with the exception of MN5018.

Case MN7778 (G.W.I.-M778/53). This patient developed myasthenia gravis at the age of 62. He was deaf but able to use a hearing aid. For twenty years previously he had been receiving liver injections for pernicious anaemia. When admitted to Glasgow Western Infirmary under my care in 1953 his blood picture was completely normal. At that time the Schilling test for absorption of cyanocobalamin was not available but there was no reason to question the earlier diagnosis. He was treated by irradiation of the thymus in 1951 and by ACTH in 1953. The latter caused temporary remission but he later developed left ventricular failure with auricular fibrillation which caused his death.

Case MN7782 (G.W.I.-G.I. 8/53/48). At the age of 63 he had progressive weakness for 6 months. A diagnosis of pernicious anaemia was made (no details available) and he was considered to be improved by liver/

liver injections. One year later he noticed difficulty in swallowing, ptosis and weakness of neck muscles. It was not until another eight months that he was seen by Dr. Gaylor who diagnosed myasthenia gravis. There was immediate improvement with neostigmine and irradiation of the thymus.

This was maintained for 2 years but he then had a relapse after 'flu'. He was admitted to the Western Infirmary under my supervision in April, 1953, severely myasthenic, and with cardiac failure associated with hypertension (B.P. 210/115 mm/Hg). The diagnosis of myasthenia gravis was confirmed by electromyography and by an edrophonium test.

On admission he had slight anaemia with a high colour index (3,800,000 red cells/cu.mm; Hb. 13.0gm/100ml; total leucocytes 9400/cu.mm). Severe myasthenic weakness was not greatly improved by 300mg. neostigmine daily. Cortisone 25mg. b.d. was started but on the second day respiration failed and could not be re-established. At post mortem Dr. J.M. Johnstone found nephrosclerosis with signs of hypertensive cardiac failure. A few tiny lymphorrhages were found in the right sternomastoid muscle and in the adrenal glands. No thymic tissue was identified. The thyroid gland was normal. The stomach was smooth and atrophic. No abnormality of bone marrow or spleen was present but the findings were consistent with treated pernicious anaemia.

Case MN5018. This patient was 70 years old when he developed myasthenia gravis. Dr. J.B. Gaylor confirmed the diagnosis by a therapeutic test (neostigmine/

(neostigmine) and I obtained an electromyographic response consistent with this diagnosis. The Harvey-Masland test gave a recruiting response. There was no personal or family history of diabetes or of thyroid disease.

Four years earlier he became pale, slightly jaundiced, and felt as if he was going to faint. He was admitted to Stobhill General Hospital, Glasgow, (Unit No. 18064) under the care of Dr. J.L. Markson. The haematological findings were:-

Haemoglobin 6.5 g/100ml. P.C.V. 19.5%
Red cells 2,110,000/cu.mm. M.C.H.C. 33%
The blood film showed macrocytosis with aniso-poikilocytosis.
The bone marrow showed megaloblastic erythropoiesis.
There was a histamine-fast achlorhydria.

The blood picture reverted to normal after injection of cyanocobalamin and has remained normal with regular injections of that drug. He also requires 12 tablets (720mg.) of pyridostigmine daily.

Case MN5503. This woman became pale and weak in 1935 at the age of 43. Pernicious anaemia was diagnosed in Leith Hospital and from that date she was treated with liver and then with cyanocobalamin by injection. In February 1961, when aged 69, she received a severe emotional shock when a friend died while accompanying her on a bus tour. A few weeks later she developed ptosis and generalised fatigue and, in a further two weeks, difficulty in speaking, chewing and swallowing. I saw her in consultation and made a clinical diagnosis of myasthenia gravis which was later confirmed/

confirmed by electromyography and an edrophonium test. She was found to have mild hypothyroidism, later shown to be due to Hashimoto's disease. This aspect of the case is described in Chapter 13. The response to treatment with neostigmine, and later pyridostigmine and spironolactone, was only moderately satisfactory as she had frequent relapses. (Spironolactone was considered to be valuable by the patient but no objective evidence of this could be demonstrated).

When admitted to the Northern General Hospital there was moderate anaemia (80-87% haemoglobin) but it was always normocytic and slightly hypochromic. Nevertheless, despite previous treatment the sternal marrow showed megaloblastic erythropoiesis and the vitamin B12 content of the serum was 120μμg/ml. (lower limit of normal range 170μμg/ml.). There was histamine-fast achlorhydria.

Absorption of cyanocobalamin was estimated by giving an oral dose of 0.5μg. of radioactive ^{58}Co-B12 without intrinsic factor (and with carbachol). Only 0.4% of this amount was recovered from the urine. With the method used a recovery of less than 7.5% is definitely abnormal. Antibodies against gastric mucosa were detected in the serum on two occasions (Table 13.1, Chapter 13).

Unfortunately the stomach was grossly autolytic at post mortem examination but Dr. A. Gordon reported that 'from the presence of some islets of interstitial metaplasia the gastric mucosa does not appear to have been normal and may well have been atrophic'. The liver and spleen contained considerable deposits of haemosiderin/

haemosiderin. Bone marrow was grossly normal. The thyroid showed the changes of Hashimoto's disease. Only a few atrophic strands of thymic tissue were identified. There was cholelithiasis. Death was due to aspiration of vomit.

The clinical, biochemical and autopsy results completely substantiate the diagnosis of pernicious anaemia. The association of that disease with Hashimoto's disease is discussed in Chapter 13.

Case MN7780 (E.R.I.). A diagnosis of pernicious anaemia was made in this patient at the age of 69. She felt well on being treated with cyanocobalamin but in the following year she began to have bilateral ptosis, especially in strong light. Three years later (two years before admission) she had an emotional shock and after this noticed weakness of her jaw and tongue when talking or chewing. I examined her at the request of Professor K.W. Donald and found bilateral ptosis, 'fatiguable' weakness of orbicularis oculi, pterygoid muscles, neck flexion and the deltoid, triceps, and adductor muscles of the arms. A diagnosis of myasthenia gravis was confirmed by an edrophonium test and a Harvey-Masland test in the Northern General Hospital.

Professor Donald confirmed the earlier diagnosis of pernicious anaemia. Haemoglobin 87%, P.C.V. 41%, M.C.H.C. 32%, E.S.R. 21mm. per hour, W.B.C. 8,100/cu.m., No L.E. cells were seen in the peripheral blood.

A first test meal was thought to show the presence of free HCl after histamine but this was not confirmed by a repeat test. A Schilling test for absorption of cyanocobalamin/

cyanocobalamin (as above) showed no urinary excretion of radioactive cyanocobalamin. This was corrected by giving intrinsic factor. Folic acid absorption was normal. Jejeunal biopsy appearances were normal. There was no radiological evidence of a thymoma.

Case MN 8279 (E.C.H. 557/59). A 77 year old woman was admitted to the Eastern General Hospital, Edinburgh for investigation of difficulty in swallowing of one year's duration. It was noted that she had recent dyspnoea on exertion and both eyelids has been drooping for the previous five weeks. Her voice was nasal in quality. She proved to have rapidly deteriorating myasthenia gravis. Dr. M.B. Matthews asked me to see her. The response to edrophonium and neostigmine was sufficient to establish the diagnosis but she was considered to be too ill for thymectomy. She died one month after admission. This was contributed to by metabolic acidosis as she had been diabetic for several years and this became uncontrolled when she was unable to take a regular diet. She had also complained of acrocyanosis.

Nine years previously pernicious anaemia was diagnosed. She had been given weekly injections of 100µg. cyanocobalamin so it is not surprising that her blood picture was normal on admission to hospital. Unfortunately no autopsy was obtained.

Case LM40167/47, 41892/47. I am indebted to Lord Brain for permission to quote this case. She was aged 54 in 1947 when she was seen at the London Hospital. She had had a thyroidectomy for exophthalmos/

exophthalmos and heart trouble when she was 42, but was said to have no goitre. Six months before being seen by Dr. George Riddoch she was found to have pernicious anaemia and was put on injections of liver extract. Her own doctor had obtained a blood count. When she reported at the London Hospital her blood count was normal and the colour index 1.05. Two months before reporting she complained of blurred vision and this was followed by double vision in all directions. Dr. Riddoch diagnosed myasthenia gravis and prescribed neostigmine. There was a previous history of asthma and bronchitis.

Later in the same year she was seen by Lord Brain with muscarinic symptoms, fasciculation of muscles and mental deterioration. She became increasingly disorientated, demented and stuporose. She died in January, 1948.

At necropsy she was found to have a cystic lymphoendothelioma of the thymus. The spleen was slightly enlarged and there was considerable parenchymatous disease of the liver. The gall bladder contained four cholesterol stones. The brain showed focal areas of congestion in the left external capsule and around the lateral ventricle.

It will be seen that the hitherto unrecognised relationship between pernicious anaemia and myasthenia gravis is more common than the acknowledged association with red-cell aplasia described in the previous section. At the time of my first paper the relationship was merely used to establish the hypothesis of a diffuse systemic disorder though this was elaborated along immunological/

immunological lines (Simpson, 1960a). At that time, however, evidence began to accumulate suggesting that pernicious anaemia is associated with an immunological disorder with production of an organ-specific antibody to the intrinsic factor and to the parietal cells of the stomach (Schwartz, 1960; Irvine et al, 1962; Taylor et al, 1962). A search for antibodies in the blood of 35 myasthenic patients gave positive results in 3, of whom one (MN5503) had clinical pernicious anaemia (Simpson, 1964a). With the method used (for which I am indebted to Dr. W.J. Irvine) positive results are obtained in 8% of middle-aged female blood donors so the significance of the other two positive results cannot be assessed at present. Unfortunately the other patients with clinical pernicious anaemia are no longer available for immunological studies. This aspect is further discussed in Chapter 13.

Haemolytic anaemia:

The exact nature of the following case is difficult to assess. There was a megaloblastic anaemia with low serum vitamin B12 and with a reticulocyte response to cyanocobalamin but haemolysis was excessive. The anaemia was a terminal event in a patient with a thymoma who had hepatic and perhaps renal insufficiency.

Case MN5095. In 1950 (age 43) this man was found to have myasthenia gravis. At thoracotomy a thymic tumour was found but it could not be removed completely. In addition to severe generalised myasthenic weakness he later complained of bizarre sensory symptoms which are described in Chapter 4. These included paraesthesia and sensory loss of the hands and feet and/

and loss of the sense of taste. The latter may have been related to the atrophy of the mucous membrane of the tongue which was noted on his admission to the Northern General Hospital in November, 1960 (Fig. 4.2). There was also angular stomatitis. He was known to be allergic to penicillin and streptomycin.

In November, 1960 his E.S.R. was 75-125mm. in the first hour (Wintrobe method). Total plasma proteins were 6.75gr/100ml. There were signs of hepatic insufficiency - serum bilirubin 1.35mg/100ml. on first estimation and 1.75mg/100ml. on repeat; thymol turbidity 4 units; cephalin-cholesterol flocculation positive (4); alkaline phosphatase 6 K-A units.

On admission his blood picture was:- Hb. 8.6gm/100ml. P.C.V. 28%, M.C.H.C. 31%, W.B.C. 4,400 (5% eosinophils). A film showed marked anisocytosis and poikilocytosis with occasional macrocytes. Platelets were present. The haematological abnormality was confirmed in six repeat examinations and there was no response to iron or to repeated blood transfusions (six pints). These were presumably haemolysed as his conjunctivae became icteric and there was no change in liver function tests.

The sternal marrow was normally cellular but contained numerous megaloblasts and showed evidence of arrested maturation of erythropoiesis. Megakaryocytes were prominent and white cell precursors normal (Dr. J. McManus). The further course of the blood changes was complicated by the deterioration in his clinical state. He had a severe myasthenic crisis on 1/12/60 requiring respiratory support by positive-pressure/

pressure respiration. He was never again reasonably powerful becoming weak on reduced dose of pyridostigmine but readily became overdosed and the latter happened several times in the next two months (see further description in Chapter 19).

On the 9th, 17th and 22nd days he was given blood transfusions to a total of 6 pints. At that time his blood urea rose to a maximum of 84mg/100ml. but dropped to normal levels in a few days. Two days later he required an oxime (PAM) for treatment of a cholinergic crisis. Four days later his conjunctivae were icteric, but as he had the second blood transfusion between these times it is uncertain whether haemolysis was due to the drug or to the transfusion. There were no signs of haemolysis after the third transfusion but his haemoglobin level failed to rise.

At that stage the result of serum vitamin B12 assays were received; they were 145 µµg and 152 µµg/ml. (normal 170-1000µµg/100ml). Free HCl was reported to be present in the gastric juice after a maximum histamine test. He was given cyanocobalamin 100µg. intramuscularly each day for 3 days and there was a reticulocyte response after the third day but it was considered to be suboptimal. Further investigation was prevented by the development of anuria with a continuous cholinergic state which led to his death on 11/2/61 (see Chapter 19).

Post mortem examination (Dr. A. Gordon) confirmed the presence of a large fibro-cystic thymic tumour consisting of poorly staining fusiform cells showing no/

no architectural pattern. No lymphocytic component was identifiable and there was no evidence of malignant infiltration. Lymphorrhages and Russell type I lesions were prominent in many of the muscles. The liver was large (2300gm) but of normal appearance. The spleen was large (300gm) and the cut surface slightly fibrotic. Gastric mucosa was too autolysed for examination. Sternal marrow showed some fatty change and fibrosis which was attributed to previous radiotherapy. Red reactive marrow was present in the shaft of the long bones. The kidneys appeared to be normal. There was no obvious cause for anuria. Unfortunately the spinal cord was not sectioned.

Storm-Mathisen (1961) described a patient (Case 56) who had been treated for haemolytic jaundice before myasthenia gravis began at the age of 32. Eight years later, after remission of the myasthenia, she had myxoedema and arthritis with a raised blood sedimentation rate. There was no recurrence of myasthenic weakness eight years later. The author does not comment on the case and does not appear to have considered a diagnosis of systemic lupus erythematosus. Case 47 of the same author had thrombocytopenia.

It is interesting to note that pernicious anaemia and haemolytic anaemia have occurred in patients without a thymoma but that all cases of aplastic anaemia reported to date have been associated with a thymic tumour.

Reticuloendothelial disorders:

I have never been able to palpate the spleen of a myasthenic patient as reported by Montesano (1898) but the spleen was found to be enlarged at post mortem examination of Cases NH/EC/DH, MN2327, MN5095 and MN7788.

Cases/

Cases NH47860 and MN4603 had a generalised lymphadenopathy without adequate explanation.

Case NH5659 developed typical myasthenia gravis when 20 years old. Within a month she was too weak to leave bed. Thymectomy carried out at that time caused immediate improvement which continued in the following year. Major improvement was not obtained until four years after thymectomy. Eight years after the operation she noticed a lump on her leg. She was found to have generalised lymphadenopathy. Death occurred seventeen months later and was attributed to reticulum cell sarcomatosis.

Dr. J. Leeny of the Charles Clinic, Prague University and Dr. Charles W.M. Whitty of the Radcliffe Infirmary, Oxford, have recently informed me of two similar cases under their care. Both were young children who had neostigmine-responsive myasthenia gravis associated with lymphosarcoma (Simpson, 1964c). Alter and Osnato (1930) described a case of myasthenia gravis with generalised lymphadenopathy. The thymus was 'granulomatous' and considered by the authors to resemble Hodgkin's disease. Campbell and Bramwell (1900) record a case described by Senator (1892) of 'multiple sarcomata', anaemia, albumosuria and 'chronic parenchymatous changes in the kidney'. Senator's diagnosis appears to have been multiple myelomatosis. It is doubtful, however, whether the muscular weakness was truly of myasthenic type.

These disorders of the blood and reticuloendothelial system are exceptional and may not be related to myasthenia gravis but it should be remembered that lymphadenopathy associated with rheumatoid arthritis is virtually confined to/

to young children. They may be related to some of the following conditions which were also found in the present series of myasthenic patients. The possible nature of the relationship is discussed in Chapters 9 and 14.

Sarcoidosis:

It is difficult to decide whether this condition should be classified as a reticulosis or as a disorder of immunological mechanisms (Teilum, 1948). One patient (Case NH/EC/MG and MN887) had sarcoidosis. It has not produced any further manifestations since the thymus was removed in 1946. She now has minimal myasthenic symptoms and works as a hospital secretary. She has prominent eyes with von Graefe's sign but has no other signs to suggest the presence of thyrotoxicosis.

Systemic lupus erythematosus:

Harvey et al (1954) described myasthenic symptoms in three cases in their classical paper on systemic lupus erythematosus (S.L.E.). Rowland (1955) found lupus erythematosus (L.E.) cells in the peripheral blood of a patient who presented as myasthenia gravis.

Case GK/ES first noticed weakness of the legs in September 1946 when she was aged 49. This was followed by ptosis and diplopia and then bulbar and, later, upper limb weakness. Myasthenia gravis was diagnosed at St. Bartholomew's Hospital, London, in October 1948. There was a good response to neostigmine. In 1950 she had pericarditis and angioneurotic oedema and in 1952 was treated by radiotherapy for suspected carcinoma of the larynx. In 1954 she attended Hammersmith Hospital with myxoedema. A diagnosis of chronic lupus erythematosus was made because L.E. cells were found in/

in her blood. At that time the possible association with thyroiditis and myasthenia gravis was not known and the myxoedema was attributed to radiation damage to the thyroid gland.

When I examined her in 1955 she was able to lead a normal life if she took 10 tablets (150mg) of neostigmine each day.

This is the only case in the present series in which classical L.E. cells have been found. Antinuclear factor has been detected in the blood of eight further cases (Table 13.1). This relationship is fully discussed in Chapter 13.

Acrocyanosis:

Raynaud's syndrome was mentioned by 12 patients in the original series (Simpson, 1960a) and by a further 5 patients.

Cases NH/MC/AW, NH537, NH7195, NH11563, NH23458, NH26546, NH29471, NH31572, NH32217, NH52310, MN382, MN4977, MN5315, MN5409, MN6522, MN6811, MN7543.

This symptom has not been reported by other authors. The true incidence might be greater since the symptom was not specifically asked for in the first 400 cases. Many of these cases showed a poor response to neostigmine or to thymectomy. I have made sure that the evidence for a myasthenic reaction is sufficiently well documented to make each case acceptable for inclusion in the series as this finding may be of some prognostic importance as indication of irreversible muscular damage. This is of some importance as acrocyanosis is a common accompaniment of polymyositis (Walton and Adams, 1958). It may be caused by auto-agglutinins in the blood (Forbes, 1947).

'Rheumatoid'/

'Rheumatoid' arthritis:

The author was also the first to draw attention to an unusual incidence of arthritis in patients with myasthenia gravis (Simpson, 1960a; 1964b). In some patients the painful swelling involved peripheral joints and was transient (Cases NH/GK/AP, NH7583, NH62028). Two patients were considered to have ankylosing spondylitis (Cases NH41178, NH61507). In a further 11 cases the joint changes have been permanent (Cases GK/EA, GK/DB, NH/D-B/JH, NH980, NH8191, NH44941, NH61496, MN294, MN675, MN4650 and MN5494).

The arthritis is indistinguishable clinically and radiologically from true rheumatoid arthritis (Figs 7.2 and 7.3) but the modifying quotation marks were used by Simpson (1960a) to indicate that identity could not be assumed. Nevertheless Burnet (1962a,b) has used my evidence (acknowledged in the second paper) to support the hypothesis I was then suggesting (Chapters 13 and 14). It will be shown in Chapter 13 that the arthritis may be different from that of true rheumatoid arthritis as judged by the Rose-Waaler test.

Nephritis:

Case NH5557 had acute nephritis just before thymectomy in the third year of his myasthenic illness.

Case GK/SJ had acute nephritis following thymectomy in the second year of illness. He also had a small non-toxic goitre.

Allergic disorders:

Asthma was noted in seven patients (Cases NH/HH/HC, NH/CS/AR, NH56864, MN277, MN336, MN6476 and MN7720). In each case the asthmatic symptoms had preceded true myasthenic symptoms/

symptoms so it is unlikely that the attacks were due to ventilatory failure or to overdosage with anticholinesterase drugs. Nevertheless the circumstances of the death of case MN6476 in another hospital from 'severe asthma' were very suggestive of a cholinergic crisis (Chapter 19). Other cases such as NH6753 who died of 'asthma' several years after thymectomy without having a previous history of asthma, have been excluded from this list.

Four patients had their initial attacks of myasthenia or relapses precipitated by allergic reactions to foreign protein. These cases and others in the literature are described in Chapter 2.

Others:

Ulcerative colitis and hepatic cirrhosis were associated with systemic lupus erythematosus which followed thymectomy for myasthenia gravis in a patient recently reported by Alarcón-Segovia et al (1963). I have seen two myasthenic patients with acute hepatitis and two with acute haemolytic anaemia. These cases will not be described here as the complications were considered to be due to drugs - chlorpromazine or oximes (Simpson, 1961a and Chapter 19) - but cases recorded in other series are listed in Table 13.1.

Summary:

It is clear that none of these associated disorders occurred with sufficient frequency to be considered 'significantly' related to myasthenia gravis in the statistical sense. Nonetheless it is a remarkable coincidence to note the occurrence of the same conditions (and some endocrine disorders which have been discussed in the last chapter) in the other major series in the literature/

literature (Table 3.3).

Simpson (1960a) drew attention to the fact that many of these conditions - which have in common a disorder of the reticuloendothelial system or of the immunological mechanisms - also featured in the list of manifestations of systemic lupus erythematosus by Harvey et al (1954) and that the precipitating factors, the age and sex distributions, and the remittant courses of these two diseases were strikingly similar. The suggestion was made that myasthenia gravis might be a local neuromuscular manifestation of a disorder in which other tissues may sometimes be involved. A disease process resembling but not identical with systemic lupus erythematosus was suggested. In the rest of this Thesis the evidence and discussion will be presented in such a way as to throw light on this hypothesis and to show how it was further investigated.

CHAPTER 8.

FAMILIAL AND CONGENITAL MYASTHENIA.

Myasthenia gravis rarely occurs in more than one member of a family but there is a well-documented literature indicating that this rare event happens more often than can be accounted for by coincidence. The cases described fall into three clear groups.

i) Neonatal myasthenia gravis.
ii) Familial myasthenia gravis.
iii) Congenital myasthenia.

Neonatal myasthenia:

The first recognition of myasthenia gravis in the newborn child of a myasthenic mother by Strickroot et al, (1942) was confirmed by Wilson and Stoner (1944) who reported two cases. Further reports soon followed. In 1960 Greer and Schotland were able to summarise 20 cases in the literature to that date and Millichap and Dodge (1960) added 10 further examples.

Where the fact is mentioned there appears to be general agreement that foetal movements are normal before birth. The baby is, however, very weak at birth or within a few hours of it and, if untreated, is likely to die of respiratory failure. There is severe weakness of bulbar, spinal, thoracic and limb muscles and ptosis is common but Levin (1949) comments on the rarity of external ophthalmoplegia. The exact duration of the illness is a little uncertain as the baby has usually died within a few hours or has been maintained on neostigmine for several weeks but from the vague accounts in the reported cases it appears to be more than one week but probably less than two months. Recurrence/

Recurrence has never been reported except for the possible case described by Osserman (1958). His patient, the child of a myasthenic mother, had difficulty with sucking and swallowing after birth. This persisted for 'several weeks' and then disappeared without specific medication. Symptoms of muscular weakness reappeared at 2 years of age.

The occurrence of neonatal myasthenia is unrelated to the severity of myasthenia in the mother and does not occur with every pregnancy, even with subsequent ones (NH12172, MN3912, MN4186). Removal of the mother's thymus before or during pregnancy does not prevent the baby from having neonatal myasthenia (Levin, 1949; Nilsby, 1949; Geddes and Kidd, 1951). This is confirmed by the history of cases GK/PB, GK/LB (described in Chapter 5) and of GK/MM who had a myasthenic child three years after thymectomy. The latter case was not taking neostigmine or similar drugs throughout the pregnancy. Six years later the mother's myasthenia relapsed after a miscarriage.

In the patients observed by me, 59 women had 81 known pregnancies with 70 live births. Of these 64 were normal. There were three definitely myasthenic babies and another three in which the baby was weak at birth but recovered without specific treatment. The three confirmed cases were born before I saw their mothers and I have not had the opportunity to observe neonatal myasthenia although I have attended the labours of some myasthenic women.

The transient nature of neonatal myasthenia is best accounted for by the temporary presence in the infant of a toxic substance which has passed through the placenta from the mother. The rarity of this event makes it unlikely that neostigmine passing from mother to child prevents normal end-plate maturation and case GK/MM was not having drugs/

drugs throughout pregnancy. Persistence of the effect for 3-6 weeks is, on the other hand, an unusually long time for a toxic substance to persist. It is about the duration of persistence of maternal antibodies in the infant's bloodstream (Chapter 14) and I have suggested that this might be the mechanism of neonatal myasthenia (Simpson, 1960a, Appendix C). The rarity of such an event (about 1 in 25 births) would be accounted for if the postulated antibody was inactive unless the infant's muscle was antigenically similar to the mother's. A possible argument against this is the occurrence of neonatal myasthenia in babies born after thymectomy has been carried out in the mother. This is a less serious objection than it may seem since there is no doubt that Hashimoto's disease and other immunological disorders may occur after the thymus has been removed (Chapter 13), nor need it be supposed that the continuing presence of the thymus is necessary for the production of antibody.

Familial myasthenia gravis:

There are also a number of reports of families with more than one case of myasthenia gravis. These have usually occurred in pairs of siblings of either sex (Oppenheim, 1898; Marinesco, 1908; Hart, 1927; Riley and Frocht, 1943; Mancusi-Ungaro, 1927). Rothbart (1937) described 4 brothers with myasthenia beginning in infancy and Noyes (1930) a father and 2 daughters. In a personal communication to Levin (1949), Dr. L.M. Eaton described 2 infant brothers and 12 year old twin sisters with symptoms of myasthenia gravis. In none of these cases was the mother known to be myasthenic. Teng and Osserman (1956) reported two families of myasthenia in adult siblings but sibling/

sibling incidence was much greater in the juveniles with myasthenia gravis and there was also involvement of first cousins. This review of the literature suggests that there is a high familial incidence when myasthenia first appears in childhood or adolescence.

The descriptions leave room for doubt in some cases regarding a distinction from the group termed Congenital Myasthenia (vide infra). Nevertheless I feel there is a place for a separate group in view of the families I have seen.

Case NH62033 was admitted to the National Hospital (Sir Gordon Holmes) in 1932 with myasthenia gravis starting one year previously when she was 22. There were remissions from 1934 to 1937 and then after a short relapse from 1937 to 1955 when I saw her in Dr. E.A. Carmichael's ward. Her grandfather was also the great grandfather of the next case (Fig. 8,1).

Case NH29555 was admitted to the National Hospital in February, 1951. Sir Francis Walshe diagnosed myasthenia gravis. His age was 27 years. He had a thymectomy in 1951 (Sir Geoffrey Keynes) and was having only rare myasthenic symptoms when I saw him in 1955. There were no other known cases of myasthenia in the family but at that time I was not aware of the possible link with other diseases (Fig. 8,1).

Case MN4275. This 27 year old virologist undoubtedly had myasthenia gravis (Fig. 8,2). There was a typical history of remissions, and of intermittent ptosis, diplopia, dysphagia and weakness of limb muscles increased by effort and relieved by rest. For three weeks soon after the onset she had persistent paraesthesia of the hands/

hands and feet. The response to neostigmine was excellent. Thymectomy in December, 1959 (Mr. Andrew Logan) revealed a large fleshy thymus described as being 'uninvoluted'. She had a temporary relapse after a road accident one year later.

She was adopted as a child but her doctor was aware that her real mother had been taking neostigmine for some time before her death at the age of 30. It is believed that she had ptosis and that her death was due to myasthenia gravis.

Case NH12374. She complained of weakness after a febrile illness with disturbance of consciousness in 1935. Sir Gordon Holmes diagnosed myasthenia gravis. She became steadily worse while taking ephedrine but in 1948 had an excellent response to neostigmine by injection. Thymectomy in that year was followed by immediate improvement but she died in 1951 (aged 51) after gastroenteritis.

Her father was still alive, aged 70, surviving removal of a rectal carcinoma. He had no symptoms of myasthenia but his mother had died at the age of 65 after thirty years of progressive weakness of all limbs, eyelids and bulbar muscles. She had a goitre. The patient's aunt (aged 76) had been unable to use her arms or to walk about for 10 years. She had thyroidectomy for goitre. Other members of the family had exophthalmic goitre. (Fig. 8,1).

Case MN4650. This patient is described in Chapter 7 as she had pernicious anaemia for 16 years before the onset of ocular myasthenia at the age of 42 years. She had also developed arthritis of the feet and hands at some/

some previous date. Her mother, aunts and uncles had familial ptosis (and possibly blindness) and her sister had ocular myasthenia gravis. Unfortunately the sister had died a few months earlier but both sisters were examined in Glasgow Eye Infirmary by Dr. J.B. Gaylor and shown to have partial response to neostigmine. Both sisters are illustrated in Fig. 8,3 and the family tree is shown in Fig. 8,4. The pattern is more suggestive of familial ptosis (or ocular myopathy) but the propositus was convinced that neostigmine improved her ptosis. Electomyography of peripheral muscles was normal and I was unable to convince myself that the ptosis was truly myasthenic. In some ways she resembled the 'benign congenital myopathy with myasthenic features' described in Appendix B or the 'congenital myasthenia' described in the next section.

The same problem of diagnosis is present in the following cases:-

Case NH19087 began to have ptosis and diplopia when she was 59. She was hypertensive (B.P. 170/120) and suffered from migraine headaches. She complained of attacks of profound fatigue but not of muscular weakness. Neostigmine caused fasciculation of the eyelids and diplopia was increased. Her father, who also suffered from migraine, had ptosis and cataract and her son was said to have 'sleepy eyes'.

It will be seen that the evidence for familial occurrence of true myasthenia gravis is not convincingly supported by the present series with the possible exception of/

of the first two cases cited. Nevertheless in view of the reports quoted above it must be considered whether there may not be a hereditary factor in myasthenia gravis. If there is, it must be of very low penetrance since I have seen one patient (NH31239) who has an identical twin without the disease (Fig. 8,5) (Simpson, 1964c). Similar cases have been recorded previously (Alter and Talbert, 1960).

Another approach might be to consider the possibility that an abnormal gene may have different expressions. In Chapter 5 it is shown that there is an unusually high incidence of disease of the thyroid (and possibly of diabetes mellitus) in the siblings and progenitors of myasthenic patients. Unfortunately much of the data was obtained before the possible significance was appreciated and so the true incidence is unknown. In addition it is regrettable that no enquiry was made regarding rheumatoid arthritis or pernicious anaemia since a hereditary factor is highly probable in these diseases too. I have suggested that a genetic factor might act through a hypothalamo-pituitary mechanism, sometimes causing thyroid disease, at other times a disorder of the thymic regulation of immunological tolerance (Simpson, 1960a, Appendix D). This will be discussed in Chapter 14.

Congenital myasthenia:

While I have no doubt that 'neonatal' myasthenia is a true type of myasthenia gravis I have indicated some doubts about the nosological status of the 'familial case'. The status of the next group is even less assured. Levin (1949) applied the term 'congenital myasthenia' to a syndrome occurring in siblings and cousins. The mothers never/

never showed myasthenic symptoms (and one mother had a normal reaction to quinine). Unlike neonatal myasthenia it was often noted that the foetal movements were weak. There was considerable myasthenic weakness increasing with effort and worse towards evening, involving mainly the eyelids and extra-ocular muscles, but usually with generalised hypotonia. Levin drew attention to the striking symmetry of involvement, differing in this respect from most cases of true myasthenia gravis. In all of the cases described by him there was an excellent therapeutic response to oral administration of neostigmine (but the marked colic reported in one case may indicate some difference from true myasthenia gravis). The natural history of the disorder in the cases described by Levin (1949) was also different from myasthenia gravis. There were no remissions and the disorder was not progressive. In fact there was a tendency for slow improvement to occur after the age of 6-10 years. Levin concludes that congenital myasthenia differs from neonatal myasthenia as it probably begins prenataly and that it is probably genetic in origin.

Walsh and Hoyt (1959) accept Levin's classification of myasthenia in children into neonatal, familial, 'normal' myasthenia of early onset, and congenital. They describe a family of six children in which the four boys had symmetrical, neostigmine-responsive weakness of eyelids and external ophthalmoplegia conforming exactly to the 'congenital' type of Levin. The oldest brother (aged 18) also had severe generalised weakness and fatiguability of his limb musculature which was symmetrical and which showed neither remissions nor improvement with time but which responded/

responded dramatically to neostigmine. Electromyography carried out in two of these (by Dr. David Grob) 'showed classic fatiguing of muscle with 'fall-out' of action potentials, immediately restored to normal by injection of edrophonium'. Unfortunately it is not stated whether this description applies to the electromyogram of a voluntary contraction or to the muscle response to faradisation of the motor nerve.

Descamps (1955) reported two sisters with ptosis first noticed at the age of 10 and at birth respectively. The symptoms are described as 'myasthenic' but were aggravated by neostigmine. From the description in this paper it seems possible that the test may have been carried out while each girl was already showing symptoms of overdosage of neostigmine taken by mouth. Since 'fatigue' is sometimes complained of by patients with congenital ptosis and pseudoptosis (Chapter 9) or with the ocular type of muscular dystrophy (personal experience), it may be that these cases are not true examples of Congenital Myasthenia.

Through the kindness of Professor J.A. Hutchison of the Royal Hospital for Sick Children, Glasgow, I have been able to examine two sisters whom I believe to have congenital myasthenia of the type described.

Case MN6140 was a full time baby. Foetal movements had been normal but at her birth she required an oxygen tent owing to feeble movements. She never sucked well. At the third or fourth month her mother noticed bilateral ptosis which did not vary. When she was weaned she had frequent choking attacks with small pieces of food. At one year she had whooping cough and pneumonia. In a hospital/

hospital in London at that time she was considered to have myasthenia gravis. Neostigmine 37.5mg. by mouth every four hours kept her well but she was nearly 18 months old before she walked though she was alert and talking well.

When she was 3 her thymus was removed without obvious benefit but there was no further deterioration. She was able to discontinue neostigmine at the age of 9 and was able to attend school. Though unable to skip or to walk quickly up stairs, she was fit for most activities; but ptosis persisted and when I saw her at the age of 10 she could not close her eyes completely. She had never had diplopia and ptosis was always bilateral.

Both parents, who were unrelated, were alive and well and had never had ptosis or muscular weakness. A younger sister had a similar disorder.

When I examined her in January, 1962, there was bilateral ptosis (Fig. 8,6). It was little if at all increased by fixing the gaze above head level. Eye movements were restricted in all directions, orbicularis oculi and the retractor muscles of the mouth were weak bilaterally. There was also weakness of the neck flexors and of the proximal muscles of the limbs. The upper limb jerks could not be elicited but lower limb reflexes were normal. There was a suggestion of early 'triple grooving' of the tongue.

Case MN6139. The younger sister of MN6140 was aged 4 when I saw her in 1962. Foetal movements had been normal and the birth uneventful. She was an active baby/

baby who walked at eleven months. Ptosis was noticed by a surgeon when she visited the Royal Hospital for Sick Children, Glasgow, with her sister. She had no difficulty chewing or swallowing but tended to have nasal speech when tired.

In 1962 there was symmetrical ptosis which receded only slightly with neostigmine (Fig. 8.7). It was slightly increased by attempting to look up for half a minute. Upward and horizontal movements of both eyes were greatly reduced. There was very little palatal movement and the tongue resembled her sister's. There was slight weakness of neck flexion and of the deltoids and hip flexor muscles but it was not marked. Upper limb jerks were depressed but others were normal.

This child was much less severely affected than her sister but there was no doubt that she was suffering from the same condition. The response to neostigmine was even less impressive.

Benign congenital myopathy with myasthenic features:

Walsh and Hoyt (1956) consider that an unusual case which I have described previously (Walton et al, 1956) may be an example of Congenital Myasthenia. The details of this case may be consulted in Appendix B. (Note - because of the doubt about the classification of this case, NH4830, it has not been included in the statistical analysis in other chapters). This patient differed from those described by Levin (1949) in having two unaffected sisters. Prenatal and infantile muscular activity was normal. Symptoms started when she was aged 9-10 months when severe generalised weakness developed including bilateral ptosis. Proximal/

Proximal muscles of the limbs were more affected than distal ones. A Harvey-Masland test for myasthenia gravis was negative and needle electromyography showed evidence of myopathy. Biopsy showed minimal myopathic changes. No abnormality of carbohydrate metabolism of muscle could be detected to account for the weakness and there was no change when the blood potassium level was lowered. Unlike Levin's cases the response to neostigmine was only moderate. A slightly better and more sustained response followed administration of ephedrine. In these respects the syndrome bore only the most superficial of resemblances to myasthenia gravis. Nevertheless there was a very striking tolerance to decamethonium such as has only been described in myasthenia gravis (Churchill-Davidson and Richardson, 1952) (see Chapter 17). As will be seen from Fig. 8,8 the injection of decamethonium caused a temporary increase in the number of muscle fibres responding to supramaximal stimulation of the motor nerve.

The patient was considered to have a benign congenital myopathy with myasthenic features. I am certain that she did not have myasthenia gravis and there are obvious differences from Levin's (1949) cases of congenital myasthenia but the suggestion of Walsh and Hoyt (1956) that our case was related to Levin's syndrome is interesting and may be justified.

Neuromuscular transmission in the infant:

In view of the obvious clinical differences between Congenital Myasthenia and all other types, in particular its symmetry and tendency to improve, it would be interesting to consider whether there are any differences between newly born children and adults with regard to neuromuscular/

neuromuscular transmission.

Anaesthetists have sometimes noticed that newborn infants tolerate relatively large doses of depolarizing relaxants and yet are very sensitive to the non-depolarizing ('competitive') type (Stead, 1955; Rees, 1959). In this respect the muscle of the newborn infant resembles that of myasthenia gravis in adults (Chapter 15). Churchill-Davidson and Wise (1963) have studied the effect of decamethonium iodide on newborn infants, many of which were premature. They used the Harvey-Masland technique to study the ability of the neuromuscular junction to transmit a series of impulses at rates from 2.5 to 50/second, with the usual precautions described in Chapter 15. The infants were lightly anaesthetised and respiration was assisted. At twitch rates of stimulation (2.5/sec) the height of the action potentials was well sustained. Tetanic stimulation was not well tolerated. After a period of 20 seconds the action potentials had often decreased to less than half their original size. In 3 infants there was post-tetanic facilitation for a few seconds and in 4 out of 7 studies a period of post-tetanic exhaustion was observed which lasted up to 15 minutes.

Churchill-Davidson and Wise confirmed that the infants were relatively tolerant of decamethonium since the dose required to paralyse the limb muscles was 2-3 times the adult dose when calculated on a weight basis. When the nerve was tetanised a decrementing response was obtained with post-tetanic facilitation. The decrement was noted even at slow rates of stimulation (2.5/sec), resembling/

resembling the effect of a 'competitive' blocking substance in the adult. A further resemblance was that the neuromuscular block caused in the infant by decamethonium was always reversed to some extent by the injection of neostigmine.

The possible mechanisms involved in the 'myasthenic' response will be discussed in Chapter 16 but at this stage it need only be said that the above findings are compatible with three possibilities, (i) exhaustion of acetylcholine production at motor nerve terminals, (ii) a difference between the infant and the adult end-plate receptors, (iii) a circulating substance which can compete with acetylcholine for receptors. The third hypothesis has many points in its favour in true myasthenia gravis and particularly in Neonatal Myasthenia. It does not seem likely that this mechanism could account for the low 'safety-factor' of transmission in the newborn. A suggestion by Keynes (1954) that the thymus might produce such a substance to inhibit foetal movement cannot be taken seriously. It is much more likely that the safety-factor is lower in the neonatal period because of immaturity of the lower motor neurone or relative inadequacy of the ratio of pre-synaptic to post-synaptic membrane as demonstrated in foetal rats by Diamond and Miledi (1962). These authors showed that the receptor surface was adequately sensitive to acetylcholine but was spread over a large area of the muscle fibre. The chemo-sensitivity of the embryonic rat muscle fibres was similar to that of re-innervated muscle (Miledi, 1960).

Both pre- and post-synaptic factors may be present since there is evidence to show that the maturation of/

of the muscle fibre and particularly of the end-plate region depends on a factor released by the nerve endings. Whether this factor is acetylcholine (which is liberated spontaneously in small amounts) or an unidentified substance is unknown at the time of writing (Miledi, 1962). Exactly the same difficulty arises with regard to the transmission failure in myasthenia gravis and it is quite possible that there is both a pre-synaptic and a post-synaptic defect in that disease (Chapter 16).

The physiological work just reviewed refers to the normal infant. It requires little straining of the facts to postulate that failure of normal maturation could occur as a hereditary abnormality. The symmetry of distribution, absence of remissions and tendency to improve in later life suggest that Congenital Myasthenia may be due to a maturation failure of this type. This concept would place Congenital Myasthenia closer to the condition known as Benign Congenital Hypotonia of infancy (as suggested by Walsh and Hoyt, 1956) than to myasthenia gravis. I believe that this is its true nosological position.

CHAPTER 9.

MYASTHENIC SYNDROMES.

For the purposes of this thesis, in which it was required to show that disorders other than neuromuscular could co-exist with myasthenia gravis, it was necessary to use strict diagnostic criteria which would be acceptable to all workers in the field. These were:-

i) There must be demonstrable weakness of muscles which increased with maintained or repeated contraction and decreased with rest. Mere tiredness or a complaint of 'fatiguability' was not considered adequate.

ii) There must be a clear-cut response to anticholinesterase drugs such as edrophonium or neostigmine.

Neostigmine-resistant muscle disease:

It is not intended here to enter the debate on the validity of the second criterion which has recently been discussed by Rowland et al (1958) but it is now necessary to examine some cases which have proved difficult to classify because of inadequacy of the response to a therapeutic test.

In Chapter 8 and Appendix B I have described a patient previously reported as a case of 'Benign Congenital Myopathy with Myasthenic Features' which was considered to be in a borderland of myopathy and Myasthenia (Walton et al, 1956). In the following cases there were features strongly suggestive of myasthenia gravis but the diagnosis was not considered sufficiently/

sufficiently well established for inclusion in the main series.

Case NM74. In 1949, when aged 35, this woman who had had a non-toxic goitre for 20 years noticed double vision followed by left sided ptosis. In the next 3 years she developed almost complete bilateral extraocular ophthalmoplegia. In 1954 her skin was moist, fingers tremulous and pulse rate 105-130/minute. She had occasional 'rheumatic pains' in her knees and shoulders. A radioiodine test at Edinburgh Royal Infirmary showed thyrotoxicosis. This subsided after treatment for 1 year with thiouracil.

In 1957 she developed arthritis of rheumatoid type in both hands (Fig. 9,1), wrists and elbows. In 1960 her neck began to ache and chewing became weak, forcing her to support her jaw and head with her hand (Fig. 9,2). Her voice became weak and all limbs became excessively tired, especially proximally (Fig. 9,3). She was admitted to the Northern General Hospital in May, 1960 under the care of Dr. J.E. Stanton because of difficulty in swallowing. At that time she also complained of retrosternal 'tightness'. She was breathless on slight exertion and had oedema of her ankles in the evenings.

She had psoriasis of the elbows and erythema and scaling of the palmar surface of the hands (Fig. 9,1). Her tongue showed triple grooving and she had Raynaud's phenomenon.

In all respects the picture was one of myasthenia gravis complicated by previous thyrotoxicosis, 'rheumatoid'/

'rheumatoid' arthritis, and psoriasis. I examined her by electromyography and found a myositic pattern in the muscles of the right arm. There was no evidence of pathological fatiguability with the Harvey-Masland test but an incrementing response was obtained (Chapter 15). She showed resistance to paralysis by decamethonium in the relatively unaffected muscles of her hands but when weakness appeared the response to a slow tetanus became decremental although it was still incremental with stimulation faster than 16/sec. The results of these tests were in keeping with a diagnosis of myasthenia gravis but there was no response to repeated injections of edrophonium or to neostigmine by injection or by mouth.

A glucose tolerance test was normal; serum proteins were 7.25g/100ml. with an electrophoretic pattern showing a slight increase of the gamma-globulin fraction. The cephalin-cholesterol flocculation test was positive (4), thymol turbidity 5 units. Serum cholesterol was 350mg/100ml. There was gross creatinuria. Serum electrolytes were normal and the urinary output of 17-hydroxycorticosteroids was 8.5mg. in 24 hours. The peripheral blood picture was normal and no antinuclear factor or L.E. cells were found. There was a positive sensitised sheep-cell test (1/128). The Wassermann reaction was negative in blood and C.S.F., the latter being normal in other respects.

A diagnosis of 'polymyositis' was made and she was treated with prednisolone. This made no obvious difference/

difference. On 7:7:60 she choked and did not respond to bronchoscopy and resuscitative measures.

Autopsy by Dr. A.F.J. Maloney showed severe 'myositis' with focal necrosis and infiltration by lymphocytes, plasma cells and histiocytes. Some small nerves in severely damaged muscles showed partial demyelination and endoneural fibrosis. Some peripheral nerve trunks also showed cellular infiltration. The central nervous system was normal. There was no vasculitis. The thyroid gland was hypertrophied (80gm) and slightly nodular. Other endocrine glands were normal. The thymus was not identified. The spleen was congested and slightly large (200gm) but was not histologically abnormal.

The final diagnosis in this case was 'polymyositis of unknown origin - ? dermatomyositis' but if she had responded to anticholinesterase drugs she would undoubtedly have been accepted as a case of myasthenia gravis.

Case MN1879. While in hospital for treatment of peptic ulcer in 1951 a doctor noticed that this man, then aged 22, had bilateral ptosis. This was progressive. It never remitted but seemed worse at night. His father and brother were said to have ptosis.

Examination revealed unsuspected weakness of biceps and triceps muscles of both arms and of the hamstring muscles of both legs. All reflexes were brisk and sensation was normal. He admitted that his voice tended to tire when talking for long periods.

My original diagnosis of myasthenia gravis seemed untenable/

untenable when no response was obtained to neostigmine and the possible family history suggested that he had ocular muscular dystrophy. On admission to the Northern General Hospital in 1956 he was found to have hypertension (B.P. 240/130mmHg) although the blood pressure recorded in 1953 was 135/80mmHg. Rogitine caused a sharp drop in the diastolic pressure but the systolic pressure rose by 10mm. As he had recently complained of pain in the left flank he was transferred to a urological unit for further investigation. Following retrograde catheterisation of the ureters he developed clot anuria. This was successfully relieved but he died suddenly on the following day.

Autopsy (Dr. N. Maclean) revealed no cause for the hypertension. The muscles were pale salmon-pink in colour and on histological examination showed acidophilic swelling of the sarcoplasm with mononuclear leucocytic reaction. There was proliferation of the sarcolemmal nuclei. A diagnosis of 'muscular dystrophy' was made but it was observed that the thymus (10.2gm) showed 'retarded involution'.

The clinical and pathological findings are strongly suggestive of a diagnosis of myasthenia gravis in every respect except the failure to respond to neostigmine.

The two cases cited are representative of five or six seen at the Northern General Hospital in the last eight years and provisionally diagnosed as 'polymyositis' because of the histological changes in the muscles and the absence of response to edrophonium or neostigmine.

Some/

Some have had a slight decrementing response to the Harvey-Masland test but more often they have shown a 'reverse myasthenic' incrementing response of muscle as is described in Case MN74. This reaction will be discussed from the electromyographic point of view in Chapter 15. It indicates that some muscle fibres are not recruited in twitch contractions but only when the acetylcholine released by the nerve terminals is increased by tetanic stimulation. I have found it to be a regular feature of many cases of polymyositis and in the 'burned out' stage of myasthenia gravis. A similar phenomenon may also be found in clinically unaffected muscles in myasthenia gravis (Simpson and Lenman, 1959; Simpson, 1960a). It differs only in degree from the phenomena considered by other authors to be 'diagnostic' of carcinomatous myasthenia.

Case MN1714 is an interesting case of polymyositis under the observation of Dr. J.B. Stanton at the Northern General Hospital since 1956. Weakness started in the pelvic girdle and spread to the diaphragm and upper limbs. Apart from slight weakness of the right side of the face the cranial muscles are unaffected. Power has improved in each of two pregnancies but otherwise there has been no remission and no variability throughout the day. There has been no response to edrophonium or neostigmine at any stage. Muscle contraction sometimes develops in a remarkable slow fashion described by Simpson and Lenman (1959). The Harvey-Masland test shows a slight 'myasthenic' reaction with slow stimulation and progressive increase in the evoked action potential with fast rates (Fig. 9.4).

The/

The slow recruitment of voluntary muscle contraction seemed to be of the same nature.

The cause of the muscular disease is unknown. She has a slight non-toxic goitre but certainly does not have myasthenia gravis.

The nosological position of polymyositis is debatable but, following the usage of Walton and Adams (1958) the term is limited to an acquired myopathy without recognisable lesion of the skin which may appear in acute, subacute, and chronic forms and is related to the connective tissue diseases such as dermatomyositis, arteritis and to malignant disease. Infective and endocrinal forms of acquired myopathy are excluded.

Polymyositis, with or without dermatitis, is sometimes associated with a myasthenic type of weakness which may be responsive to edrophonium or neostigmine (Benedek, 1944; Christensen and Levison, 1950; Ragan, 1950; Reese and Harman, 1954; Walton and Adams, 1958). In most of the reported cases the decrementing type of weakness has been transient or the response to neostigmine has not been maintained after the first few doses (Fig. 9,5) (van Bogaert and Radermecker, 1954; Eaton, 1954; Bonduelle, Bouygues and Coulon, 1955; Coërs, 1956). In some of these cases the diagnosis has been changed on many occasions from dermatomyositis to myasthenia gravis and back again. The true classification still perplexes the experts (Rowland et al, 1958).

Systemic Lupus Erythematosus:

A similar muscular weakness responding to neostigmine has been reported in systemic lupus erythematosus (Harvey et al, 1954; Rowland 1955). In one/

one of the cases reported by Simpson (1960a) (GK/ES Chapter 7) L.E. cells were found in the blood of a case of 'typical' myasthenia.

These observations have previously been considered to indicate that 'symptomatic myasthenia' may exist which simulates 'true' myasthenia gravis. Rowland (1955) and Rowland et al (1958) discuss the quandary which may exist when typical myasthenia gravis is shown to have the histological lesions of interstitial myositis which are described in Chapter 11. They label these cases as 'myasthenia gravis with polymyositis' but confess that there are no clinical criteria which differentiate these patients from ordinary myasthenia. When it is further considered that polymyositis may be associated with a thymoma (Bonduelle, Bordet et al, 1955; Waller et al, 1957), that Hashimoto's disease may be associated with dermatomyositis and with rheumatoid arthritis (Sharvill 1958), and that the Raynaud phenomenon and other disorders which I have associated with myasthenia gravis (Simpson, 1960a) are also common in the whole group of connective tissue diseases including polymyositis, it can only be concluded that there is a wide spectrum of closely related tissue reactions. The predominance of one or other clinical pattern may permit a 'disease' to be recognised, but the frequent overlap is no longer surprising.

Experimental myasthenic syndrome:

Mankowski (1963) has recently reported on the effects of injection of the yeast Candida albicans into the spleen of rats. In most cases no disseminated infection occurred but many of the animals developed neoplastic/

neoplastic conditions or a variety of connective tissue disorders thought to resemble human dermatomyositis, scleroderma and periarteritis nodosa. Three rats showed muscular weakness which improved with injection of neostigmine. The author describes them as having 'myasthenia gravis'. It seems more probable that the condition of these rats is more like the myasthenia of human dermatomyositis. Nevertheless the prospect of having an experimental myasthenic preparation to investigate is most exciting particularly since it's causation appears to be due to a disorder of the reticuloendothelial system.

Carcinomatous myasthenia:

In view of the definite though unexplained relationship between dermatomyositis and neoplasia (Walton and Adams, 1958) it is not surprising to find occasional cases of a myasthenic syndrome associated with neoplasm in some organ. This was first reported by Anderson et al (1953). These authors described a man aged 47 with progressive muscular weakness and transient diplopia. Weakness did not increase with maintained contraction of the muscles and myasthenia was apparently not considered in the first instance. After radiography of the chest and bronchoscopy he was found to have a bronchial neoplasm. When anaesthetised for bronchoscopy he was given succinylcholine, a relaxant drug of depolarising type. There was prolonged apnoea following this and electrodiagnostic tests revealed considerable neuromuscular block. Blood cholinesterase levels were normal. On testing the effect of another depolarizing drug, decamethonium by the technique introduced by two of the/

the authors (Chapter 17) the changes typical of myasthenia gravis were noted. Administration of neostigmine then improved skeletal muscle power. This paper immediately produced a number of letters to the Lancet describing similar cases in some of which the weakness increased with continuous use of the affected muscles.

In the same year Henson (1953), reporting on motor neuropathy and myopathy associated with carcinoma of the bronchus, noted that some of the patients had a history of muscular fatiguability suggestive of myasthenia and these were further reported by Henson et al (1954) and Brain and Henson (1958). In the latter paper, three of the fifteen women with carcinomatous neuromyopathy (not all myasthenic) had unexplained myxoedema. Chamberlain and Whittaker (1963) reporting an association between Hashimoto's disease, dermatomyositis and ovarian carcinoma suggest that their experience might offer an explanation for the myxoedema noted by Brain and Henson (1958). This interesting suggestion should be confirmed as it would support the proposition that carcinomatous myasthenia is related to the non-malignant autoimmune diseases. Walton and Adams (1958) already accept carcinomatous myopathy as a variant of polymyositis. Tumour antigens have been demonstrated in the serum of patients with various neoplastic diseases and have been shown to be capable of provoking the formation of antibodies of circulating type (Makari, 1958; Curtis et al, 1961). References to the rapidly expanding literature are provided by Rowland et al (1958).

Further experience has shown differences between carcinomatous/

carcinomatous myasthenia and classical myasthenia gravis. The neostigmine response is less satisfactory and tends to disappear as the disease progresses. The extraocular and bulbar muscles are less frequently and less severely affected in carcinomatous myasthenia and the tendon jerks, especially of the lower limbs, are depressed or absent (Croft, 1958). The latter phenomenon is strikingly different from the state of the reflexes in true myasthenia gravis. In that condition they are usually present and commonly very brisk (Simpson, 1960a). This clinical point led to the diagnosis of bronchial carcinoma in the following case.

Case MN7531. This 48 year old woman was referred to me at the Northern General Hospital as a case of myasthenia gravis due to a thymoma (Fig. 9,6). She had been well until six months previously when she was aware of difficulty with swallowing. Soon after this her left leg and then her right leg became weak. At about the same time she found that she was unable to apply any pressure with her right hand. There was little variation in her strength during the day but she thought it possible that it was worse in the evening. Shortly before admission she had increased difficulty in swallowing, slurring of speech and weakness of the neck and shoulder muscles. She had never noticed ptosis, diplopia or weakness of the face. Although she had responded to neostigmine in the referring hospital this had become less satisfactory.

On examination she had rather drooping eyelids but no 'fatiguability' was demonstrated. There was weakness of the neck and proximal muscles of the limbs but, unlike myasthenia gravis, this was greatest in/

in the lower limbs which were wasted. All tendon jerks were severely depressed. Electromyography showed the response described below. Since these clinical and electrical features pointed to a carcinomatous myasthenia the 'thymoma' was re-examined by tomography and found to consist of a mass of glands which were compressing and invading the right main bronchus. Bronchoscopic biopsy showed that the lesion was a bronchial carcinoma. No L.E. cells or A.N.F. were found in the serum. Protein-bound iodine level was 5.2 µg%; the serum protein level was 7.5g/100ml. and electrophoresis showed slight excess of beta-globulin. Cephalin-cholesterol flocculation was negative but the thymol turbidity test gave 6 units. Serum G.P. and G.O. transaminases were each 11 units and serum aldolase 9 units/ml. which are normal findings. The E.S.R. was normal (13mm. in the first hour, Westergren).

Case MN7024. This 47 year old woman was admitted to the Department of Thoracic Surgery, Edinburgh Royal Infirmary in January, 1963 with an anaplastic carcinoma of the mediastinum. Mr. J.D. Wade considered that it could not be removed when he examined it at thoracotomy. Five months previously she had noticed that her legs felt 'heavy' and a little later she had difficulty washing her face. She had double vision on a few occasions but had not observed ptosis or difficulty in swallowing. In January, 1963 slight bilateral ptosis developed after looking upwards for 1½ minutes. Jaw muscles were fatiguable.

All/

All upper limb and trunk muscles showed progressive loss of power on attempted contraction, and there was practically no voluntary power in the lower limbs. The knee and ankle jerks were absent and the upper limb jerks depressed. There was no response to edrophonium or neostigmine.

Plasma protein content was 7.0g/100ml. The electrophoretic curve was within normal limits (? slight elevation of alpha 2 globulin). Thymol turbidity was 3 units. The E.S.R. was 27 mm. in the first hour (Westergren). The protein-bound iodine content of the serum was 8.1µg/100ml. but a radioiodine test of thyroid function was normal. The blood picture was normal apart from 6% of eosinophils. No L.E. cells were seen and no antibodies against thyroid, stomach or liver were detected (Dr. W.J. Irvine).

She died one month later. No autopsy was obtained.

Electromyography in this patient showed 'myopathic' units in all the muscles tested. When the ulnar nerve was stimulated at a slow rate (2·5/sec) a 'myasthenic fade' was seen. Faster stimulation (20/sec) caused an initial decrement followed by progressive increment until the evoked muscular action potential was 600% above its original level. On returning to slow rates of stimulation the decrementing 'myasthenic' response reappeared (Fig. 9,7).

Case MN8280. This 34 year old woman provided a difficult diagnostic problem. When admitted to Edinburgh Royal Infirmary in October 1963 under the care/

care of Dr. J.M. Hamilton she gave a history of steadily progressive weakness of the lower limbs beginning five months earlier. Soon afterwards the upper limbs became weak and clumsy and two months after the onset she had attacks of vertigo, blurred vision and intermittent diplopia. Relatives noted that her left eyelid was drooping. Two years earlier her mother had died of a similar illness after 20 years of disability. Both were considered to have disseminated sclerosis. The diagnosis was supported by evidence of ataxia and equivocal but probably extensor plantar reflexes. Ptosis was attributed to a recovering Horner's syndrome. A slight opacity at the apex of the left lung was calcified and considered to be tuberculous and a right hilar shadow was interpreted in the same way.

In May 1964 she was readmitted with profound generalised weakness and wasting, bilateral ptosis and absent tendon reflexes. Plantar responses were still extensor from the lateral borders of the feet and she had scanning dysarthria and nystagmus in all directions. Injection of edrophonium increased the time for which she could hold out her left arm from 25 seconds to five minutes and 50 seconds. The chest radiograph now showed an obvious bronchial carcinoma. I saw her in consultation at that time and agreed with Dr. Hamilton that she had carcinomatous neuropathy of central and neuromuscular types.

At the Northern General Hospital I measured the conduction velocity of the left ulnar nerve by the method described previously (Simpson, 1956). It was normal/

normal but on tetanising the nerve a 'fatiguable' response was evoked from the abductor digiti minimi muscle. This was abolished by injection of edrophonium (10mg. intravenously). No incrementing response was obtained at any time in this case. The injection of edrophonium also reversed temporarily the bilateral ptosis. This case was seen while the thesis was being written and is still alive.

Case NH38140 complained of difficulty in chewing early in 1950 and soon developed generalised myasthenia with incomplete response to neostigmine. In the same year she had bilateral mastectomy for carcinoma of the breast. She died in July 1953 and post mortem revealed anaplastic adenocarcinoma of the tracheo-bronchial lymph gland. It is unfortunate that the thymus was not examined as this case is said to have had brisk reflexes. She was seen before the syndrome of carcinomatous myasthenia was recognised.

Case GK/AB was also seen in 1950 by Dr. E.A. Carmichael and Mr. Geoffrey Keynes prior to recognition of the syndrome. She had carcinoma of the breast treated four years previously. The presenting symptom was diplopia and later there was ptosis and bulbar weakness. There is no record of limb weakness or of the state of the reflexes but this patient is said to have responded well to neostigmine. She was treated by irradiation of the thymus but died in April 1951.

(Two other cases who died of carcinoma, NH/PS/LB and NH/EC/IM probably had this as a late complication of myasthenia gravis).

The/

The unusual electromyographic phenomenon in carcinomatous myasthenia was first described by Eaton and Lambert (1957). Using the stimulation and recording technique of Harvey and Masland (1941) described in Chapter 15, they found that the first muscle potential evoked by a supramaximal electrical stimulus applied to its motor nerve was subnormal but on repeating the stimulus at short intervals there was marked facilitation. The same phenomena could be induced by voluntary contraction of the muscle. Post-tetanic exhaustion lasting for 2-4 minutes was also noted. A characteristic incrementing response was recorded from the case just described when the nerve was tetanised at a fast rate, but a decrementing response with slow rates of stimulation.

The incremental response described by Eaton and Lambert (1957) has been considered by them and by later authors to be diagnostic of carcinomatous myasthenia. Wise and MacDermot (1962) showed that the incremental response to fast rates of stimulation may be changed to a 'fade' of myasthenic type with stimulation at 5/second or slower. It is my opinion (Simpson, 1964b) that these electromyographic changes are not specific for carcinomatous myasthenia since I have previously reported similar findings in different types of acquired myopathy ('polymyositis') and even in myasthenia gravis (Simpson , 1960a,b). The matter is discussed further in Chapter 16. It is not questioned that the incrementing response is highly characteristic of, and perhaps best developed in, carcinomatous myasthenia but it is important to make the point that the disturbance of physiology is not unique to that/

that condition and does not clearly differentiate its mechanism from that of true myasthenia gravis.

It is unfortunate that many papers discuss carcinomatous neuropathy, myopathy and myasthenia without making it clear whether these are discrete syndromes or whether the author's investigations are confined to one or other group. Eaton and Lambert (1957) noted extreme sensitivity to curare in their cases of carcinomatous myasthenia. Croft (1958) described similar excessive response to curare in three patients with carcinomatous neuropathy but without overt myasthenia. Two other patients with carcinoma but without obvious neurological disorder showed similar abnormal sensitivity. His conclusions were critically discussed in an ensuing correspondence by anaesthetists who considered that there were alternative explanations for his observations. Croft claimed that prolonged response to suxemethonium occurred in one of his cases, like the first case reported by Anderson et al (1953). Wise and MacDermot (1962) found that their cases of carcinomatous myasthenia with the Eaton-Lambert electromyographic sign were paralysed by an unusually small dose of decamethonium. Though the paralysis so produced was partially reversed by neostigmine this sensitivity is the converse of the response in true myasthenia gravis (Churchill-Davidson and Richardson, 1953). They examined the motor end-plates by the special techniques described in Chapter 11 and found 'a non-specific degenerative process affecting the distal nerves and motor end-plates' but without the particular features claimed to be specific for myasthenia gravis.

It must be concluded that carcinomatous myasthenia differs in clinical, electromyographic, pharmacological and histological details from true myasthenia. Nevertheless there are obvious resemblances and it may be that the differences are quantitative. It is not possible at present to reach any definite conclusion.

Ocular myopathy and exophthalmic ophthalmoplegia:

Ocular myopathy is normally of importance in the present context only as a problem of differential diagnosis. There is no difficulty if the weakness is lessened by injection of neostigmine as most authorities would consider the appropriate diagnosis was ocular myasthenia. The difficulty arises in cases which do not respond to anticholinesterase drugs but in which weakness is increased by an abnormally small dose of curare. Cases have been reported by Rowland (1955), Walsh (1957) and Ross (1963) and in association with thyrotoxic ophthalmoplegia by Millikan and Haines (1953). Rowland and Eskenazi (1956) consider that curare-sensitivity indicates ocular myasthenia, but there is little doubt from the careful study of Ross (1963) that curare-sensitivity is common in ocular and limb muscles in the ocular type of hereditary muscular dystrophy.

Rowland et al (1958) review the literature to that date and consider that 'if variability is not a feature of an ophthalmoplegic syndrome and tests with neostigmine and curare are negative, the diagnosis of ocular myopathy seems justified. If variability is a feature, myasthenia may still be considered, no matter what the histological and electromyographic findings, even when neostigmine and curare tests are negative, but the diagnosis/

diagnosis cannot be made with certainty unless these drugs evoke a response.' This aptly summarises the position from the practical point of view but leaves room for argument where, as in some cases of exophthalmic ophthalmoplegia, there is apparent improvement in eye movements after injection of neostigmine. I agree with Rowland et al (1958) that such a case should be considered to have myasthenia gravis in association with hyperthyroidism.

Case MN5809 was referred from the Endocrine Clinic of the Western General Hospital, Edinburgh, by Dr. J. Strong. She was a 26 year old woman complaining of weight loss, vomiting and goitre. Previous symptoms had suggested thyrotoxicosis but specific testing had produced equivocal results. She was noted to have bilateral ptosis (Fig. 9,10) and intermittent paresis of both lateral recti although she had rarely noticed double vision. The lateral rectus weakness was apparently reversed by edrophonium but ptosis was unaffected or worse. The curare sensitivity test showed no abnormality but a decamethonium test using the left ulnar nerve and a hand muscle (Chapter 17) gave results intermediate between those of a normal and a myasthenic person. No diagnosis has yet been made.

Congenital ptosis and 'pseudoptosis'.

The same considerations apply to congenital ptosis. This is often hereditary. When it appears in childhood it may be extremely difficult to differentiate from the congenital/

congenital type of myasthenia (Chapter 8). In my opinion neither of these syndromes is related to true myasthenia gravis. The ptosis, sometimes familial, which appears in elderly women is termed 'pseudoptosis' by Walsh (1957) who attributes it to local changes in soft tissues which permit sagging of the lids. Some authors consider that it is a form of ocular myopathy (Fuchs, 1890; Kiloh and Nevin, 1951). Like the latter disorder it may cause difficulty in diagnosis as the ptosis is more prominent when the patient is tired. In my experience of four cases the ptosis was not significantly increased by fixing the gaze upwards or by repeated opening and closure of the eyes and the 'tiredness' complained of was fatigue or drowsiness rather than true myasthenic weakness. In my opinion this is not a form of myasthenia gravis.

Case MN5765, a retired schoolmistress aged 64, complained that her eyes had been 'heavy' when driving her car for the previous year. There was no other weakness and neostigmine given by Dr. Henry Miller, Newcastle, who kindly referred her to me, had been unhelpful. Her mother had had diabetes and thyrotoxicosis. There was no familial history of ptosis.

There was apparent 'fatigue' of the eyelids when she concentrated on visual work and a tendency to spasmodic contraction of orbicularis oculi was noticed on both sides. No paretic ptosis could be demonstrated (Fig. 9, 9). Curare sensitivity was normal and a decamethonium test within normal limits.

The possibility of a tic (blepharospasm) was considered. There was certainly no evidence of myasthenia gravis. In April 1963 the difficulty in keeping/

keeping her eyes open was so much worse that she had to stop regularly in the street to 'look and listen'.

Case MN7146, a woman aged 51, complained of difficulty in keeping her eyes open for 3 years. This was worse if she was anxious or trying to concentrate and was more marked on the right than on the left. Her mother had similar ptosis in later life which progressed until she was hardly able to open them. (The mother died of carcinoma of the breast 4 years later so it is possible that she had carcinomatous myasthenia). A brother who died in July 1963 had severe weakness of his limbs. No details can be obtained.

The patient's eyelids tended to close suddenly and not gradually as in myasthenia gravis nor could they be fatigued by maintaining a posture or by repeated closure of the eyes (Fig. 9,18). No evidence of myasthenia could be found in other muscles by clinical testing or by electromyography. Radio-iodine studies gave a 'T' index of 1.9, Kt ('thyroid clearance') of 4.2. These figures are in the hypo-thyroid range, but the protein-bound iodine level in the serum was 5.0µg/100ml., plasma cholesterol was 183mg/100ml., and glucose tolerance and plasma protein studies were normal.

When re-examined a year later she stated that ptosis had increased. The measured palpebral fissure had decreased by 2mm. on each side but this was difficult to assess because, like the previous patient, she blinked frequently.

The similarity of these cases and the case illustrated by Rowland et al (1960) make it certain that they/

they have a definite lesion. None of them showed any improvement with the use of sedative or stimulant drugs and the ptosis appears to be progressive. Whatever the nature of the abnormality it is not myasthenic.

Other myasthenic syndromes:

The muscular weakness previously discussed in this chapter has so many relationships with true myasthenia gravis that it is justifiable to look for a common mechanism if not a related aetiology. Some other syndromes have now to be described which appear to differ in both respects.

Encephalitis with myasthenic symptoms was reported from time to time before the modern era of electromyographic and pharmacological tests for myasthenia gravis. Reviews of these cases by McKendree and Wolf (1935) and McAlpine (1929) make it clear that the diagnosis was unacceptable or that myasthenia and encephalitis were coincidental.

Case NH/EC/LT was thought to have 'sleepy sickness' in 1930 when she complained of weakness and tiredness of the legs. She was then aged 22. Definite myasthenic symptoms developed in 1933 and continued until her death in 1944. Response to neostigmine was always poor but there can be no doubt about the diagnosis since autopsy at New End Hospital, London, revealed an infiltrating thymoma. In view of this finding it is probable that the original diagnosis was incorrect.

Disorders of the lower motor neurones:

There is no doubt that increasing weakness of sustained/

sustained or repeated muscular contraction with a decrementing electromyographic response to indirect faradisation may be found in some cases of disease of the anterior horn cells or peripheral nerves (Simpson and Lenman, 1959; Simpson, 1960, 1962). These cases have a myasthenic phenomenon which is usually detected by electromyography and rarely by clinical examination (Figs 9, 11 and 12) though the myasthenic symptoms (with reputed neostigmine responsiveness) sometimes described in porphyria may be of this nature (Gillhespy and Smith, 1954). For this reason the discussion is deferred until the chapter on diagnostic methods because of their importance in a consideration of the pathophysiology of true and symptomatic myasthenia. My conclusion has been that damage of the lower motor neurone may cause failure of synthesis of acetylcholine. The effect on neuromuscular transmission resembles that of myasthenia gravis but the mechanism may be different (Chapter 16). There is no clinical or aetiological relationship except in so far as some cases of polyneuropathy of the Guillain-Barré type may be caused by an immunological mechanism (Simpson, 1962). This has not so far been associated with abnormal thymic function.

Steidl et al (1962) describe muscular changes which they interpret as evidence of peripheral neuropathy in an otherwise typical case of myasthenia gravis but the evidence is less than convincing. Two cases in the present series were first diagnosed as cases of polyneuritis but the subsequent course was typical of myasthenia gravis.

Case MN3126 is described in Chapter 4 with an illustrative electromyogram. (Fig. 4.1).

Case NH/PS/JF. Had numbness and paraesthesia of all limbs/

limbs at the onset and his C.S.F. contained 125mg. protein per 100ml. The later course was 'myasthenic' but the final outcome is unknown.

Case NH75766 developed myasthenia gravis at the age of 23. She was not greatly improved by thymectomy. Ten years later (1960) she was admitted to the National Hospital with evidence of motor and sensory polyneuritis. The C.S.F. protein level was 220mg/100ml. There was hypergammaglobulinaemia but no L.E. cells were found in her blood.

Toxic and nutritional causes:

Muscular weakness of 'myasthenic' type has been described from France in chewers of tobacco which had fermented as the result of contamination by Clostridium perfringens (Coulonjou and Salaun, 1952; Lhermitte, 1952). This organism usually causes severe myositis (gas gangrene) and it is possible that minimal muscle damage may be responsible for the symptoms described. It is interesting to consider the possibility of an exotoxin such as that produced by the related organism Clostridium botulinum as the mechanism of paralysis in botulism has resemblances to that just described for the neuronopathies.

A disease named Kubisagari in Japan was described by Mwira (1897). This was an outbreak of paralysis with ptosis and bulbar symptoms. Similar epidemics occurred in prisoner-of-war camps in the Far East (Musselman, 1945; Katz, 1946; Denny-Brown, 1947). Weakness fluctuated in severity and was sometimes worse in the evening. The reports differ regarding the effect of neostigmine but it seems probable that these outbreaks were essentially the same as Kubisagari and probably due to nutritional deficiency/

deficiency though a neurotoxin (such as Tick paralysis) can not be excluded (Murnaghan, 1960). Denny-Brown (1947) reported that parenteral administration of thiamine caused the symptoms to disappear in one week. This suggests the possibility that defective acetylcholine synthesis may also be the mechanism here.

In summary. A decrementing muscle response to repeated voluntary or electrical stimulation may be due to myasthenia gravis, a variety of muscular diseases, and a few disorders of the lower motor neurone. The mechanism of the transmission failure is probably different in the neuronopathies but the close clinical, electromyographic, and pharmacological resemblances in the myogenic group is in favour of a similarity of mechanisms. A double lesion - of nerve endings and motor end-plates, with a balance between degeneration and regeneration - will be discussed as a possible cause in Chapter 16.

CHAPTER 10.

THE INFLUENCE OF REMOVING THE THYMUS GLAND.

The operation of thymectomy for the treatment of myasthenia gravis was first performed by Sauerbruch. It was said to have improved but not cured the patient (Schumacher and Roth, 1912). Sauerbruch operated on two further patients with thymic tumours but both died a few days later. Von Haberer (1918) was no more successful and the operation fell into disuse until Blalock successfully removed a thymoma in 1936 with resulting cure of the associated myasthenia gravis. Blalock was also the first to report removal of an apparently normal gland from a myasthenic patient in 1941 and he was soon able to report six cases (Blalock et al, 1941). The later reports from Baltimore became steadily less favourable (Blalock, 1944; Harvey, 1948; Grob, 1953) and their conclusions were supported by workers at the Mayo Clinic (Eaton and Clagett, 1949; 1950; 1953; 1955) and in Boston (Schwab and Passouant, 1952; Schwab and Leland, 1953).

The experience of Geoffrey Keynes in London appeared to be entirely different (Keynes, 1946; 1949; 1954; 1955). Despite a high operative mortality in his first series, he was sufficiently impressed with the beneficial results in some cases to persist with the operation and insisted that the unfavourable American results were due to their failure to distinguish cases with and without a tumour of the thymus. He emphasised that the presence of a tumour profoundly affects the problem/

problem of treatment and that fair assessment is impossible unless patients with thymic tumours are treated in a separate category from those without. In addition he drew attention to the fact that some patients develop a 'myopathy', as shown by muscular biopsy, which could scarcely be expected to respond to treatment (Keynes, 1953).

An independent analysis of 100 consecutive patients operated on by Keynes was made by Ross (1952). The results were described by Keynes (1954) as 'considerably better than anything I had ever claimed myself'.

It is not surprising that the apparent lack of agreement between the few centres with wide experience of thymectomy has caused those looking for guidance to assume that the evidence was too equivocal to carry conviction (Lancet, 1954). This was the position in 1953 when I was invited by Dr. E. Arnold Carmichael to review the cases treated at the National Hospital for Nervous Diseases, London. Most of the operations had been performed by Sir Geoffrey Keynes and by Mr. Holmes Sellors. Sir Geoffrey Keynes kindly invited me to extend the survey to include cases operated on by him at St. Bartholomew's and New End Hospitals, London. These cases were compared with a series treated without operation, being all patients diagnosed as myasthenia gravis at the National Hospital since 1934. Special precautions were taken to make the survey complete and these are detailed in Appendix C. It is unfortunate that no randomization of treatment was used and to this extent the comparison is less than ideal. Nevertheless, comparison of the operated and non-operated series/

series in respect of age, sex, duration of illness, severity, incidence of 'myopathy' and of thyroid disease showed that they were acceptable samples from a single population for statistical purposes (Appendix C). A preliminary account of the survey was presented in 1956 and the definitive evaluation of thymectomy in 1958 (Simpson, 1956; 1958).

The 1958 paper is included in this thesis as Appendix C. which should now be consulted. A summary of its contents follows:-

P.113-114 - Criteria for inclusion in the survey. Extent of availability. Classification of cases. It should be noted that this is based on a change of status with respect to presence of signs and symptoms of myasthenia, exercise tolerance, and drug requirements. The statistical techniques to be adopted were based on the 'null hypothesis' (that the two treatments did not differ) and so in case of doubt a patient was assigned to the lower category.

P.114-117 - Comparison of constitution of 'operated' and 'not-operated' series (non-tumour).

P.117-120 - Comparison of change of status of 'operated' and 'non-operated' series. The conclusions are embodied in a table and diagram which are reproduced on p.109. They show that the operated series contains a higher proportion of females in Category A and B. (cured or greatly improved) than would be likely to occur by chance (at the 5 per cent level) and the death rate from myasthenia is very significantly reduced. Even when the operative hazard is added, the total mortality rate is significantly lower than in/

in the not-operated series. Males show a similar trend though the difference is not statistically significant except in Category C. (moderate improvement). Inspection of the data (P.118) suggested that a possible explanation might be that without operation the prognosis is poorer for women but this difference is reversed by operation. P.120-125 examine some factors which may affect the response to operation. It had been suggested by Schwab and Leland (1953) and by Eaton et al (1953) that onset at an early age gives a better chance of good operative results in contrast with a poor prognosis without operation. My data go some way to support this but show that a short pre-operative history of myasthenia gravis is a more significant factor. Obviously, young surgical cases are likely to have a short history so that it is not surprising to find that the prognosis is better if the patient is young at the time of operation (P.123).

There was no clear evidence that the severity of myasthenia materially affected the final state of the survivors. The follow-up period of survivors was the same in each group.

An interesting point which had not been previously reported was that those patients who eventually died of myasthenia gravis did so on average four to seven years after the onset of the disease whether thymectomy was carried out or not. Deaths from myasthenia gravis per se rarely occurred more than ten years after the onset of symptoms. Thus the most dangerous period was also/

also the period in which symptoms were most likely to be reversible by thymectomy. This observation led to the concept of an 'active stage' referred to in Chapter 2 (Simpson, 1958; 1960).

P.126-128 - The cases with thymoma are treated separately. Apart from a higher age of onset there was no obvious clinical difference between tumour and non-tumour cases in respect of incidence but it was confirmed that medical control was more difficult. Most deaths occurred at the same interval of time from the onset as in non-tumour cases. Keynes has stressed the poor prognosis for myasthenia in the presence of a thymoma. The present survey confirmed that myasthenic death is more likely to occur than in non-tumour cases and that the very high mortality rate (50-80%) is not strikingly lowered by thymectomy (30-40% after comparable survival). Nevertheless in some cases of thymoma, the immediate effects of operation on the myasthenic status were comparable with the non-tumour patients and indeed three of them had long periods ($2\frac{1}{2}$, 6 and 7 years) of complete remission from myasthenia before the relapse which led to death in a short period.

These findings substantially support the claims of Keynes as against the American ones. While the survey was being made, Eaton et al (1953) reviewed their material and now treated tumour cases as a separate group and found, to their acknowledged surprise, that there was strong statistical support for the value of thymectomy in the non-tumour series.

In pp.128-138 of Appendix C. the major series in the literature are critically compared. It is shown that/

that apparent differences are due to -

i) Selection of cases for operation.

ii) Failure to separate tumour from non-tumour cases.

iii) Differences of criteria - notably the use of 'end status' instead of 'change of status' for classification.

iv) Selection of unoperated 'controls'.

When the reported series are compared in the light of these differences it is found that there is general agreement on the mortality rate and extent of remission in operated and not-operated series. All four centres (London, Mayo Clinic, Boston and Baltimore) agree that thymectomy results in a worth-while improvement in prognosis for women, particularly in the reduced mortality rate, but the three American centres do not consider that males are significantly benefited by operation. This conclusion may not be valid as the mortality in operated males reported by Eaton and Clagett (1955) is entirely an operative mortality and in the series of Schwab and Leland (1953) it is predominantly so. (The incidence of thymoma was also much greater in males and this is included in their figures).

It is concluded (P.138-141) that apparent differences of opinion are due to sampling errors or methodology. No criteria were found for selection of patients likely to benefit from operation. Young women with a history of less than five years were most likely to do well but equally good results were found in some men and in older cases of long duration. The/

The severity of myasthenia (as judged by the dose of neostigmine required to control symptoms) did not appear to influence the quality of survival though death was more likely if a large dose of neostigmine was required.

Viets and Schwab (1960) corroborate my results and attribute previous contrary opinions to failure to consider male and female cases separately. Earlier series not quoted in Appendix C are too small for adequate statistical treatment but their conclusions are in substantial agreement (Viets, 1950; Brea et al, 1952; Sellors, 1952; Bergh, 1953; Dunlop and Brown, 1953). No further reports of major series have been published since Simpson (1958) and the conclusions made therein have been generally accepted. In view of this, I have recommended thymectomy to all patients coming under my care since 1956 (Northern General Hospital, Edinburgh) if the history of myasthenia is less than five years, the disease generalised, and the age not greater than 50 years, irrespective of sex. If the weakness is confined to the extraocular muscles I treat the patient medically but as soon as spread to other muscles is detected I feel it is wiser to remove the thymus without further delay.

If the history is longer than five years or if the patient is older than 50 I treat the patient medically for six months. If it does not deteriorate, this treatment is continued but if weakness continues to spread to previously unaffected muscles, or if the dose of anticholinesterase drugs continues to rise, I recommend operation. This is done in the knowledge that the operative/

operative mortality is exceedingly low in the hands of Mr. Andrew Logan of the Royal Infirmary, Edinburgh and that operation has never unfavourably influenced the course of the disease. As would be expected from Simpson (1958) the results in these late cases are less satisfactory than in the earlier ones but some cases appear to have had progression arrested. If the patient has a thymoma I advise its removal on general principles.

Keynes (1949; 1955) considers that the prognosis for life is improved by the application of high-voltage X-ray therapy to thymic tumours before their removal. He recommends the treatment described by Williams (1952) but acknowledges that it may sometimes provoke temporary exacerbation of the myasthenic symptoms. I have seen this happen in cases not under my own care. McWhirter (personal communication) considers that the value of pre-operative radiotherapy is very doubtful and on his advice I have not prescribed it in a recent case of thymic tumour (MN6476). Thymectomy was carried out on 14/5/62 and he remained well until April 1964. He was admitted to another hospital with 'myasthenic crisis resistant to neostigmine'. It was noted that he had fasciculation and bronchospasm before death so there is little doubt that death was due to overdosage of neostigmine (Chapter 19).

I do not recommend thymectomy for the emergency treatment of myasthenic crisis. Griffin et al (1956) report recovery of respiratory power after thymectomy in a case of atypical myasthenia gravis in which respiratory failure had occurred and breathing could not be restored by the use of antimyasthenic drugs. In that case the authors/

authors recognise the possibility that respiratory paralysis was due to overdosage of neostigmine. If the nature of a 'crisis' is correctly diagnosed and the appropriate management adopted (Chapter 19) there can rarely be indication for thymectomy in these circumstances.

CHAPTER II.

PATHOLOGY.

Muscle:

It is well known that there is a striking lack of correlation between the apparent pathological changes in muscle and the severity of weakness which the same muscle exhibited during life. It seemed reasonable that this should be so when the advance of physiological knowledge provided an explanation for the myasthenic syndrome in terms of a 'functional' disturbance of neuromuscular transmission. This concept received such general acceptance that most of the earlier work on the histology of myasthenic muscle was ignored or described as 'non-specific'.

To Weigert (1901) is attributed the first description of focal collections of small mononuclear cells and lymphocytes within the muscle. His suggestion that they were metastatic tumours was disproved by Buzzard (1905) who believed that the cells originated from small blood vessels ('lymphorrhages'). Querido (1929) noted that they were often perivascular in position and associated with a vasculitis. The importance of the lymphorrhage has been questioned by many workers on account of the variability of its occurrence. There is certainly but a poor correlation with the severity of muscular weakness but Mendelow (1958) states that lymphorrhages can be found in at least 50% of myasthenics. I have an unsubstantiated impression that the ease with which this type of lesion can be found correlates with the duration of illness rather than with the extent of loss of power/

power, being most readily found in the 'active' stage of the disease (Chapter 2). If this impression can be confirmed the lymphorrhage takes on a new importance.

It has been further pointed out by many authors that the lymphorrhage is not exclusive to myasthenia gravis but is also present in the muscles in cases of exophthalmic goitre (Dudgeon and Urquhart, 1926), rheumatoid arthritis and other rheumatic diseases, connective tissue disease, chronic infections, myositis and endocrine myopathies (Ogryzco, 1948). The writer was the first to suggest that instead of dismissing the lymphorrhage as 'non-specific' on these grounds it might be more profitable to consider what factor might be common to each of these diseases. It was suggested that the common factor might be an immunological reaction since lymphocytic infiltrations are common in the target organs of allergic disorders (Simpson, 1960a).

Other neglected findings reported by Buzzard (1905) were degenerative changes of muscle fibre. These were re-investigated and classified by Russell (1953). Professor Russell described three types of muscle change. These are confirmed in my limited experience and personal cases are used to illustrate them.

Type I (Fig.II,1) is an acute coagulative necrosis of the muscle fibre with eosinophilic change, loss of cross-striation, and inflammatory cellular reaction leading to phagocytic removal of the fragmented muscle fibre. This process may be limited to one fibre or so widespread as to cause naked-eye changes in the muscle.

Type II (Fig.II,2) is the lymphorrhage. Professor Russell considers that it is secondary to atrophy of a solitary muscle fibre in which the cytoplasm undergoes basophilic/

basophilic change and cross-striation is lost.

Type III (Fig.II,3) is a simple focal muscle fibre change with eosinophilia and swelling but without loss of striation or inflammatory reaction.

Russell (1953) does not consider that any of these lesions are 'specific' for myasthenia gravis. Nevertheless it is obvious that the weakness of myasthenia gravis is not without some related morbid anatomical changes. Recent advances in histochemical technique have shown further changes which are claimed by the authors to be diagnostic of myasthenia gravis.

Nerve terminals and motor end-plates:

Mott and Barrada (1923) stained the motor nerve terminals in the muscle of a case of myasthenia gravis by injection of methylene blue before biopsy. Either they were unlucky or, as suggested by contemporary critics, the diagnosis was erroneous (though the patient had a possible thymoma and lymphorrhages were found in the muscles) but it was by a similar method supplemented by staining for cholinesterase in the subsynaptic apparatus by the method of Couteaux that Coërs and Woolf (1954, 1959) showed florid morphological changes of the intramuscular nerve endings in myasthenia gravis. These changes are of two types (Fig. II,4). In one, the 'dystrophic' type there is increased branching of the terminal arborization and the terminal knobs are distributed over a wider area of the muscle fibre than usual. This type is probably reactive as the related muscle fibre is usually abnormal and the same type of end-plate has been found in other neuromuscular disorders. In the other type, the 'dysplasic', there are few terminal knobs and these are arranged serially along a scanty number of terminal branches ending/

ending on a long end-plate region. Woolf et al (1956) and Bickerstaff and Woolf (1960) consider that these changes do not represent the primary pathogenesis of myasthenia gravis but more likely indicate degeneration and repair. Bickerstaff and Woolf (1960) and MacDermot (1960) described a remarkable degree of sprouting of the terminal axons after their emergence from the nerve bundle as in collateral reinnervation which accompanies primary degeneration of the lower motor neurone but also seen in dermatomyositis. Axonal sprouting was most prominent in the vicinity of a lymphorrhage. Bickerstaff and Woolf (1960) interpret the 'dysplasic' elongated end-plates as the primary abnormality though they are absent in cases with a short history. The 'dystrophic' changes are interpreted as secondary to 'inflammatory' exudates (lymphorrhages) and degeneration of muscle fibres and hence not fulfilling a primary role in the pathogenesis of myasthenia.

MacDermot (1960) confirmed these observations, even in muscles which were normal 'or nearly so' on both clinical and electromyographic examination and with slight or absent histological abnormality with routine stains. She further noted that regenerative sprouting frequently arose from end-plate knobs (telodendria). These prolongations may terminate as an end-plate on the same or another muscle fibre, and at this site a similar process may again be seen, giving rise to a chain of end-plates connected by a single fine nerve fibre. The final elongated end-plates may give off large numbers of very fine ultra-terminal sprouts. Ultra-terminal fibres have been described in various types of neurogenic disorder in animals and/

and man when reinnervation of muscle is taking place (Gutmann and Young, 1944; Coërs and Woolf, 1959). For this reason MacDermot agrees with Bickerstaff and Woolf (1960) that the appearances of the nerve terminals indicate a combination of degeneration and regeneration. This may account for the observation of Coërs and Desmedt (1959) that not all of the end-plates showed changes or were equally affected in biopsies stained with methylene blue.

The neuromuscular junction has been further studied by means of electronmicroscopy. Bickerstaff et al (1960) were unable to detect any feature which differed from animal end-plates (they had no normal human controls) and in particular they remarked on the presence of numerous round or oval profiles 300-500 Å in diameter in the axoplasm of the terminal expansion of the axon. (It has been suggested that these are vacuoles containing packets of acetylcholine which are released by the nerve's action potential.) Circular structures were described in the terminal expansions of some cases, possibly replacing mitochondria. Their significance is unknown.

Zacks et al (1962) studied muscle biopsies from five cases of myasthenia gravis by electronmicroscopy. They noted two types of abnormalties of the ultrastructure of the neuromuscular junction. The first type was focal decrease of electron density in the muscle surface membrane within the secondary synaptic clefts. This was present in two biopsy specimens described as being from 'chronic moderately severe myasthenia gravis' though one was a child aged 2½ with a somewhat uncertain diagnosis of Congenital Myasthenia. The second type of abnormality, noted in three cases of 'rapidly/

'rapidly progressive myasthenia or acute exacerbations of chronic myasthenia gravis', were major degenerative changes in axon branches and subsynaptic apparatus. These authors support the concept of the workers previously quoted using the Coërs technique that degeneration of end-plates and subsequent repair may occur during the course of exacerbations and remissions of the myasthenic syndrome. However, unlike the work of the light microscopists which suggests that the lesion is mainly pre-junctional, Zachs et al (1962) consider that their work points also to consistent post-junctional abnormalities (reversible in Type I and irreversible in Type II).

Further advances in this field may be expected though interpretation will be impossible until more normal human material has been studied. Nevertheless two important conclusions can already be made; i) There is clear evidence of structural pathology of the motor nerve terminals and of the muscle fibres in myasthenia gravis and a 'pure' defect of function need no longer be considered; ii) it is not yet possible on histological grounds to say whether the disturbance of neuromuscular transmission is due to a pre-junctional or a post-junctional abnormality (Chapter 16).

Central Nervous System:

The evidence of pathological change in peripheral nerve endings, whether primary or reactive, and the hypothesis of the present work that myasthenia gravis may be part of a multi-system disease, including such occasional symptoms as psychosis and epilepsy (Chapter 4) make it mandatory to re-examine previous claims that the central nervous system may show pathological changes in myasthenia gravis.

Neuronal/

Neuronal abnormalities and lymphocytic infiltration of the brain or spinal cord occasionally reported in some of the early cases were critically analysed by McAlpine (1929) and McKendree and Wolf (1935). Many of the papers reviewed preceded the modern era of diagnostic methods, others dated from the period of the influenza pandemics of the third decade of the present century. The dearth of reports since then could be due to more precision in the diagnosis of myasthenia gravis or to the psychological factor, to which I have already drawn attention, that once a particular concept of a disease becomes universal any apparent discrepancies are rejected as irrelevant or coincidental. The nosological position of some of the cases recently described by Rowland et al (1958) is very doubtful.

In my series the following cases were encountered -

Case NH/EC/LT. This young woman was aged 22 in 1930 when she complained of tiredness (? sleepiness) and weakness of the legs. A diagnosis of encephalitis lethargica was made at the National Hospital. In 1933 generalised myasthenia gravis developed after a road accident and during a time of business worries. There was initial response to neostigmine given by injection but in subsequent years the response became poor. Relapses were precipitated by infection or by emotional disturbances.

In 1944 it was decided to remove her thymus but she was considered to be too ill for operation. She died at New End Hospital, London and a post mortem examination revealed that she had an infiltrating thymoma.

There seems no doubt that she had myasthenia gravis but the original diagnosis of encephalitis was probably mistaken.

Case NH32170 had a transient Brown-Séquard syndrome.

Case/

Case NH20468 had a cauda equina syndrome at one stage. No further details are available but there is no definite evidence that the spinal disease was related to the myasthenia.

It is most probable that these cases and the others in the literature represent the accidental coincidence of myasthenia gravis with another disease. The earlier attempts to explain muscular weakness on the basis of a central lesion must certainly be rejected. It may, however, be worth pointing out that the current trend of thought is to regard the fundamental mechanism of multiple sclerosis and demyelinating encephalitis as 'autoimmune' in type. Thus it may be necessary to consider the possibility that they may have a common pathogenesis with myasthenia gravis though they do not cause it. The evidence is too scanty to support such a proposition if only the neuropathology is considered but it needs to be taken in the whole context discussed in Chapter 7.

Heart:

In Chapter 4 I have referred to a few cases in the present series and in the literature who complained of precordial pain or palpitations. Apart from these I have not seen clinical evidence of heart disease, since dyspnoea was usually accounted for by myasthenic weakness of the muscles of respiration.

Most workers have reported no evidence of pathological changes in heart or smooth muscle but lymphorrhages and muscle fibre changes resembling those of skeletal muscle have been reported in the myocardium by Weigert (1901), Buzzard (1905), and other authors including Russell (1953) and Rowland et al (1956). A striking feature of many of these reports is that myasthenia gravis was associated with a thymoma (Brem and Wechsler, 1934; Rottino et al, 1942; Giordano and Haymond, 1944/

1944; Mendelow and Genkins, 1954; Waller et al, 1957). The myocardial necrosis and myocarditis described by these authors was usually accompanied by changes in the skeletal muscles of sufficient degree to be classified as myositis. The best reviews of this aspect of myasthenia gravis are by Rottino et al (1942) and Mendelow (1958). The latter author closes his review with the following statement:- 'Many investigators feel that myocardial necrosis and reactive myocarditis are basic aspects of the pathology of myasthenia gravis and require explanation in any valid theory of the etiology and pathogenesis of this condition. The apparent close relationship between myocarditis and the presence of a thymoma may serve to further distinguish this type of myasthenia gravis from those cases without thymic tumor and may prove to be worthy of consideration in clinical management.'

Other organs:

Infiltration of lymphocytes has been reported in the adrenal glands, pancreas and liver, (Buzzard, 1905; Bell, 1917; Goñi, 1946; Ringertz, 1951; Rowland et al, 1956). I cannot say how regularly they were searched for in the pathological material available to me but the following pathological report was present in the records:-

Case MN7782 (W.I.C.-G.I. 8/53/48). This case is described in Chapter 7 as myasthenia gravis preceded by pernicious anaemia. He also had essential hypertension with nephrosclerosis. Death was due to respiratory failure.

Post mortem examination (Dr. J.M. Johnstone) showed that in addition to the expected changes there were small collections of plasma cells and lymphocytes of the cortex and medulla of both adrenal glands.

All/

All the authors quoted above describe these lymphocytic infiltrations as 'non-specific'. It is impossible to state unequivocally that this is not so, but it may be more profitable to consider that like the lymphocytic changes in muscle and thyroid they are part of a diffuse process which may be immunological.

Thyroid and Thymus:

The pathological changes found in the thyroid gland are more conveniently discussed in the chapter on clinical disorders of that organ (Chapter 5) and the role of the thymus is so central to the thesis being developed as to justify a separate chapter (Chapter 12).

Reticuloendothelial System:

The author's paper of 1960 was the first to draw attention to the occasional occurrence of generalised lymphadenopathy, splenomegaly or reticulosis in cases of myasthenia gravis. It must immediately be stated that most cases show no evidence of disturbance of this type though they have also been reported without comment by Castleman and Norris (1949) and by Ringertz (1951). Indeed some authors have drawn particular attention to the absence of lymphoid hyperplasia of lymph nodes and spleen. On the other hand these changes are seen in hyperthyroidism, acromegaly and Addison's disease which have similar thymic changes to those of myasthenia gravis (Sloan, 1943; Ringertz, 1951).

CHAPTER 12.

RELATIONSHIP OF THE THYMUS GLAND TO MYASTHENIA GRAVIS.

Pathology:

An association of thymic pathology with myasthenia gravis has been recognised for more than sixty years and an explanation of the role of the thymus is essential for any satisfactory theory of the nature of myasthenia gravis. (Simpson, 1958). The evidence is of two types; (i) the close association between myasthenia gravis and pathological changes in the thymus, and (ii) the beneficial effects of thymectomy. Evidence of the first kind will be reviewed here. In Chapter 10 it has been shown that there is statistical confirmation that thymectomy favourably influences the course of the disease but only if it is removed during the 'active' stage of the disease (Chapter 2). It is also clear that the course of myasthenia is more severe if the patient has a thymoma (Chapter 3) and complications in other organs are more likely if thymoma is present (Chapters 7 and 13).

Attention to this correlation was first drawn by the report of Weigert (1901) describing a case of myasthenia gravis in which there was a thymic tumour. Bell (1917) and Norris (1937) reviewed the literature at different times and established that Weigert's case was not unique. They found that 45-48% of the reported cases had obvious thymus abnormalities and about 30% of these (15-20% of all cases) were thymic tumours. The remaining abnormalities were described as 'hyperplasia' and Norris (1937) considered that a thymoma was not a true neoplasm but rather an extreme form of hyperplasia. Lievre, 1936 (cited by Seybold et al, 1950) carried/

carried out complete autopsies on 67 myasthenic patients and found thymomas in 36% and 'persistence' or 'hypertrophy' in a further 48%.

At that time the mere persistence of the thymus in adult life was considered to be abnormal since the gland was generally assumed to atrophy during childhood. The other assumption, which remains in vogue, is that the thymus is a ductless gland of endocrine type. If this is true it is very strange that no normal function has been correlated with its presence, that it can be dispensed with after puberty, and that its surgical removal causes no deprivation symptoms, or if there are any they are so subtle as to escape detection.

The first of these misconceptions was soon dispelled by the interest of investigators of myasthenia gravis. Hammar (1906) found that the thymus of non-myasthenic children and adults had a wide variation in size and cellularity and Boyd (1936) and Sloan (1943) found that the thymus never underwent complete involution. Sloan pointed out that the thymus from myasthenic patients was not distinguished from the normal by size (thymomas excluded) but by histological change. He noted lymphoid hyperplasia in both cortex and medulla of the gland and in particular the frequent presence of 'germinal centres' in the medullary portion of the gland. These are identical to the structures of that name in hyperplastic lymph nodes.

The germinal centre (Fig.12,1) consists of reticular cells, large lymphocytes and macrophages. Frequent mitotic figures indicate active cell division and the centre is considered to be forming lymphocytes (or thymocytes). The germinal centre is surrounded by darker staining, more mature/

mature small lymphocytes.

Sloan (1943) found germinal centres in seven out of ten operative specimens of thymus removed from cases of myasthenia gravis but could rarely find them in normal thymuses from cases of sudden death. His findings were confirmed by Bratton (1948), Castleman and Norris (1949) and Ringertz (1951) and it is now certain that the thymus of myasthenia gravis is characterised by the presence of germinal centres rather than by 'hyperplasia'. Failure of involution might be a more acceptable term. Unfortunately this is still unfamiliar to most pathologists, including neuropathologists, and it is impossible from the material available to me to form an estimate of the frequency of the change described. I know that some reports have been changed from 'normal' to 'pathological' when I have asked to see the sections and pointed out these features to the pathologist. Castleman (1955) stated that 68% of patients with myasthenia have this type of change. When the number of the remainder with tumours is considered it may well be wondered if the changes described are not present to some degree in all cases. It has seemed to me that, as with the lymphorrhages (Chapter 11) germinal centres have been most readily found in the glands removed early in the history of the disease - what I have called the 'active stage' (Chapter 2). I do not have the material to confirm this impression but it would fit with a report by Castleman (1955) that although there was no correlation between the numbers of lymphoid follicles in the thymus and the clinical course of the myasthenia gravis, those patients with fewest follicles in the operative specimen seemed to have a poorer prognosis for improvement after thymectomy. Oosterhuis (1963) found no/

no correlation between the number of germinal centres and the effect of thymectomy. It has been shown in Chapter 10 that the results of thymectomy depend more on the duration of illness than on any other factor.

Thymic Tumours:

The subject of thymic tumours is a controversial one which need not be considered here. There are excellent reviews and suggested classifications by Castleman and Norris (1949), Murray and McDonald (1945) and Iverson (1956). Common to all types and differentiating it from the non-tumour type of pathology described above is hyperplasia of epithelial elements, though the lymphocytes (thymocytes) may be the main proliferating cell type. The majority of these tumours are encapsulated (Fig. 12,2). There is often breakdown of central parts to form cystic areas containing milky fluid and calcification is common. In some cases the epithelial cells form cords or tubes, giving the appearance of a secretory tissue (the only time the thymus looks like a normal endocrine gland). (Fig. 12,3).

The types of thymic tumour associated with myasthenia gravis are usually benign. If malignant, they are considered to be only locally malignant within the thoracic cavity. Spread may occur by lymphatics to the neck or diaphragm, or to the axillary and coeliac glands and to the omentum (Keynes, 1955). They do not metastasize by the blood stream (Seybold et al, 1950; Morgan and Dudley, 1955).

The type of tumour, benign or malignant, seems to be of no consequence so far as the occurrence of myasthenia gravis is concerned. It may be more significant that many observers have noted lymphoid follicles within the tumour or/

or in the surrounding 'normal' thymic tissue beyond the capsule of the tumour (Castleman and Norris, 1949; Ringertz, 1951; Mendelow and Genkins, 1954). My own material confirms this in those instances where a search for germinal centres has been made (Fig. 12,4).

Reviewing these changes, I have suggested that there was little evidence that the thymus acted as an endocrine organ in the ordinary sense but that the features most regularly associated with myasthenia gravis - germinal centres - were more in keeping with an active organ of the reticuloendothelial system (Simpson, 1960). While this lecture was in preparation, Smithers (1959) writing on tumours of the thyroid in relation to some general concepts of neoplasia and in particular the role of the thymus and lymphocytes, remarked that the thymus changes in myasthenia gravis resembled the changes to be expected in autoimmunity. At the time these two papers were written the thymus was still considered to be an endocrine gland. The evidence for its immunological role followed rapidly and this will now be described.

The physiology of the thymus:

An apparent absence of function in normal people has caused many workers to fall into the trap, familiar to neurologists, of postulating 'functions' to account for presumed mechanisms seen in disease. Thus all clinical thinking has been concentrated on the lines that (i) the thymus must be a ductless gland which is not necessary after puberty, and that it has some influence on growth, either pre- or post-natal, and (ii) that it secretes a curare-like substance that blocks neuromuscular transmission or interferes with the synthesis of acetylcholine.

McEachern/

McEachern (1943) and Keynes (1954) wondered if it might serve to restrain the muscular activity of the foetus in utero.

'Curare-like' toxin:

Adler (1938) claimed to produce weakness in dogs by repeated implantation of thymic tissue and that the weakness was relieved by neostigmine. His findings could not be confirmed by Bomskov and Milzner (1941) and McEachern (1943). Constant et al (1949) described a 'curare-like' action of saline-extracts of human thymus in the cat which most other authors failed to confirm (reviewed by Eaton et al, 1953).

Inhibition of acetylcholine synthesis.

Wilson et al, (1953) criticise the previous work on technical grounds such as incorrect solvent of thymic tissue or inadequate dosage. They obtained thymus glands removed at operation by Mr. Geoffrey Keynes from 42 of the patients included in the present report and extracted them with acetone. The acetone-insoluble fraction was homogenized with saline solution, centrifuged, and the supernatant fluid, suitably adjusted for pH, was applied to the phrenic nerve/diaphragm preparation of the rat. They found evidence of neuromuscular block and compared it with standard doses of d-tubocurarine chloride. They claimed to show that the glands which on removal produced the most beneficial therapeutic effect also produced the greatest depression in the response of the nerve-muscle preparation. Glands from normal infants (autopsy specimens) also showed high activity whereas adult glands did not. The neuromuscular blocking effects were transient and were not reversed by neostigmine (Wilson and Wilson, 1955). In a comment on the latter/

latter paper Zacks (1955) stated that he had obtained the same effect from both acetone-soluble and acetone-insoluble extracts of myasthenic thymuses but found that the muscle became inexcitable to direct stimulation as well as to indirect stimulation through the nerve. He was able to account for the block by finding high concentrations of potassium in the extracts.

Despite this criticism, and the failure of other workers to confirm their reports, Wilson and his co-workers have continued to study the pharmacological actions of extracts of human and foetal whale thymus glands which were stated to produce effects of the same order (Nowell et al, 1959). The Liverpool workers have recently reported two quaternary nitrogen bases in extracts from thymus glands obtained from patients with myasthenia gravis. These were also identified (by a colorimetric method) in post mortem specimens from neonatal infants but not in normal adult thymus glands. The compounds have not yet been completely characterised but Wilson and his co-workers consider them to be quaternary nitrogen compounds. Restricted pharmacological investigation did not show any neuromuscular blocking effect. On the contrary, the response of frog rectus muscle to acetylcholine was potentiated and the effect of tubocurarine was reversed. They suggest (Nowell and Wilson, 1962) that one of the substances resembles diethylcholine and speculate on its having properties similar to triethylcholine which interferes with the synthesis of acetylcholine in the motor nerve terminals (Chapter 16). They have not demonstrated any effect of this nature at the time of writing.

Torda and Wolff (1944) and Trethewie and Wright (1944) have previously claimed to demonstrate that a thymus-extract/

extract interferes with the synthesis of acetylcholine. Stoerk and Morpeth (1944) and Welsh and Hyde (1945) were unable to reproduce their results. This hypothesis seems basically improbable. In the first place the type of neuromuscular block caused by inhibitors of acetylcholine synthesis such as triethylcholine is not reversible by anticholinesterase compounds. In the second place it would be difficult to account for persistence of myasthenia after thymectomy and impossible to account for those cases which first show myasthenic signs after all thymic tissue has been removed (Eaton et al, 1953).

Control of growth:

Since the thymus is relatively larger in growing children than in adults it is not surprising that it has been considered to produce a growth hormone. This work is reviewed by Cameron (1945) and need not be recounted here as all claims made in the era 1920-40 were subsequently denied by other workers. Nevertheless one aspect of the work from this era may justify reappraisal. Rowntree et al (1935) gave daily intraperitoneal injections of acid watery extracts of young calf neck thymus to successive generations of rats. The first generation of rats became heavier, bred more frequently, and gave rise to larger litters of above average weight. The average weight of the seventh generation at 60 days was 180 g. against 100 g. in normal rats, but the excessive growth was not maintained. However, a claim which could be significant is that the earlier growth acceleration was associated with, if not due to, precocious differentiation of tissues. This work seems to have been abandoned since Segaloff and Nelson (1940) and others were unable to confirm it.

Morel/

Morel and Gineste (1939) found that injections of growth hormone of the anterior pituitary into rabbits caused enlargement of the thymus but implantations of thymus inhibited the thyroid gland of the rabbit. Engfeldt and Hultquist (1953), using crystalline growth hormone in pregnant rats, confirmed that it caused hyperplasia of the thymus. Comsa (1958a) reported experiments from which he concluded that the thymus was a significant factor mediating the growth effect of anterior pituitary growth hormone and that its 'anti-thyroid' action was due to suppression of the activity of thyroxine on target tissues such as muscle (Comsa, 1958b). Rawson et al (1942) considered that the thymus inactivated the thyroid-stimulating hormone of the pituitary but that this effect was also present in lymph glands. The extensive literature on the action of the thyroid and adrenal glands on the thymus is reviewed by Gyllensten (1953). It is quite clear from his review and his meticulous research work that in all these relationships (of endocrines on thymus and of thymic tissue on endocrine glands) the thymus is similar to the spleen and lymph glands apart from quantitative differences. Gyllensten is highly critical of Comsa's work which he considers to be unsound on statistical grounds. He confirmed that thyroid stimulation followed thymectomy in the guinea pig but it was transitory. (It is possible that this action, brief though it is, could account for the transient retraction of the upper eyelid which I have noted after thymectomy for myasthenia gravis - Chapter 10). The thyroid stimulation was accompanied by slight hyperplasia of lymphatic tissues. He also confirmed the finding of Rawson et al (1942) that the thymus is a target/

target organ for the thyrotrophic hormone and has power to inactivate it. Gyllenaten (1953) summarises the results of his experiments as indicating a balance between growth of thymus tissue and lymphatic tissue with the pituitary-thyroid axis acting as a regulator.

The thymus as a lymphoid organ:

The resemblances between the thymus and a lymph gland are obvious. Most histologists now agree that there are no significant differences between thymus lymphocytes and blood lymphocytes but there are certain differences in their response to various factors (Yoffey and Courtice, 1956). The thymus often reacts more intensely and more rapidly than lymph glands to the involutional effects of adrenocorticotrophin, gonadotrophic hormones or sexual hormones (Money et al, 1951; Dougherty, 1952). The concept of a 'thymolymphatic system' acting together in infections, though not in exactly the same manner, was widely discussed more than thirty years ago (Hammar, 1931). One difficulty in the acceptance of a reticuloendothelial role for the thymus was its apparent failure to produce antibodies. This objection became less valid when it was shown that lymphocytes entering the blood stream from the thoracic duct do not contain antibodies but are capable of producing them in vitro (Weeslen, 1952).

Role of immunological processes:

This was the position in the years 1953-59 when I was investigating the clinical aspects of myasthenia gravis set out in the previous chapters, and establishing that thymectomy had definite value in its treatment (Chapter 10). Reflection on the natural history of the disease and of abnormalities/

abnormalities of other organs which were sometimes present, led me to formulate as a hypothesis that the disease was a manifestation of the type of abnormal immunological reaction currently termed 'autoimmunity'. The role of the thymus had never been satisfactorily fitted into any theories of the mechanism of the disease. I considered that the relationship would be logical if the thymus was functioning as a lymphoid organ rather than as a ductless gland in the true sense. While this hypothesis was being elaborated Smithers (1959), who had been studying the role of the thymus and lymphocytes in disease with special reference to cancer, concluded that they were implicated in 'autoimmunity' and remarked that the thymus changes of myasthenia gravis resembled the lymphadenoid changes of the thyroid in Hashimoto's disease and might be due to a similar autoimmune process. (If I interpret the paper correctly, Smithers was suggesting that autoimmune reactions may predispose to lymphoid tumour formation. My own interpretation is the exact converse). During this same period, Metcalf (1956) found what may be the true 'hormonal' function of the epithelial cells of the thymus. From a culture of these cells he isolated a cell-free factor which could also be detected in the blood plasma and which acted as a 'lymphocyte stimulating factor'.

On 28th April, 1960 in a Honyman-Gillespie Lecture in the University of Edinburgh I summarised my work and hypothesis as it then stood. To the best of my knowledge this was the first clear statement of an active role for the thymus in autoimmune diseases and the first fully elaborated account of myasthenia gravis as an autoimmune disease.

A synthesis of the previous work reviewed above was made/

made in the interpretation illustrated in Fig.12.5.It was suggested that a genetically-determined pituitary hormone -somatotrophin or a related substance - might control the size and activity of the thymus. The thymus in turn might be responsible (with another fraction of growth hormone) for differentiation of tissues in the embryo and infant (cf. Rowntree et al, 1935). The new speculation was that the only part of this action still required after childhood is the differentiation of the blood cells. If the reticulo-endothelial cells be considered as protein-forming organs, this idea may be expanded to cover a control of certain plasma proteins. The concept described in the lecture is shown in Fig.12.5. It was condensed for reasons of space in the published version (Simpson, 1960a). One of the functions of the globulins formed by lymphocytes is undoubtedly to act as an antibody against foreign proteins. It was suggested that the thymus might produce antibodies against the receptor protein of muscle cells. In 1960 the prevailing view of the autoimmune mechanism was that a normal antibody-producing mechanism reacted against protein escaping from normal cells in which it would normally be isolated from the antibody-forming cells. It was accordingly suggested that the muscle cells may be primarily damaged by an abnormal pituitary secretion or by a delayed-type allergy caused by infection, deductions based on the known precipitants of myasthenic relapses. As a result of further studies reported in Chapter 13 and the changing view on autoimmunity, I now think it is necessary/

necessary to consider that the thymus is producing abnormal antibodies without provocation from a 'leak' in the target organ. Nevertheless, the hormonal mechanism described here cannot be ignored and will be further adverted to in Chapter 14.

The hypothesis gained rapid support in the next two years from the work of Miller (1961) on the effect of thymectomy on one-day old mice. Such mice appear normal for about three months and then rather rapidly develop a wasting syndrome which is usually fatal. Miller confirmed earlier observations that there is no significant diminution in the immunological capabilities of the animal thymectomized in adult life but found that the fatal wasting disease which followed thymectomy soon after birth (within one week) was due to a failure to form antibodies (Miller, 1963). He likened the wasting disease to the so-called 'runt disease' seen in graft-versus-host reactions in animals deprived of immunological reactivity and concluded that the thymus has a key role in controlling immunological reactivity. Miller (1961) suggested that during embryogenesis the thymus would produce the originators of immunologically competent cells many of which would have migrated to other sites at about the time of birth. This would suggest that lymphocytes leaving the thymus are specially selected cells. They might populate the lymph glands or the latter could be stimulated to produce their own cells by Metcalf's lymphocytosis-stimulating factor already referred to. Osoba and Miller (1963) have recently shown that lymphoid cells are enabled to become immunologically competent by a humoral factor present in thymic tissue.

Burnet/

Burnet (1962b), for long the protagonist of a 'selection' theory of immunity (as distinct from an 'instruction' theory) has incorporated these ideas into his theories. He regards the thymus as the chief 'first level' immunological organ in which the lymphoid cells arise which proliferate to produce functionally active descendant or collateral cells in the 'second level' immunological organs, spleen, lymph nodes, bone marrow and local lymphoid-cell aggregations. In his concept, mutant cells in the thymus give rise to 'forbidden clones' of descendant cells in the 'second level' lymphoid organs which are capable of producing antibodies against protein native to the body and hence of provoking 'autoimmune' disease. In deriving this concept Burnet (1962b) made full use of the material and ideas of Simpson (1960a). The further development of these concepts will be discussed in the next chapter.

CHAPTER 13.

IMMUNOLOGICAL DISORDERS IN MYASTHENIA GRAVIS.

The concept of an autoimmune mechanism for myasthenia gravis suggests itself because the age and sex distributions and the relapsing natural history are strikingly similar to those of rheumatoid arthritis, systemic lupus erythematosus and disseminated sclerosis, in all of which disordered immunological mechanisms have been demonstrated or suggested. The factors associated with the first attacks and with the precipitation of relapses of myasthenia gravis are also associated with relapses of these diseases. A circulating antibody transmitted through the placenta would account for neonatal myasthenia while being compatible with the consistent failure to transmit the disease by cross-transfusion between adults (Simpson, 1960a). This aspect is further discussed in Chapter 16.

Simpson (1960a) was the first to report the association of myasthenia gravis with disorders of joints and reticuloendothelial system and to collect scattered references to neurological and haematological disorders associated with the disease. It was also pointed out that there was a consistent histopathology of nerve and muscle of a type suggesting immunological reaction and that the same type of reaction could account for the similar histological changes occurring in other diseases which had previously been considered to indicate that the changes were 'non-specific'. The immunological factors in the related thyroid, diabetic, and haematological disorders/

disorders described below have only been described since 1960. It was further suggested that the typical pathological changes in the thymus, the appearance of germinal centres, strongly suggested that the organ was immunologically active rather than acting as an endocrine gland in the usual sense. While this work was in preparation, Smithers (1959) made the same suggestion regarding the histological appearance of the thymus in myasthenia gravis but did not suggest how the muscle disease could be caused.

Antibody against muscle:

In 1955, with the assistance of Dr. J.R. Anderson, I made an attempt to produce myasthenia in mice by inoculation of homologous muscle with Freund's adjuvant in the hope of provoking the formation of antibodies active against the host muscle. No positive results were obtained and the experiments were not reported in the original publication because of a restriction against discussion of animal experiments in a Honyman-Gillespie lecture. Oosterhuis (1963) reports negative results in similar experiments on rats and guinea pigs.
Dr. Anderson and, from 1956, Dr. R.W. Alexander collaborated with me in a search for muscle antibodies in the serum of patients with myasthenia gravis. We were encouraged to continue despite essentially negative results (vide infra) when Nastuk et al (1959) reported that, during an unsuccessful search for a neuromuscular blocking substance in myasthenic serum, the serum caused lysis of frog muscle cells. The cytolytic effect was not present in each sample and was only found in two cases out of twenty-two. It/

It was present in lesser degree in some sera from normal controls, nevertheless the authors thought it worth further investigation. Soon after the publication of my lecture the American workers independently concluded that myasthenia gravis is a disease involving a destructive autoimmune mechanism. Their conclusions were based on the finding of changes in serum complement activity (Nastuk et al, 1960) and the demonstration by an immunofluorescence technique of a muscle-binding, complement-fixing globulin fraction in the serum of patients with myasthenia gravis (Strauss et al, 1960).

Nastuk et al, (1960) reported that the cytolytic activity previously reported occurred in 44% of patients afflicted with myasthenia gravis and in 22% of normal controls. The relative strengths of the active sera found in each group were unknown. They found that the level of serum complement fluctuated over an abnormally wide range. There was some suggestion that a low level was correlated with disease exacerbation (though three cases with exacerbation had an abnormally high level). Conversely remission of the myasthenia gravis was often related to a supernormal complement level though sometimes to a subnormal one. They suggested that complement-fixation was occurring in active myasthenia but offer no explanation for the supernormal levels in quiescent cases. Their hypothesis of an autoimmune alteration of the muscle cell membrane as the result of a conjunction of a foreign antigen and an entity found in the plasma membrane or intracellular elements of muscle is virtually identical with my own proposal (Simpson, 1960a) including the suggestion that there might be two grades of damage/

damage, one altering the configuration of the post-junctional membrane, another, more severe, causing reversible or irreversible damage to the muscle fibres. The terminal arborization of the motor nerve might be indirectly or directly involved.

In a companion paper Strauss et al (1960) applied an immunofluorescence technique to study the presence of globulin fixed to the skeletal muscle of patients with myasthenia gravis. They pooled sera from ten myasthenic patients of whom six had thymic tumours. The globulin fraction precipitated by 20% sodium sulphate was conjugated with fluorescein isothiocyanate and sources of non-specific fluorescence removed by absorption with rat and mouse liver powders. They were able to demonstrate that the globulin was bound to a sample of myasthenic muscle to which it was introduced and no similar reaction could be demonstrated in a similarly prepared normal serum globulin pool. The myasthenia gravis globulin fraction was shown to fix guinea-pig complement to human skeletal muscle and this was considered to be in favour of an immune phenomenon. Not all myasthenic sera gave rise to fluorescent skeletal muscle sections by this technique. Sixteen individual sera tested subsequently gave negative or equivocal results. One serum from a patient with 'exacerbating paroxysmal myoglobinuria' caused complement-fixing fluorescence of myasthenic muscle but no normal sera or sera from patients with other muscular diseases produced fluorescence. The appearance described by Strauss et al (1960) was of fluorescence of alternate striations of human skeletal muscle. One

serum/

serum from a case of dermatomyositis caused sarcolemmal fluorescence but did not bind to the cross-striations of the muscle fibres.

In 1960-61 Alexander, Anderson and I investigated fifteen myasthenic sera for anti-muscle antibodies. Seven of these proved to be anti-complementary and useless for further study. Only one of these is represented in Table 13.1. Of the remaining eight cases, one (MN294) showed a low titre of anti-muscle activity by the tanned cell haemagglutination technique. None showed specific changes with the immunofluorescence technique (Simpson, 1964a). The American results are, however, confirmed by Beutner et al (1962) and Feltkamp et al (1963a). These authors describe four different types of reaction of globulin to muscle based on immunofluorescence techniques.

i) fluorescence of the sarcolemma, which also occurs with control sera.
ii) fluorescence of the A bands of muscle fibres.
iii) similar involvement of only about half of the muscle fibres ('zebra' type).
iv) nuclear fluorescence.

Only types ii) and iii) seem to be specific for myasthenia gravis. The nuclear fluorescence is due to the presence in some sera of antinuclear factor which also acts against other cells (Feltkamp et al, 1963b).

Specificity:

The cytolytic effect of myasthenic serum in frog muscle cells described by Nastuk et al (1959) suggests that the anti-muscle substance, if such it be, is not species/

species-specific. The globulin which is capable of binding to human skeletal muscle also attaches itself to skeletal muscle of the rat (Strauss et al, 1960; Feltkamp et al, 1963a and b). With regard to organ-specificity the available evidence is inconsistent. Strauss et al (1960) found that the globulin which binds to skeletal muscle does not do so with cardiac or uterine muscle and they also had negative results against thymus tissue obtained from two myasthenic patients. Beutner et al (1962) confirmed their results on skeletal muscle with sera from 2 of 10 myasthenic patients. Both of the active sera also showed fluorescence with the heart muscle by the direct and indirect fluorescent antibody techniques, but the complement-fixing and staining technique using heart tissue was negative. They suggest that their results indicate the presence of at least two antibodies, one specific to skeletal muscle and the other reacting with skeletal and cardiac muscle.

Van der Geld and Oosterhuis (1963) using an antiglobulin consumption test with or without the aid of immunoelectrophoresis, found that 40% of sera containing antibodies reacting with skeletal muscle also reacted with thymus. They did not encounter sera with antibodies acting exclusively against thymus. Cross-absorption experiments suggested that there were two distinct circulating antibodies, one of which reacted with skeletal muscle or thymus, the other with skeletal muscle alone. No reaction was found with heart muscle, liver, pancreas or kidney tissues.

In/

In searching for a possible explanation of the failure to find muscle-binding globulin in my small series and the apparent disagreement of these authors regarding organ-specificity, I have drawn attention to one important aspect which is not commented on by any of the papers cited (Simpson, 1964a). Strauss et al (1960) obtained their positive results on skeletal muscle from samples of pooled sera from 10 myasthenic patients. Six of these had a thymoma. Their further experience of 16 individualssera was apparently negative. The only two positive sera of the ten examined by Boutner et al (1962) were from the only patients with a thymoma. Feltkamp et al (1963a) found muscle binding globulin by the Coon's indirect technique in 42% of 111 myasthenic sera but included sarcolemmal fluorescence. Their data are a little difficult to interpret but a study of their Table I suggests that in fact unequivocal fluorescence of muscle fibre was present in only 23 of the 111 cases (20%). In a further comment on the same material (van der Geld et al, 1963) they state that patients in whom myasthenia gravis was associated with a thymoma appear to fall into a special group, with a consistently higher incidence of anti-skeletal-muscle antibodies. Of their 8 cases with thymoma, all showed anti-muscle antibodies as against 30 of 90 cases without a thymoma. Unfortunately this comparison was made with an antiglobulin consumption test which their Table III suggests does not correlate exactly with the immunofluorescence technique.

This review strongly suggests that the sera containing muscle-binding antibodies as judged by an immunofluorescence technique are derived from myasthenic patients/

patients who have a thymic tumour. None of the patients tested in the present series had a thymoma and unfortunately no case of thymic tumour has been available for study since this correlation was noticed. It might also be relevant to note that muscular wasting was not a feature of the cases I have examined for anti-muscle antibodies. As pointed out in Chapter 3 and in Simpson (1958) 'myasthenic myopathy' is more common in association with a thymoma though not confined to such cases. It would be interesting to examine the correlation between muscle antibodies of the Strauss type and the so-called myasthenic myopathy.

The considerations just discussed are of considerable importance. In my original hypothesis (Simpson, 1960a) I suggested that the disorder of neuromuscular transmission of myasthenia gravis could be accounted for by the blocking of chemoreceptors of the muscle receptor zone by an incompletely fixed type of antibody. This specification seems necessary to account for the rapid changes in the clinical state which have been described in Chapter 2. The Strauss type of antibody acting against the contractile part of muscle fibres does not seem to meet the operational requirements. If it is a pathogenic factor it would be expected to cause partial or complete cell necrosis. In Chapter 11 it has been shown that muscle cells may indeed be affected by a 'myositic' reaction but that this is scattered, inconsistent, and apparently unrelated to the 'fatiguable' type of weakness. The electromyographic evidence (Chapter 15) leads to the same conclusions. If, in addition, the Strauss type of antibody is virtually confined/

confined to cases with a thymic tumour it seems possible that there may still be an antibody against end-plate protein which remains to be identified. In this respect my hypothesis remains unproved. Nevertheless it must now be accepted that in some cases of myasthenia gravis an immunological disorder is related to muscle damage and this fact immediately increases the possibility that the original hypothesis is valid.

Antinuclear and rheumatoid factors:

Since the autoimmune hypothesis was in part derived from a consideration of the possibility of multiple organ pathology in myasthenia gravis (Simpson 1960a, Chapter 7) it follows that one would expect to find serological evidence of antibodies against other organs.

A possible relationship with 'rheumatoid' arthritis was suggested by Simpson (1960a). The quotation marks were used to indicate that the arthropathy might differ from true rheumatoid arthritis though it resembled it closely in affecting mainly the small joints of the limbs. It was, however, sometimes transitory. Van der Geld et al (1963) have recently reported that the rheumatoid factor was present in the serum of 5 of 111 (4.5%) cases of myasthenia gravis (Table 13, 2 and 3). Six patients in their series had rheumatoid arthritis (sic) but it seems from a letter by Feltkamp et al (1963b) that only one of these patients had the rheumatoid factor in the blood so it would appear that the other positive findings were made on myasthenic patients without clinical evidence of arthritis. Arthritis was present in 3 of 15 cases of myasthenia gravis reported by White and Marshall, (1962/

(1962). (I omit one of the 16 cases reported who appears to have had carcinomatous myasthenia rather than myasthenia gravis). Two of the three arthritic cases gave a positive latex reaction for rheumatoid factor and each had hyperglobulinaemia at the time of examination or previously. One of these cases was later diagnosed as Systemic Lupus Erythematosus. Antinuclear factor (A.N.F.) was demonstrated in 6 of the 15 cases and another 2 gave positive nuclear fluorescence with undiluted serum. Antinuclear factor in the serum was detected by its action on thyroid tissue. The positive reactors included all but one of the arthritic cases, one case of cutaneous lupus erythematosus, and 3 cases without evidence of joint involvement.

Strauss (1962) found no evidence of A.N.F. against skeletal muscle-cell nuclei but Koutner et al (1962) and Feltkamp et al (1963a and b) reported its presence. The incidence of positive results against muscle nuclei is not recorded but with human leucocytes as antigen Feltkamp et al (1963b) found A.N.F. in 15 of 111 cases (13.5%). Antinuclear factor was not detected in any of 70 normal controls (type unspecified).

Antinuclear factor was estimated in the sera of 45 patients in the present series and rheumatoid factor in nine. The A.N.F. tests were performed on human leucocytes according to the technique of Alexander et al (1960) who found 4% positives in 580 controls (healthy young blood donors of both sexes). The cases relevant to this section are summarised in Table 13.1. Antinuclear factor was present in significant titre as defined by Alexander et al (1960) in 8 of the 40 cases (Simpson, 1964a). No L.E. cells were detected in any of these 45 cases but one/

one other case reported earlier (Simpson 1960a) and described in Chapter 7 had L.E. cells in her blood.

None of the nine cases examined for the rheumatoid factor by the sensitised sheep-cell test had a significantly raised titre. The series is very small but includes Case MN 294 which has been described and illustrated in Chapter 7 and Figs. 7,2. The negative result does, however, justify continuing to differentiate the arthritis of myasthenia gravis from 'true' rheumatoid disease. Oosterhuis (1963) found a negative Rose-Waaler reaction in four cases of 'rheumatoid' arthritis associated with myasthenia gravis. Two of these and another 6 of his 116 myasthenic cases had a family history of rheumatoid arthritis. The high incidence of A.N.F. (20%) though less than that reported in the smaller series of White and Marshall (1962) gives strong support to the hypothesis that immunological mechanisms are disordered in myasthenia gravis and links this disease with the so-called 'symptomatic myasthenias' described in Chapter 9.

Autoimmune aspects of associated blood disorders:

Pure red-cell aplasia, which was present in one case (Chapter 7) was not, at the time it occurred, considered to be of immunological importance. Oosterhuis (1963) reports a case in which the direct Coomb's test was positive (an interesting series of radiographs shows temporary shrinkage of the thymoma during treatment with prednisone). Another of his cases and one reported by Castaigne et al (1961) had hyperglobulinaemia. A recent report describing the finding of a positive A.N.F. test in a case of this disorder associated with a thymoma, but without myasthenia gravis, adds to the probability that immunological mechanisms/

mechanisms may be involved in the blood dyscrasia (Holborrow et al, 1963).

In the same way, when I recorded the association between myasthenia gravis and pernicious anaemia (Simpson, 1960a) it was not known that that blood disease was of immunological interest. It has been suggested recently that an organ-specific antibody to gastric intrinsic factor and to the parietal cells of the stomach may be responsible for the production of the cyanacobalamin deficiency which causes the anaemia (Schwartz, 1960; Irvine et al, 1962; Taylor et al, 1962). In the present series of myasthenic patients, antibody active against human stomach was detected in 3 of 44 cases, using complement fixation (C.F.T.) and immunofluorescence (Ic) techniques with gastric tissue (Table 13,1). One of these patients, (Case MN 5503, Chapter 7), had pernicious anaemia. With the method used positive results are obtained in 8% of middle-aged female blood donors (Irvine, 1964). The other patients with pernicious anaemia described in Chapter 7 are no longer available for immunological studies.

Pernicious anaemia has recently been reported to be associated with a number of other diseases e.g. rheumatoid arthritis (Partridge and Duthie, 1963), myxoedema (Tudhope and Wilson, 1960), thyrotoxicosis (McNicol, 1961; Doniach et al, 1963), autoimmune thyroiditis (Irvine et al, 1962; Markson and Moore, 1962; Taylor et al, 1962; Doniach et al, 1963), systemic lupus erythematosus (Doniach et al, 1963), and with diabetes mellitus (Arapakis et al, 1963; Beckett and Matthews, 1963). There is thus an overlap between pernicious anaemia and several diseases/

diseases associated with abnormal immunological reactions and to these myasthenia gravis should now be added (Simpson, 1964a).

Autoimmune thyroiditis:

The relationship between thyroid disease and myasthenia gravis has been discussed in Chapter 5 from the clinical point of view and a case of Hashimoto's disease described (Fig 13). Attention was drawn to the earlier reports of lymphadenoid goitre associated with myasthenia gravis and further examples were described. Through the kindness of Dr. W.J. Irvine an investigation has been made for the presence of anti-thyroid substances in the blood of 44 patients with myasthenia gravis, using the methods described by Irvine (1964). The results of the tanned cell haemagglutination (T.C.H.) and complement-fixation tests (C.F.T.) are shown in Table 13,1. Specificity was ensured by absorbing out antibodies which were not organ-specific. Of the 44 patients examined, 12 had significant titre of antithyroid antibodies by one or both tests. Six of the positive reactors have had confirmed or suspected thyrotoxicosis at some time in the past. Another 4 cases with a similar history (MN4536, MN5625, MN7543, MN7781) did not have a significant titre. One case of non-toxic goitre (MN7855) and one case of thymoma with biochemical evidence of hypothyroidism (MN6476, Chapter 5) had no detectable antibodies against thyroid tissue. The other cases of thyroid disease shown in Table 13,2 were not examined for thyroid antibodies.

The only other report in the literature is that of van der Geld (1963b) who found antithyroid antibodies in 36 of 111 cases of myasthenia gravis.

CHAPTER 14.

THE AETIOLOGY OF MYASTHENIA GRAVIS.

It is convenient at this point to review the previous chapters from the point of view of the aetiology of myasthenia gravis.

i) Age and Sex (Chapter 2). Myasthenia gravis occurs in both sexes but more commonly in women. The modal age at the onset is 20-25 years irrespective of sex.

ii) Precipitating factors (Chapter 2). Myasthenia may arise spontaneously but the first attack and subsequent relapses are commonly precipitated by infections or by emotional disturbance and occasionally in association with allergic disorders. Relapses are also brought on by pregnancy, menstruation and extremes of cold or warmth.

iii) Course (Chapter 2). This is variable but is characterised by relapses and remissions during the first 5-7 years. Later remissions are rare. There is some evidence for a stage of 'active' disease during this period in which the natural history may be influenced by removal of the thymus gland (Chapter 10). The later course is, on the whole, determined by pathological changes occurring during the 'active' stage.

iv) Related disorders (Chapters 4,5 and 7). The neuromuscular syndrome may be associated with a wide spectrum of disturbances of the central and peripheral nervous system, arthritis of 'rheumatoid' type/

type, acrocyanosis, splenomegaly, lymphadenopathy, pure red-cell aplasia, pernicious anaemia, haemolytic anaemia, nephritis, hepatitis, ulcerative colitis, thyrotoxicosis and other thyroid diseases including Hashimoto's disease, and diabetes mellitus. The relationship of these disorders with autoimmune disease is shown in Chapter 13.

v) Biochemistry (Chapter 6). There is no evidence of endocrine disease other than thyroid and diabetes, and the thyroid may be affected in many ways - non-toxic goitre, myxoedema and Hashimoto's disease as well as thyrotoxicosis. Hyperglobulinaemia may be found and, occasionally, raised protein content of the cerebrospinal fluid.

vi) Antibodies (Chapter 13). A significant increase of organ-specific antibodies against muscle, thyroid and stomach and of antinuclear factor and rheumatoid factor is found in the sera of myasthenic patients.

vii) Neonatal myasthenia (Chapter 8). Myasthenia occurring in some children born to myasthenic mothers persists for 4-6 weeks. This suggests passage of a toxic factor across the placental barrier yet no such factor can be identified by cross-transfusion experiments in adults (Chapter 16). These results would be explained if the 'myasthenic toxin' were an antibody.

viii) Symptomatic myasthenia (Chapter 17). Myasthenic weakness may be found in systemic lupus erythematosus, dermatomyositis, sarcoidosis and carcinomatosis.

ix) Pathology (Chapter 11). There are consistent pathological changes in the thymus, motor nerve terminals and muscle, and less commonly in other organs/

organs, of a type suggestive of immunological disorder.

x) Thymic function (Chapter 12). A review of the physiology of the thymus shows that its main function is the production of immunologically competent lymphocytes. It is important in controlling the development of the body's defence mechanism against foreign protein in foetal and infant life and may play an intermediary role in growth and maturation at that time. Disorders of the thymus are now known to be associated with failure of immunological tolerance in later life.

An autoimmune hypothesis:

Though the recent evidence on thymic function was not available, I have interpreted the data summarised here as indicating the possibility that myasthenia gravis is the result of a failure of immunological tolerance, with the production of antibody against the receptor protein of muscle or some similar structure at the neuromuscular junction (Simpson, 1960). The further immunological studies reported in the last chapter support this concept. A discussion of the mode of production of the failure of neuromuscular transmission will be postponed until the physiopathology has been examined in Chapter 16.

The response to the autoimmune hypothesis was immediate. Marshall and White (1961) showed that direct injection of bacterial antigen into the guinea-pig thymus produced a histological reaction which was essentially the same as that seen in myasthenia gravis. Their studies suggested that a blood-thymus barrier exists which would preclude/

preclude any cellular reaction of the normal thymus to circulating antigen and so facilitate the development of immunologically competent cells active against an individual's own tissues. By this time experimental biologists were coming to the conclusion that the thymus played a very important role in the development of immunological response (Miller 1961, 1963; Burnet, 1962 a & b) and Strauss et al (1960) and later workers had shown that anti-muscle substances could sometimes be demonstrated in the serum of myasthenic patients. Harvey and Johns (1962) reviewing the evidence in 1962 concluded that the data for an autoimmune disease of muscle due to disordered function of the thymus now 'provide a substantial direction for future research'.

In view of the evidence reviewed by Simpson (1960), Burnet (1962a) has included myasthenia gravis among the autoimmune diseases. (In this and all subsequent papers from the same author the arthritis described in my paper is described as rheumatoid arthritis without the cautionary quotation marks. Burnet does not seem to have any independent evidence) Burnet (1962b) classified myasthenia gravis in his Group I (organ-specific) type of autoimmune disease while acknowledging that a possible relationship with rheumatoid arthritis might necessitate revision of this provisional classification. The evidence now presented supports the hypothesis that myasthenia gravis is associated with disturbed antigen-antibody reactions but demonstrates that there may be several organ-specific antibodies present and that there is a clinical and serological overlap with many other autoimmune disorders.

Antibodies/

Antibodies against muscle fibres are rare except in the presence of a thymic tumour and may not account for the defect of neuromuscular transmission. The possibility of a more localised end-plate reaction remains unconfirmed but is perhaps more plausible since the production of multiple antibodies is now established and this may justify some further discussion of the possible mechanisms involved since further facts are presented in this thesis which are not generally known and yet may be relevant in the wider context of autoimmune disease.

xi) Thymectomy (Chapter 10). Removal of the thymus may cause arrest or resolution of myasthenia if carried out during the proposed 'active stage' of the disease (except in so far as permanent muscle damage has already occurred) but does not always do so. Furthermore, myasthenia gravis has first manifested itself after the thymus has already been removed to eradicate a tumour (Green and Booth, 1958).

These clues that the thymus is not the exclusive source of antibody responsible for autoimmune reactions is supported by the occurrence of Hashimoto's disease 5-7 years after thymectomy (Chapter 13). Alarçon-Segovia et al, (1963) reported the development of ulcerative colitis and systemic lupus erythematosus after the thymus had been removed for myasthenia gravis. Hepatitis and acute haemolytic anaemia developed several years after removal of a thymoma in Case MN 5095 (Chapter 19) were probably due to drug toxicity. These observations suggest that the thymus is not necessary for the continuation of the disease or for the subsequent development of autoimmune disorders. It may/

may be that the thymus is of prime importance during the first five years or so but that other parts of the reticuloendothelial system may then continue to produce autoantibodies without its presence (Simpson, 1958, 1960).

Several theoretical possibilities have been discussed and a full review is not required here. One theory of autoantibody production which was favoured in recent years was that protein 'leaked' from damaged cells within which it was normally confined and that this acted as an antigen which 'instructs' the reticuloendothelial system to form appropriate antibody. The multiplicity of antibodies in myasthenia gravis and other diseases makes a 'leak' theory most improbable though it was allowed for in the diagram illustrating my hypothesis - Fig. 12,5, (Simpson, 1960). It is more probable that the antibody-producing mechanism forms a wide range of proteins but normally these do not react with the individual's own tissues. Burnet has developed a theory, which has been modified from time to time, based on the supposition that clones of lymphoid cells develop which produce antibodies which cover all the antigens likely to be encountered in a normal environment. In the early stage of his theory he postulated that each clone was preadapted to react with only one type of antigenic determinant. He now considers that it is necessary to envisage a progressive development to specifically committed clones, based on the differentiation during embryonic life of receptors concerned essentially with the recognition of patterns that are or may be present in body components. The theory requires that cells carrying receptors which could react with normal body components must be destroyed during embryonic/

embryonic life or sequestered in some organ with an effective blood-organ barrier. In view of the work of Miller (1961) he suggests this role for the thymus (Burnet, 1962a). The lymphocytes produced there are, in this view, 'uncommitted' until they come into contact with the appropriate antigen and then the cell proliferates in other lymphoid tissues such as the spleen and lymph nodes. During this proliferation he suggests that progressive specialisation occurs of the antibody formed by the clone which is now 'committed' by a process of mutation with selection. Clones of cells which would produce antibody against 'self-components' are described by Burnet as 'forbidden clones' and he considers that they are normally immured within the thymus by some form of homeostatic control. If a somatic mutation to a form resistant to homeostatic control arises it will proliferate in the thymus instead of being inhibited or destroyed, thus giving rise to active germinal centres. The escape of a forbidden clone into the blood stream would then initiate tissue-destruction.

Burnet (1962a) states that the favourable response to early thymectomy suggests that in myasthenia gravis most of the development of the forbidden clones occurs in the thymus or that this type of cell is rapidly eliminated when it escapes into the circulation. White and Marshall (1962) suggests that a breakdown of a blood-thymus barrier may occur in myasthenia gravis. The failure of late thymectomy might suggest that later population of mature lymphoid tissue (spleen, lymph nodes) may occur (Harris and Ford, 1963). The occasional occurence of splenomegaly or/

or lymphadenopathy in myasthenia gravis now assumes some significance (Chapter 7).

Miller (1963) offers alternative theories for the role of the thymus and favours the view that it may endow non-thymic lymphocytes with the property of immunological competence (Osoba and Miller, 1963). He considers that it is still not quite clear whether the thymus plays any direct part in the induction of specific tolerance but that it is more likely that it plays a part in the breakdown of immunological tolerance.

It is unprofitable to discuss further this very specialised and rapidly advancing field but it will be apparent that at least one plausible theory of immunological tolerance requires a homeostatic control of the thymus in early life.

xii) Genetic factors (Chapter 8). Familial myasthenia occurs as a rare event, yet only one of a pair of identical twins is affected. There is an increased incidence of thyroid disease, and possibly of diabetes mellitus, among the progenitors and siblings of myasthenic patients.

xiii) Endocrine relationships (Chapter 5). The associated endocrine disorders do not appear to be causally related to the neuromuscular syndrome. They cannot all be accounted for in terms of disturbed immunological tolerance. It is suggested that they are indirectly related by having a common hypothalamo-pituitary mechanism (Fig.12.5).

These two propositions may indicate that there is a hereditary factor which determines the reactivity of the hypothalamus and/or the pituitary. In most instances this renders the subject liable to develop thyroid disease of various/

various types under suitable provocation. (In others diabetes mellitus may result but the evidence in this respect is insufficient). In a few cases myasthenia gravis results, the appropriate stimulus being an emotional or infective one or a pregnancy (Simpson, 1960$_a$). This pituitary mechanism could provide the intrinsic (non-immunological) stimulus to the thymus or the homeostatic mechanism required by Burnet's theory (Simpson, 1964$_c$). In the original presentation (Simpson, 1960$_a$) it was suggested that the thymus might play a role in tissue differentiation during embryogenesis of which the control of blood cells and plasma proteins may be a fraction which survives after birth, thus harmonizing the immunological role with earlier work on growth and differentiation which has been reviewed in Chapter 12. A similar idea is implicit in the suggestion by Burnet (1962a) that the thymus is primarily concerned with the maintenance of the chemical integrity of the body, including the mechanism of specific protein synthesis, and that the development of the immunological competence of the body is part of the process of morphological and functional differentiation of the embryo and young animal. Weiss (1950) and Burwell (1963) have developed alternative theories of control by the reticuloendothelial system of cellular growth and differentiation. My further suggestion that this mechanism is controlled by the pituitary gland may be as rewarding as the first part of the hypothesis on the role of the thymus gland in myasthenia gravis and in autoimmune disease.

CHAPTER 15.

NEUROMUSCULAR TRANSMISSION IN NORMAL AND MYASTHENIC MUSCLE.

The feature which differentiates myasthenia from other types of muscular weakness is its progressive increase if the muscular contraction is maintained or if a movement is regularly repeated without adequate interval for rest. This phenomenon is often termed 'pathological fatigue'. The term is graphic but undesirable as the increasing weakness has no close resemblance to normal fatigue of muscle or of its nervous control. It is unfortunate that there is no suitable word in the English language to describe the progressive loss of power of muscular contraction or of the associated action potentials.

The Jolly test:

The resemblance of myasthenia to curare poisoning occurred to Oppenheim (1887) and to Jolly (1895). The latter worker made a most significant contribution when he showed that the 'fading' muscle contraction could be reproduced if the motor point of a myasthenic muscle was stimulated by a burst of faradic electric current (i.e. a rapid train of oscillatory stimuli) whereas the muscle continued to contract powerfully if a galvanic stimulus was used. The explanation is that the faradic current is a suitable stimulus for the motor nerve entering the muscle at the motor point, but the galvanic stimulus affects only the muscle. This important observation showed that the muscle was capable of contracting repeatedly without 'fatigue' if its fibres were stimulated directly though/

though there was progressive loss of response if it was stimulated indirectly through its motor nerve. Since both the motor nerve and the muscle fibre have been considered, until recently, to be normal it seemed likely that there was a defect of transmission of excitation from nerve to muscle.

Pritchard (1933) identified the cause of the myasthenic reaction as Wedensky inhibition. In the Wedensky phenomenon a partial block of a nerve so prolongs its refractory period that only the first of a rapid train of impulses will pass through the blocked area though a slow train may pass without difficulty. The result of a series of impulses at a critical frequency of stimulation will then be a single muscle twitch, not the decrementing series of twitches found in myasthenia gravis. The concept of Wedensky inhibition in myasthenia gravis still has some currency in the Soviet states but can no longer be accepted.

Action of anticholinesterase agents:

In view of the resemblance to curare poisoning, Jolly (1895) suggested that physostigmine might be an effective 'antidote' to 'myasthenia gravis pseudoparalytica' (he was the first to use that term) but apparently he never tried it. That honour goes to Murri (1895) but was not followed up as the patient showed little response. In 1934 Mary Walker gave physostigmine to a myasthenic patient with dramatic benefit (Walker, 1934a) and later an analogue of the alkaloid, neostigmine (Walker, 1934b). At that time the possibility of chemical transmission at the neuromuscular junction was a current topic among physiologists and in the same year Dale/

Dale and Feldberg (1934) confirmed the role of acetylcholine in neuromuscular transmission. Viets and Schwab (1935) showed that a therapeutic response to neostigmine was sufficiently characteristic of myasthenia gravis to be used as a diagnostic test. From this time there has been no serious doubt that the myasthenic phenomenon was due to a disorder of transmission at the neuromuscular junction though the exact mechanism has been debated. Indeed myasthenia gravis became a favourite subject for the teacher of medicine as the ideal meeting ground for clinician, physiologist and pharmacologist. It seemed only a matter of time and of refinement of physiological and pharmacological techniques before the true lesion would be demonstrated. 'In that same period' (I wrote in 1958) 'knowledge of the physiology of the neuromuscular junction has made its greatest advances yet the solution of the problem of myasthenia evades us'.

<u>The neuromuscular junction</u>:

Further consideration of the problem requires a brief review of the mechanism of neuromuscular transmission as it is at present understood (Fig.15.1[88]). The motor nerve axis cylinder ensheathed in myelin and Schwann cell syncytium, has a terminal arborization (telodendria) embedded in the sarcoplasm of the terminal Schwann cell (teloglia) which continues over the fine branches though myelin ceases at the arborization. In mammals the terminal branches are normally grouped closely together in a 'plaque' applied to a discrete region of a muscle fibre. Each terminal fibre, often ending in a knob, is embedded in one of a series of grooves/

grooves called synaptic gutters on the surface plasma membrane of the muscle. The neurilemma which lies outside of the terminal Schwann sheath merges into the sarcolemma at the margin of the end-plate zone and takes no actual part in the junction. The enveloping connective tissue sheath of the nerve fibre, the endoneurium, becomes continuous with the endomysium. Thus the cytoplasm of the axonal terminal knob is covered by a very thin layer (0.1-0.4μ) of teloglial cytoplasm which is separated by a gap of 200-250 Å from the plasma membrane of the muscle cell in the corrugated 'subneural apparatus' of Couteaux.

Physiology of neuromuscular transmission:

The cytoplasm of the axon terminal contains many mitochondria and a number of ovoid particles can be identified by the electron microscope (Lehrer and Ornstein, 1959). These are believed to be vesicular structures containing acetylcholine or its precursor. Some of these are considered to discharge spontaneously into the synaptic cleft, but the majority are released only by some unknown change accompanying the depolarization of the terminal knob by the occurrence of an action potential at its surface membrane (pre-synaptic membrane). The acetylcholine liberated in this way crosses the narrow gap to the post-synaptic membrane of the muscle end-plate. At this site it is considered that there is a protein which has a molecular structure complementary to the shape of the acetylcholine molecule. This acts as a 'receptor' surface to which acetylcholine or similarly formed molecules readily bind themselves. In recent years there has been an increasing tendency to restrict the term/

term 'end-plate' (previously used more comprehensively) to the sub-synaptic region of the muscle membrane. The union of acetylcholine to receptor protein in some way increases the permeability of the end-plate zone to ions in a relatively unspecific way. As a consequence of this permeability change, an ionic current flows across the postsynaptic membrane with a direction and intensity which depends solely upon the ionic gradients and potential difference across the membrane. The inward flow of sodium ions causes a depolarization of the previously polarized muscle cell. The 'end-plate potential' which results causes a current flow in the adjacent resting muscle membrane. If this reaches a critical level of current flow a muscle action potential is generated. This in turn activates the contractile substance of the muscle. Note that a consequence of this is that if all muscle fibres are depolarized simultaneously the compound action potential is more or less directly related to the accompanying twitch tension. It is because of this relationship that measurement of the synchronised action potential of the muscle is now used as a measure of muscular response in place of the tension as in the original test of Jolly (1895).

The muscle cell becomes repolarized by the outward passage of potassium ions and almost immediately by the expulsion by a metabolically controlled 'pump' of the excess of sodium ions. This does not normally lead to regenerative activity even though the receptors may still have acetylcholine molecules attached. There appears to be some mechanism causing temporary refractoriness but its nature is not understood (Axelsson and Thesleff (1958). If/

If the acetylcholine is not displaced this is followed by prolonged block of transmission in the sense that further discharge of acetylcholine across the synaptic cleft will not evoke an end-plate potential. After the work of Burns and Paton (1951) this was considered to be due to persistent depolarization. Though it is now known that the postsynaptic membrane actually repolarises the block is still described as a 'depolarization block'. It is the mechanism of block when certain quaternary ammonium compounds related to acetylcholine (decamethonium, succinylcholine) are injected into the normal human subject. That this does not happen with acetylcholine is due to the fact that it is rapidly hydrolysed by a specific acetylcholinesterase which is concentrated in the subneural (or terminal) apparatus lying deep to the postsynaptic folds of the muscle membrane. Cholinesterase destroys acetylcholine at a very high rate. As there is, in addition, free diffusion of acetylcholine out of the synaptic cleft into the extracellular space, with which it is in continuity, the concentration of acetylcholine at the receptor site falls very rapidly, permitting the muscle to respond to a rapid series of nerve impulses and their mediatory packets of acetylcholine. It is the failure of the hydrolysis which leads to the prolonged 'depolarization block' when the closely related decamethonium is given to normal human beings but acetylcholine will have an entirely similar effect if it's hydrolysis is prevented by a complete inhibition of cholinesterase by neostigmine and similar substances. (Chapter 18 and 19).

Electromyography/

Electromyography of voluntary contraction:

Lindsley (1935) made myographic and electromyographic studies using coaxial needle electrodes to record the activity of individual muscle fibres or of motor units. He found that the rhythm of discharge of the motor units on voluntary contraction was normal. The size of the potential recorded from each unit was subject to wide variation which was greater with fatigue of the muscle but was abolished after injection of neostigmine. He considered that the function of the motoneurone was normal but that there was intermittent block of neuromuscular transmission to some of the muscle fibres which it innervated. With continued effort there is a progressive fall-out of motor units. If a special effort is requested, a new and poorly sustained burst of discharge occurs. Denny-Brown (1953) states that the units forming this renewed discharge are not units which have recovered from the previous 'fatigue' but are new units responding only to the special effort. This has not been my own impression though it is impossible to be dogmatic about it. It would, for instance, be quite impossible to state that the first units to drop out had not recovered since their morphology cannot be examined during full contraction by normal methods of recording. I have described cycles of sudden failure of contraction with renewed effort, which resembles a hysterical manifestation, and their electromyographic concomitant (Simpson, 1960) but the latter is published here for the first time (Fig. 152, 3, 1 and). It will be seen that the confused 'interference pattern' of the electromyogram decreases in amplitude and becomes simplified by the sudden/

sudden cessation of activity of some units (Denny-Brown, 1953; Lundervold, 1954, Simpson, 1956). At this stage the contraction becomes tremulous and the motor units tend to synchronise. This is found in normal fatigue and in maximum contraction of muscle weakened by a variety of causes. I have suggested that it might be due to a change from a contraction regulated by spindle receptors to one regulated by tendon organs (Simpson, 1962b). The contraction then stops abruptly but is resumed in about one second with greater intensity. Rather than Denny-Brown's explanation of recruitment of a hidden reserve of high threshold units I have suggested that the brief pause allows development of short-lasting post-tetanic facilitation. It is the same mechanism which abolishes induced ptosis if the patient is allowed to blink during testing. It is probably also the mechanism of the coarse monocular nystagmus which is sometimes present (Simpson, 1960a).

Many of the motor units in the affected muscles have the polyphasic action potentials of a 'myopathic' motor unit. This may only be seen in the last units remaining before final cessation of the weakening contraction but in many cases similar units can be found at the beginning of contraction even after a period of rest. This is most frequently observed in the deltoid and triceps muscles of the upper limbs. In a minority of cases muscles affected in this way show scanty spontaneous fibrillation, positive sharp waves, and increased mechanical excitability. All of these features are indistinguishable from the electromyographic pattern of polymyositis (Simpson, 1960a) (Fig. 15,3).

Unfortunately/

Unfortunately the existing techniques do not permit satisfactory isolation of a single motor unit to study the changes in its action potential throughout strong voluntary effort. Considerable information of a statistical nature can, however, be obtained from the study of a population of motor units integrated by recording from the skin surface if each is stimulated more or less synchronously by means of its motor nerve.

Possible abnormalities causing the myasthenic reaction:

In the 1930-50 period it was considered that the myasthenic response must indicate one of three possible 'chemical lesions' at the neuromuscular junction: i) insufficiency of acetylcholine, ii) excess of cholinesterase, or iii) a block of transmission resembling curare-poisoning, and presumably due to the presence of a curariform 'myasthenic toxin' present in the blood (Wilson and Stoner, 1944). Logically it should be considered that the receptor site of the end-plate might be abnormal but this has only recently been postulated (Zaimis et al, 1952). The investigations carried out to determine between these possibilities are electrophysiological and pharmacological or a combination of these two.

The Harvey-Masland test:

Early reports of the changes in the action potential of a myasthenic muscle tetanised by repetitive stimulation of a motor nerve may be criticised on technical grounds (Herzog, 1917; Eichler et al, 1935). Harvey and Masland (1941) drew attention to the importance of preventing displacement of the stimulating electrodes placed over the nerve and of using supramaximal/

supramaximal stimulation to ensure that every motor fibre in the mixed nerve is adequately stimulated. This can be a painful experience for the patient and it may be preferable to block the nerve proximally by injected local anaesthetic (Desmedt, 1958a). Special precautions must be taken to prevent the electromyographic record of the evoked muscle potential from being obscured by an artefact caused by stimulus-escape (Pinelli, 1957).

Most of the present work was done with an electronic square-wave stimulator similar to that of Ritchie and Sneath (Walter and Ritchie, 1945). The output of the stimulator was connected to the primary of a Muirhead transformer (Type D-139-E) and the secondary windings of the transformer were applied to saline pad electrodes fixed over the appropriate nerve. The electrodes were placed 2 cm. apart with a cathode distal to the anode. In this way the stimulus was isolated from the ground. The wave form of the stimulus delivered at the electrodes was virtually square but the wave form is not important as the stimulating current reaching the nerve is distorted by the resistance and capacitance of the skin and other tissues (Stephens, 1956). In later experiments a battery-operated transistorised stimulator was used giving a stimulus isolated from the ground without the need for transformer coupling.

Using the shortest available pulse (16μ.sec) at a frequency of 0.5/sec., the stimulator output was increased until it was 30% greater than the current required to produce maximal response in a muscle supplied by the nerve which was being stimulated.

If/

If this was not obtained within these parameters, the stimulus pulse was gradually lengthened. The actual stimulus applied varied from case to case but was always at least 30% supramaximal.

The action potential evoked by the stimulus was recorded from an appropriate muscle by surface electrodes (0.5cm. silver-silver chloride discs) leading to a conventional push-pull resistance-capacity coupled amplifier and a two-beam oscilloscope. One electrode was placed over the belly of the muscle and the other over a tendinous part of the related finger. They were fixed firmly in position with adhesive tape. Time calibration was applied to the second beam of the oscilloscope from an Ediswan low-frequency oscillator or a crystal-controlled time marker (Digitimer) producing a ruler-type time scale. Records were made on 70mm. moving film to demonstrate sequential changes in the action potential amplitude. In a few instances the action potential of the nerve was simultaneously recorded by similar electrodes placed over its course proximal to the point of stimulation.

Hervey and Maaland (1941) found that the action potential of the muscle after the second of a pair of supramaximal stimuli was depressed for 0.5-2.0 seconds after the first (conditioning) stimulus. With a train of stimuli ('tetanus') the effect varied with the interval between stimuli but even with stimulation rates as low as 13 per second there was an immediate and progressive decline in voltage for the first few responses. The voltage of the evoked potential then continued with little change/

change at this lower level of response. The decline was more pronounced when the muscle was partially 'fatigued' (sic) as a result of previous periods of stimulation and the decrement was greater with faster rates of stimulation. The time course of recovery following stimulation was tested with single test shocks applied at various intervals after a standard tetanus. The action potential did not regain its initial voltage until 1.5 seconds after the termination of the tetanus.

In a later paper (Harvey et al, 1941) the Baltimore workers reported that the first evoked potential was sometimes subnormal in myasthenic patients. This was sometimes followed by transient facilitation or recruitment of neuromuscular transmission and in others by a profound degree of depression. They interpreted these findings as an indication that some muscle fibres were incapable of stimulation until neuromuscular transmission was facilitated by repetition of stimulation within a short period of time. The increased voltage could not be due to better synchronization of muscle response since it was accompanied by an increase in the duration of the potential. (There was no evidence of repetitive response of the muscle fibres). In one patient both depression and facilitation were seen.

These results were confirmed and extended by Johns et al, (1956). They noted that patients with generalised myasthenia gravis showed an abnormal response to repetitive nerve stimulation at rates as low as 5 per second. Initially the amplitude of the muscle action potentials declined rapidly and then returned toward the initial/

initial value. This was in turn followed by a slow exponential fall in amplitude. As the stimulus frequency was increased the initial trough deepened and the rate of the late exponential fall was increased. Similar results were reported by Struppler (1954) and Pinelli (1957).

Johns et al (1956) noted a facilitated response to a test stimulus sometimes occurred 1.0 sec. after a tetanus. Such an increase was never seen in normal subjects and they concluded that there must be muscle fibres available for recruitment in the myasthenic, or in other words, that there is sometimes a partial neuromuscular block to transmission of a single impulse. The degree of post-tetanic facilitation may be increased by stimulating the nerve at frequencies above that at which the muscle fibres can respond, or by continued stimulation after the muscle fibres have ceased to respond. These facts suggested to Johns et al (1956) that the facilitation is a prejunctional rather than a post-junctional phenomenon, probably due to increased output of acetylcholine by the nerve endings when stimulated rapidly (Hutter, 1952; Liley and North, 1953).

Personal electromyographic studies:

My own studies from 1950 to date are in full agreement with the workers at Johns Hopkins University. The illustrations show examples of the pure decrementing response (Fig. 15,4), the decrement temporarily restored by facilitation (Fig. 15,5), initial decrement followed by facilitation and maintained response at the original level (Fig. 15,6), and facilitation without decrement (Fig. 15,8). Post-tetanic facilitation is illustrated in Fig. 15,7.

In/

In some cases a decrementing response occurred at slow rates of stimulation (less than 10/sec.) but facilitation at faster rates (Fig.15,8 and Desmedt, 1957a).

It is therefore certain that both depression and facilitation occur in true myasthenia gravis. It may be true that the facilitation response is seen in its most impressive form in carcinomatous myasthenia (Chapter 9 and Fig.9,7) but I have no doubt that the difference is only one of degree. I have the impression that the muscles which show the facilitation response with little if any decrement (in true myasthenia gravis) are those which exhibit the 'dual response' to the decamethonium test (vide infra) and that this response becomes greater in the 'burned out' phase of the disease. It will be recalled that 'myositic' changes may then be prominent in the histopathology. This phenomenon could account for the fact that some patients eventually found an improvement in their muscular power after exercise (Chapter 2 and Case MN.1714), (Simpson, 1960). In these patients the Jolly test, which records the power of contraction of the muscle when tetanised rather than its action potential, is misleading.

Post-activation exhaustion:

Desmedt (1957a and b; 1958b) has made a special study of the excitability changes following an indirect tetanus of a myasthenic muscle. He reports that the post-activation facilitation is short-lived. It disappears 20-30 seconds after faradization and is succeeded by a stage of 'post-tetanic exhaustion' (his terminology) during which the electrical and mechanical responses are greatly/

greatly reduced and a short train of stimuli at rates as slow as 3 per second cause marked decrement of successive responses. This 'post-tetanic exhaustion' slowly disappears with a half-time of 10-15 minutes. Desmedt considers that this, rather than the prompt decrement during a tetanus, is the real reason for the long-lasting component of the pathological fatigue seen clinically (Desmedt, 1957b). I have not studied this aspect in detail but there is no doubt that a 'myasthenic reaction' which cannot be demonstrated with a brief faradization of a motor nerve may sometimes be demonstrable after a prolonged voluntary contraction of the muscle even though there has been no obvious failing of the voluntary contraction. A related phenomenon is illustrated in Fig.15,D. This shows that the myasthenic reaction may only be detectable after repeated applications of a tetanus with brief intermissions, an important point when using the reaction as a diagnostic test.

CHAPTER 16.

THE MECHANISM OF NEUROMUSCULAR BLOCK IN MYASTHENIA GRAVIS.

The mechanism of transmission across the neuromuscular junction has been described in Chapter 15. Transmission may be blocked by various types of abnormalities. Before these are outlined it is desirable to point out that present concepts are based to a large extent on a study of transmission in the normal frog or mammalian neuromuscular junction and on the modifications detectable by present techniques when drugs are applied. From the number of papers appearing every year it is certain that present knowledge of the site of drug action is incomplete. For instance it has been widely assumed that the action of quaternary ammonium compounds is entirely post-synaptic whereas there is now increasing evidence of an additional pre-synaptic action. Nor is it permissible to extrapolate results obtained from normal neuromuscular junctions in other mammalian species to human muscle altered by disease.

With these reservations the possible mechanisms of transmission failure appear to be as follows:-

1) Deficient formation or release of acetylcholine from the motor nerve endings.
2) Excessively rapid removal of acetylcholine following its release.
3) Competition for receptors between acetylcholine and a sterically related molecule.
4) Abnormal prolongation of the action of acetylcholine.
5) Abnormal structure of the transmission substance.
6) /

6) Abnormality of structure or function of the receptor protein of the muscle end-plate.

7) Failure of activation-contraction coupling in the muscle fibre.

Unlikely possibilities:

Of these possibilities numbers 2, 4 and 7 may be dismissed from further consideration. Excessively rapid removal of acetylcholine from the synaptic cleft is very unlikely since it can be shown by histochemical techniques that the concentration of cholinesterase in the subneural apparatus is normal (Cohen et al, 1956) and it is certainly not raised in venous blood (Stedman and Russell, 1937; Wilson et al, 1951). Abnormal prolongation of the action of acetylcholine would lead to the condition described as 'depolarization' block. In this state the motor end-plate becomes inexcitable to further addition of acetylcholine (by nerve stimulation or by arterial injection). This type of block is often preceded by an increase in motor activity but further nerve stimuli evoke a subnormal response which does not decline further. This statement is true if cholinesterase activity is normal but, as pointed out by Grob et al, (1956a) there may be progressive intensification of the block if cholinesterase is absent or inhibited. This exceptional state can be excluded from consideration in view of the previous facts but it follows that the degree of block will be exaggerated by administration of acetylcholine or anticholinesterase compounds.

On the other hand block would be relieved by injection of a competitive blocking agent such as d-tubocurarine/

d-tubocurarine. There is no post-tetanic facilitation in 'depolarization' block. In all of these respects that condition differs from the phenomena of myasthenia gravis except in the event of increasing weakness associated with overdosage of anticholinesterase drugs - the so-called 'cholinergic crisis' (Chapter 19). It is now known that the muscle membrane does, in fact, repolarize despite continued occupation of receptor sites by acetylcholine but the chemoreceptors are in some way desensitized (Thesleff, 1955; Katz and Thesleff, 1957). The seventh possibility, failure of activation-contraction coupling, can be dismissed in view of the fact that myasthenic muscle responds promptly to the intra-arterial injection of acetylcholine (Grob et al, 1956b) and to direct electrical stimulation (Jolly, 1895). This leaves for serious consideration mechanisms 1, 3, 5 and 6.

Deficient formation or release of acetylcholine:

The effects of this type of transmission failure have been studied in experimental preparations. Calcium appears to exert a specific facilitatory action on the release of acetylcholine by a nerve impulse and magnesium is antagonistic to this reaction. If the calcium in the environment of the motor nerve terminals is sufficiently lowered (or the magnesium raised) transmission failure occurs which has been attributed to failure of release of acetylcholine from the telodendria (del Castillo and Katz, 1954).

Synthesis of acetylcholine by nervous tissue is strongly inhibited by hemicholinium (MacIntosh et al, 1958) /

1958). Desmedt (1958b) has studied its action in the cat with the Harvey-Masland technique (vide supra) and compared it with that of curare. Both drugs caused decremental depression of the evoked muscle action potential response to a train of supramaximal shocks to the nerve and when these were stopped there was a brief period of post-tetanic facilitation followed by 'post-tetanic exhaustion' such as he has described in myasthenia gravis (Desmedt, 1957b). On the other hand he did not demonstrate any post-tetanic exhaustion in partially curarised muscle. In his opinion this evidence strongly supports the possibility that the myasthenic condition results from a presynaptic biochemical defect chronically impairing synthesis of acetylcholine. Desmedt has repeated his views in many later publications but I am unable to find that the evidence has been extended. The only details provided are in the letter to Nature (Desmedt, 1958b). It is true that the timing of the post-tetanic events in the hemicholinium-treated cat are the same as in the single case of myasthenia gravis quoted. On the other hand the decrement in the evoked action potential did not exceed 7% as against 35% in the myasthenic and 30% in the example from the partially curarised cat muscle. There is no evidence that the influence of different dosage of d-tubocurarine on post-tetanic events was investigated and the statement that in curarized muscle 'the synthesis of transmitter would roughly keep pace with ejection provided physiological rates of stimulation (less than 50/sec) are used' would certainly not be accepted by other authors.

The action of curare is described below but it may/

may be said at this point that there is a general acceptance that it blocks some of the end-plate receptors thereby reducing the 'safety factor' for transmission. It is considered that the normal nerve ending when tetanised produces a quantity of acetylcholine with each impulse which at first increases owing to the facilitatory effect of fast stimulation on acetylcholine release which has been described above. This at first counteracts a progressive depletion of stores of preformed acetylcholine. In the normal state the 'safety factor' is such that the amount of transmitter required to activate all receptors is considerably less than the amount released during the first part of a tetanus. For this reason the facilitation effect can not be observed either during or after the tetanus in the normal and the response remains maximal until the exhaustion of reserves lowers the output of transmitter below the level required to activate all receptors (Farmer et al, 1960). By removing the 'safety factor' curare discloses the facilitation-exhaustion cycle of acetylcholine release by the nerve terminals. The progressive decrement of action potentials of a curarised muscle when its nerve is stimulated must therefore reflect a normal event at the motor nerve terminals which Desmedt (1958b) asserts is only present in the hemicholinium treated nerve.

It is unfortunate that Desmedt's publications do not illustrate the events during tetanisation of the hemicholinium treated nerve. The post-tetanic facilitation appears to be small (though this could be due to the small magnitude of the depression during tetanus/

tetanus) and there is no evidence regarding its effect on facilitation during tetanus. In Botulism, which is considered to be a paralysis caused by poisoning of the motor nerve terminals with failure of release of acetylcholine (Brooks, 1954) the action potentials of a muscle evoked by repetitive stimulation of its motor nerve decrement progressively and usually without the transient recovery of facilitated release (Burgen et al, 1949). I have occasionally noted the same type of decrement in disease of peripheral nerves and interpreted the absence of facilitation as evidence of abnormality of the nerve terminals (Fig.9,12) (Simpson 1960$_b$, 1964$_d$). The mechanism suggested by Desmedt would account very well for the myasthenic syndromes associated with peripheral neuritis and perhaps for carcinomatous myasthenia but does not fully account for the pharmacological observations which will be described below. He can only account for the changed reaction of the myasthenic muscle to drugs by postulating secondary changes induced at the motor end-plate. This suggestion overlooks two facts. In the first place the altered reactionsto drugs are present in muscles earlier than clinical or electromyographic evidence of transmission block. Secondly, suppression of release of acetylcholine by botulinus poisoning causes an effect on the muscle membrane resembling denervation. The region sensitive to acetylcholine spreads from the end-plate to the entire muscle membrane in a similar manner and with the same time course as in chronically denervated muscle (Thesleff, 1960). Changes of this type should lead/

lead to 'supersensitivity' and the electromyographic sign of 'fibrillation' yet this is rare in myasthenia gravis and if it does occur is of the type found in acquired myopathies (Chapter 9). Furthermore the effect of neostigmine in increasing muscle tension during a tetanus is negligible in botulism (Burgen et al, 1949).

It must be concluded that the evidence for presynaptic failure in myasthenia gravis is inconclusive.

Competitive block of transmission:

It was the resemblance of the clinical state of myasthenia gravis to curare poisoning which suggested the trial of physostigmine and its analogues for its treatment. The principal active component of curare is d-tubocurarine. It is a quaternary ammonium compound with structural resemblances to acetylcholine. It is readily attached to the same receptor sites in cholinergic synapses including the neuromuscular junction but the union is relatively loose and does not lead to the permeability changes of the subsynaptic membrane which stimulate muscular contraction. Therefore, unlike other quaternary ammonium compounds such as decamethonium which resemble acetylcholine more closely, there is no initial stimulation of muscle when d-tubocurarine is applied to the end-plate. On the contrary it competes with acetylcholine for receptor sites and so inhibits the action of the natural transmitter.

Electrical recording from the normal muscle end-plate shows the presence of spontaneous miniature end-plate potentials which are considered to be the result of the spontaneous release of 'quanta' of acetylcholine/

acetylcholine from the motor nerve terminals. The effect of d-tubocurarine is to reduce the size of the miniature end-plate potentials (m.e.p.p's). The much larger end-plate potential resulting from nerve stimulation is a summation of similar miniature potentials due to the discharge of many 'quanta' of acetylcholine by the nerve impulse. From a study of the end-plate potentials by means of a micro-electrode, del Castillo and Katz (1957) found that curare abolishes the reactivity of the post-synaptic membrane to acetylcholine without affecting membrane resting potential, resistance, or capacity. These actions are considered to be due to competition for receptors. The result of this is that the end-plate potential resulting from nerve stimulation is smaller than normal. With sufficient curare the end-plate potential may not rise to the critical level required to initiate a propagated action potential and hence a muscular contraction. With smaller doses the effect is to lower the 'safety factor' of transmission (vide supra). The natural facilitation-depression events of nerve stimulation thus cause a similar cycle of changes in the action potential and tension curves of the stimulated muscle. With slight dosage the inhibition of receptors is completely counteracted by the facilitated acetylcholine release during a tetanus so that the muscle response shows only activation. This phenomenon is best seen in amphibian muscle (Bremer and Homès, 1932) but is present in lesser degree in mammalian muscle (Brown, 1938; Eccles et al, 1941). The mammalian response resembles that of the frog more closely in a low calcium environment (Lundberg and/

and Quilisch, 1953) and this may support those who favour a presynaptic explanation for myasthenic weakness. Nevertheless it is as well to recollect that nothing is known of the action of d-tubocurarine on pathological muscle and it is possible that such a muscle may require a supranormal concentration of acetylcholine for its full response to be seen.

Though Harvey and Masland (1941b) and Johns et al, (1956) considered that both the decrementing and the facilitatory types of response in myasthenia resembled the phenomena of partial curarisation they do not seem to have considered the difference between amphibia and mammalia. Harvey et al (1941) later stated that the facilitation phenomenon in one of their myasthenic patients more closely resembled that occurring in calcium-deficient animals. Nevertheless Grob et al (1956d) show an evoked electromyogram illustrating a sequence of depression followed by facilitation and post-tetanic facilitation in a normal human being who had been injected with d-tubocurarine. It is strikingly similar to the usual type of facilitation seen in myasthenia gravis (Fig. 9 and 10 of their paper). Their studies on the post-tetanic period were not extended long enough to explore the 'post-tetanic exhaustion' described by Desmedt (1957b).

Quantitative differences between the responses of myasthenic and curarised muscle described by Grob et al (1956d) may be important. If it is accepted that d-tubocurarine lowers the 'safety factor' for transmission and thereby discloses the changes of output of acetylcholine from the nerve terminals, it follows that the/

the curves should have the same time-course in both conditions. Grob et al (1956d) found proportionally greater inhibition of the later potentials of a train in myasthenia than in curarisation. They also noted that intra-arterial injection of acetylcholine was strikingly effective in restoring transmission in the myasthenic but not in the curarised patient. This suggested to them that the presumed competitive block present in the myasthenic patient (i) may be exerted at different sites on the end-plate than the curare block and that the former may be more easily displaced from the end-plate by acetylcholine than is d-tubocurarine and (ii) may increase during voluntary contraction or electrical stimulation, due to the formation of a competitive blocking substance by the liberation of acetylcholine.

Their point of view inevitably requires the proposition of a 'myasthenic toxin' produced pari passu with the voluntary or stimulated release of acetylcholine. They suggest that this is choline formed by the hydrolysis of acetylcholine (see Chapter 15). Nevertheless their data up to this point could be adequately accounted for by assuming that the progressive decrease of acetylcholine or release during the tetanus had a shorter half-time than normal because of presynaptic failure and the better response of the myasthenic end-plate to directly applied acetylcholine would be understandable.

Dillon and Sabawala (1959) showed that the hypersensitivity to curare of myasthenic muscle could still be demonstrated in excised samples and that this effect persisted after repeated washing. They conclude that/

that this makes it unlikely that a 'curare-like substance' is the cause of the block. Certainly it would require to be firmly bound to the junctional region.

Abnormal structure of the transmission substance:

The arguments summarised so far depend on the assumption that the transmitter substance in myasthenia gravis is acetylcholine as in the normal, unaccompanied by any abnormal substances. Grob et al, (1956b and c) investigated the effect of acetylcholine and choline injected directly into the arterial blood supply to the limb muscles in normal subjects and in patients with myasthenia gravis.

In normal subjects acetylcholine introduced in this way produced transient stimulation of motor activity, followed by a brief period of depression of neuromuscular transmission. After recovery from this 'prompt' depressant effect there was a 'late' and more prolonged reduction in function. The 'prompt' depression was increased and prolonged by the prior administration of neostigmine and this appeared to be due to persistence of the initial depolarization caused by the injected acetylcholine. In contrast the 'late' depression was not increased. Its time course and the degree of block resembled that produced by intra-arterial injection of choline and this suggested to these workers that the 'late' depression might be due to choline released as a result of hydrolysis of acetylcholine (Grob et al, 1956b). Neither acetylcholine nor neostigmine reversed the 'late' depression produced by acetylcholine.

The type of neuromuscular block produced by choline varied with the degree of block in normal subjects. When moderate it had the properties of the depolarization type/

type, resembling the 'late' depression of acetylcholine but when it was marked it had many of the properties of the competitive type of block as judged by the effect of added acetylcholine or neostigmine and the presence of post-tetanic facilitation.

In myasthenic patients Grob et al (1956c) found less 'prompt' depression after intra-arterial acetylcholine and a transient improvement in neuromuscular function was interposed between the 'prompt' and 'late' phases of depression. Myasthenic patients also differed from the normal in that the 'late' phase of depression was reversed by neostigmine or by further injection of acetylcholine.

The time course of the depressant effect of choline in the myasthenic patients differed significantly from that observed in normal subjects. The latency of the depressant effect was greatly increased and the block was always of 'competitive' type. The depressant effect of choline on clinically unaffected muscles was less than normal but in some of these patients the type of block was intermediate between that observed in normal subjects and clinically affected muscles in myasthenic patients.

Grob et al, (1956c) consider that their results indicate the presence of 'competitive block' of the myasthenic neuromuscular junction. They suggest that the time-course and other properties of the 'late' depressant effect of acetylcholine in myasthenic patients indicate that it may be produced by choline released following the hydrolysis of acetylcholine by cholinesterase. An anomalous feature which they point out is that

acetylcholine/

acetylcholine produced three times as much depression as choline per mg. of injected drug whereas calculation of the amount of choline yielded by hydrolysis would indicate that acetylcholine should be less active. This could be accounted for by postulating that the choline released by acetylcholine hydrolysis is in closer proximity to the end-plate receptors than would result from the injection of choline but the abnormal response to both substances could also be due to alteration of the receptor protein.

Abnormality of structure or function of the receptor protein of the end-plate of muscle:

An increased sensitivity of the myasthenic patient to curare and quinine was demonstrated by Harvey and Whitehill (1937) and Bennett and Cash (1943). In contrast, Paton and Zaimis (1950) suggested from a consideration of the different modes of action that a depolarizing blocking drug such as decamethonium might prove less effective in myasthenic patients and this was soon confirmed by Sellick (1950) though Dundee and Gray (1951) thought that the response was within the limits of normality. Systematic studies on neuromuscular transmission by Churchill-Davidson and Richardson (1952a) indicated a generalised tolerance of the muscle fibres of myasthenic patients to decamethonium iodide, particularly marked in those patients in whom the only clinical evidence of myasthenia was ptosis and diplopia. Indeed decamethonium sometimes increased the strength of myasthenic muscles. Grob et al (1956d) could not confirm with intra-arterially injected decamethonium that the non-affected muscles were unusually tolerant. The tolerance described by Churchill-Davidson/

Davidson and Richardson was more difficult to demonstrate when the muscle 'fatigue' was widespread as it was less in those muscles affected by the disease. This implies that the increased weakness due to the drug is first seen in the clinically affected muscles. On further investigation they found that the weakness so induced was rapidly and completely reversed by anticholinesterase substances and that tetanic rates of stimulation of the muscles were not so well sustained as a twitch (Churchill-Davidson and Richardson 1952b, 1953). This was later explained by the finding of Grob et al (1956d) that the first response to stimulation ('twitch') was more resistant than later ones ('tetanus'). The drug, normally a 'depolarizing' blocking agent, appeared to act in the clinically affected muscles as a 'competitive' blocking substance after a fleeting depolarization. This they describe as a 'dual block', a term coined by Zaimis (1952) to describe similar actions on some of the muscles of some animal species. Their results have been confirmed by Grob et al (1956d) and by my own studies.

Churchill-Davidson and Richardson (1952b) found no difference from normal in the urinary excretion rate of decamethonium and it was excreted unchanged. They concluded that the different action cannot be accounted for by an alteration of the composition of the drug and so postulated a change in the characteristics of the motor end-plates which could be responsible for the myasthenic reaction by altering the response to acetylcholine or one of its breakdown products.

It will be apparent that the related substances acetylcholine, choline, and decamethonium all act in similar/

similar ways in the myasthenic patient. It is therefore undesirable to explain the abnormal findings of Grob et al (1956c) as being due to choline or to the production of a toxic product during nervous activity since the same change of function at the motor end-plate could explain both sets of findings.

The position would be clarified by a study of the sensitivity of the end-plate to acetylcholine. The literature is conflicting in this respect. Lanari (1937) was the first to inject acetylcholine into the brachial artery of a myasthenic patient. His opinion that the myasthenic muscle was abnormally sensitive to acetylcholine was confirmed by Harvey and Lilienthal (1941). These authors injected 20-40 mg. into the brachial artery distal to a cuff obstructing the venous return. The violent motor response which they obtained was much greater than they had found in normal subjects and the grip-strength seemed unchanged when the spasm subsided. They concluded that the myasthenic muscle fibres retain the capacity for vigorous contraction when adequately stimulated and that they were hypersensitive to acetylcholine applied in this way. They were drawn to this conclusion although it conflicted with their belief that there was a close analogy between the myasthenic state and partial curarization.

Acheson et al (1948) made similar studies using 0j-10mg. of acetylcholine intra-arterially and concluded that the sensitivity of myasthenic muscle to this substance was normal or slightly depressed. Wilson and Stoner (1947) and Engbaek (1951) concluded that/

that the myasthenic end-plate showed diminished sensitivity to acetylcholine. Engbaek (1951) reconciled the conflicting opinions by showing that the result depended on the dose of acetylcholine. The normal threshold dose was 100-350µg. She found that 0.2-0.3mg. caused a motor response in most normal subjects but was insufficient to do so in myasthenic patients who required far greater doses, indicating a raised threshold. The apparent hypersensitivity reported previously was due to stimulation by an overdose which would have caused depolarization block in normal muscles. The Johns Hopkins team later changed their views in agreement with Engbaek (Grob et al 1956c). This matter requires further study. If, for instance, it was found that the end-plate could be first hypersensitive and later hyposensitive to acetylcholine this would suggest the possibility of regeneration after partial denervation (Miledi, 1960). In support of Engbaek, Grob et al (1956b,c) showed that a suitable dosage of intra-arterial acetylcholine will cause rapid depolarization block of normal muscle while facilitating the activity of the myasthenic junction.

These studies suggest that the changes in the response of myasthenic muscle to depolarizing substances including the natural transmitter are associated with an elevation of threshold. This could also account in part for the well-known tolerance of myasthenic patients to doses of anticholinesterase drugs which would be toxic in normal individuals.

I have proposed a theory of drug action which accounts for the reported observations(Appendix D, Simpson/

Simpson 1960). It was proposed that the effective condition for depolarization of the end-plate membrane may be the density of ionic charges attached to the receptor substance (Fig16,1). Thus an applied substance will be effective in depolarizing the end-plate membrane only if (1) the ionic charge of the substance is adequate (Riker, 1953) and (2) there is an adequate charge per unit of receptor area. If this limiting charge density is not reached, no depolarization occurs and the attached charge merely blocks the receptors in a 'competitive' way. This is the situation with quaternary ammonium compounds such as d-tubocurarine ( ).

If an adequate charge density appears the membrane permeability is altered and a local response causes depolarization. I suggested that certain time factors may be necessary and Paton (1960) has elaborated an alternative 'rate theory' of drug action. If the charge density reaches a critical level (lower horizontal line in Fig16,1) it becomes self-completing, an action potential is propagated along the muscle fibre and it twitches (see Chapter 15).

If the charge density rises too high (the upper horizontal line in Fig.16,1) or if the stimulating chemical substance is resistant to hydrolysis by cholinesterase, depolarization persists causing a depolarization type of block (p.227). The fact that decamethonium in myasthenic muscle does not inhibit the 'prompt' depolarizing action of acetylcholine though its later block is of competitive type is readily understandable though Grob et al (1956d) considered this to be anomalous.

As the concentration of depolarizing substance falls/

falls, charge is lost from the end-plate and it is allowed to repolarize by the normal sodium-pump mechanism. Further stimulation is prevented by 'desensitization' of the membrane (Axelsson and Thesleff, 1958) but if the destruction or other means of loss of the drug is delayed and the ionic charge remains within the 'critical zone' sufficiently long it may facilitate neuromuscular transmission for a brief spell (Grob et al, 1956b,c).

When the charge-density falls below the critical level it enters the zone of 'competitive block' (shaded in the diagram) where it will tend to inhibit muscular response to neural stimulation or to the application of further depolarizing substances until the 'sticky molecules' (Zaimis, 1952) become slowly detached. The two latter phases would be more prominent with large doses and with compounds resistant to hydrolysis (see diagrams). This sequence of events would account for the 'dual block' of Zaimis and can be made to accommodate all the phenomena associated with the action of drugs on the end-plate of muscle.

This model which is suggested by the differing actions of a range of dosage levels of neostigmine in the normal subject and in myasthenia of various degrees of severity (Grob et al, 1956d) removes the necessity to postulate abnormal breakdown products of acetylcholine or decamethonium in myasthenia gravis. It may now be used to study some of the possible mechanisms involved in the transmission failure in myasthenia gravis.

If the charge-density (not necessarily the <u>total</u> charge/

charge) is decreased, the 'critical level' is raised (Fig.16,1). Acetylcholine produced by nerve activity or drugs injected into the artery supplying the muscle will accumulate charge on the receptor site too rapidly to permit detection of the early competitive zone but the presence of a raised threshold would be detected (Engback, 1951). A higher dose which would stimulate the normal end-plate and cause transient depolarization block ('prompt' depression of Grob and his colleagues) would cause only stimulation in the myasthenic (Grob et al, 1956c) whereas a massive dose would still cause strong contraction which may pass into a brief depolarization block (Harvey and Lilienthal, 1941). This would be followed by a brief period of facilitation and then by a phase of 'competitive block' (Grob et al, 1956c) with a duration depending on the decay constants of the particular substance. Where the latter phase is marked it may be recognised as the 'dual response' of Zaimis (1952). Smaller doses which merely enter the stimulation zone and then drop rapidly through the competitive zone give rise to such phenomena as 'decamethonium resistance' (Churchill-Davidson and Richardson, 1952).

Allowing for different time factors and ionic charges with different drugs and animal species, this schema can be used to study the alternative hypotheses for the abnormality in myasthenia gravis which can be resolved into an investigation of the factors determining the position of the 'critical level' for depolarization. In rough terms the shaded areas of the diagrams represent the amount of neostigmine required to produce depolarization of/

of the end-plate (cf. the findings of Grob et al, 1956d).

Increased concentration of cholinesterase in the subneural apparatus would decrease the rate of rise of the curve, lower the crest and steepen the falling phase. The results which can be deduced do not fit the observed facts. The raised threshold could be due to an alteration of the properties of the end-plate receptors requiring a greater density of charge. Or it could be due to the receptor area being abnormally large (as in partial denervation; Miledi, 1960) or to occupation of some receptor sites by molecules with a negligible charge. Each of these concepts would fit the observations. The first two are the 'end-plate abnormality theory', the third is the 'curare-like substance theory'. The sequence of events is less likely to occur from diminished acetylcholine production at the nerve endings (though lowering of spontaneous production of acetylcholine might have this effect) but a spatial dispersion of the ionic charge could do so. In view of the histological changes described at the nerve endings by Coërs and Woolf (1959) this possibility requires serious consideration.

The conclusion I have drawn (Simpson, 1960) is that the results of the Harvey-Masland electromyographic test coupled with the pharmacological studies are compatible with each of the three main theories and that further studies of this type are not likely to settle the matter if my interpretation of the physics of the situation is correct. Selection between the alternatives must therefore depend on other factors.

Micro-electrode studies of the neuromuscular junction:

The most direct approach to the study of the living pathology/

pathology of the neuromuscular junction in myasthenia gravis has been made by Dahlback et al (1961). These workers used isolated intercostal muscles obtained by biopsy under regional anaesthesia. The muscle samples were studied immediately by the normal technique for intracellular recording with glass capillary micro-electrodes, the sample being bathed with Liley's fluid and the temperature controlled.

They found that the resting membrane potential of single muscle fibres was 70-90mV which is similar to that of normal muscle. Spontaneous miniature end-plate potentials (m.e.p.p's) were usually decreased in frequency or completely absent. Their amplitude and time course were similar to those of normal muscle. An increase in the potassium concentration from 5-30mM did not produce an increase in frequency of the m.e.p.p's such as occurred in control muscles from normal subjects. The authors considered that the normal amplitude and time course of the m.e.p.p's indicates that the chemical sensitivity of the post-junctional membrane in muscles from myasthenic patients is similar to that in normal healthy subjects. The low frequency of spontaneous m.e.p.p's and the lack of a frequency increase in response to potassium suggested a pre-junctional deficiency affecting the release of acetylcholine. The transmitter release produced by nerve stimulation was studied by determination of the amplitude of (summated) end-plate potentials (e.p.p's) during and following periods of repetitive nerve stimulation. In normal muscle, according to the text, this could only be done by/

by blocking the receptors with d-tubocurarine. In myasthenic muscles a short period of high-frequency (about 100/sec) nerve stimulation produced a lasting block of transmission to the majority of the muscle fibres and post-tetanic facilitation of the e.p.p. was slight or short-lasting. On the other hand the same procedure on curarised normal muscles produced, after a short delay, a marked increase in the amplitude of the e.p.p. which persisted for about a minute after the stimulation had stopped.

These statements appear to conflict with their Fig.5 which shows marked inhibition of the end-plate potentials during stimulation of the curarised normal muscle whereas in the myasthenic muscle the fall was slight. They state that there was no progressive decline and that 'the amplitude of successive subthreshold ep.p's fluctuated at random'. It is not stated whether the stimulus was supramaximal for the nerve fibres. In any event the lack of decrement of e.p.p. response suggests that the muscles tested were not typical of myasthenia. It will be recollected that the intercostal muscles are among the last to be affected by myasthenia gravis (Chapter 2) and in fact they were not evidently involved clinically. Nevertheless it must be conceded that the diminished frequency of spontaneous m.e.p.p's and the poor response to increased potassium in the bathing fluid point strongly to the presence of a low quantal content of acetylcholine released spontaneously at the nerve terminals.

The interpretation of these findings depends on the supposition that the end-plate is capable of normal response/

response to the normal transmitter. As will be apparent from a previous section this is by no means an unquestionable assumption. Hoffmann and Stemmer (1963) supported the Swedish conclusions but their evidence requires confirmation because of the unsatisfactory nature of the resting potentials of the muscle fibres investigated by them. They claimed to show that there was poor release of acetylcholine but adequate production at the nerve terminals as the frequency of m.e.p.p's increased with application of guanidine or veratrine. In view of the evidence that guanidine increases receptor sensitivity (Chapter 18) and veratrine is known to act on muscle, these findings could be used to support a post-synaptic theory.

A later communication from the Swedish workers (Elmquist et al, (1964) reported no diminution in frequency of the m.e.p.p's (not printed in their abstract). They confirmed their previous report that m.e.p.p's were difficult to find but when present (usually after stimulation) they were of low amplitude and this could be increased by adding neostigmine to the bathing fluid. The estimated quantum contents of the e.p.p's were similar to those found in curarised normal human muscle for a wide range of stimulation frequencies. Though they again found normal post-synaptic activity (this time to carbachol) they had to concede that the observations on quantum content of m.e.p.p's did not allow them to rule out the possibility of a post-synaptic defect in addition to a pre-synaptic failure.

It is to be hoped that further experiments will resolve/

resolve the doubt. There is a growing body of evidence for a pre-synaptic failure but it is impossible to overlook the pathological changes in muscle fibre described in Chapter 11 and there is no reason to expect a raised threshold to intra-arterially applied acetylcholine, indeed the converse would be more probable.

If the transmission is blocked by preventing transmitter release by poisoning with Clostridium botulinum toxin, the muscle fibres undergo atrophy and show spontaneous fibrillation potentials. At the same time the entire muscle membrane becomes sensitive to applied acetylcholine (Hofmann et al, 1964). The extreme rarity of these features in myasthenia gravis must militate against the acceptance of decreased release of acetylcholine at the pre-synaptic membrane as the sole cause of transmission failure.

Transmission at regenerating neuromuscular junctions:

A possibility which has not been discussed by previous writers is that myasthenia gravis could be due to a minimal lesion of both the nerve terminals and the end-plates of muscles in which there is a balance between degenerative and regenerative changes of the nerve endings. This concept, which arises out of a consideration of the remarkable histological appearance of the end-plates (Chapter 11) can scarcely be discussed by comparison with the findings in normal junctions which have been treated with curare or lowered calcium. The properties of regenerating neuromuscular synapses in the frog have recently been investigated by Miledi (1960). The spontaneous miniature end-plate potentials were decreased in frequency. When e.p.p's appeared at the regenerated end/

end-plates as the result of nerve stimulation or of iontophoretic application of acetylcholine they were always adequate to generate spike potentials. On repetitive stimulation the progressive decrease in amplitude of the e.p.p's was greater than normal and this was increased by post-tetanic potentiation. Some fibres showed abrupt failure. These features bear a striking resemblance to the phenomena of the myasthenic junction as reported by the Swedish workers. On the other hand Thomson et al (1950) found that the decrementing twitch response of muscle stimulated repetitively by a regenerating nerve was made worse by acetylcholine. They suggest that a depolarization block might be caused by absence of cholinesterase in the regenerated muscle or persisting end-plate hypersensitivity after recent denervation. There is, however, no physiological work on the nature of transmission when degeneration and regeneration of motor nerve terminals is associated with, and perhaps secondary to, a disorder of the muscle fibre. Harvey and Lilienthal (1941) remarked that the myasthenic neuromuscular mechanism possesses characteristics similar to those of a normal muscle which has been both denervated and partially curarised.

If this hypothesis is acceptable it would bring all the symptomatic myasthenias, including the disorders of the lower motor neurone, under a single mechanism but need not indicate a common aetiology. It has already been shown that there are clinical and pathological correlations between the acquired myopathies (or should they now be considered as neuromyopathies?) and/

and true myasthenia gravis which are absent from the diseases of the lower motor neurone with the possible exception of 'allergic' polyneuritis of the Guillain-Barré type. It is now necessary to examine the remaining hypothesis which may clarify this relationship.

Myasthenic toxin:

It has been shown in a previous section that the results of the Harvey-Masland test and of pharmacological studies are compatible with each of the more likely theories accounting for myasthenia, including the possibility of a 'curare-like substance' which suggested itself to many observers of the last century. There are three observations which have been considered to support this concept (i) the Walker effect, (ii) neonatal myasthenia and (iii) a therapeutic improvement after dialysis.

The Walker effect:

It has been stated by many authors since Laquer (1898), Buzzard (1900) and Walker (1938) that exercise of a major group of muscles in a myasthenic patient caused the release into the blood stream of a substance which induced weakness of unexercised muscles. The procedure adopted by Walker and by subsequent writers was to occlude the circulation in an upper limb while exercising the muscles of the forearm. On releasing the constriction an increase in the clinical signs of myasthenia in other parts (e.g. ptosis) is said to be present in many cases. This is often referred to as the Walker effect. Wilson and Stoner (1944) reported similar findings substantiated by cinematography and others/

others making similar claims are Grosse-Brockhoff and Welte (1950), Struppler (1955) and Oosterhuis (1963).

These claims are far from convincing. The alteration in the palpebral fissures of the cases illustrated by Wilson and Stoner (1944) is not impressive. Walker (1938) recorded the onset of ptosis one and a half minutes after the release of the occluding cuff. Wilson and Stoner (1944) reported a range of latencies from ten seconds to four minutes and Struppler (1955) of 4-6 minutes. It is difficult to accept latencies of this order as being due to the pharmacological action of a substance passing from the arm veins to the eyelid muscles. In view of the fact that ptosis may rapidly occur in situations of emotional stress or in bright light (such as an experimental situation with close-up photography) it would be desirable to have more convincing evidence. It might be pointed out that the fact that a blink will restore the drooping eyelid to normal, due presumably to post-tetanic potentiation, and the similar finding in other muscles, argues against the notion that a toxic substance is produced during neuromuscular activity and in proportion to the degree of contraction. In many experiments conducted personally I have never been convinced of the reality of the Walker effect, as it has been named, and this has also been the experience of Nastuk et al (1959).

More serious consideration must be given to the experiments of Tsukiyama et al (1959). These authors tested the response of the action potential of a muscle of one hand (stimulated through its nerve) before and after/

after stimulation of a nerve of the other arm distal to an occlusive cuff. About one minute after the cuff was released the potential of the contralateral muscle began to fall, reaching a minimum in 1-4 minutes and then recovering in the next 10-15 minutes. The depression was less after administration of an anticholinesterase drug. This report is impressive but an apparent anomaly is discussed in the next section.

If myasthenic 'fatigue' were due to the accumulation of some toxic substance at the end-plates resulting from the activity of its motor nerve or from a metabolite produced by the muscle (Struppler, 1955) one would expect a run away effect with the rate of decrement increasing progressively. In fact the exact opposite happens. Inspection of any of the records in Chapter 16 will show that the greatest fall in amplitude of the action potentials takes place at the beginning of the decrement and a later plateau level is commonly established.

Neonatal myasthenia:

The occurrence of temporary myasthenia in the child of a myasthenic mother is best accounted for by the transmission of a toxic substance from mother to child, presumably through the placenta (Chapter 8). The nature of this toxin has never been determined, but it is natural that it should be considered to act in a similar manner to curare. Its source has been considered to be the neuromuscular junction (presumably as a by-product of acetylcholine or a metabolite of muscle) or the thymus gland whose function has been obscure until recently.

Dialysis:

The/

The recent report by Stricker et al (1960) that 5 of 8 patients with myasthenia gravis were strikingly improved by dialysis of their blood requires confirmation. The marked influence of psychological factors and rest with controlled respiration must be considered before this important claim can be accepted. The same result might have been expected from an exchange transfusion which Schwarz (1952) showed to be ineffective.

Attempted isolation of myasthenic toxin from the thymus:

Asher et al (1929) and many later workers have searched for neuromuscular blocking substances in extracts of thymus glands prepared in many ways. The literature is summarised by Oosterhuis (1963). Trethewie and Wright (1944) and Torda and Wolff (1944) reported that thymic extract inhibited the synthesis of acetylcholine in vitro.

Wilson et al (1953) examined thymus glands removed by Keynes for the treatment of myasthenia gravis. The glands were placed immediately in acetone and extracted by a particular method. The extract was assayed on a variety of nerve-muscle preparations and the authors stated that a neuromuscular blocking-effect was detected. This was most marked in the glands which had been obtained from the patients attaining most benefit from the operation. A lesser degree of activity was found in the thymus of normal infants but not in the adult gland. Later studies on the gland of young cattle and whales produced similar results (Wilson and Wilson, 1955; Nowell et al, 1959). These have been severely criticised and the experimental results attributed to the presence of potassium in the extracts (Zacks, 1958).

Close/

Close-arterial injection of small doses of an extract of foetal whale thymus potentiated the twitch of cat muscle indirectly stimulated. Larger doses first stimulated then depressed the twitch (Nowell et al, 1959). This could not be accounted for by the presence of electrolytes. The active substances have recently been identified by chromatography and are believed to be quaternary nitrogen bases (Calvey and Wilson, 1963). The extract has the properties of a depolarizing substance and does not, in my opinion, have the activity necessary to produce the known effects of myasthenia gravis.

Search for a neuromuscular blocking agent in the blood:

There have been many attempts to demonstrate the presence of a neuromuscular blocking substance in the blood of myasthenic patients by applying the blood to an isolated nerve-muscle preparation of the frog (Wilson and Stoner, 1944; Cohen et al, 1945) or by intravenous injection into normal human subjects (Schwarz, 1952) or live mammals (Lammers and Most Van Spijk, 1954; Struppler, 1955). These experiments have not yielded results acceptable to critical workers. The grounds for rejecting earlier positive claims are well discussed by Nastuk et al,(1959). Oosterhuis (1963) gives a good summary of the literature.

Bergh (1953) showed that negative results might be accounted for by lack of sensitivity of the test methods used. Tsukiyama et al (1959) reported an interesting experiment. They drew blood from the ipsilateral vein of a myasthenic patient below the cuff on an arm exercised by electrical stimulation and injected it into the/

the brachial artery of the contralateral arm. The evoked muscle action potential on that side showed the same depression as it had done after release of the cuff as described in a previous section. The resemblance extended to the amplitude and the timing of the response although it is to be presumed that the former test was a measure of the effect of a randomly determined dose of 'blocking substance' administered by close-arterial injection whereas the latter was the effect of release of a much greater volume of the substance into the venous side of the circulation. This seems so unlikely that it would be wise to suspend judgement until these results have been confirmed. The Japanese authors also reported that blood from the exercised arm of a myasthenic patient caused neuromuscular block when injected into a vein or an artery in rabbits, especially after exercise in ischaemic conditions (as emphasised by Struppler, 1955). The neuromuscular block produced in this way was promptly reversed by injection of neostigmine or acetylcholine. They suggest that their results point to the existence of a 'myasthenic substance' obtained from myasthenic patients when their muscles are exercised. This has the properties of a competitive blocking substance either alone or when combined with choline formed by the destruction of acetylcholine. The claims made in this paper for a positive Walker effect, an arm-to-arm transmission of a 'myasthenic substance' and for a blocking substance readily detectable in animals refer to matters of great difficulty for experienced experimenters/

experimenters in the past. There does not appear to be any novel technique in the experiments described and all the illustrations are in the form of graphs. Except for one Walker test using a nerve-stimulation technique, no original records are shown. For these reasons the claims cannot be accepted until they have been confirmed by other workers.

Immunological mechanisms in neuromuscular block:

Mastuk et al (1959) repeated some of the experiments just described. With regard to the Walker effect they state that some inhibitor substances may be released from normal muscles exercised under hypoxic conditions (Schmidt and Chase, 1947) and further criticise Struppler (1955) on the grounds that he used too much curare in his animal 'transmission' experiments. They were unable to obtain convincing results in the Walker test. They proceeded to search for a neuromuscular blocking effect on frog muscle of serum from myasthenic patients, pointing out that previous negative results might be due to lack of sensitivity of the assay procedure (Bergh, 1953) or failure to allow for a latency of the response. With the appropriate precautions suggested by these considerations they repeated the experiments of Wilson and Stoner (1944). Serum from some myasthenic patients was shown to cause reduction of isometric tetanic tension and action potential of the neurally stimulated frog muscle. Isometric twitch tension was usually not significantly depressed and indeed was sometimes augmented. Only one serum produced an appreciable depression of tetanus and twitch tension.

The depression in tetanus tension produced by

serum/

serum from patients with myasthenia gravis had a relatively slow time course (1½ hours for 50% reduction) and the changes were sometimes irreversible. Similar changes of a lesser degree were found with plasma from some normal control subjects. Resting potentials, end-plate potentials, and action potentials recorded by an intracellular electrode from single muscle fibres were all subnormal in those muscles which showed a persistent depression of tetanus tension. These fibres were all at the surface of the muscle and were noted to have become cloudy in appearance. They later began to disintegrate at various loci bearing no discernible relation to the neuromuscular junctions. It was concluded that the two sera causing this effect contained a cytolytic agent. A similar 'delayed' cytolysis was obtained with serum from one of eight control subjects. Nastuk and his colleagues concluded that no neuromuscular block had been demonstrated. The muscles showing progressive change of tension had done so because of damage to muscle cells of an irreversible nature. They were unable to account for the augmentation of twitch or end-tetanus sometimes found with plasma or serum samples from both myasthenic and normal persons.

This paper appeared while I was preparing my own lecture on an autoimmune hypothesis for myasthenia gravis and it was considered possible that the cytolytic effect might have an immunological cause (Simpson 1960$_a$, Chapter 13). Nastuk and his colleagues made a similar deduction from their experimental observation without being aware of my clinical data and their subsequent observations supporting the concept have been described in/

in Chapter 13.

As pointed out on page 245, the physiological and pharmacological data hitherto available on myasthenia gravis can be accounted for on any of the previous concepts of the disease. A permanent abnormality of end-plate structure would, however, be difficult to reconcile with the facilitation effects previously described during and after a tetanus. There are three clinical facts which must be included in any explanation of the pathological mechanism. These are (i) The correlation with abnormalities of the thymus; (ii) the characteristic long or short-term remissions and equally sudden relapses; (iii) the probability of transplacental transfer of a factor causing temporary myasthenia in a foetus. To this must be added the substantially negative results of cross-transfusion experiments to human beings and animals. I have suggested from a consideration of the clinical and pathological data that all of these could be accounted for by postulating that the thymus is a reticuloendothelial organ directly or indirectly mediating the production of antibodies (Simpson, 1960$_a$ and Chapter 13). If an antibody could be formed against the receptor protein of the muscle end-plate its molecular configuration might be presumed to resemble acetylcholine since both would be mirror images of the receptor surface. A molecule of this type would be a very effective blocking agent of competitive type. Furthermore it would be practically specific for the individual. The chances of transfusing blood containing the antibody into another person or animal with immunologically identical protein structure would/

would be very small. The probability would, however, be greater in the case of mother and child. The persistence of neonatal myasthenia for six weeks would require a myasthenic 'toxin' to have a large molecule or to be bound to tissues, and only slowly degraded or excreted. An antibody globulin would fit this specification very well (Simpson, 1960). It is known that the substances responsible for causing the L.E. cell phenomenon and the antinuclear factor are capable of crossing the placental barrier and persisting in the infant's blood for a short period (Beck and Rowell, 1963). The antibodies studied by these authors had a half-life in the infant's circulation of 17.5 days. This would correspond very well with the duration of neonatal myasthenia since the destruction/elimination curve is exponential.

The idea just described is not, of course, the only possible immunological mechanism. As was pointed out in the original paper antibodies could be developed against nerve endings, muscle fibres, and other organs including occasionally the central nervous system, in close analogy with systemic lupus erythomatosus and dermatomyositis. Indeed this must follow from the fact that it was the occasional involvement of other organs which led to the hypothesis. This aspect has been discussed in Chapter 13 but it is now appropriate to point out that the persistent failure to demonstrate anti-muscle antibodies except in the presence of a thymic tumour (and then only antibodies against muscle fibre, not the end-plates) and the increasing evidence for a pre-synaptic disturbance as well as a muscular one may/

may imply that nerve terminals are also damaged by a similar mechanism. Autoimmune peripheral neuritis in guinea-pigs is now being studied in my laboratory with Dr. J. Hall. An investigation planned for the future is the study of the regeneration of immunologically damaged nerve and muscle (see Chapter 16).

CHAPTER 17.

DIAGNOSIS.

The diagnosis of myasthenia gravis may be confirmed by using physiological and pharmacological tests based on the mechanisms described in the last chapter. A brief account of treatment is also desirable because certain aspects of the response to treatment reflect on these mechanisms. In addition, some understanding of the nature of drug action in the myasthenic patient is necessary as an introduction to the final chapter on the cause of death in myasthenia gravis.

The most important test for the confirmation of a provisional diagnosis of myasthenia gravis is the demonstration that a muscle or group of muscles becomes weak at an abnormally early time when contraction against resistance is maintained or repeated without rest. The importance of continuing the contraction for an adequate period of time cannot be overemphasised (Chapter 3). Sustained contraction for one minute is usually sufficient, but repeated intermittent contraction (e.g. crossing and re-crossing the legs) may have to be continued for 3-5 minutes.

If the physical examination is carried out in this way the diagnosis is rarely in doubt. It should always be suspected when a patient complains of a symptom which could be accounted for by muscular weakness, e.g. double vision, dysphagia, dyspnoea, or weakness of a limb. These symptoms may be greater towards the end of the day but this is not a constant feature. Indeed surprisingly few patients remark on it until specifically asked to comment on it.

Differential Diagnosis.

The/

The differential diagnosis of myasthenia includes the following conditions (Simpson, 1964b).

1. The symptomatic myasthenias: Dermatomyositis, polymyositis, systemic lupus erythematosus, carcinomatous myasthenia and disorders of the lower motor neurone have been discussed in Chapter 9. Here there is a true myasthenia and the problem is to recognise its relationship to myopathy, neuropathy or cancer. Relative sparing of cranial muscles, diminution or abolition of tendon jerks, (especially in the lower limbs) and poor or temporary response to neostigmine may be important clues.

2. Non-myasthenic conditions are rarely diagnosed as myasthenia gravis but this mistake may be made when muscular disease is associated with a complaint of abnormal tiredness. Polymyositis, thyrotoxic myopathy, myxoedema and Addison's disease are the most common diseases in which this mistake is made. Figure 17,1 illustrates a myxoedematous patient with ptosis simulating myasthenia gravis. Parkinsonism may be a cause of progressive weakness of repeated movement. 'Pseudoptosis' (Chapter 9) and the congenital syndromes with facial and extraocular palsies including congenital ptosis, ocular myopathy and the von Graefe-Moebius syndrome are the most difficult disorders to differentiate from myasthenia gravis. It is in this group that the special diagnostic tests are often required. There should be little difficulty in recognising motor neurone disease or polyneuritis but intermittent paresis caused by vertebro-basilar insufficiency and hypokalaemic states, familial periodic paralysis, paroxysmal myoglobinuria and craft palsies may occasionally cause difficulty to the inexperienced.

3. Wrong diagnosis: It is much more common for true myasthenia gravis to be overlooked. It is commonly mistaken for/

for hysteria because it is so often precipitated by emotional disturbances, and physical signs may be absent if the patient has rested before examination. The intermittent nature of the symptoms and the frequent occurrence of diplopia and dysarthria or other bulbar symptoms may suggest multiple sclerosis or vertebro-basilar insufficiency. The mistake in diagnosis, which is unfortunately the experience of the majority of myasthenic patients, never persists once a doctor has considered myasthenia gravis as a possible diagnosis.

Performance Tests.

Fatigue tests appropriate to the various muscle groups will readily suggest themselves and it is important to test all muscles in this way before classifying a case of myasthenia as 'localised'. Performance tests are conveniently coupled with pharmacological tests and it is then valuable to have an objective record of the test since subjective appreciation by the patient is often misleading.

Ergographic and radiological:

The decrementing muscular response to maximum effort may be demonstrated by means of an ergograph. This is a useful adjunct to some of the pharmacological tests. A simple ergograph recording on a kymograph drum can often be improvised. I have found this valuable in the regulation of treatment (vide infra).

Radiographic screening of diaphragmatic movement during respiration or of a 'barium swallow' before and after anticholinesterase medication is valuable in the diagnosis of myasthenic dyspnoea or dysphagia (Viets, 1947).

Clinical performance tests, with or without ergographic/

ergographic recording, have the disadvantage that it must be presumed that the patient is continuing to make a maximum voluntary effort throughout the test. Many patients with Parkinsonism will show progressive 'fatigue' by this test. For this reason the Jolly and Harvey-Masland tests have the advantage of objectivity.

Electromyography:

Conventional needle electromyography is rarely of diagnostic value because of the difficulty of ensuring sustained voluntary effort. Myopathic motor units may be found in excess. The pattern is described and illustrated in Chapter 15.

Stimulation-response tests:

The test originally described by Jolly (1895) is still a valuable one. A motor nerve or the motor point of a muscle is stimulated at rates of 3-20/second with an alternating electric current ('faradism') or 0.01-1.0 msec. pulses of current (the pulse shape is unimportant). The stimulus must be supramaximal to ensure that every motor nerve fibre to the observed muscle is stimulated by each pulse of current. The resulting contraction of muscle rapidly lessens but reappears after a short rest. This is the 'myasthenic reaction'. When no further contraction is visible a long pulse of current ('galvanism', a pulse exceeding 100msec. in duration) applied directly to the muscle immediately produces a full contraction and this can be repeated indefinitely, indicating that the loss of contraction when the nerve is stimulated is not due to failure of the ability of the muscle fibre to respond to an adequate stimulus applied peripheral to the motor end-plates. Simultaneous/

Simultaneous recording of the nerve action potential conducted retrogradely to the elbow demonstrates that all nerve fibres continue to produce normal action potentials in response to each stimulus (Alajouanine et al, 1959).

The test used by Harvey and Masland (1941) has been described in Chapter 15. It is essentially similar but uses the surface action potential of the muscle as an index of response. This is an integration of the individual muscle fibre potentials which are evoked almost synchronously. The area of integrated action potential is directly proportional to the twitch tension and its amplitude is very nearly so if certain precautions are taken. Botelho (1955) has claimed that tension may decrease without corresponding change of action potential but no other investigator agrees with this (Desmedt, 1961). A positive Jolly or Harvey-Masland test, if properly carried out, is unequivocal evidence of a myasthenic reaction but does not necessarily indicate myasthenia gravis (see Chapter 9). If, however, the decrementing response is abolished by injection of edrophonium, the diagnosis is certain.

A more difficult problem is the interpretation of a negative response when the clinical history suggests myasthenia gravis. As pointed out in Chapter 3, the distal parts of the limbs are often spared by the disease yet it is just these muscles which have the most readily accessible motor nerves. Sometimes an apparent negative response becomes positive after several repetitions at short intervals (Fig. 159) or after strong maintained voluntary contraction of the muscles being tested. In some muscles a slowly repeated stimulus causes a myasthenic response but a fast tetanisation evokes a progressively increasing response. This/

This incrementing type of reaction may be the only abnormality present. I have the impression that it is most often seen in muscles which show 'resistance' to decamethonium. It is seen in its most dramatic form in carcinomatous myasthenia (Chapter 9) but also occurs in polymyositis (Simpson, 1960b).

The circumflex nerve may be used to stimulate the deltoid muscle or the facial nerve to stimulate the orbicularis oculi (Botelho et al, 1952) but it is difficult to obtain satisfactorily integrated action potentials from these muscles. Direct observation by the Jolly technique may be more satisfactory for the proximal muscles which are so commonly affected.

The Jolly and Harvey-Masland tests may conveniently be supplemented by pharmacological tests. (Figs. 17,2-5).

Pharmacological Tests.

The most widely used tests are those involving a therapeutic response to anticholinesterase drugs, confirming that weakness is of myasthenic type. Conversely, increased sensitivity to curare and similar substances may be used to detect latent myasthenia. This group of tests will be described first. They are dangerous and should not be used where performance tests or therapeutic tests indicate the diagnosis. Their use should be confined to cases who give a classical history suggestive of myasthenia gravis but who are in remission at the time of examination or who do not show convincing 'fatiguability' (Simpson, 1964b). I have never required a curare or quinine test to establish the diagnosis of myasthenia gravis and on the rare occasions I have used them to investigate a 'possible' case without satisfactory/

satisfactory therapeutic response the results have invariably been normal. If they are considered necessary, all medication with anticholinesterase drugs should be withdrawn for 24 hours. Facilities for artificial respiration and syringes loaded with edrophonium (10mg.) and neostigmine (1.5mg.) should be prepared before carrying out the test. Since a dangerous test should not be repeated without good reason it is desirable to use an objective method of recording a response, such as the Harvey-Masland test or an ergographic trace.

Provocative tests:

Curare Test. The curarising dose for normal individuals is taken as 3mg. d-tubocurarine intravenously per 40lb. of body weight. The suspected myasthenic patient is given 2 per cent of the normal curarising dose and observed for 3-5 minutes. If no weakness appears in that time, 5 per cent of the estimated normal curarising dose is injected (Bennett and Cash, 1943). Bigger doses of curare should not be used, as muscle weakness may occur in some normal subjects with the 10 per cent dose originally recommended. Pelikan et al (1953) have questioned the reliability of the curare test by finding that some myasthenic patients have a normal sensitivity to the drug while some normal subjects are exceptionally sensitive.

Quinine Test. Quinine bisulphate 0.65g. (10gr.) 2-hourly by mouth to a maximum of three doses, may be used to precipitate weakness in suspected myasthenics (Eaton, 1943). In this dose no neuromuscular effect can be detected in normal individuals but myasthenics may become very weak. This may be dangerous as the paralysis cannot be reversed by anticholinesterase drugs.

Decamethonium/

Decamethonium Test. The basis for this test is the abnormal response of myasthenic muscle to this and other depolarizing drugs which has been described in Chapter 16. As reported by Churchill-Davidson and Richardson (1952a), patients with myasthenia gravis tolerate an unusually large dose of decamethonium. This test is also performed after withdrawal of anticholinesterase drugs for 24 hours. Decamethonium iodide is injected intravenously in an initial dose of 1.5mg. Four minutes later 0.5mg. is injected and this dose is repeated at 2 minute intervals until muscle weakness is seen or there is a drop in the muscle action-potential evoked by supramaximal nerve stimulation at 10 per second when tested every half minute. In normal subjects the block caused by a depolarizing drug is non-decremental and is potentiated by neostigmine, but in the myasthenic subject the depolarization block is brief and followed by a longer competitive (curare-like) type of block ('dual response'). (Fig. 17,2).

I do not use this test except for probable cases of neostigmine-resistant myasthenia gravis. On most of these occasions the test has been valuable, a positive or negative result being subsequently confirmed by the course of events. Difficulty in interpretation has occurred when 'partial resistance' has been encountered. I have seen three or four cases in whom the fall in the action potential was 50-60% of the normal fall with the appropriate dose. In each of these cases the true diagnosis remains in doubt (see Chapter 8). They are certainly not 'declared' myasthenics. Churchill-Davidson and Richardson (1961) state that they have never found abnormal tolerance in any other neuromuscular condition than myasthenia gravis.

Therapeutic/

Therapeutic tests:

Edrophonium Test. The short duration antimyasthenic effect of edrophonium chloride ('Tensilon') makes it very suitable for a diagnostic test. A syringe is loaded with 1 ml. (10mg.) for intravenous injection. Initially 2mg. should be injected to detect abnormal sensitivity but if there is no response the remaining 8mg. is injected after 30 seconds (Osserman and Kaplan, 1953). Within $\frac{1}{2}$ to 1 minute there is improvement if weakness is due to myasthenia gravis but weakness returns in 4-5 minutes. Some normal subjects experience no obvious effects while others feel a tight sensation around the eyes and fasciculation may be seen for a few seconds, particularly in the orbicularis oculi. Adequately treated myasthenic patients show this normal reaction. If weakness is due to cholinergic crisis it is transiently increased and fasciculation may occur. Unfortunately respiratory weakness may be increased to an extent endangering life.

The positive responses described are very valuable and reliable indications of the myasthenic syndrome when assessment is made by objective means. In my early experience of the test I was disappointed to find a number of patients who were apparently improved but in whom subsequent events discounted a diagnosis of myasthenia gravis. With further experience it became apparent that this was due to an error of procedure. In every case of a 'false positive' result the assessment had been based on the patient's report of improved muscular performance. I have never had a 'false positive' reaction since insisting that the response be considered negative unless there was objective improvement of some performance test such as the ability to look upwards for/

for 1 minute without ptosis, ability to hold the arms outstretched for 1 minute, increased length of speech without dysphonia or dysarthria, reversal of abnormal Harvey-Masland electromyographic test and so on. It is essential to measure the time to 'exhaustion' of one or other group of muscles before the injection and to retest the same movement ½-2 minutes after the injection. (Fig. 17-5)

It is advisable to test at least two muscle groups in this way in case of the misfortune that the only muscle tested is 'myopathic' and incapable of response to an anticholinesterase drug. This is particularly common with the extraocular muscles (Chapter 3).

Failure to obtain improvement with the standard dose does not necessarily exclude the diagnosis of myasthenia gravis since the neuromuscular block may be very severe, requiring twice the normal dose. Conversely, the normal test dose of 10mg. may be excessive for very mildly myasthenic muscles or during remissions so that fasciculation may result. These 'false negative' results are more common than the 'false positive' ones if due regard is paid to the precaution about objective criteria.

Adequately treated cases of myasthenia gravis will show a normal type of response and if the dose of anticholinesterase medication is excessive there may be fasciculation and temporarily increased weakness. This is due to depolarization block (Chapter 15). Because of this range of reactions it is possible to use the edrophonium test to control the level of dosage and in emergency to differentiate between weakness due to myasthenia gravis ('myasthenic crisis') and to overtreatment with anticholinesterase drugs ('cholinergic crisis'). This use of the test is

further/

further described in Chapter 19.

Neostigmine Test. A disadvantage of the edrophonium test is that the short duration of the response provides little time for assessment of the changed state, if any. Neostigmine, on the other hand, has a therapeutic action for 1-3 hours or more, enabling a truer assessment to be made. Though the latency is greater, a favourable response to injection of neostigmine remains the most convincing evidence of myasthenia gravis (Viets and Schwab, 1935). The duration of the anticholinesterase activity, so favourable for initial diagnosis, renders it unsuitable when cholinergic crisis is suspected. (Fig. 3,7).

To perform the test, neostigmine methylsulphate or salicylate is injected intramuscularly (1.5mg.) alone or combined with 0.6mg. of atropine sulphate. Improvement begins in 10-15 minutes but is most obvious after 30 minutes. The same preparation may be used intravenously (0.5mg.) when the response is more rapid but the danger of ventricular fibrillation or arrest is greater. The drug should never be given by this route unless accompanied or preceded by atropine.

The response to 15mg. of neostigmine bromide orally may be sufficient to make the diagnosis clear. If any of the parenteral tests are equivocal and the diagnosis of myasthenia gravis seems highly probable on clinical grounds it is worth carrying out a therapeutic trial for a week.

CHAPTER 18.

TREATMENT.

The sheet anchor of medical treatment is neostigmine. It restores in whole or in part the defect in neuromuscular transmission so long as an adequate level of the drug is maintained in the circulation. It is not therefore a radical form of treatment and so its consideration will be postponed.

Thymectomy - indications and management:

The autoimmune hypothesis will have served its purpose so long as it stimulates new looks at the nature of myasthenia gravis. Meanwhile not the least of its attractions is that, for the first time, it provides a rational basis for the treatment of the disease by thymectomy. The operation is assessed in Chapter 10 and in Appendix C. but it will be convenient to summarise at this point what I now consider to be the main indications for its use and to discuss the post-operative management.

Though the results may be rather better in women than men and before rather than after 40 years of age, the most important factor is the duration of myasthenic symptoms (Simpson, 1958). Operation should be offered to all patients with a history of less than 5 years unless myasthenic weakness is confined to the extraocular muscles. Apart from this limitation the severity of the disease is not a significant factor in deciding against operation. The danger is probably greatest in patients who have marked difficulty in swallowing, but this group tends/

tends to have the worst prognosis even without operation. Patients who do not come into these categories should be operated on if myasthenia is progressing despite optimal medical treatment provided they are considered likely to survive the operation. In competent hands and with a modern skilled anaesthetist the operative risk is very low. In the last eight years in Edinburgh only 1 case from a series of 28 included in the present work has died post-operatively and she was not directly under my care. All of these patients have been operated on by Mr. Andrew Logan.

Mr. Logan and I are now convinced that the major difficulty is the management of drug treatment at that time. It is my practice to maintain the pre-operative dose of anticholinesterase drug until the patient is in the anaesthetic room. No further dose is then given until the operation is completed. Before the patient leaves the operating theatre the anaesthetist fully inflates the lungs, aspirates any secretion in the upper respiratory passages and carries out bronchoscopic suction of the main bronchi if necessary. The patient does not leave the operating room until good spontaneous respiration is re-established. If inflation is not adequate, 1.5mg. of neostigmine methylsulphate is injected intramuscularly.

On return to the ward an intratracheal tube is maintained in position until the patient is conscious and is obviously free from respiratory distress. The previous medication is resumed at two hours from return to the ward. If possible the tablet is crushed and given through a gastric tube but in some cases an equivalent dosage must be/

be injected intramuscularly. 15mg. of neostigmine orally should be replaced with 1mg. of neostigmine by injection (in my experience the equivalence of 1.5mg. suggested by Viets (1950) is excessive).

There is often a remarkable remission in the hours immediately after the operation. This may be so great that a patient who has previously had persistent ptosis may show tonic retraction of the eyelids. This may be seen as soon as the patient has recovered from the anaesthetic and may persist for 2-3 days. This may be a thyrotrophic effect due to removal of an inhibitory action of the thymus (Chapter 12) but is more probably an indication of increased response to anticholinesterase drugs. This is a point which I wish to emphasise as, apart from a personal contribution (Simpson, 1964b) it has not been described in the literature.

Immediate 'remission' after operation may so lower the requirements for anticholinesterase medication that the dose required before operation is now dangerously excessive. An observer unfamiliar with this hazard will interpret the increasing weakness as indicative of a myasthenic crisis when in fact it is due to a so-called 'cholinergic crisis' in which further medication may be fatal. In my opinion, the very low mortality post-operatively in my Edinburgh series is due to recognition of this fact. The single post-operative death occurred in a child aged 8 (MN 4603) in the day following operation. She was not under my care and signs of impending cholinergic crisis were not recognised until she had a convulsion and died without recovering consciousness/

consciousness.

The immediate favourable response to thymectomy may persist but many cases relapse a little in the next few days, requiring adjustment of dosage. These cases then improve slowly. It is often three years later before they feel really well. For this reason they may be disappointed at first but, in retrospect, they realise after the passage of time that the 'tide turned' after the operation.

The less favourable response to thymectomy for a thymic tumour is described in Chapter 10. Even after thymectomy two out of three cases die within five years. Nevertheless the survivors may benefit to the same extent as the non-tumour cases (Chapter 10 and Appendix C). This may happen even without pre-operative radiotherapy (Simpson, 1958).

Radiotherapy:

The desirability of radiotherapy for thymic tumour was stressed by Keynes (1955) but I feel that this requires substantiation. It has also been used sporadically for the non-neoplastic thymus in the treatment of myasthenia gravis. My experience of this method is restricted to observation of five patients under the care of other physicians so I shall not comment extensively on it. Grob (1953) reported definite but rather disappointing improvement in 40% of cases and Osserman (1958) noted improvement in 'almost one half' (his figures do not give the independent results for the 34 non-tumour and 20 thymoma cases). There is a distinct danger of temporarily increased weakness (Jones et al, 1955) and this contraindicates its use in the patient who is 'unfit/

'unfit for surgery'. The benefit does not appear to be comparable with the results of thymectomy, a more certain way of ending the unwanted activity of the thymus.

Denervation of the carotid sinus:

In view of the early favourable reports of an anti-myasthenic action of corticotrophin and some evidence from animal experiments that adrenocortical hypertrophy occurred after bilateral denervation of a carotid sinus, French workers have carried out this operation on myasthenic patients (Thévenard, 1954). The favourable effect claimed is not seen for about a year. Mertens (1955) was not impressed with his results. The operation has not found favour since improvement (if indeed it is attributable to the operation) is apparently inferior to that following thymectomy. It does not seem rational to seek atrophy of the thymus by such an indirect method when thymectomy is such a safe operation in experienced hands (Simpson, 1964).

Medical Treatment.

ACTH therapy:

A brief account of this form of treatment will be given at this point because any benefit obtained is likely to be due to suppression of thymic and reticuloendothelial function, or to some other anti-immunological mechanism. Torda and Wolff (1951) reported remissions of myasthenia following the use of adrenocorticotrophin (ACTH) but the drug is now rarely prescribed because initial deterioration is common and may be fatal (Grob and Harvey, 1952) and the favourable response may not occur until the drug is withdrawn (Westerberg/

(Westerberg and Magee, 1955). Cortisone and its derivatives are much less effective and have no place in practical therapeutics.

In 1952-53 I gave ACTH or Cortisone to 4 cases of myasthenia under the care of Sir John McNee and Dr. J.B. Gaylor in the Western Infirmary, Glasgow. The results were not impressive. No severe deterioration was seen but it was confirmed that the patients felt better after withdrawal of the drug. The hormones were given as the initial form of treatment. When this was followed by the orthodox treatment with neostigmine there was no doubt that the previous hormonal treatment was inferior so I have abandoned its use. Nevertheless, the initial deterioration and subsequent improvement may be considered to support the autoimmune hypothesis (Simpson, 1960a).

Antireticular cytotoxic serum:

In view of the autoimmune aspects of myasthenia gravis it is necessary to record the use of Bogomolet's 'antireticular cytotoxic serum' in one case of myasthenia gravis by Buscaino and Redi (1952). Though used without awareness of the theoretical justification they claimed improvement in their case. This claim has never been followed up.

Dialysis:

The report by Stricker et al (1960) that improvement in the myasthenic state may occur after dialysis requires confirmation in view of the beneficial effect of physical rest and a hopeful therapeutic atmosphere. It is unlikely that sufficient antibody would be lost by dialysis to make a material difference.

Anticholinesterase/

Anticholinesterase drugs:

Substances with anticholinesterase activity are still the most useful drugs in treatment. Even after thymectomy most patients require to take them for a period, but it is desirable to reduce the dose slowly but steadily. Many patients are unwilling to give up the drug they have come to depend on but I have the impression that the long-term prognosis is best for those who are gradually able to withdraw medication (Simpson, 1964b. I have, on the other hand, no evidence to support Harvey (1948) in his opinion that the use of neostigmine prevents remission.

Many patients are best treated by medical means and the response is usually very gratifying. Nevertheless, even in an early case the response is rarely complete and the extraocular muscles in particular often cease to respond, no doubt due to the development of myopathic changes (Keynes, 1955).

Various drugs with anticholinesterase activity are available. This activity is attributed to the carbamate grouping. Some of these, including neostigmine and pyridostigmine, are quaternary ammonium compounds and may have an additional depolarizing action on the end-plate directly, or a facilitatory effect on the release of acetylcholine from motor-nerve endings (Riker et al, 1959). This may account for some of the differences in the clinical response to different drugs but there is insufficient appreciation of the wide variation in the duration of action of any one of these drugs from one patient to another. Neostigmine may have a useful action for 8 hours in one patient and only 1-2 hours in another, when/

when taken orally. For this reason it is essential to establish the duration of effective action in each patient. A simple ergograph such as the one described in Chapter 17 is a useful adjunct to this (Fig.18,1).

Neostigmine bromide acts rapidly when taken by mouth. Its most powerful action lasts for only ½-1½ hours and is followed by a carry-over for a further 1-6 hours. The activity then tends to fall off rapidly. This 'let down' can be most discouraging to a patient. Pyridostigmine bromide does not have the early marked effect of neostigmine. The duration of the 'plateau' of useful activity is very little longer than that of neostigmine, despite the fact that it was introduced as a long-acting preparation, but the fall off is more gradual so a smoother control can be established if the tablets are given at the correct times for the particular patient (Fig. 18,1).

In a double-blind trial (Appendix A.) most patients considered that pyridostigmine was the drug of choice. Some preferred neostigmine because of the early 'surge of power' but most selected pyridostigmine because the control was smoother without the 'let down' effect which necessitates very accurate timing of successive doses of neostigmine. The use of each of these drugs is very similar to the use of soluble and slow acting insulins in the treatment of diabetes mellitus. It is usual practice to take some of the tablets 30 minutes before each meal when there is bulbar weakness and other doses before going to sleep and immediately on waking in the morning. If other doses are necessary they are then timed between these according to the results of a trial such/

such as is illustrated in Figs. 18, 1 and 2. If bulbar symptoms are troublesome or if the patient is very weak on waking in the morning it is advisable to rouse him for a dose at the appropriate time during the night. Absorption is erratic in some patients and it is then necessary to rely on subcutaneous injection of neostigmine methyl-sulphate or salicylate and this may be the route of choice in severe cases. The dose may be calculated on a basis of 1mg. by injection having an effect equivalent to 15mg. orally. When given by this route, neostigmine should be administered with atropine sulphate, 0.4mg., to prevent parasympathomimetic effects such as intestinal colic, sweating and bradycardia. If possible the atropine should be injected 15-30 minutes before the dose of neostigmine (Gaylor and Simpson, 1964). The routine use of atropine is not without its dangers (Chapter 19).

The various anticholinesterase drugs in use will now be reviewed in the light of personal experience in the order of duration of action.

Edrophonium chloride ('Tensilon'). The use of the response to this drug as a diagnostic test (Chapter 17) is based on its rapid but brief action. Its maximum effect is completed in 5 minutes. By the Harvey-Masland electromyographic test I have found that some effect can still be found 50-60 minutes later. Osserman et al, (1953) have also found clinically that edrophonium shows an additive effect when readministered within 30 minutes but this effect was dissipated in less than an hour. This may be of some importance in the management of/

of cholinergic crisis (Chapter 19) but the main action is too brief for therapeutic purposes.

Neostigmine bromide ('Prostigmin'). This drug has stood the test of time. The 15mg. tablet has a cholinergic activity which varies from 2-6 hours in different patients. The total and the spacing of doses must be established by the individual trial described above. It may vary from ½ tablet t.d.s. (22.5mg./day) to 3 tablets every 2 hours (540mg./day). Exceptional cases requiring even bigger dosage have been reported (Rowland et al, 1955) but an average dose is 10 tablets daily (150mg.) (Simpson, 1958, Appendix C). Some of the advantages and disadvantages of neostigmine have been described above but one of the main advantages not yet described is the relatively small cumulative effect.

Pyridostigmine bromide ('Mestinon'). The advantages of this drug have also been described above. The slightly slower 'fall off' of the therapeutic effect makes it a useful drug for overnight medication even if it is not the drug used during the day but when pyridostigmine is used as the sole medication care must be taken to avoid cumulative effect.

Theoretically it seems desirable to use a long-acting preparation to avoid the need for frequent dosage but all anticholinesterase drugs tend to be cumulative and this is more marked the longer the duration of the plateau activity (Fig. 18,1) (Simpson, 1964c). This may not be obvious for weeks when using neostigmine or pyridostigmine so that the physician may be lulled into a false sense of security. Slow release tablets of neostigmine/

neostigmine and pyridostigmine have not been available in this country but preliminary reports from the U.S.A. are encouraging and it appears that cumulative effects have not been prominent (Schwab et al, 1957). With most of the drugs which will now be described the cumulative effect is so prominent as to make their use dangerous unless the patient is under close supervision.

Ambenonium chloride (Win 8077, 'Mysuran', 'Mytelase'). This drug is not readily available in Britain and my experience of its use is limited to five cases. It is dispensed in 10mg. and 25mg. tablets, the latter being approximately equal in potency to 15mg. of neostigmine. The duration of action is said to be only slightly longer than that of 60mg. of pyridostigmine (Schwab et al, 1955) but I have felt that unintentional overdosage was common since it occurred in three of the five cases. Central actions are certainly more common but it may be that the onset of cholinergic crisis is more difficult to detect. Muscarinic side-effects are said to be less frequent than with neostigmine or pyridostigmine but Desmedt (1957c) found that the optimal therapeutic dosage usually produced signs of 'cholinergic intoxication'. My very limited experience confirms this. In addition I have felt that cumulative effects were noticeable in as short a period as one week. For these reasons I do not consider ambenonium to be the drug of choice.

Bis-neostigmine compounds. The cholinesterase inhibiting power of neostigmine may be increased and prolonged by combining in one molecule two neostigmine or pyridostigmine radicles separated by a polymethylene chain of various lengths/

lengths. Pateisky et al (1955) and Herzfeld et al (1957) have investigated the actions of BC-40 (Hexadistigmin), BC-47, BC-48, and BC-51 (Hexamarium) and report durations of activity of a single dose exceeding one day. The Vienna group have found BC-51 the most useful of the series but noted wide variation in absorption when the drugs were given orally. An average oral dose of BC-51 is 7.5mg. every 4 days. More frequent dosage is hindered by cumulative effects, yet the carry-over is inadequate and neostigmine is usually required in addition.

My experience of these drugs is limited to a restricted trial of a sample supplied from Vienna. Five cases treated with BC-51 in a recommended dosage schedule all showed signs of overdosage within a week.

I feel that the cumulative action entailed by the long action of this group of drugs makes them unsatisfactory for domiciliary use.

Alkyl-Phosphates. This group of anticholinesterase preparations which includes di-isopropylfluorophosphate (DFP), tetraethylpyrophosphate (TEPP), hexamethyltetraphosphate (HETP) and octamethylpyrophosphoramide (OMPA), had a vogue in the treatment of myasthenia gravis because their long duration of activity was considered desirable. This very property leads to inflexibility of control (Simpson, 1964c). Furthermore they have a greater effect on central synapses than the quaternary ammonium compounds, giving rise to headache, nightmares and personality disturbance. Some workers are still using TEPP and indeed some of the present series of patients treated by physicians at the National Hospital have continued to take TEPP or DFP for/

for many years. I have questioned twelve patients who have been taking TEPP. One patient (NH61437) preferred it to neostigmine but the others considered that it was 'useless' (GK/CH, NH6352, NH7720, NH8162, NH8827, NH9558, NH11102, NH11563, NH12374, NH61502, NH61510). Opinion was more divided on the value of DFP (Case GK/ES, NH/EC/MG (MN887), NH1190, NH4384, NH33122). Only one patient was treated with OMPA (Case GK/ES). She expressed herself satisfied with it.

There is a general tendency to abandon these drugs (Westerberg and Magee, 1955). The relatively poor therapeutic value compared to the quaternary nitrogen group is of some theoretical interest since the alkyl phosphates appear to act only as inhibitors of cholinesterase, whereas the quaternary nitrogen compounds may have an additional direct depolarizing action on the end-plate or a presynaptic action as described above (Riker et al, 1959).

Galanthamine hydrobromide ('Nivaline'). This is a phenanthrene alkaloid isolated in Russia from a Bulgarian plant, Galanthus nivalis. It is related to morphine which has a stimulating effect on smooth muscle and a little sudorific action. The pure crystalline substance ('nivaline') has been shown to have anticholinesterase activity (Paskov, 1959). A therapeutic action on myasthenia gravis was confirmed by Bergamini and Baggiore (1960) in Italy but they found it to be less active than pyridostigmine.

Dihydro derivatives of galanthamine, named lycoramines, tested in America have been shown to be effective in myasthenia gravis (Somers et al, 1963). I have/

have no experience of any of these drugs and it is still too early to assess their role.

Dequalinium chloride ('Dequadin'). This is a bis-quaternary ammonium salt used clinically as an oral antiseptic. Like other similar compounds it has a neuromuscular blocking activity when injected intravenously into mice. Graham and Grant (1959) reported a 'blind' trial of its use in one case of myasthenia gravis and claimed that it was capable of causing clinical improvement. I have not been able to demonstrate any favourable effect in two cases of myasthenia (MN3231, MN3609) and this has been the experience of other workers (Schwab, 1960).

Adjuvant forms of treatment.

Hormonal: The use of adrenocorticotrophin (ACTH) and cortisone has been described on pp.277-278. They are not recommended. Gottlieb and Laurent (1961) suggested the use of spironolactone (400mg.) to inhibit secretion of aldosterone by the adrenal glands in order to conserve potassium in the body. It is too early to evaluate this form of therapy. O'Driscoll (1962) and Cremieux and Bille (1962) have reported single cases who appeared to benefit. Riser et al (1962) report three cases who received cobalt in addition to spironolactone. Despite a favourable reception in the French literature my own experience in three patients has not shown any significant modification in the response to treatment with anticholinesterase drugs though the patient may have a sense of increased wellbeing (MN5503, MN5652, MN7550).

Potassium/

Potassium chloride or citrate. Though useless as a primary therapy, potassium has a role as an adjuvant in dosage of 5gr. b.d. or q.i.d. (Laurent and Walther, 1935). The nausea and diarrhoea which it may cause may be difficult to distinguish from cholinergic crisis (Chapter 19). There is some clinical evidence that potassium increases the response to neostigmine and it is probably worth a place as an adjuvant to that drug but its value is marginal. Its action is probably on the muscle fibre (Desmedt, 1945).

Ephedrine sulphate. This drug, introduced by Edgeworth (1930) from her personal experience is still used as an adjuvant in a dose of 25mg. t.d.s. by mouth. Its value is questioned but many experienced clinicians continue to use it. Ephedrine is believed to function by inhibiting amine oxidase and so to potentiate the action of adrenaline. Its mode of action is uncertain but is probably related to the Orbeli effect (Bulbring and Burn, 1940). An increase in motor power lasting 30 minutes or longer after intra-arterial injection of 0.4-0.6mg. of adrenaline was noted in a myasthenic patient by Harvey and Lilienthal (1941). Luco (1939) has stated that the 'defatiguing' effect of adrenaline is closely related to its lowering of the threshold of skeletal muscle to stimulation by acetylcholine.

Guanidine hydrochloride. This drug has a limited anti-myasthenic action also attributed to sensitisation of the end-plate to acetylcholine (Frank et al, 1923; Desmedt, 1956). It is given orally in a daily dose of 20-50mg. per kilogramme of body weight, divided into three doses. I have/

have only used it when the maximum tolerable dose of neostigmine or pyridostigmine did not fully restore muscular power. In three cases in which it was used in this way there was no obvious benefit. The drug tends to cause paraesthesia and is now rarely used (Dodd et al, 1941).

Casein hydrolysate, ('Amigen'). An enzymic hydrolysate of casein was given intravenously to five cases of myasthenia gravis by Torda and Wolff (1947) in the belief that the synthesis of acetylcholine would thereby be increased. No further work has been published supporting these claims which are generally discounted.

d-Tubocurarine. Churchill-Davidson and Richardson(1957) and other workers have given paralysing doses of d-tubocurarine (while sustaining respiration mechanically) to patients who have become resistant to neostigmine in the belief that the end-plates of the muscles may thus be rested and recover their sensitivity to neostigmine. I have never used the drug in this way and find the suggested rationale difficult to accept. I have, on the other hand, made a tentative use of the drug in the treatment of cholinergic crisis (Chapter 19).

Neostigmine Resistance.

The whole question of neostigmine resistance is a formidable one which keeps recurring in the literature of myasthenia gravis. It is based on the frequently observed fact that optimal dosage with neostigmine (or any other anticholinesterase drug) will frequently fail to restore full power to the muscle weakened by myasthenia gravis. As the short-fall becomes greater in cases deteriorating/

deteriorating in spite of treatment, it is understandable that the concept of 'neostigmine-resistance' should have been raised. This idea depends ultimately on a belief that the myasthenic defect is entirely a 'chemical' lesion of neuromuscular transmission. The idea is unnecessary in view of the now established fact that histological changes may occur at the motor nerve endings or in the muscle fibres (Chapter 11). Indeed the margin between maximum power recovered under treatment and the pre-morbid power may be considered as a measure of the permanent changes which I have tentatively described (following Keynes, 1949) as 'myopathic'.

It is well known that myasthenic patients can tolerate unusually large doses of anticholinesterase drugs without experiencing unpleasant muscarinic (parasympathetico-mimetic) symptoms. So far as the muscles are concerned there is a striking absence of fasciculation (Harvey and Lilienthal, 1941). Since there is a possibility that fasciculation is due to a presynaptic effect of neostigmine and similar drugs (Riker et al, 1959), this has been used to support the concept that myasthenia gravis is due to a presynaptic defect of acetylcholine production or release (Harvey and Lilienthal, 1941). From my experience of cholinergic poisoning, which will be described in the next chapter, I consider that this is a relative matter, indicative of the raised threshold of the myasthenic muscle.

I have no evidence that true drug resistance to anticholinesterase agents can occur and the evidence that sensitivity can be improved by 'resting the end-plates' with/

with curare is not impressive.

There is, to my mind, no doubt that some muscle fibres are rendered permanently incapable of responding to acetylcholine. Where the number of these fibres is an appreciable proportion of the whole the clinical picture of 'myasthenic myopathy' results. Doubtless these fibres are affected by the necrotic changes described in Chapter 11. This state is relatively more frequent in patients with a thymic tumour. Since it is these patients who may have circulating antibodies against muscle fibres (as distinct from end-plate protein) (Chapter 13) it is possible that they are damaged by an autoimmune myositis.

So long as some fibres have a raised threshold to acetylcholine but are still capable of responding to a normal amount if it is prevented from rapid hydrolysis, neostigmine responsiveness remains but it will be obvious that there must be transitional stages between 'classical myasthenia gravis' and 'polymyositis with myasthenic symptoms'.

Rowland (1955) has discussed the problem of diagnosis in cases with symptoms and a natural history closely resembling myasthenia gravis but in whom there is little or no improvement after administration of neostigmine. As he points out, the cases described in his paper would have been classified as myasthenia gravis before the introduction of neostigmine and yet no favourable response could be detected. His cases included one case of apparent neonatal myasthenia in a child born to a myasthenic mother. His Case 4 (in which 'lupus erythematosus cells' were found in the peripheral blood on two occasions but not on two others) showed an incrementing type of response to the Harvey-Masland/

Masland test. My own cases (described in Chapter 9) who had a similar type of electromyographic response showed no real improvement when treated with neostigmine. The nosological position of these patients is still doubtful but I would agree with Rowland (1955) that they represent the 'myositic extreme' of the spectrum of neuromuscular diseases exhibiting the myasthenic reaction.

The resistance just described is, on the whole, permanent and is different in nature to the acquired resistance presumed by some previous authors and which, it is implied, can be recovered from by 'resting the end-plates' with curare and withdrawing neostigmine. For reasons which will be described in the next chapter I consider that these are unrecognised examples of neostigmine overdosage with depolarization block and not of weakness due to diminished sensitivity to neostigmine. On the other hand I find nothing to support the opinion of Harvey (1948) that the continued use of neostigmine prevents remission of myasthenia gravis (see also Ferguson et al, 1955). Although cases treated with very large doses of neostigmine have been described (Rider et al, 1951) an attempt to do so is fraught with danger and it may be significant that no case of this high dosage has been reported since the introduction of the edrophonium test for discrimination between myasthenic and cholinergic weakness (Osserman and Kaplan, 1953). As I believe that most cases of 'neostigmine resistance' are in reality suffering from overdosage, further discussion will be postponed until the next chapter.

GENERAL MANAGEMENT.

The general management of the patient's life is important/

important in order to reduce fatigue and stress both physical and emotional. It is discussed by Gaylor and Simpson (1964).

Contraindications:

It is obvious that drugs with known activity as neuromuscular blocking agents must be used with care in myasthenic patients. Curare, quinine and quinidine are examples of these which will readily occur but a similar action has sometimes been reported with antibiotic drugs such as neomycin and streptomycin (Foldes, 1958; Loder and Walker, 1959; Fisk, 1961; Ross et al, 1963). Polymyxin B has a similar action in animals (Sabawala and Dillon, 1959). The block induced by these drugs is resistant to neostigmine.

Increased weakness in myasthenia gravis has been attributed to administration of chlorpromazine (McQuillen et al, 1963). These authors have shown that chlorpromazine antagonises the action of anticholinesterase drugs in non-myasthenic patients (McQuillen and Johns, 1963). A neuromuscular blocking effect has been previously recognised in animals in this and other tranquillising agents (Kopera and Armitage, 1954; Jindal and Deshpande, 1961) but apart from the case just cited this has not been a significant factor in human cases.

The neuromuscular blocking action of ether and other anaesthetic agents is found only in anaesthetic concentration and it can be overcome by neostigmine (Gross and Cullen, 1943). It may precipitate myasthenia in an unrecognised case (van Noohuys, 1952). Morphine and other respiratory depressants should be used with caution because of the danger of depressing respiration which may be/

be barely adequate but their use is not otherwise contraindicated. An unforseen hazard which should be borne in mind in the treatment of cholinergic poisoning is that the respiratory stimulant tetrahydroaminacrine (T.H.A.) has anticholinesterase activity.

It is generally accepted that an enema may cause sudden collapse with syncope in a myasthenic patient (Keynes, 1949; Simpson, 1964c). I have never seen this happen because, knowing of the risk, I have never permitted an enema to be given to a case under my care, but cases NH26546, NH48570 and NH61501 collapsed after an enema and case GK/EW did likewise after using a glycerine suppository. I have thought it too hazardous to investigate the mechanism or even to confirm the extent of the risk by a trial. Distension of a bowel rendered hypertonic by neostigmine is a possible cause of a vagal reflex. Enemata and purgation are known to cause serious potassium depletion (Dunning and Plum, 1956; Coghill et al, 1959) but the collapse is probably too sudden to be explained in this way since the normal kidney conserves potassium when body levels are depleted.

Ptosis may be prevented by a lid crutch attached to an eyeglass frame. If there is diplopia, an eye patch may be worn but should be changed from eye to eye to prevent suppression of vision. Surgical correction of ptosis or strabismus should be postponed until it is certain that no further variation is likely to occur (Fig. 18,3). Where this precaution is not taken the final result is not satisfactory.

Case MN7550. A young Indian complained of double vision. A corrective operation for ophthalmoplegia was/

was carried out in India. A few months later he developed severe generalised myasthenia gravis with more severe diplopia which has persisted despite thymectomy and optimal treatment with anticholinesterase drugs. (Fig. 17.3)

Orthopaedic appliances have limited value in myasthenia gravis and rarely justify the extra burden imposed on the patient. A myasthenic patient should be warned against eating grapes and should take care at all times to avoid food which might lead to accidental asphyxia. Persistent dysphagia may cause starvation with rapid loss of weight. A fluid diet with concentrated protein supplements should then be given by gastric tube. In very severe cases showing poor response to treatment it may be advisable to make a gastrostomy for this purpose. A case where this was necessary is described in Chapter 4 (MN5652).

Respiratory embarrassment must be detected early. This may be done by measuring the ventilatory capacity or the expiratory force, but an adequate method for clinical purposes is to ask the patient to take a deep breath and then to start counting. A normal person should reach '40-50' before taking a new breath. If the patient only reaches '20' it is apparent that the previous pulmonary inflation has been inadequate and ventilation must be assisted. If the expiratory force required for coughing is inadequate or if there is severe dysphagia it is also desirable to assist respiration by a method which will prevent aspiration of foreign matter into the lungs.

In mild cases of myasthenia gravis respiratory distress is very rarely due to weakness of inspiration. Sudden/

Sudden respiratory distress in such patients is more likely to be due to inhalation of food, or a foreign body so prompt postural drainage with manually assisted cough may be lifesaving if suction equipment is not at hand. Weakness of inspiration usually follows progressive weakness of limb and bulbar muscles associated with an increasing dosage of neostigmine. Since even the most severely ill patient may have a good remission it is extremely important to prevent asphyxial death where this can be forseen. An episode of respiratory failure does not prejudice the eventual prognosis. The possibility that apparent neostigmine resistance is due to hypoxia with carbon dioxide retention should be considered (Scurr, 1954). Assisted ventilation may be life-saving and frequently tides a patient over a crisis which would otherwise be fatal. For these reasons treatment of ventilatory failure should be started whenever there is appropriate indication. It must not be regarded as a desperate remedy to be kept as a last resort. It is unwise to temporise if the patient has shallow fast respiration or is restless. Cyanosis is rare. Neostigmine (2mg.) should be injected intramuscularly at once and a respirator obtained. This dose may be repeated hourly for two or three hours. If an edrophonium test shows that treatment is still inadequate the dose should be increased steadily. This is less likely to give rise to cumulative effects than shortening the intervals between injections although this may also be necessary. Provided an unequivocal response is obtained to edrophonium, it is safe to give atropine in addition but its effect in thickening bronchial secretions is undesirable and it should be avoided if it is possible/

possible to do so.

Since ventilatory failure in myasthenia gravis is frequently associated with dysphagia and often with sialorrhoea, it is preferable to use a positive-pressure method of ventilation of the lungs through an endotracheal tube or, if assisted ventilation is required for more than 24 hours, through a tracheostomy tube (Fig. 18,4). Both types of tube should have an inflatable cuff to prevent retrograde escape of air and to prevent foreign matter which enters the trachea from passing into the lungs. As pressure necrosis of the trachea may be caused by the inflated cuff it is necessary to deflate the cuff every two hours. This must always be preceded by aspiration of the mouth, pharynx or upper trachea through a whistle-tip catheter attached to a suction pump. Despite these precautions food matter persistently passed the cuff barrier and entered the lungs in MN5652 (Fig. 18,5). This case is fully described in Chapter 4 and is worth referring to again as an illustration of the importance of persisting with controlled respiration and gastrostomy for many months even though eventual recovery may seem impossible.

Another indication for artificial respiration is the development of 'cholinergic crisis'. When increasing neostigmine 'resistance' or the results of a series of edrophonium tests indicate the onset of this state the safest procedure is to stop anticholinesterase drugs and to use an artificial ventilator to maintain regular breathing while muscle cholinesterase regenerates. The recognition of this state and its further treatment will be described in Chapter 19.

CHAPTER 19.

CAUSES OF DEATH.

Myasthenia gravis sometimes belies its name and is a comparatively mild disorder. Many patients die of other diseases such as cerebral haemorrhage (NH/GH/AB), acute mania (NH40934) or by injury (NH37580). Four cases died of neoplasia which was not thought to be the cause of the myasthenia (NH/PS/LB, NH/EC/LM, NH5659, MN7785). In view of the previous duration of myasthenia it is improbable that these were cases of carcinomatous myasthenia though this diagnostic category was unknown at the time of their deaths. In the early days of thymectomy many patients failed to survive the operation or died within a period of 2 weeks. With increasing experience of the management of these cases, operative death is now unusual (Chapter 18).

Death directly attributable to myasthenia gravis occurs in three ways - i) Acute asphyxia, ii) myasthenic crisis, iii) cholinergic crisis.

Acute asphyxia:

A major hazard of any disease involving the respiratory and pharyngeal muscles simultaneously is the possibility of inhalation of foreign matter into the lungs. The responsible disorder is not failure of ventilation but deficiency of the expiratory force required to clear the offending substance from the trachea or bronchi. The foreign matter is usually food but may be saliva. The latter may be found in untreated and treated cases alike. Myasthenic patients who are not having any drugs may produce large amounts of thick glairy fluid from the mucous membranes of the pharynx, larynx and probably from the main bronchi. This/

This is rare in the patient receiving anticholinesterase drugs but these have their own danger as they stimulate secretion of large amounts of watery saliva and possibly also bronchorrhoea. This can be minimised by the use of atropine but the tenacious sputum which may result may be even more difficult to evacuate by postural drainage or by suction. Fortunately this type of bronchial obstruction is common only in severely ill patients. There is still, however, a hazard in the well controlled patient. Even in the late 'burned out' stage of myasthenia the expiratory reserve may be inadequate to clear the bronchi or trachea of an inhaled foreign body (Simpson, 1960a). Severely ill patients should not be allowed to eat fruit and all others should take great care when eating it. Case NH3533 described in Chapter 2 illustrates the risk involved.

Myasthenic crisis:

Severe uncontrolled myasthenic weakness adds to the risk of obstructive asphyxia but the main hazard is death from respiratory failure due to weakness of the diaphragm or intercostal muscles. This may come on rapidly in response to emotional or physical stress (including injury), acute infections or in pregnancy. A crisis of this type requires immediate increase of anticholinesterase medication and control of the respiration by the methods described in Chapter 18. It is advisable to change from oral treatment to subcutaneous or intramuscular injection of neostigmine to ensure that the drug is being absorbed in known amounts. Before modifying treatment in this way the diagnosis must be very carefully considered to make quite certain that the cause of increasing weakness is not overdosage of drugs (Nandt/

(Randt, 1953; Tether, 1956).

Duration of action of anticholinesterase drugs:

Severe weakness with respiratory failure may also be caused by prolonged depolarization of the end-plates (Chapter 15). This condition, described by clinicians as 'cholinergic crisis' may be caused by an acute overdose of any anticholinesterase substance. More commonly the paralysis results from prolonged treatment with one of these drugs, due to gradual accumulation of drug within the body. This is most likely to happen with the long-acting drugs such as the alkyl-phosphates and the bis-neostigmine derivatives but all active anticholinesterase substances tend to persist for a considerable period in the body. As pointed out in Chapter 18, the tendency to cumulate is approximately proportional to the duration of effective therapeutic action, thus it is appreciable with pyridostigmine, less with neostigmine, and non-existent with edrophonium.

In my earlier experiences of cholinergic poisoning the management of the 'crisis' state was prolonged by failure to appreciate how slowly neostigmine and pyridostigmine were excreted (vide infra).

Signs of overdosage of anticholinesterase drugs:

Acetylcholine is the transmitter substance liberated at many nerve endings. In addition to the motor nerves to the skeletal muscles it is also present at many synapses or neuro-effector junctions of the autonomic nervous system and in many synapses within the central nervous system. When inhibition of cholinesterase allows accumulation and prolongation of the action of acetylcholine at these synapses the/

the result is a mixture of stimulation and depolarization block at each of these sites. It is convenient to classify the effects under three headings i) muscarinic, ii) nicotinic iii) central.

Muscarinic effects:

The earliest symptoms of this type are colic, 'heartburn', sweating, salivation, lachrymation and constriction of the pupils. With increasing dosage these are followed by diarrhoea, bronchorrhoea and later bronchoconstriction. The latter may be mistaken for asthma and might account for some of the examples of that disorder listed in Chapter 7. With severe overdosage there may also be laryngospasm, involuntary defaecation and disorders of the heart beat. Theoretically one would expect bradycardia but in fact I have never seen this. On the contrary, persistent tachycardia is very suggestive of overdosage. Vasoconstriction, with a cold pale skin and rapid pulse, may nevertheless be associated with a drop in blood pressure. A previously unrecorded sign which I have noticed on several occasions is venospasm which can be so severe as to prevent infusion of fluid into the veins.

No one would wish to continue with a dosage level producing the more severe muscarinic effects. The second group is always associated with nicotinic effects and the third with central nervous system effects. There is, however, a measure of disagreement regarding the significance of slight muscarinic symptoms such as colic, sweating, salivation or lachrymation. Many workers believe that these should be tolerated or suppressed with atropine if the dose level is otherwise satisfactory for the skeletal muscles/

muscles. On the other hand it is well known that myasthenic patients tolerate unusually large doses of anticholinesterase drugs before suffering muscarinic symptoms and on this account the presence of these effects should always suggest that too large a dose is being used. I agree with Schwab (1954) and others who consider that the early muscarinic symptoms are a valuable warning of impending danger and so do not advocate the routine use of belladonna derivatives, though some exceptions must be made. The diaphoretic and purgative actions of potassium salts may confuse the issue.

I have found that the size of the pupil is the best guide. If its diameter is 3mm. or more in normal ward lighting there is no danger. At 2mm. pupil diameter the patient is usually showing nicotinic signs, and when it has constricted to 1mm. there is a well established cholinergic crisis (Simpson, 1961b).

Nicotinic effects:

In normal subjects anticholinesterase drugs cause fasciculation followed by paralysis as depolarization block occurs with increasing accumulation of acetylcholine. It has often been remarked that fasciculation rarely occurs in patients with myasthenia gravis treated with neostigmine and similar drugs and this is taken to be part of the 'tolerance' of these patients. Fasciculation confined to the lower limbs is compatible with excellent control of the weak muscles (see Case MN3231 below). Persistent fasciculation with 'neostigmine-resistant' myasthenic weakness was noted by Cases NH980 and NH8162.

Case MN5108 had fasciculation of hand and leg muscles but showed only ocular weakness.

Case/

Case MN4585, a girl of 19 years with generalised myasthenia did not obtain satisfactory control of ocular and facial muscles until three years after thymectomy. At that time there was a sudden improved response to neostigmine and her usual dose caused fasciculation of the lower limbs and muscarinic symptoms.

Case MN8279, who has been described in Chapter 7, was severely myasthenic in addition to having diabetes mellitus and pernicious anaemia. Weakness was brought under satisfactory control by pyridostigmine (420mg.), neostigmine (135mg. orally and 15mg. intramuscularly). When the dose was reduced she relapsed. When the same dose was re-established there was definite improvement in the performance of all muscles but marked fasciculation was noted in the distal parts of all limbs. An edrophonium test increased further the power of the tongue and lessened ptosis but fasciculation of the legs increased and the quadriceps muscles became weaker. This was interpreted to mean that the severely affected muscles of the head were still underdosed but the less myasthenic muscles of the legs were already overdosed. On this account tracheostomy was performed and the dose reduced. Further tests with edrophonium in the next three days confirmed that the danger of overdosage had receded but unfortunately the diabetes got out of control as she could no longer swallow and death was mainly due to diabetic coma.

Fasciculation may be present for years in an adequately controlled myasthenic patient but only in the clinically unaffected muscles. Fasciculation may later disappear/

disappear as cholinergic crisis develops so the absence of fasciculation does not controvert a diagnosis of cholinergic crisis (Simpson, 1961b).

Progressive weakness is the most important nicotinic sign of the cholinergic state. Weakness in normal muscles is usually preceded by fasciculation but in myasthenic muscles this may not happen so that the only evidence of nicotinic effect is increasing weakness (Osserman et al, 1953; Rowland et al, 1955). The block may be a depolarization type in the first instance but this is likely to change to a desensitization type (see Chapter 17). (The distinction between the 'desensitization' stage and 'cholinergic crisis' made by Grob and Johns (1961) may be valid in theory as an explanation of 'refractoriness' but it is unnecessary in practice and has the disadvantage of concealing from the inexperienced that this is a form of block due to overdosage with anticholinesterase drugs. Since the term 'cholinergic crisis' is not necessarily equivalent to 'depolarization block' I see no necessity to reject the term which has become customary).

Central nervous system effects:

With severe degrees of inhibition of cholinesterase there is a similar sequence of stimulation and depolarization block of central synapses. This may often be suggested by observing tension, anxiety, restlessness, emotional lability or giddiness. Some patients complain of insomnia and nightmares. It is possible that some of the epileptic states associated with myasthenia gravis may be caused in this way. Headache, apathy, intellectual impairment, tremor and progressive depression of the level of consciousness indicate a very severe degree of cholinergic poisoning.

The/

The fall in blood pressure referred to above may be a central effect. Cerebral death may ensue, but in the majority of cases death is due to respiratory paralysis of peripheral type.

The recognition of weakness due to cholinergic poisoning is extremely important because its treatment is diametrically opposite to that of myasthenic weakness. It might be thought possible to recognise a stage of normal muscle power transitional between myasthenic and cholinergic weakness. In fact it is quite common for one type of weakness to succeed the other without any phase of normal power. Rowland et al (1955) noticed this when giving intravenous infusions of neostigmine to myasthenic patients and I have repeatedly confirmed their observation.

The practical importance of this observation will be obvious. Most physicians who have treated myasthenic crisis must have been impressed by the inadequacy of successive increments of dosage with neostigmine. Rowland et al (1955) mention a case requiring 2500mg. daily and Rowland et al (1956) describe patients who failed to respond to 18.0mg. of neostigmine given intravenously during one hour. This phenomenon is usually attributed to refractoriness. It is true that some muscles may become atrophic or 'myopathic' in the course of myasthenia gravis and these muscles will fail to respond to anticholinesterase medication, but there is no real evidence that general refractoriness can occur within the space of a few days. Viets (1944) considered that 'refractoriness (is) merely an acknowledgement of inadequate dosage'. From my own experience the usual explanation of apparent refractoriness to neostigmine is the presence of cholinergic poisoning. To follow Viets' advice/

advice in these circumstances could be disastrous.

A further conclusion made by Rowland et al (1955) from their experiments on intravenous infusion of neostigmine was that muscles which had not been clinically weak previously were usually affected simultaneously with the 'myasthenic' muscles though 'paradoxical' observations were made in one case. My experience disagrees with this conclusion too (Simpson, 1961b). The point is of some importance in the diagnosis of the cholinergic state but discussion will be postponed until the use of the edrophonium test has been evaluated.

The edrophonium test for cholinergic status:

The pharmacological basis of the use of edrophonium for the confirmation of myasthenia gravis has been described in Chapter 16. Osserman et al (1953) suggested that it might also be used to test the cholinergic status of treated myasthenic patients. If temporary improvement occurs after an injection, the need for a bigger dose of anticholinesterase drug is indicated.

The usual dose for the test is 10mg. (1ml.) of edrophonium. The first 2mg. (0.2ml.) should be injected intravenously and the needle kept in place. If the patient is hypersensitive to the drug or in a cholinergic state, this dose may cause fasciculation, blepharospasm, dizziness, faintness and slight muscarinic symptoms. In this event the test should be discontinued. If no ill-effects occur in half a minute the remaining 8mg. is injected. If the symptoms described occur in the next $\frac{1}{2}$-2 minutes it is certain that no myasthenic weakness exists in the muscles tested.

When used to test the cholinergic status the timing

of/

of the test is important. In the average myasthenic patient in whom the test is used to adjust dosage it is best applied at the end of the second hour after neostigmine has been administered. A positive response at that time indicates that the dose of neostigmine is insufficient. In 'adequate' treatment no response will be obtained; in overdosage there will be temporary deterioration. A false impression may be gained if the test is carried out at the end of the first hour when the action of neostigmine is maximal as a patient may fail to show further improvement with edrophonium at that time even though treatment is inadequate. Conversely, three hours after neostigmine is too late. Even a 'null response' at that time may indicate overdosage. The best timing for the test in the control of pyridostigmine therapy is less certain but the two-hour test is probably satisfactory provided that absence of objective improvement is always interpreted as indicating optimal or overdosage (Osserman et al, 1953). At times of crisis the test may be used at any time but should not be repeated more than hourly. The concept of 'titrating' the cholinergic status is sound, but I have found difficulties in practice. (Fig. 19,1).

Death due to muscarinic action:

The following case died very soon after an edrophonium test.

Case MN3231. When aged 34 she had bilateral ptosis which was soon followed by difficulty in chewing, swallowing and speaking increased by continuing the activity. She began to have double vision and weakness of the arms in the evening. Myasthenia gravis was diagnosed 18 months after the onset (Sir Derrick Dunlop). Satisfactory/

Satisfactory control was achieved with neostigmine. Six months later her thymus was removed by Mr. Paterson-Brown. The improvement experienced was not maintained and the dose of neostigmine required increased gradually from 45mg. to 180mg. daily. Her condition then remained unchanged for seven years until she became pregnant. During the first trimester she had a myasthenic crisis of dyspnoea. She improved after termination of pregnancy but never regained her former state of wellbeing and required 225-300mg. of neostigmine with gr.1½ ephedrine daily.

During the last three years of her life (1946-49) there was coarse fasciculation of the legs which had never shown significant myasthenic weakness. Myopathic changes had occurred in both triceps muscles of the upper limbs, the levator palpebrae, masseters, and tongue, but the other muscles of the face, neck and upper limbs still improved with injections of edrophonium or neostigmine after temporary withdrawal of the latter.

In June 1958, the fourteenth year of her illness, she was transferred to the Northern General Hospital under my care to be near facilities for artificial respiration as it was apparent that increased anticholinesterase medication was necessary for the bulbar muscles despite the presence of signs of overdosage in the lower limbs. The vital capacity of the lungs was temporarily increased by injection of 10mg. edrophonium from 600ml. to 860ml. This indicated that the respiratory weakness was myasthenic and not cholinergic. Cautious increase of dosage was therefore permitted and the patient was instructed how to inject neostigmine in case of emergency. A mechanical support for/

for the jaw was provided. In this way she was able to continue in tolerable comfort for more than a year when her doctor requested emergency admission. Apart from the obvious distress her condition had not changed but she stated that she had felt unwell and very breathless for several days although she had greatly increased her dose of neostigmine (by mouth). She was extremely nervous and would not allow her tongue and jaw to be held forward though this aided respiration. The amount of neostigmine taken was unknown. The possibility of cholinergic crisis rather than myasthenic crisis was considered. Fasciculation was marked in the legs but little worse than it had been for 3 years. The pupils were not contracted.

Oxygen was given by nasal catheter and the muscle end-plates were tested by injection of edrophonium intravenously. (Atropine sulphate gr.1/100 was mixed with 10mg. edrophonium.) An initial dose of 2mg. had no effect so injection was continued. When 5mg. had been given the respiratory excursion was considerably improved but she complained of a burning sensation in her eyes, salivation increased and she was unable to swallow sufficiently rapidly to clear it. She panicked and would not keep her head in a position to permit free respiration. The injection was discontinued but she suddenly lost consciousness. Artificial respiration was started immediately and the flow rate of the oxygen was increased. Nikethamide (4ml.) injected intravenously had no effect. Death appeared to be instantaneous. Fasciculation continued after death in the legs and was occasionally seen in the upper limbs for the first time.

In/

In this case there was good reason to believe that the requirement for neostigmine was increasing despite the presence of persistent fasciculation of the leg muscles. Respiration was, in fact, improved by the injection of edrophonium but the patient was asphyxiated by inhalation of saliva and bronchial secretions despite the prior injection of atropine sulphate (0.1mg.) intravenously.

The additional muscarinic effect could also cause death by ventricular fibrillation or cardiac arrest as in the following case in which this event happened from unrecognised overdose of neostigmine without the addition of edrophonium.

Case MN2257 The early history of this patient has been described in Chapter 7 and the unexpected autopsy finding of Hashimoto's disease associated with a thymic tumour. The delay of five years in making the diagnosis was perhaps justified as she was, indeed, a nervous excitable woman. For the same reason the ominous significance of headache, belching and 'heartburn' was not appreciated when she was admitted to the Northern General Hospital in the seventh year of her illness in 1957. At that time there was general acceptance of some muscarinic symptoms as inevitable in the treatment of severe myasthenia gravis.

Dosage was progressively increased because of 'neostigmine-resistance' of the muscles but when diarrhoea, sweating and occasional facial twitching appeared on a dose of neostigmine 75mg. and pyridostigmine 300mg. every three hours, the dose was reduced and atropine increased from 0.3mg. to 1.2mg. every three hours. Her condition did not improve and three days later/

later she suddenly lost consciousness. She was roused in a few minutes when oxygen was administered but vasoconstriction was noted and pulsus bigeminus. About twenty minutes later her heart and respiration stopped and could not be restored by artificial respiration.

It is now obvious that the signs of overdosage were seriously underestimated and that the large dosage of anticholinesterase drugs caused ventricular fibrillation or cardiac arrest despite atropine protection of autonomic synapses. Neostigmine is known to potentiate vagal reflexes affecting the heart and lungs (Furman and Geiger, 1952) and it must be assumed that edrophonium could temporarily potentiate this action to a degree which could be dangerous.

Both of these fatalities occurred despite the intravenous injection of atropine sulphate (0.1mg.) before injection of edrophonium. This should never be omitted when the test is used for suspected cholinergic poisoning.

Differential nicotinic action:

The edrophonium test has one inherent fallacy which I have reported (Simpson, 1961b) but which has not been published previously. It assumes that the muscle tested during its brief period of action is representative of all skeletal muscles. Apart from the possibility of selecting for test muscles which have become unresponsive from 'myopathic' change, it will be apparent from the case history just described that some muscles may improve with the additional anticholinesterase substance while others do not or get worse. A further example of this phenomenon may be described.

Case MN294 took increasingly large doses of pyridostigmine to improve eye movements and to relieve ptosis. As these effects/

effects were achieved her limb muscles first fasciculated and then became weak. When the dose was reduced the eyes deteriorated but her general strength improved.

These cases, which are representative of many, show that different muscles may respond in different ways. Those which, without treatment, would have a marked myasthenic reaction may improve, while the less affected muscles are unchanged and the muscles not affected by myasthenia become weaker. This is obviously what might have been predicted and is apparent from the protocols of the experiments described by Rowland et al (1955) on the effect of intravenous infusion of neostigmine in myasthenic patients. A diagram from their paper is reproduced (Fig. 19,1). These authors were unable to understand why overdosage might not be accompanied by fasciculation or previously existing fasciculation might disappear. A consideration of my hypothesis on the nature of drug action (Fig. 16,1) will show that this effect is a predictable result of increasing accumulation of acetylcholine at the end-plate. The normal muscles suffer a 'cholinergic' block with a dose of neostigmine which is still insufficient to maintain optimal transmission in the severely myasthenic muscles.

It will be recollected that it is only the 'normal' muscles which show fasciculation in a few well controlled myasthenic patients. The explanation for this distribution is patently the same. It accounts for the fact that fasciculation may be tolerated for an indefinite period but it is unwise in these circumstances to attempt to achieve full control of the myasthenic muscles. The quandary in Case MN3231 (above) was that the affected muscles were requiring/

requiring still greater dosage of neostigmine to combat increasing myasthenic weakness. The improvement in ventilatory capacity after edrophonium is clear evidence that the respiratory muscles were still underdosed. This experience leads one to disagree with the conclusions of Rowland et al (1955) that anticholinesterase drugs affect all muscles in the same way at the same time. They must be 'titrated' individually.

Three lessons may be learned from this experience - i) in testing for incipient cholinergic crisis with edrophonium the first muscles to be tested should be those for respiration and deglutition. Only when it is apparent that these are not deteriorating should attention be paid to other muscles. The deltoid muscles of the arms and the flexor muscles of the neck are very commonly affected by myasthenia gravis but rarely become resistant to neostigmine. They should be tested next. The ocular muscles which commonly become 'myopathic' should not be used to test for cholinergic status. The short time available for testing should be used for more vital and consistently responsive muscles. ii) Some groups of muscles may be overdosed by neostigmine while others are underdosed. iii) A negative response should always be considered to indicate incipient cholinergic crisis. Furthermore, a statement by the patient that he 'feels stronger' should never be accepted as evidence of improvement. If no objective evidence is seen the test should always be interpreted as indicating potential danger.

Differential diagnosis of cholinergic crisis:

When a patient does not continue to improve or actually deteriorates despite increasing dosage of anticholinesterase drugs it must always be considered whether the/

the patient is being overdosed. Many authors have stated that the possibility of giving too much neostigmine to a patient with respiratory failure is remote and that there is a greater likelihood of giving inadequate amounts when a patient is critically ill but not in a respirator (Harvey, 1954; Viets, 1944). My experience of the last 10 years leads me to the opposite conclusion. In my opinion the majority of cases of so-called 'neostigmine resistance' and of 'crisis' occurring despite previously adequate treatment have been due to overdosage with anticholinesterase drugs.

On reading the brief case histories provided in illustration it might be concluded that the diagnosis of incipient cholinergic crisis was easy. Unfortunately this was not the case. Although suggestive signs or symptoms have been recorded chronologically in the case reports, they were sometimes elicited retrospectively by close questioning of junior nursing staff who had not appreciated their significance. Early symptoms were increased sweating, colic, heartburn, diarrhoea, muscle twitching or increased restlessness. The nurses, and indeed the house physicians, usually believed that these symptoms resulted inevitably from the use of neostigmine. Though they may be compatible with a safe level of dosage they should always be considered as evidence of possible danger. I have found that measurement of the pupil diameter is helpful. If it is 3mm. or larger in normal ward lighting there is little danger. If it is only 2mm. it is possible that the safe dose has been exceeded and at 1mm. there is little doubt about the presence of cholinergic crisis. Doubt may arise, however, if there is respiratory insufficiency as the patient may then show

mental/

mental confusion, apathy or restlessness, sweating and miosis due to anoxia with carbon dioxide retention (Table 19,1. Simpson, 1964e). This difficulty is illustrated by Case MN5095 (vide infra).

Muscarinic symptoms may not be prominent, especially if atropine has been used prophylactically. In these cases the diagnosis of the cause of increasing muscular weakness can be very difficult. Valuable clinical clues are -

i) If fasciculation is present in any part of the body the condition should be considered cholinergic until this is disproved.

ii) If the daily dose exceeds 300mgm. of neostigmine orally (or its equivalent) or if weakness develops within an hour of taking tablets it is highly probable that it is due to overdosage, especially if there is no obvious cause for myasthenic relapse. On the other hand if the deterioration follows an emotional upset or occurs in the course of a pyrexial illness and is first noticed more than two hours after the last dose of anticholinesterase drug, it may be due to a myasthenic relapse. This is most probable if the daily dose is less than 225mg. of neostigmine or its equivalent.

It is in the doubtful case that the use of the edrophonium test is most justified. If all the circumstances point to the probability of cholinergic crisis it is not advisable to incur the further risk provided by injection of edrophonium. It is much safer to ensure maintenance of respiration by an artificial ventilator, to inject atropine sulphate 0.1mg. intravenously, and to give no more neostigmine.

So long as respiration is secured (and if necessary there/

there should be no hesitation in performing a tracheotomy for this purpose) it is safe to wait. If weakness is increasing in two hours an edrophonium test may be applied to confirm that the weakness is myasthenic in type. If the condition is static or improving the test should be delayed for at least 6 hours. The timing of the test with regard to the most recent medication should otherwise follow the rules laid down above.

The Jolly or Harvey-Masland test may be useful in differentiating between myasthenic and cholinergic weakness. In the presence of cholinergic block the first twitch and its action-potential should be greater than subsequent responses but the later ones should remain at a subnormal plateau level without showing the decrementing response typical of the myasthenic state. I have found this procedure helpful in two cases and now have a small battery-operated transistorised stimulator which enables a Jolly test to be carried out in the patient's home. Unfortunately no permanent record of the response has been obtained. The main objection to the method is one already made with regard to the edrophonium test, namely the possible fallacy involved in extrapolating the findings from one nerve-muscle complex to others. This problem will be studied further as occasion arises.

Treatment of cholinergic crisis.

If increasing weakness due to overdosage of anticholinesterase drugs is recognised before respiratory failure takes place it is sufficient to give atropine sulphate 2mg. intravenously and to omit the next dose of the drug. The edrophonium test should be repeated every two hours and no more anticholinesterase substance given until/

until there is an unequivocal improvement with edrophonium.

If there is respiratory failure the patient should be respired through a cuffed endotracheal tube. This must be replaced by a tracheostomy tube in 24 hours if further artificial respiration is necessary. This is a much more dangerous state than the myasthenic crisis because of the haemodynamic changes present and the possibility of bronchospasm so intubation should not be delayed. There will be no worth while recovery in another hour and the patient may lose his chance of survival. Passive ventilation of the lungs is more difficult in cholinergic than in myasthenic crisis because bronchospasm may be present. This will cause difficulty with time-cycled or pressure-cycled ventilators and care must be taken to ensure that the minute-volume of respired air is satisfactory. Bronchorrhoea adds to the difficulty but should be minimised by the repeated injection of atropine sulphate. This should be given intravenously in doses of 2mg. every hour until muscarinic signs abate or signs of atropine toxicity appear. The latter possibility should be considered if restlessness or confusion develop in the well oxygenated patient.

Curare as antidote:

Atropine has no significant action on the neuromuscular junction of a skeletal muscle. There are two possible approaches to the problem at this site i) to reactivate cholinesterase, ii) to displace some of the acetylcholine from end-plate receptors with d-tubocurarine (Simpson, 1961b). The latter approach, which is similar to the use of atropine in the treatment of muscarinic effects, has not been reported by other workers. Better results might be expected if this form of treatment could be controlled/

controlled by electromyography.

Case MN7788. This 15 year old girl complained of 'swelling' of her eyelids and pain in the calves when walking. Her arms became weak and she noticed increasing tiredness as the day wore on. Dr. D.H.A. Boyd made a diagnosis of myasthenia gravis which was confirmed when she was admitted to the Eastern General Hospital, Edinburgh (Dr. A. Bruce). The initial response to neostigmine was excellent, but after two months when I first saw her she had become extremely weak, requiring 4 tablets (60mg.) of neostigmine six-hourly.

On 1/5/57 she developed pharyngitis and the myasthenia became more severe. In view of the increasing deterioration despite increasing the dose of neostigmine to 1.5mg. intramuscularly every 2 hours, it was decided on 9/5/57 to remove her thymus. That night she became very weak and restless. She was given Omnopon gr. 1/6 subcutaneously at 11.0p.m. At 1.0a.m. on the 10th she suddenly lost consciousness and breathing stopped. The pupils were contracted and there was spasm of the jaw muscles and excessive salivation. Controlled respiration was started by an anaesthetist but she was certainly apnoeic for some time. I saw her after respiration was re-established passively. The history suggested myasthenic crisis precipitated by a respiratory depressant drug but on questioning the nursing staff it was found that the patient had complained of abdominal pain and headache earlier in the evening. Since these symptoms pointed to a cholinergic crisis and the small pupils could be due to neostigmine poisoning rather than to opium or/

or hypoxia it was decided to use the edrophonium test as described above. She was given 1.2mg. of atropine sulphate subcutaneously between 3.30 and 4.30a.m. and then edrophonium 10mg. intravenously. This had no obvious effect but since no voluntary movement could be tested the injection was repeated with 10mg. intramuscularly. As there was still no obvious improvement the test was considered to indicate a cholinergic state.

No conventional stimulator could be obtained at that time of night but an apparatus for electrical defibrillation of the heart was available. It was found that this instrument could evoke a twitch of the fingers when the large electrode was applied directly to the flexor muscles in the forearm but not when the ulnar nerve was stimulated at the elbow.

In 1957 there was no 'antidote' to neostigmine so I decided to attempt to displace acetylcholine from end-plate receptors by injecting d-tubocurarine. This had never been done before so there was no means of assessing the required dose. Intravenous injection of 15mg. of d-tubocurarine did not cause any obvious clinical change but muscle twitches could now be evoked by stimulation of the ulnar nerve. This was taken as confirmation that the previous block had been of depolarization type.

Having no information about the extent and duration of the effect of d-tubocurarine in this condition I did not give any more but continued throughout the night with intermittent positive pressure respiration and atropine.

During the following day she recovered consciousness and regained voluntary movement of her limbs but a nor-adrenaline drip was required to maintain her blood pressure/

pressure. Seventeen hours after she had collapsed her condition deteriorated again and she died. At autopsy (Dr. A. MacFarlane) the brain showed no macroscopic alterations but on histology the cells of the granular layer of the cerebellum were ballooned with pyknosis of nuclei. These changes and others such as petechial haemorrhages and ecchymoses in the epicardium were attributed to the episode of respiratory arrest. The thymus was considered to be 'normal' but some of the muscles showed Russell's type I lesions. The thyroid was not examined.

Case MN5095. The early history of this patient is described in Chapter 7. He had severe myasthenia gravis with partial removal of a thymic tumour 12 years previously and was referred to me on account of increasing 'neostigmine-resistance'. In addition to myasthenia gravis he had megaloblastic anaemia, hepatomegaly and splenomegaly. His tongue was smooth and red (Fig. 4.2) which might have accounted for disturbance of taste sensation though he also had paraesthesia of all limbs (see Chapter 4).

On admission to the Northern General Hospital, Edinburgh, he was taking 46 tablets of neostigmine daily but found great difficulty in chewing and swallowing his food, and speech was very difficult although the distal muscles of his limbs were powerful.

Stage 1 (days 1-19). After two days on 40 tablets daily his condition had deteriorated. On the seventh day there was brief improvement after intravenous injection of edrophonium (10mg.) so some of the neostigmine dose was continued but given parenterally in case he was not swallowing/

swallowing the full dose. Tracheostomy was performed and intermittent positive pressure respiration started (Fig. 19,3). On that day he had neostigmine 2.5mg. intramuscularly at 0200, 0800 and 1600 hours, and pyridostigmine (Mestinon) 3 tablets by mouth at 1300 hours. Three oral doses of atropine sulphate (0.6mg.) were given in that period. At 1700 hours the pupils were nearly pin point in size (Fig. 19,3). I felt sure that he was in cholinergic crisis but a repeat edrophonium test at 1830 hours caused unequivocal improvement of eye-lid raising and extraocular movements so a further 5mg. neostigmine was injected intramuscularly at that time, causing the patient to feel much happier. At 2100 hours the response to edrophonium was equivocal but the eye movements were again thought to improve so, despite continuing miosis, 4mg. of neostigmine was injected intramuscularly every two hours with apparent improvement in muscular power.

On the eighth day finger twitching was noted but power was maintained, the pupil was slightly larger and edrophonium still caused slight improvement in eye movement so the high dosage was continued in the belief that this must indicate subopitmal dosage. On that day he had 23mg. of neostigmine intramuscularly and 3 tablets (180mg.) of pyridostigmine orally. On the ninth day there was no clinical change on 57mg. neostigmine intramuscularly but an edrophonium test gave no significant increase in power. It was repeated on the tenth day (67mg. neostigmine). There were no adverse effects and hand grip seemed stronger, yet two hours later he had become very weak, there was fasciculation of/

of forearm and calf muscles and the pupil measured 2mm. diameter. Edrophonium now caused no objective change but once again the patient claimed to feel stronger. Nevertheless the signs of cholinergic crisis were clearly present, miosis, sweating, fasciculation and pallor. The veins were constricted (a feature I noted in subsequent cholinergic states). He was immediately given 500mg. of P.A.M. by slow intravenous injection. (This is one of the oxime drugs discussed in the next section). There was no dramatic change in the condition but 40 minutes later edrophonium (20mg.) caused increased grip strength despite increasing fasciculation of all limbs. The patient noticed no improvement until at least one hour after injection of P.A.M. and continued to feel better for about 4 hours. Ninety minutes after the injection there was a rapid drop in blood pressure to 90/40mmHg. and it remained low for another 2 hours. Throughout this period the pupils remained constricted (1½mm) and fasciculation continued in the calves but not in the upper limbs. We felt that the patient's condition was back to that of the previous day. Parenteral neostigmine was restarted as the available information about oximes led me to conclude that cholinesterase had been regenerated. I was again influenced unduly by the edrophonium test which I interpreted as indicating that the end-plates of the muscles were again responsive to anticholinesterase medication although autonomic synapses were still markedly overstimulated. On day 11 the pupils remained at 2.5mm. but not so small as on the day before, fasciculation and spontaneous twitching of fingers persisted, but the grip was good and definitely seemed/

seemed stronger after edrophonium (Fig. 19,3). Nocturnal restlessness and disorientation were noted at this time and attributed to the frequent use of atropine. On day 12 he seemed stronger, and fasciculation was less, being confined to the legs in the morning and absent altogether in the evening. I was lulled by this 'improvement' into ignoring increased bronchorrhoea and further constriction of the pupil (1mm.). On day 13, on an even bigger dose of neostigmine (197mg. intramuscularly) he seemed well in the morning, edrophonium still improved the grip and the movement of the eyes. On that day, however, he did not pass urine and had oliguria for the next 10 days. On the fourteenth day air hunger developed and it was found that acute haemolysis had occurred. He was given a transfusion of whole blood on day 15.

For the next five days he seemed to be well so far as muscle power was concerned and fasciculation was slight and confined to the calves, but the pupils remained small (1.5mm.). We concentrated on treating the haemolytic anaemia and anuria.

Comment on stage 1:

During this period I believed that the patient required large doses of neostigmine parenterally and felt confident that he was being made more powerful by it. Viets (1950) stated that 15mg. of neostigmine bromide by mouth are equivalent to 1.5mg. of the methylsulphate injected intramuscularly. I calculated the parenteral dosage on this basis but as the result of experience in this case feel that 15mg. oral dose is equivalent to only 1.0mg. parenteral. (Simpson, 1964b).

Results/

Results of testing with edrophonium appeared consistent. Fasciculation was ignored as it was confined to muscles which were not weakened by myasthenia. The small pupils were noted but discounted in view of the apparent improvement, on the grounds that muscarinic effects need not parallel the action on pathological muscles. In retrospect some of the improvement may have been the result of the blood transfusion on day 15. On the one occasion that I had felt obliged to doubt the subjective improvement on edrophonium because muscarinic effects were so gross, the injection of P.A.M. had not given the immediate improvement I had expected from the literature. Indeed its most marked effect was a prompt and alarming hypotension. The anuria and haemolysis developing three days later were attributed to this drug, perhaps wrongly since there may have been renal ischaemia from cholinergic poisoning.

I was now faced with a dilemma. The only information I could obtain about the fate of ingested neostigmine was that it was 'unknown, but there is presumptive evidence that it is both destroyed in the liver and excreted in the urine'. (Goodman and Gilman, 1955). The patient was known to have abnormality of liver function and now had severe oliguria.

Stage 2 (Days 20-41). On the morning of day 20 the condition was that just described, pupils 1.5mm., fasciculation slight and confined to the lower limbs, power excellent without gross tiring and edrophonium (20mg.) caused increased grip strength without increasing fasciculation. Nevertheless 20 minutes later he was weaker, and 1½ hours after the test was very weak indeed, perspiring profusely with pin point pupils but no fasciculation/

fasciculation. Pulse rate was 84/min. Edrophonium 2mg. intravenously had no effect, and a further 8mg. did not increase strength (Fig. 19,4). Fasciculation was possibly increased. Another 10mg. given within 4 minutes caused definite fasciculation of interosseous muscles of the hands but arm flexion seemed more powerful. Venospasm was again noted. This time there was no doubt that cholinergic block had occurred. Neostigmine was discontinued and P.A.M. injected intravenously. An initial dose of 1G. did not improve the clinical state and again there was a fall in blood pressure, which commenced 15 minutes after the injection and lasted for ½-1 hour. One hour later an edrophonium test still indicated a cholinergic state. A further injection of P.A.M. was given (300mg. intravenously, 2mg. intramuscularly). About an hour after the second dose a slow improvement in strength was apparent. (Fig. 19,5). Atropine was injected and further response observed. Four hours after the injection of P.A.M. he was definitely stronger and fasciculation was less but the pupils remained about 1mm. diameter so a further 500mg. P.A.M. was injected intramuscularly. On this occasion no hypotension occurred but the clinical state was not significantly altered and edrophonium gave no response. Two further doses of 1000mg. P.A.M. were injected intramuscularly at intervals of three hours. Some twelve hours after the original injection of P.A.M. (during which he had received a total of 4G. of the drug in five doses) slight but steady improvement was noted, but two further injections of 1G. intramuscularly were required on the following day to prevent relapse (Fig. 19,5). During much of this period the patient was drowsy or unconscious and there was subsequent amnesia for/

for the whole period. His temperature dropped to 97.6°F. (rectal) and the blood pressure remained very low. Unequivocal improvement did not occur until 48 hours after he had collapsed. Concomitant with returning alertness and power, sweating decreased and the pupil gradually increased to 2mm., and in another 12 hours to 3mm., by which time power was good, hypothermia had given place to slight pyrexia for the first time and there was slight increased strength after edrophonium (20mg.).

I did not feel that it was safe to reinstitute neostigmine therapy until 55 hours from the time of the collapse although obvious myasthenic fatiguability had returned and the pupils had increased to 5mm. diameter. Occasional fasciculation was still present in the legs.

Comment on Stage 2:

During this period (days 20-24 inclusive) no neostigmine was given (the amount shown on the chart represents that part of the previous regime given before neostigmine was withdrawn on day 20). There was therefore a maintained cholinergic state for 4 complete days, and another 8 hours elapsed before treatment was restarted. This period coincided with a phase of severe oliguria (150-600ml. urine passed daily). The urinary output increased to 980ml. on the day of his recovery, but some oliguria persisted until his death six weeks later.

Two conclusions may be justifiable, i) neostigmine is probably excreted in the urine and it is not significantly destroyed or excreted by other routes, ii) the preparation of P.A.M. used was ineffective, at least in the presence of renal failure. The fall in body temperature was already apparent/

apparent on day 19 and so was considered to be caused by central synaptic block. Hypotension was probably similarly caused but it was temporarily increased after intravenous injection of P.A.M. (Fig. 19,5).

Stage 3:

In view of the continuing oliguria, treatment was restarted with a very small dose on the evening of day 24 (Fig. 19,4). There was slight sweating with some pyrexia and conjunctival icterus which continued for three days, with biochemical evidence of haemolysis.

A single intramuscular injection of 1.25mg. neostigmine did not improve the myasthenic state which had been allowed to develop and it was repeated in an hour. At midnight regular medication with 2 tablets of neostigmine was restarted every 4 hours and on the 25th day he was quite well, though still suboptimally treated as judged by edrophonium testing. Nevertheless the pupils which had been 4.5-5mm. diameter returned to 2.5-3mm. The dose was cautiously increased. On day 29 it was 4 tablets three hourly (less than his original dose), his power was now excellent but the pupils were sometimes as small as 2.0mm. and upper limb fasciculation had returned so it was once more reduced to 2½ tablets 4 hourly. The first definite evidence by edrophonium testing of a return to the myasthenic state was on day 33. Pyridostigmine was substituted for neostigmine but on the 35th and 36th days occasional sweating and upper limb fasciculation recurred and the edrophonium test was equivocal.

The interval between each dose of pyridostigmine was increased to 4½ hours on day 36 and to 5 hours on day 38. On that day the pupil contracted to 2-2.5mm., and/

and there was slight sweating but no fasciculation. Faecal incontinence occurred without colic. It may have been due to potassium citrate started on that date, but its continuation on the next day with slight deterioration in power suggested that another crisis was impending although he was only having 12 tablets of pyridostigmine per day and the pupil diameter was approximately 3mm. In the early morning of day 40 he became difficult to rouse, weakened rapidly and collapsed. The pupils contracted to 1.0-1.5mm., sweating was profuse and fasciculation returned to the hands and face. There was spontaneous twitching of the fingers. Atropine was injected immediately, followed by intramuscular P_2S (1G) which was now available. No appreciable change occurred for one hour then power rapidly improved, hand fasciculation and sweating stopped and he regained consciousness. The pupils, however, remained almost pin-point in size (Fig. 19,6). Forty five minutes later toxic signs reappeared and 15 minutes after that (two hours after the first injection) a further 1.0g. P_2S was injected intramuscularly. This time a response occurred in 30 minutes but seemed to be passing off in half an hour. Ninety minutes after the second injection the pupil diameter was still 1.5-2.0mm. Fasciculation and sweating had returned but power was good and so I decided to continue with atropine.

He had no neostigmine from 0900 on day 39 to 2100 on day 41 (60 hours) and only then was power decreasing, edrophonium causing improvement, and the pupil size larger/

larger than 3mm. Fasciculation was minimal throughout this period. There was again oliguria during this crisis with greater output on the day of recovery.

Comment on Stage 3:

At the time of these events the renal failure and haemolysis were attributed to P.A.M. Later examination of fluid balance charts suggests that the oliguria at least may have been a result of the cholinergic state. Nevertheless cholinergic crisis had once again occurred with a dose of anticholinesterase drugs substantially less than that which he had taken four years previously, suggesting failure of an excretory mechanism. It is possible that potassium citrate, given by mouth (2g. b.d.) on days 38 and 39, caused faecal incontinence and that the potassium ion precipitated this new crisis but this is unlikely. The patient's general state was now deteriorating. His breathing had been maintained by a positive-pressure ventilator for five weeks, and tube feeding had been necessary throughout that time. Oesophageal ulceration was now present and renal function was poor. Haemolytic anaemia was added to a previous megaloblastic anaemia. The prognosis seemed hopeless but I felt obliged to persist with attempts to establish a satisfactory balance despite apparently increasing sensitivity to anticholinesterase drugs

Stage 4 (days 42-61):

Since it was now clear that tolerance for anticholinesterase drugs had decreased (whether from diminished excretion or other reason) I decided to restart treatment with a very small dose and to increase it gradually, relying on the ventilator to maintain respiration. Pyridostigmine was/

was restarted in a dose of 60mg. (1 tablet) 4 hourly. Fasciculation and sweating persisted throughout day 42 but thereafter subsided, and the pupil remained larger than 4mm. The patient was alert and strength was fair but with rapid fatigue. The dose was gradually increased after confirmation that edrophonium caused unequivocal improvement but on day 48 was still only 2 tablets 4 hourly by day and 1½ tablets 4 hourly by night. On day 49 the patient begged for a bigger dose but an additional 0.5mg. neostigmine intramuscularly before a meal made no appreciable difference and for the first time in a week the pupil was slightly smaller and fasciculation reappeared in the hands. (Fig. 19.7).

On day 50 the serum potassium (which had been steady at 3.4mEq/litre) dropped to 2.9mEq/litre. Potassium supplements were again given and continued until day 64.

Comment on Stage 4:

Throughout this period it seemed that the patient was gradually improving in his general condition though muscle power was deliberately kept submaximal. Even so, on day 54 an intravenous injection of edrophonium (10mg.) improved the grip but caused sweating, hiccough and fasciculation of the eyelids. A change was gradually taking place which was difficult to define. Power (measured by a dynamometer) was no worse, fasciculation was absent from the upper limbs, the pupils were satisfactory but apathy and despair characterised the patient's attitude in place of his previous hopefulness.

Stage 5 (days 62-80):

During this next stage it was considered that further cholinergic crisis must be avoided at all costs by accepting/

accepting submaximal control of myasthenia. Anaemia and inadequate gaseous exchange in the lung from pulmonary complications were now important factors in preventing adequate oxygenation. A trial of ANP 235 (in addition to two tablets of pyridostigmine 4 hourly) was without any effect. The megaloblastic anaemia was now shown to be accompanied by low cyanocobalamin in the serum (145-152µµgm. by cyanide assay, normal 170-1000µµgm.). Injection of cyanocobalamin (1000µg. daily for 3 days then weekly) gave a reticulocyte response of 7% in 3 days but without changing the gradually deteriorating clinical course (see Chapter 7) (Fig. 19,8).

By this time the unfortunate patient had been on the respirator for 2 months during which he had had many spells of pulmonary collapse, pneumonitis and oesophageal ulceration which were only relieved by the most devoted care of nurses and physiotherapists (Fig. 18,4). When he collapsed again on day 68 the attack began with breathlessness and sweating but there was no miosis or fasciculation. Bronchial aspiration and changing the tracheostomy tube relieved his air hunger. From day 69 to 78 the pulmonary pathology dominated the picture and oesophagitis caused great distress. On day 79 a further spell of air hunger caused him to panic. He seemed very weak but he could make strong muscular contractions when persuaded to make the effort and tetanisation of various peripheral nerves produced strong contraction without demonstrable fatigue. Sweating was profuse and the pupils became smaller. Edrophonium improved muscle power but reduced the pupil diameter to the size of a pin-point and caused bronchorrhoea/

bronchorrhoea. Urine output decreased again in the latter part of the day. It was considered that pulmonary collapse and anoxia were again important factors but the picture was now so like that occurring in previous cholinergic crises that pyridostigmine must be discontinued and more atropine given despite the improved power after edrophonium.

He slept well, but was weak in the morning and the edrophonium test was equivocal. Pupils were now 2.5-3.5mm., sweating was profuse and there was an odd rhythmic jerking of the tongue. The blood pressure had dropped slowly to 82/50mmHg. It did not drop further when P_2S (1G.) was injected intramuscularly (Fig. 19,9). In one hour power was perhaps a little greater but the pupils were still 3mm. in diameter. The injection was repeated twice at hourly intervals (3 in all) but, although the pupil became larger, sweating remained profuse, oliguria was severe, the hypotension never recovered and the pulse was rapid and thready (130-140/minute). When it was obvious that death was near, neostigmine 2.5mg. intramuscularly was tried without effect and still another dose of P_2S but all to no avail. The patient died on day 80 (11th February, 1961).

Comment on Stage 5:

For whatever reason, the patient had shown in stages 2 and 3 that he could no longer tolerate his previous level of anticholinesterase medication. During this stage I deliberately allowed the patient to develop myasthenic weakness which was then slowly brought under control. I was astonished when further collapse occurred with some signs/

signs common to cholinergic crisis, but this time there were important differences. The pupils remained large except after edrophonium which caused miosis and fasciculation, indicating that the anticholinesterase level was high despite the small dose. Nevertheless P2S in repeated doses (with atropine) was without significant effect. It is not certain whether anoxia due to pneumonitis was the cause of the change but it was certainly an important new factor confirmed at autopsy. Even up to the time of death the handmuscles still responded well and without fatigue when the ulnar nerve was tetanised at the elbow. The post mortem findings are summarised in Chapter 7.

The similarities and differences between respiratory failure, overventilation and cholinergic crisis are summarised in Table 19,1.

Urinary Excretion of Anticholinesterase Substances.

A major difficulty in the handling of this patient who had both hepatic and renal insufficiency, was the uncertainty regarding the fate of neostigmine or pyridostigmine in the body. The current edition of a standard work of reference (Goodman and Gilman, 1955) stated that 'the exact fate of neostigmine in the organism is unknown but there is presumptive evidence that it is both destroyed in the liver and excreted in the urine'. The manufacturers (Roche Products Ltd.) were unable to give more information but their biochemist, Mr. R.F. Long, kindly assayed the urine excreted during days 22-33, the first period of oliguria. He was able to recover from the urine 5-8% of the amount of neostigmine taken by mouth from/

from day 24, but even during the first two days a similar concentration was present in the urine though no drug was administered.

In view of this evidence that neostigmine might be cumulative, the results were discussed with Professor A. Wilson of Liverpool University. His previous studies on the metabolism of neostigmine had not shown such prolonged secretion. The patient was then having pyridostigmine and Professor Wilson found that 10% of each day's dose could be recovered from the urine, a result consistent with his experience of the elimination of single doses. Since the drug is still being excreted two days later in persons with normal renal function it seems highly probable that renal failure contributed to the difficulty of preventing the cholinergic state in this case.

I have collaborated with Professor Wilson and his colleagues in studying the urinary excretion of neostigmine and pyridostigmine in later cases. They have found that up to 67% of neostigmine is excreted unchanged in the urine when it is given by intramuscular injection but when neostigmine or pyridostigmine is given orally the recovery in the urine is only about 5% (Nowell et al, 1962). They have also found evidence that pyridostigmine is absorbed more efficiently than neostigmine from the alimentary tract but is excreted more slowly. Appreciable amounts are still detectable in the urine two days or more after the last dose.

Neostigmine bromide taken by mouth is believed to be metabolised to m-hydroxyphenyltrimethylammonium bromide and an unidentified quaternary nitrogen compound. The former metabolite is known to have an anti-curare action (Nowell/

(Nowell et al, 1962; Scott et al, 1962). It is assumed that the degradation after oral administration takes place in the alimentary tract (Goldstein et al, 1949) but the role of the liver is uncertain. Injected neostigmine, on the other hand, is practically unchanged in the body. Some of our results obtained in 1961 showed that the urinary recovery was relatively independent of the volume of urine excreted (Case MN5409). We considered the possibility that this might be due to tubular secretion of the drugs and this has now been shown by Roberts et al, (1963).

Oxime preparations:

Reactivation of cholinesterase can be achieved, when the enzyme is inhibited by an organic phosphate drug, by the use of oxime compounds, such as pyridine-2 aldoxime (2 PAM) or its methane sulphonate P_2S and diacetyl monoxime (DAM). These drugs may be very effective antidotes to overdosage in myasthenic patients of TEPP and similar drugs (Wilson and Ginsburg, 1955; Childs et al, 1955). The action of oximes and related compounds is considered to be a displacement of phosphorus from the phosphorylated cholinesterase and this action is more or less powerful according to the nature of the alkyl group directly connected with the phosphorus atom, being relatively ineffective against compounds with a diaminoalkyl group such as OMPA (Kewitz et al, 1956).

Displacement of phosphorus cannot be the only mechanism involved as Grob and Johns (1958a) showed that certain oximes are capable of reversing in man the cholinesterase inhibition and neuromuscular block due to quaternary ammonium anticholinesterase compounds such as neostigmine/

neostigmine which contain no phosphorus. These authors suggest that the oximes 'reactivate' muscle cholinesterase by some unspecified mechanism. I offer as a working hypothesis that the oxime competes with either type of inhibitor for occupation of the esteratic site on the cholinesterase molecule. It might then be expected to have some affinity for the similar grouping of the end-plate receptor substance, with the possibility of causing neuromuscular block. Grob and Johns (1958a) showed that 2 PAM produced a transient local neuromuscular block following the intra-arterial injection of high concentrations. They attribute the block to an anticholinesterase effect which can also be demonstrated with certain concentrations of 2 PAM. The block is potentiated by previous injection of some anticholinesterase compounds but not by neostigmine. This would fit with my suggestion that the anticholinesterase substances occupy esteratic sites on cholinesterase molecules and the 2 PAM then occupies the less favourable sites on muscle receptors. This would satisfactorily account for their observation of progressive depression of successive potentials evoked by repetitive nerve stimuli during the oxime induced block, and the transition from cholinergic to oxime block without a transitional phase of normal function.

Grob and Johns (1958a) also measured the inhibition by 2 PAM and DAM of cholinesterase enzymes of human plasma, erythrocytes, muscle and brain and showed that these oximes protected against the inhibition of cholinesterase by organophosphorus compounds but the protection and reactivation of cholinesterase inactivated by quaternary ammonium drugs (neostigmine, pyridostigmine, ambenonium) was slight. This conclusion was in keeping with previous opinion by pharmacologists/

pharmacologists. Hobbiger and Sadler (1959) reported that the LD 50 of physostigmine or neostigmine in experimental animals was not raised by 2 PAM in conventional doses.

Despite the theoretical objections, Grob and Johns (1958a and b) claimed that 2 PAM and DAM were both effective in the treatment of the nicotinic effects of neostigmine overdosage in normal and myasthenic subjects though the response was never dramatic. The muscarinic effects were not appreciably altered. They found that the weakness caused by overdose with oximes was even more likely to happen with myasthenic patients and attributed this to an 'uncovering of the basal myasthenic weakness' by removal of anticholinesterase drugs. On this account they recommend that myasthenic patients be titrated with successive 500mg. doses of 2 PAM (or DAM) at 5-10 minute intervals until strength is restored to the maximum level attained following the administration of optimal doses of anticholinesterase compound.

In view of the importance of this claim for the treatment of the most common form of death in myasthenia gravis it must be examined with the greatest care. As I have shown above their observations are open to alternative interpretation and are in contrast to the generally expressed opinion of pharmacologists working in this field. For this reason I have thought it proper to give detailed protocols of my own experience on Case MN5095 which has been reported to the British Pharmacological Society but not previously published (Simpson, 1961a). It will be noted that there was definite evidence of reversal of cholinergic poisoning although the extent of this was not sufficient to be of great clinical value. This has been confirmed in Case MN5652.

The/

The latency was much greater than the 5-10 minutes described by Grob and Johns (1958b). Some of the trials were made with the more soluble British drug P_2S, the methane sulphonate salt of pyridine-2-aldoxime which is more rapidly absorbed from intramuscular injection (Ladell, 1958). Despite the limited number of observations the preceding report of the first use of P_2S in cholinesterase poisoning of any kind has the advantages of referring to investigations in the unique circumstances of full control of respiration and with negligible urinary excretion of the anticholinesterase. These observations confirm the claims of Grob and Johns (1958b) that oxime drugs have some effect in combating the nicotinic effects of neostigmine but differ in showing a little activity against the muscarinic effects too. These workers also suggest that 2 PAM and P_2S act with approximately the same latencies when injected intramuscularly though Gribetz et al (1960) state that pyridine-2-aldoxime methiodide (2 PAM) is too insoluble for intramuscular administration and requires relatively large quantities of fluid for intravenous use. This paper was published after the first of the above cases was treated and the preparation and administration of PAM followed the advice of Edson (1959). (The drug supplied from the Ministry of Health emergency supply depot was manufactured in Japan and carried no instructions in English). It is possible that the haemolytic action was due to the use of the drug in too concentrated form. This may also account for the abrupt hypotension which followed intravenous injection. This was also noted, in lesser degree, by Grob and Johns (1958a). Its occurrence in dogs treated with oximes for organophosphorus poisoning by Lubash et al (1960) was/

was attributed to the effects of hypoxia. This does not seem to be a satisfactory explanation for my observations. Neither haemolysis nor hypotension has occurred in my restricted experience of the use of the more soluble P_2S (five times in three patients).

The confirmation of the claim that oximes may reverse neostigmine poisoning is obviously important. Nevertheless it must be emphasised that, in my experience, the delay of 30-45 minutes and the limited nature of the beneficial action were such as to limit their clinical value. Intubation with control of respiration should never be delayed in the hope that administration of an oxime preparation will render it unnecessary. The sheet-anchor of the treatment of cholinergic poisoning is still atropine coupled with passive respiration.

CHAPTER 20.

SUMMARY AND CONCLUSIONS.

Chapter 1.

A review of the earlier writings on myasthenia gravis shows that the concept of a 'biochemical lesion' of transmission at the neuromuscular junction of skeletal muscles has dominated thinking about the nature of myasthenia gravis for the last thirty years. Prior to the discovery of the restorative effect of physostigmine and neostigmine it was accepted by many that there may sometimes be sensory or mental disturbances. An analysis of the natural history suggested to some workers that myasthenia gravis was the result of a toxin from bacterial infections which affected neuromuscular transmission and in some way disturbed the lymphatic system. Buzzard (1905) demonstrated that lymphorrhages occurred in many organs besides the skeletal muscles. From that period it has been known that the thymus gland is often enlarged in myasthenia gravis and is sometimes affected by a tumour.

A new era was started with the suggestion of the writer that myasthenia gravis was the result of an immunological disturbance of muscle and occasionally of other organs and that the thymus was an organ of the reticuloendothelial system playing a necessary part in the 'autoimmune' reaction.

Chapter 2.

A review of 488 cases shows that myasthenia gravis occurs in all races. It is more common in women but the modal age (about 20 years) is the same for both sexes. After 40 years of age an increasing proportion of cases of both sexes have a thymic tumour and these cases have a higher mortality rate.

The/

The age-distribution curve is monomodal, suggesting that myasthenia gravis is a true entity.

The onset may be insidious or sudden and the course is characterised by variability. Long term remissions occur in less than half the cases and are practically confined to the earlier years of the disease. Death from myasthenia gravis (as distinct from accidental complications) or improvement after thymectomy are most common in the first seven years. It is suggested that this period is the 'active stage' of the disease but that permanent muscular damage may continue into a 'burned-out' stage.

The initial onset and later relapses may be precipitated by emotional upsets, infections or by allergic disorders.

Chapter 3.

Myasthenic weakness is defined and its distribution studied. It is shown that certain muscles are affected more often than others and that these tend to be affected earliest in progressive cases. The extraocular, bulbar and neck muscles are most commonly affected and in the limbs it is mainly the proximal muscles. Limitation to the extraocular muscles was uncommon in the present series and it is suggested that this may be due to certain precautions taken in examination of other muscles in order to demonstrate slight degrees of myasthenic weakness.

Permanent weakness with failure to respond to neostigmine and sometimes muscular atrophy ('myasthenic myopathy') occurred in /5% of male and /0% of female cases. The incidence was much higher (/8%) in patients with a thymoma.

The tendon reflexes were usually retained and often exceptionally brisk. Absence of tendon jerks in a myasthenic syndrome/

syndrome should suggest a diagnosis of carcinomatous myasthenia.

Chapter 4.

Sensory symptoms complained of by many patients in this series and in the earlier literature are analysed. Pain and paraesthesiae could usually be attributed to the mechanical effects of muscular weakness. Intermittent deafness is attributed to eustachian block associated with pharyngeal paresis and it is suggested that low-tone deafness may be due to paralysis of the tensor tympani. Some cases of sensory disturbance can not be accounted for on a basis of muscular weakness and it is possible that sensory nerve fibres or end-organs may occasionally be involved by the disease process. Epilepsy occurs with greater frequency than would be expected and mental disorders were noted.

Chapter 5.

The literature associating myasthenia gravis with thyrotoxicosis is reviewed. It is shown from the author's material that there is a high correlation with thyroid disease but that the latter may be non-toxic goitre or myxoedema as well as thyrotoxicosis and the thyroid disease may precede, accompany, or follow the myasthenia. Simpson (1960a) drew attention to the high incidence of thyroid disease in the relatives of myasthenic patients. It is suggested that thyroid disease and myasthenia are independent results of a common genetic factor and that this might act through a hypothalamo-pituitary mechanism as there are occasional examples of disorders of other endocrine glands associated with myasthenia gravis. Diabetes mellitus may also be genetically linked to the neuromuscular disease. The effect of emotional disturbance would be compatible with a hypothalamo-pituitary mechanism and this would also account/

account for the variable effects of menstruation, pregnancy and environmental extremes.

Chapter 6.

There are no consistent biochemical disorders. Serum enzymes derived from muscle are normal and creatinuria is absent if nutrition is maintained. Endocrine function tests supplement and support the clinical conclusions of the last chapter. Attention is drawn to a high incidence of hypergammaglobulinaemia which tends to be associated with complications of an immunological type. The protein content of the cerebrospinal fluid may also be increased. The incidence of this cannot be assessed owing to inadequate data.

Chapter 7.

Disorders of other systems in the cases reviewed are classified and compared with those of other series in the literature. Simpson (1960a) showed that there was surprising agreement between some of them and this has since been supported by other authors. Although the figures are not 'statistically significant', it is clear that there is a relationship between myasthenia gravis and aplastic anaemia, pernicious anaemia (reported for the first time), reticuloendothelial disorders, systemic lupus erythematosus, acrocyanosis, 'rheumatoid' arthritis, nephritis, asthma and other allergic disorders.

It is suggested that myasthenia gravis is part of a disease process involving the reticuloendothelial system particularly the thymus, as a disorder of immunological tolerance (Appendix D). Acrocyanosis may be an indication of a poor prognosis since it tends to be associated with myositis/

myositis and 'neostigmine-resistance'.

Chapter 8.

The infant born to a myasthenic mother may have temporary 'neonatal myasthenia' even though the mother's thymus has been removed. This is considered to support the concept of a 'myasthenic toxin' which can cross the placental barrier.

Rare cases of familial incidence of myasthenia gravis are described but only one of identical twins was affected. This supports the suggestion of a genetic factor with variable expression depending partly on secondary acquired factors.

Congenital myasthenia is described and analysed. It is suggested that this is a different condition due to delayed or arrested maturation of neuromuscular junctions. An unusual case of 'benign congenital myopathy with myasthenic features' described previously by the author (Appendix β) is considered to be a variant of this type of myasthenia.

Chapter 9.

Myasthenic syndromes occur in a number of diseases including polymyositis, dermatomyositis and systemic lupus erythematosus. It is shown that these form a continuous spectrum with 'neostigmine-resistant' types of myasthenia gravis.

'Fatiguable' weakness may also occur in carcinomatous myasthenia, disorders of the lower motor neurones (including peripheral neuropathy) and in toxic and nutritional disorders. It is suggested that these have a different mechanism from true myasthenia gravis but have some resemblance with congenital myasthenia.

Ocular myopathy, congenital ptosis and 'pseudoptosis' and/

and encephalitis are among the disorders which may be mistaken for myasthenia gravis but they are entirely different in nature.

Chapter 10.

Early claims that removal of the thymus was beneficial in myasthenia gravis were later disputed. The confused position was resolved by an analysis of part of the present material and a comparison with other series (Simpson 1956a, 1958 and Appendix C). It is shown that the course of the disease is favourably influenced and the mortality reduced if the thymus is removed during the 'active stage' of the disease. The benefit is most obvious in young women but duration of illness is more important than age or sex. Removal of a thymoma less commonly alters the unfavourable prognosis associated with that condition.

Contrary views are shown to be due to failure to analyse separately the cases with and without thymic tumours and, to a lesser extent, to differences in response of each sex.

It is concluded that the thymus plays an essential role in the first 5-7 years of the disease but thereafter the disease is self-perpetuating or the other parts of the reticuloendothelial system assume greater importance.

Chapter 11.

A brief outline of the morbid anatomy shows that the purely 'biochemical' theories of myasthenia gravis have ignored the fact that there are consistent pathological changes in many tissues. It is suggested that 'lymphorrhages' and cytolytic changes in skeletal muscle are evidence of immunological damage. Supravital staining of the motor nerve/

nerve terminals and electronmicroscopy of muscle by other workers show that there is a pre- and post-junctional lesion in the majority of cases. The nerve terminals are characterised by a combination of degeneration and active regenerative sprouting.

Evidence of immunological disorders may be seen in the heart, adrenal and thyroid glands.

The thymus shows a characteristic lymphoid reaction ('germinal centres') even in the glands which show adenomatous change ('thymoma'). It is suggested (Appendix D) that this is evidence of immunological activity, though at the time of the original hypothesis (Simpson, 1960a) the function of the thymus was unknown. Some examples of splenomegaly are reported.

Chapter 12.

The normal physiology of the thymus is not fully understood. Earlier evidence is reviewed suggesting that it plays a role in growth or, more probably, maturation under the control of the pituitary gland. A possible inhibitory effect on the thyroid and adrenal has also been discussed. The author's suggestion of a role for the thymus in 'autoimmune diseases' was soon given a firmer basis by the work of Miller (1961, 1963) and of other workers. It is suggested that the immunological function may be part of a wider mechanism of protein differentiation linking the recent work with the earlier studies, and further that this is under hypothalamo-pituitary control. This could provide the homeostatic mechanism required by some current theories of immunological tolerance (Simpson, 1964d).

There is no evidence that the thymus produces a 'curare-like' substance in the conventional sense.

Chapter 13/

Chapter 13.

American workers independently reached the concept of an immunological mechanism in myasthenia gravis on observing the cytolytic effect on frog muscle of serum from some myasthenic patients. They were able to demonstrate the presence of muscle-binding complement-fixing antibodies in myasthenic sera and this has been confirmed by other workers. The author and his colleagues have not been able to obtain these results and it is now suggested that anti-muscle antibodies are only found in the blood of myasthenic patients who have a thymic tumour.

It is shown that many patients with myasthenia gravis have raised titres of antibodies against thyroid and gastric parietal cells, and antinuclear factor but do not have a positive response to the sensitised sheep-cell test even when they have a 'rheumatoid' type of arthritis.

Hashimoto's disease is described in 4 cases including one in which the clinical picture developed after removal of the thymus. It is shown that there is a clinical and serological overlap between myasthenia gravis and many diseases which are considered to be due to defective immunological tolerance.

Chapter 14.

In this chapter the evidence is summarised and the hypothesis is made that myasthenia gravis is the disorder resulting from immunological damage to the neuromuscular junctions as the result of abnormal function of the thymus gland and that this may be associated with other disorders of immunological tolerance. It is suggested that the abnormality of thymic function is genetically determined and involves a defect of hypothalamo-pituitary control which may/

may also manifest itself in the same patient or in his progenitors or siblings as endocrine disease. An immunological mechanism would account for neonatal myasthenia and yet render understandable the failure of cross-transfusion experiments.

The 'symptomatic myasthenias' may be similar in nature (polymyositis, dermatomyositis, systemic lupus erythematosus) or simply have a common disturbance of neuromuscular physiology. The immunological disorder postulated for myasthenia gravis may cause blockage of end-plate receptor sites (protein) by antibody, but could affect nerve terminals.

Chapter 15.

When a myasthenic patient maintains a postural contraction of a muscle, the electromyographic registration of summed action potentials is gradually reduced by motor units decrementing in size but also by sudden cessation of firing. Many of the motor units (in the electromyographic sense) are of 'myopathic' type and occasionally spontaneous activity may be recorded at rest. These findings indicate that in addition to a disorder of neuromuscular transmission there is often electromyographic evidence of an abnormality of muscle fibres. An intermission of a few seconds is followed by renewed activity owing to post-tetanic facilitation, and the alternation between 'fatigue' and facilitation may cause phasic contraction.

If a motor nerve is stimulated repetitively (with supramaximal stimuli) the muscular response decrements but the muscle will still respond to direct post-junctional stimulation. This is the Jolly test which demonstrates that there is transmission failure. The integrated action potential/

potential of the muscle may be used as the index of response (Harvey-Macland test). When this is done it can be seen that there is a facilitation response as well as the decrementing response. Usually this causes only temporary recovery but in some muscles fast rates of nerve stimulation cause an incrementing response. This is most striking in carcinomatous myasthenia but may also be present in myasthenia gravis. It is suggested that muscles showing the incrementing response are also resistant to the action of depolarizing drugs. When the tetanus is stopped there is a brief post-tetanic facilitation, but according to Desmedt (1957a) this is followed by prolonged 'post-activation exhaustion'.

The anatomy and normal physiology of the neuromuscular junction are described.

Chapter 16.

Possible mechanisms of neuromuscular block in myasthenia gravis are discussed. It is shown that there is evidence in favour of a pre-junctional disturbance but also evidence of post-junctional abnormality in the altered response of myasthenic muscle to depolarizing substances. The electrophysiological and pharmacological data are compatible with several of the mechanisms suggested for myasthenia gravis. A personal theory of the nature of drug action at the end-plate of muscle is discussed (Appendix D). It is suggested that a sequence of stimulation, depolarization block, refractoriness and 'competitive' block is common to all drugs acting on the end-plate, the intensity and duration of each phase depending on the density of ionic charge on the end-plate receptor sites and the kinetics of its breakdown and removal. Previous reports on the phenomena/

phenomena of drug action in myasthenia are shown to be predictable on this hypothesis and it is shown that anything which reduced the density of ionic charge at the end-plate after each nerve impulse would cause a myasthenic phenomenon.

Two possible theories are favoured, i) competitive block by a 'myasthenic toxin' and ii) transmission at regenerating neuromuscular junctions. Recent evidence on the latter (Miledi, 1960) support this possibility but it is pointed out that nothing is known about the transmission from regenerating nerve terminals to pathological muscle fibres. The concept of a balance between degeneration and regeneration of motor nerve terminals associated with myositis, described here for the first time, is supported by the pathological findings. The lesion could be of immunological origin and would account for the fluctuating course of myasthenia gravis.

The possibility of a myasthenic toxin is favoured by the evidence of neonatal myasthenia and it is pointed out that the duration of the latter is in keeping with the persistence of maternal antibodies in the blood of the newborn child. The author is unable to confirm that some muscles become weak if others are exercised in the myasthenic patient (Walker effect) and is critical of previous claims to demonstrate such an action. Cross-transfusion and experiments on isolated nerve-muscle preparations show no evidence of a curare-like substance in the serum of myasthenic patients.

It is suggested that an antibody against the protein of muscle end-plates would function as a competitive blocking substance specific to an individual or to a genetically similar infant. American evidence for the presence of a substance in myasthenic serum which causes cytolysis of frog muscle is considered/

considered to support the hypothesis. It is concluded that one of several possible immunological mechanisms is compatible with the known disturbances of neuromuscular function.

Chapter 17.

The differential diagnosis of myasthenia gravis is discussed and the use of diagnostic tests based on the disorders of neuromuscular transmission and of response to drugs acting on the end-plate region of muscle. The nature of drug action is discussed as a preliminary to later work on treatment and on 'neostigmine-resistance'.

Chapter 18.

Treatment is discussed under the main headings of a) removal, destruction or inactivation of the thymus, b) pharmacological compensation for transmission failure, c) general management.

Thymectomy is advised for all patients, irrespective of sex, if the duration of illness from myasthenia is less than six years, the weakness is not confined to the extraocular muscles, and the patient is under 40 years of age (Appendix C). When these indications do not apply thymectomy is still advised in cases progressing despite treatment with drugs and in all patients with thymic tumour.

Radiotherapy is not a suitable substitute for thymectomy by a skilled thoracic surgeon and may be dangerous. It is doubtful whether its use before operation for thymoma is of value. Denervation of the carotid sinus is discussed without personal experience. It is not recommended on the grounds that it is an inferior method of suppressing the function of the thymus. The same objection is/

is made to the use of adrenocorticotrophin, antireticular cytotoxic serum and plasma dialysis.

The anticholinesterase drugs are reviewed. It is considered that the search for long-acting preparations is misguided since all those available are cumulative, giving rise to overdose effects. Neostigmine and pyridostigmine are satisfactory for routine use, the latter being the best for smoothness of control but neostigmine is valuable where an extra 'boost' is required.

Corticosteroids, potassium, ephedrine and guanidine have occasional value as adjuvant forms of therapy but the author does not recommend the use of d-tubocurarine to 'rest the end-plates' in cases of apparent 'neostigmine-resistance'. The latter phenomenon is discussed and considered to be due to overdosage with anticholinesterase compounds.

In general management the avoidance of certain drugs with neuromuscular blocking effect is advised and a warning given of the danger of administration of an enema to a myasthenic patient. The general management of the patient's life is discussed.

Chapter 19.

The causes of death in myasthenic patients are discussed. These are i) unrelated causes, ii) asphyxiation by foreign-bodies or saliva, iii) myasthenic paralysis of respiration, iv) cholinergic paralysis of respiration.

It is shown that the risk of asphyxiation by inhaled material may persist even in the 'burned out' stage of the disease but that the other types of respiratory failure (mainly inspiratory) are more probable during the 'active stage'. The diagnosis and management of each is discussed and it is suggested that 'cholinergic crisis' is a more common cause/

cause of death than 'myasthenic crisis' though rarely recognised as such.

Personal studies on the cholinergic state are reported, laying emphasis on the fact that different muscles may be in a different state as judged by the response to stimulation or to edrophonium. It is shown that some muscles may be overdosed while others still show a myasthenic type of weakness. Precautions to be taken while testing with edrophonium are described in the light of these findings.

The first British report on the use of oxime drugs for the treatment of overdosage with quaternary ammonium anticholinesterase substances is presented. It is concluded that the action of drugs at present available is too slow and too limited to be of practical value. The importance of giving sufficient atropine to suppress muscarinic effects and to limit blockage of central synapses is emphasised and stress is laid on the necessity to ensure pulmonary ventilation at an early stage. A tentative trial of d-tubocurarine as an antidote to cholinergic poisoning is described.

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MYASTHENIA GRAVIS.

VOLUME 2

Figures, Tables, Appendices.

by

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MYASTHENIA GRAVIS.

Vol. 2.

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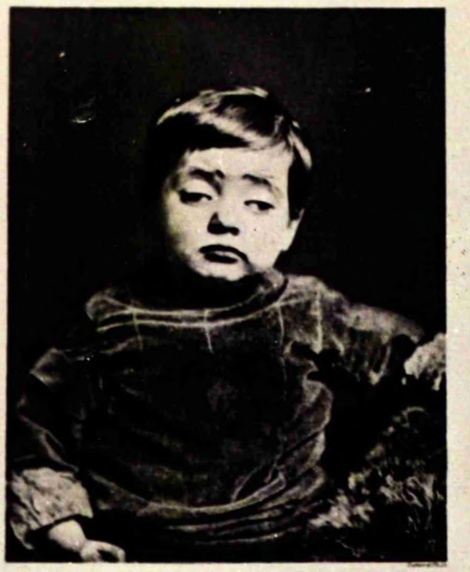
Fig. 1.1. A child with remittent ophthalmoplegia described by Byrom Bramwell (1892) in Volume 3 of his 'Atlas of Clinical Medicine'. The aetiology was uncertain and it was attributed to syphilis. The bilateral ptosis and drooping of the mouth suggest that this was an unrecognised case of myasthenia gravis (Simpson, 1960a).



OPHTHALMOPLEGIA EXTERNA

(BEFORE TREATMENT)

OPHTHALMOPLEGIA EXTERNA

(AFTER RECOVERY)

TABLE 2. 1.

Age at onset of myasthenic symptoms (488 cases).

Age. Years.	Non-tumour.		Thymoma.	
	Female.	Male.	Female.	Male.
0 - 5	7	1	-	-
6 - 10	6	2	-	-
11 - 15	35	6	-	-
16 - 20	49	25	1	-
21 - 25	58	19	2	-
26 - 30	43	17	2	3
31 - 35	26	15	3	3
36 - 40	24	14	5	2
41 - 45	12	8	6	5
46 - 50	10	11	5	3
51 - 55	8	8	2	-
56 - 60	5	4	2	1
61 - 65	4	4	2	-
66 - 70	2	2	-	-
71 - 75	1	3	-	-
76 - 8	2	-	-	-
Unknown	7	2	-	2
Total	299	141	29	19
Over 40	44(14.7%)	40(28.3%)	17(58.6%)	9 (47.4%)
Modal age	22 yrs.	17 yrs.	45 yrs.	44 yrs.
Mean age	27 yrs.	33 yrs.	42 yrs.	39 yrs.

Fig. 2, 1. Distribution of age at first myasthenic symptom. The ordinate is calibrated in number of cases and as percentage of the total number.

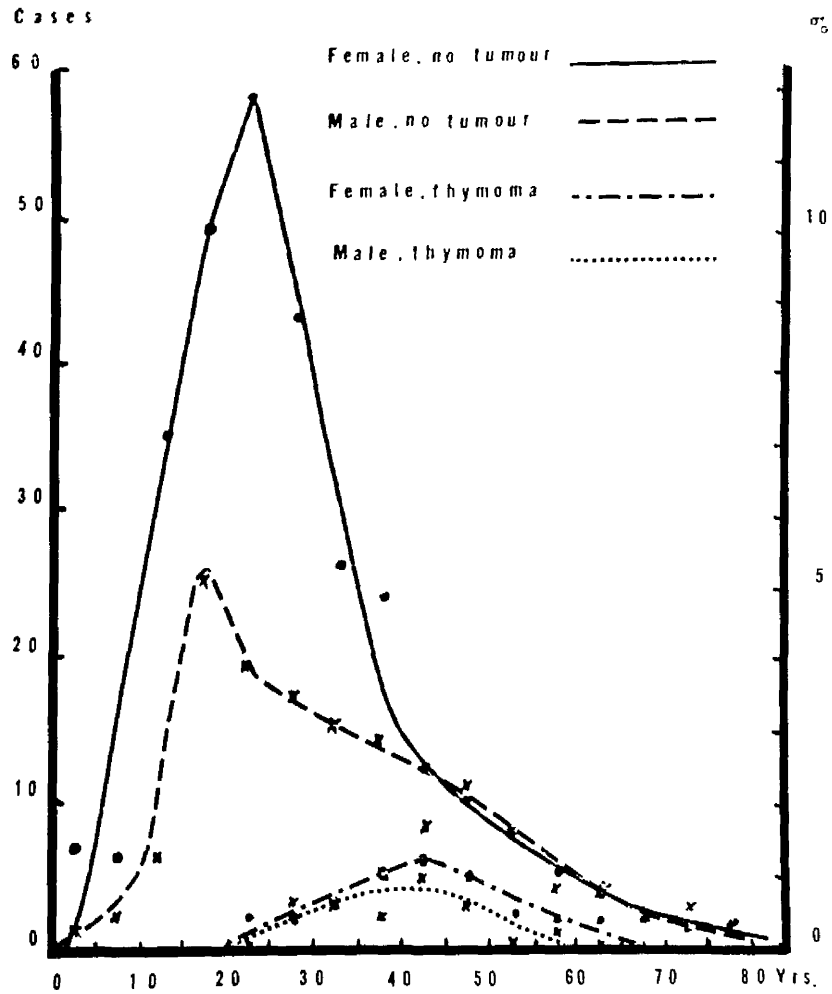

Cases
%
60
50
40
30
20
10
0
10
5
0
Female, no tumour
Male, no tumour
Female, thymoma
Male, thymoma
0
10
20
30
40
50
60
70
80 Yrs.

Table 2,2.

Duration of myasthenic symptoms before death. Non-tumour.
(Excludes deaths within one month of thymectomy and deaths due to unrelated causes).

Not Operated.				Operated.			
Females.		Males.		Females.		Males.	
Case	Years	Case	Years	Case	Years	Case	Years
NH/D-B/JH	1 3/12	NH/GH/AH	3/12	GK/JB	3	GK/AC	3
NH/D-B/MT	1 7/12	NH/GH/AP	10	GK/LB	3	GK/CG	20
NH/EC/GB	3	NH/HE/HC	6	GK/EC	7	GK/RW	3 4/12
NH/EC/AH	8	NH/PM/JK	7	GK/MC	12	NH/EC/CP	1
NH/EC/DH	4 6/12	NH/FW/CF	6	GK/MG	5	NH 9474	3
NH/EC/SW	14	NH 42789	2	GK/SK	8 6/12	NH 18338	3
NH/GH/JH	5	NH 44239	6/12	GK/ML	8	NH 26385	1
NH/PS/WM	2	MN 6780	1	GK/AM	6	NH 31378	2
NH/CS/AR	4	MN 7782	5	GK/JP	1	NH 32217	23
NH/FW/MD	10	MN 7783	6/12	GK/CR	2	MN 6807	2
NH 3533	18			GK/GW	5		
NH 11563	13			NH/EC/IH	13		
NH 13612	4			NH/EC/FL	5		
NH 19815	1 5/12			NH 3279	1 4/12		
NH 42337	8/12			NH 6753	7 6/12		
NH 45067	6/12			NH 12374	26		
NH 57049	10/12			MN 336	8		
MN 5401	1			MN 2327	2		
MN 5503	2 6/12			MN 3231	15		
MN 7788	3/12						
MN 8279	1						
Mean duration.	5		4		7		6

Table 2.3.

Duration of myasthenia before death (excluding post-operative and other causes of death) - Thymoma.

Females.		Males.	
Case	Years	Case	Years
GK/AC	1/12	GK/RA	10/12
GK/DC	3/12	GK/VB	3 7/12
GK/EC	3	GK/GC	2
GK/GD	9	GK/GP	7/12
GK/BG	4 6/12	GK/HS	5/12
GK/ES	15	GK/AW	1 6/12
GK/AT	2	GK/FW	2
GK/NT	3	NH/GH/JM	1
GK/DW	7/12	NH 5232	10
GK/EW	3	NH 17834	5 6/12
NH/EC/ET	11	MN 5095	12
NH/GH/MV	6/12	MN 6476	2 3/12
NH 10884	14		
NH 11406	5		
NH 40934	4		
NH 47064	8/12		
NH 48570	1		
MN 2257	7		
MN 4906	4/12		
MN 7784	1		
Mean duration.	4		3

Fig. 2, 2.

a) Case MN 5625. Presentation as recurrent paralysis on either side of the face. She is attempting to show her teeth.

b) Case MN 6289. Presentation as a case of 'ocular myopathy'. He is unable to retract his lips to show his teeth.

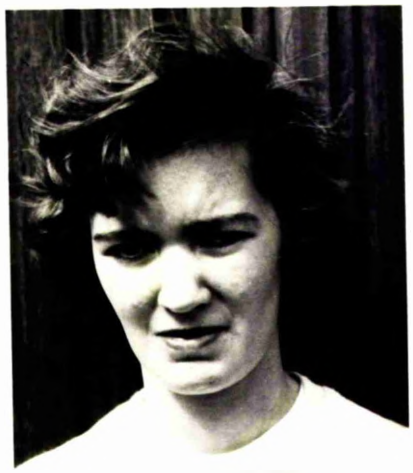


Fig. 2, 3. Prominent supraorbital pads.

a) Case MN 4656. History suggested that she may have had mild thyrotoxicosis in the past but she was euthyroid when she became myasthenic though her eyes were slightly proptosed.

b) Case MN 3054. Note prominent supraorbital pads. No previous history of thyroid disease but she developed goitre with minimal toxic symptoms one year later.

See also Figs. 3, 2; 3, 7; and 5, 2.

Fig. 2, 4.

Case MN 5652. Induction of ptosis by fixing the gaze above head level for one minute.

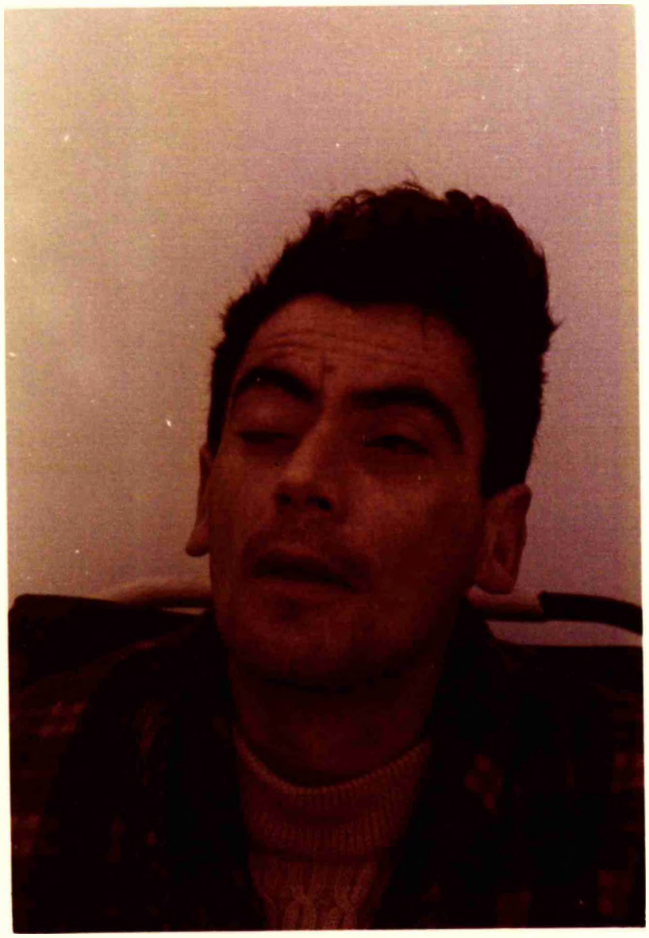


Fig. 3, 1. Electromyograph recorded from the right deltoid muscle by a co-axial needle electrode. The arm was held out until the posture could no longer be maintained. The records read continuously. Note the development of hypersynchrony and tremor leading to brief pauses of successively longer duration until further contraction is impossible. Each pause is followed by brief post-tetanic potentiation. The pattern reduces in amplitude but the units firing at the end of the contraction apparently stop firing suddenly, without decrement in amplitude.

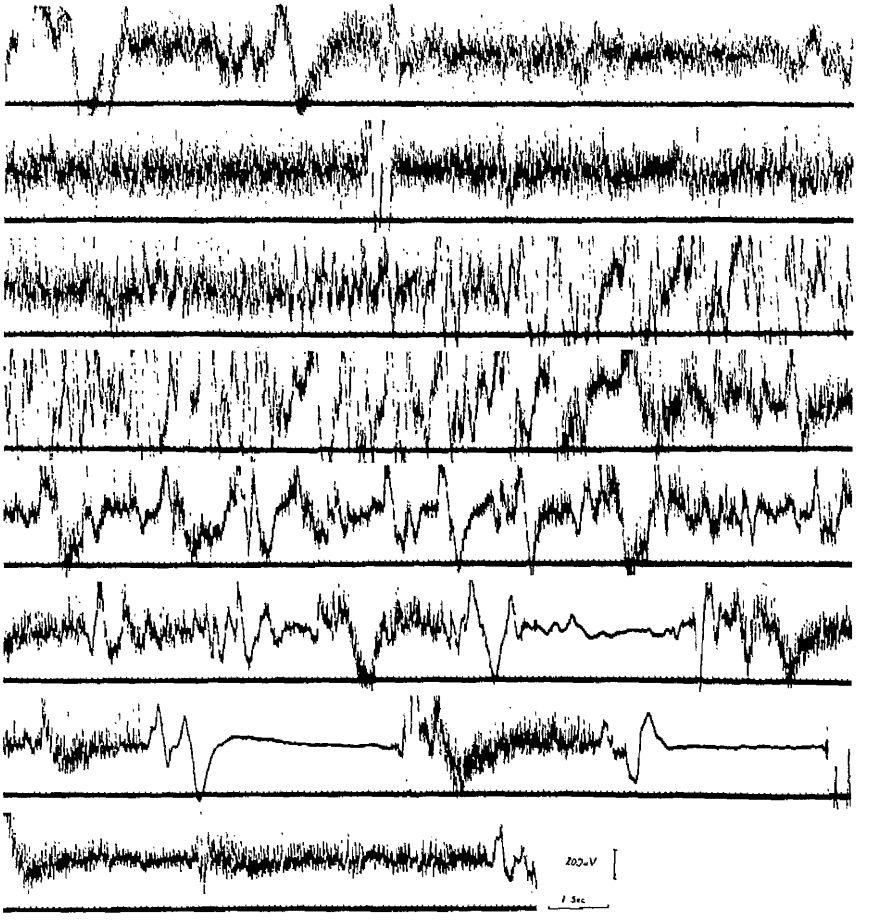
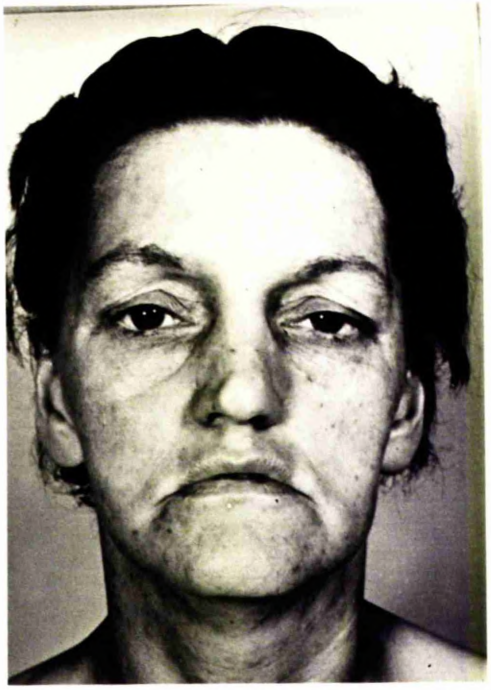
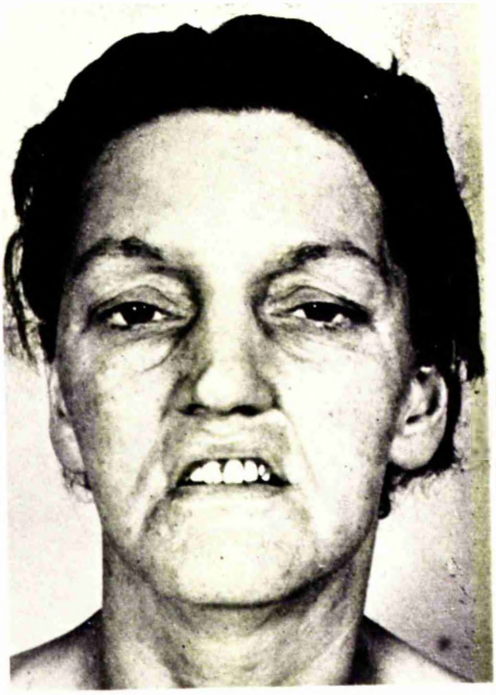

200μV
1 Sec

Fig. 3, 2.

Case MN 1906. Facial expression at rest shows slight ptosis and drooping of the corners of the mouth. On showing the teeth the lips are not retracted but the elevators cause a typical 'snarl'. Note the prominent supraorbital pads. There was no history of thyroid disorder.

Her tongue shows the 'triple grooved' appearance.





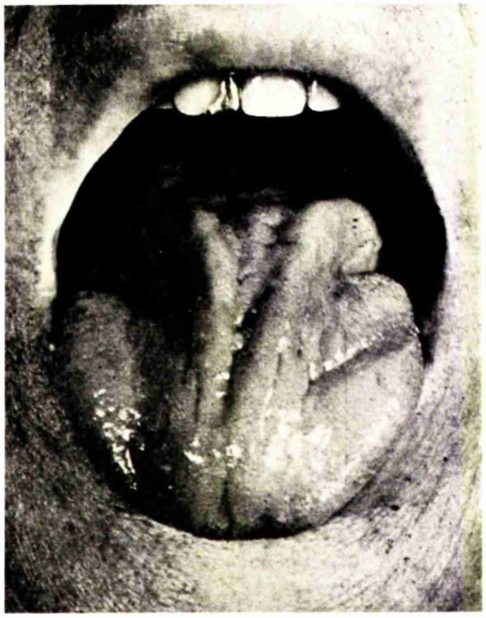
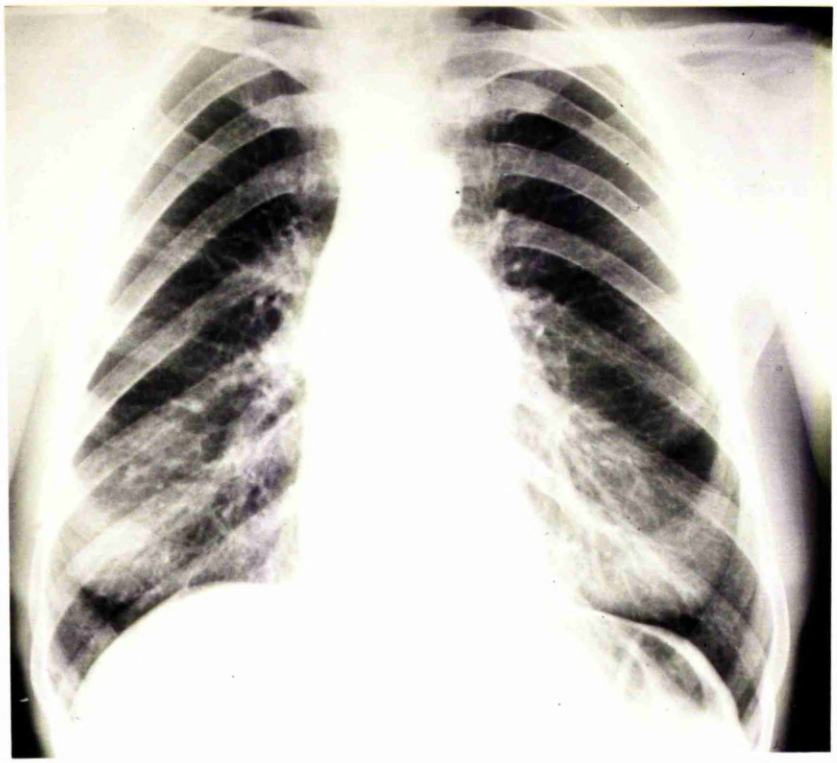


Fig. 3, 3a.

Case MN 6522. Chest radiograph to show shadow of a thymoma in the anterior mediastinum. Confirmed by operation and histological examination.



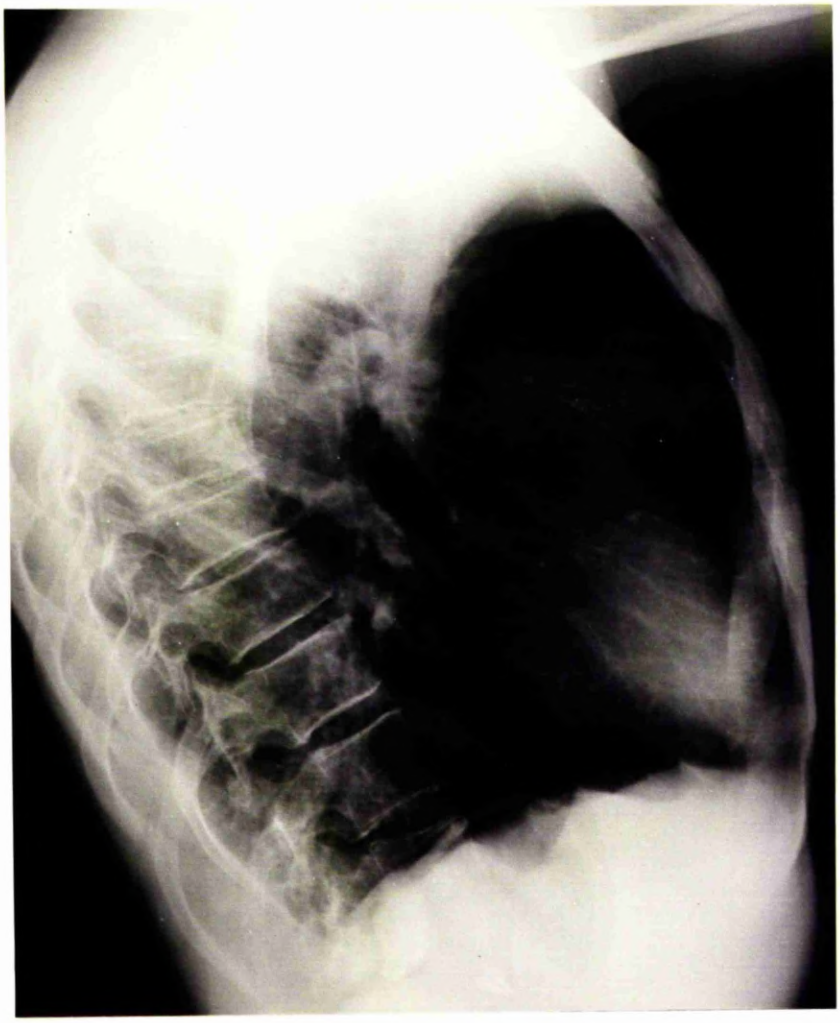


Fig. 3, 3b.

Case MN 6476. Radiograph of a large thymoma. In addition to myasthenia gravis he had asthma which persisted after thymectomy.

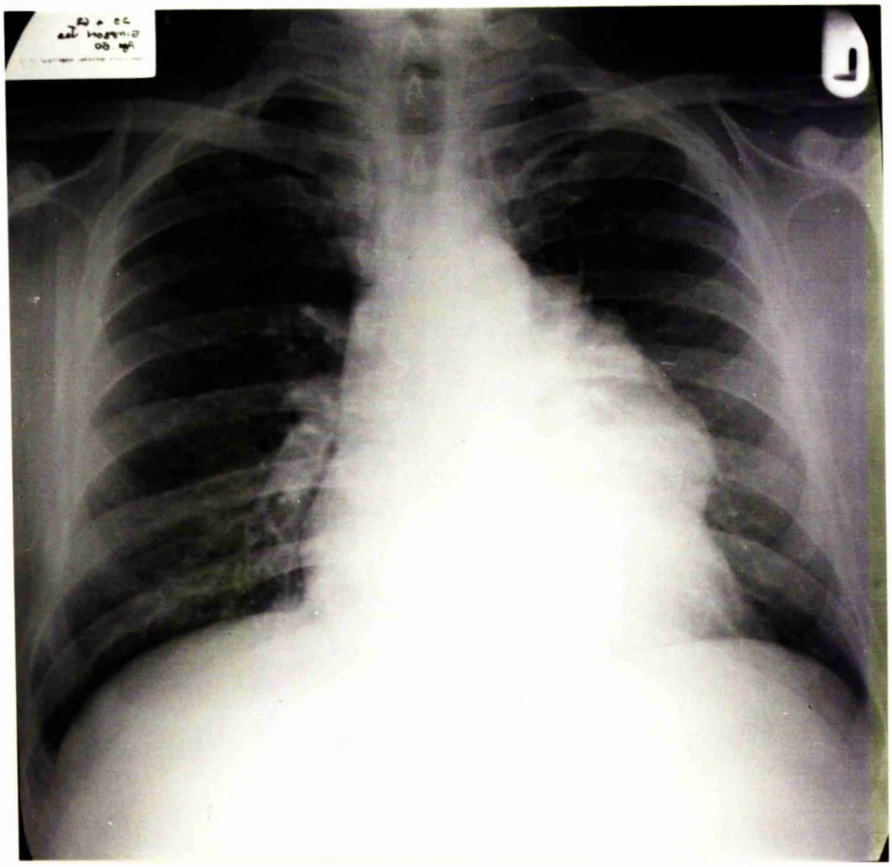

L

Fig. 3, 4.

a) Case MN 8170. Typical myasthenia gravis. Pneumomediastinum radiography demonstrates a rounded mass near the lower pole of the left lobe of the thymus gland. (Dr. M.D. Sumerling).

b) The thymus removed at operation. The rounded mass proved to be cystic, containing brownish-yellow fluid. No neoplastic changes were detected. (Dr. A.F.J. Maloney).

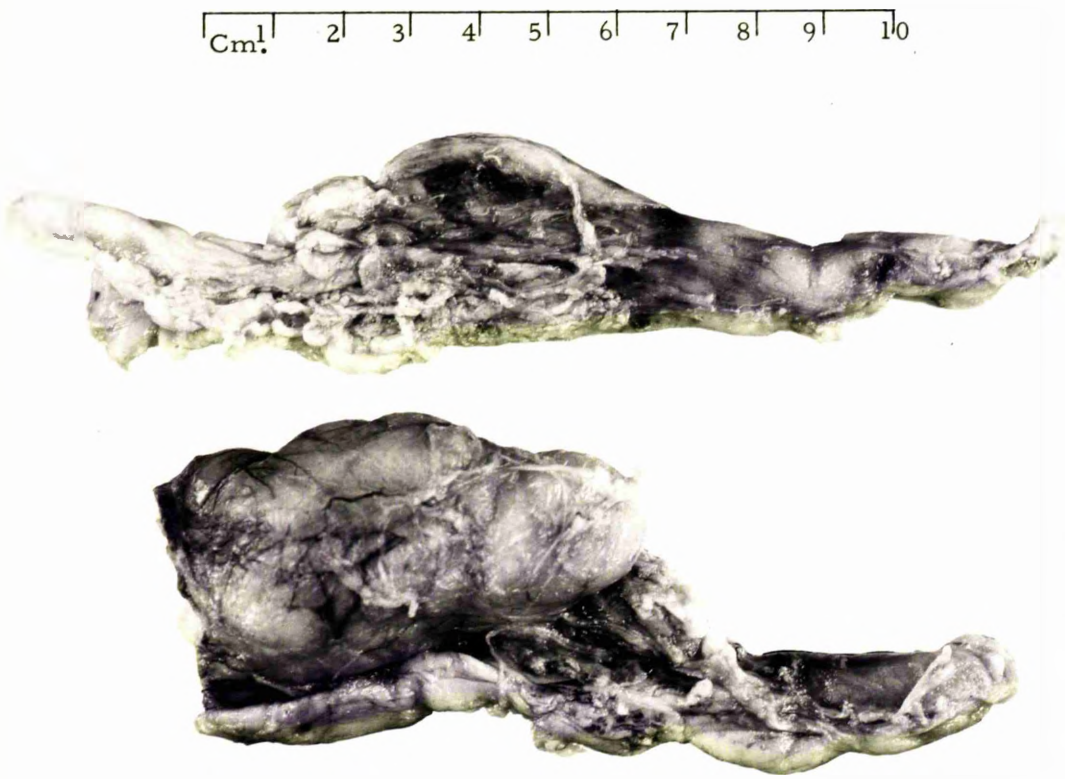

Cm. 1 2 3 4 5 6 7 8 9 10

Fig. 3, 5. Frequency of involvement of different muscle groups. The scale on the left of the key shows the frequency with which these groups are affected at the onset of myasthenia gravis. The scale on the right of the key shows the frequency with which they are affected at some time during the whole illness.

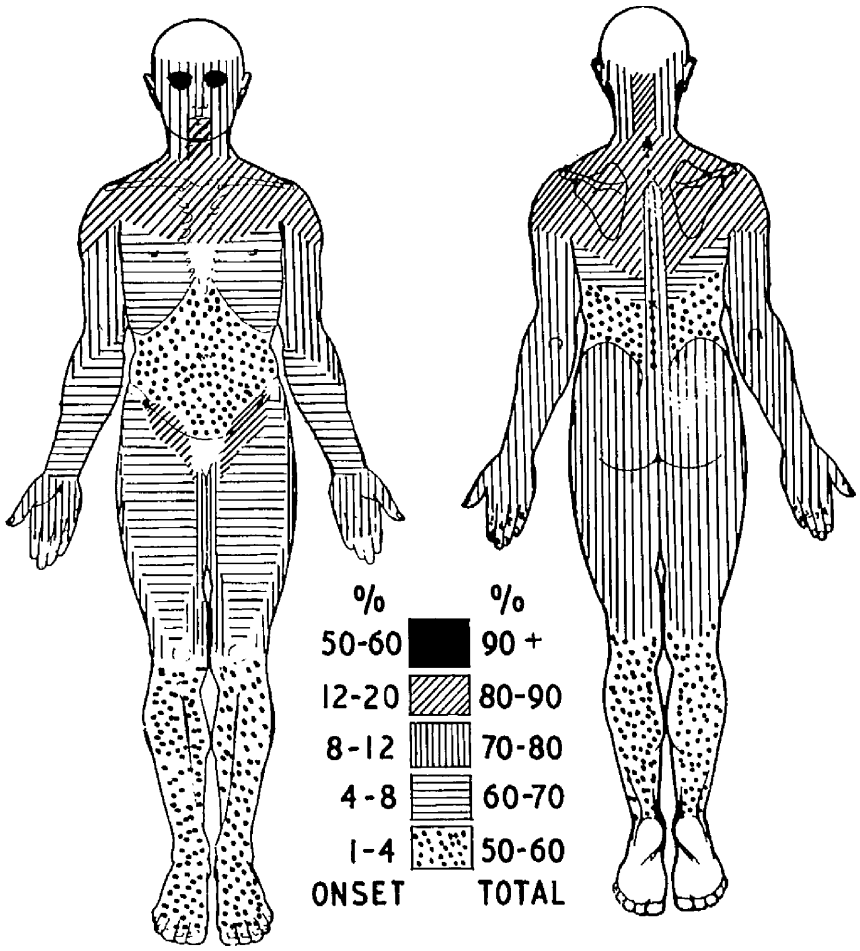

%
50-60
12-20
8-12
4-8
1-4
ONSET
%
90 +
80-90
70-80
60-70
50-60
TOTAL

Fig. 3, 6. Myasthenic ptosis.

a) Case MN 4603. Bilateral but asymmetrical ptosis.

b) Case MN 4585. Bilateral ptosis associated with weakness of orbicularis oculi causing epiphora.

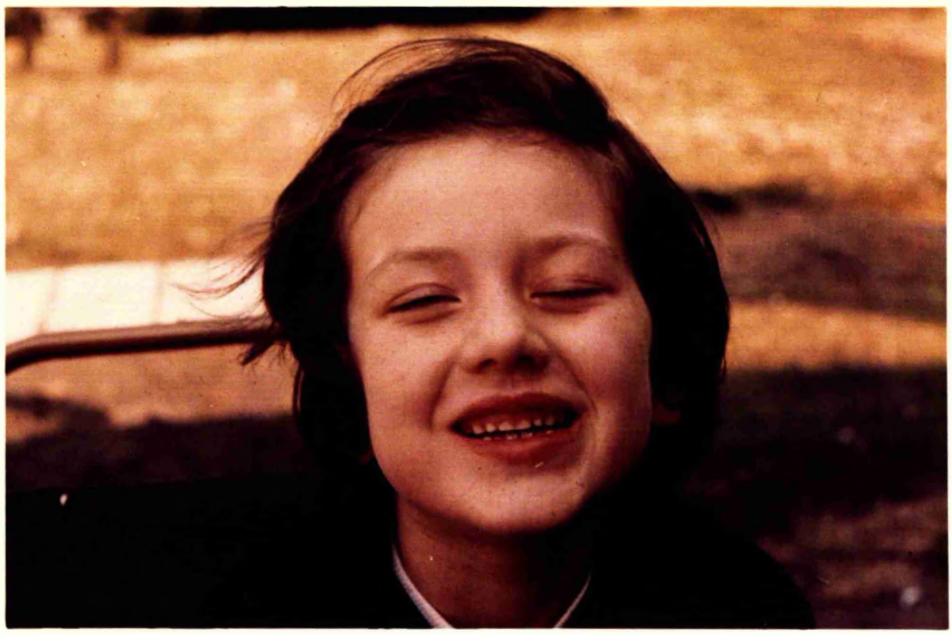


Fig. 3, 6.

c) Case MN 5766. Left ptosis with bilateral facial weakness.

d) Case MN 6780. Bilateral ptosis.

See also Fig. 8, 2 for unilateral ptosis.

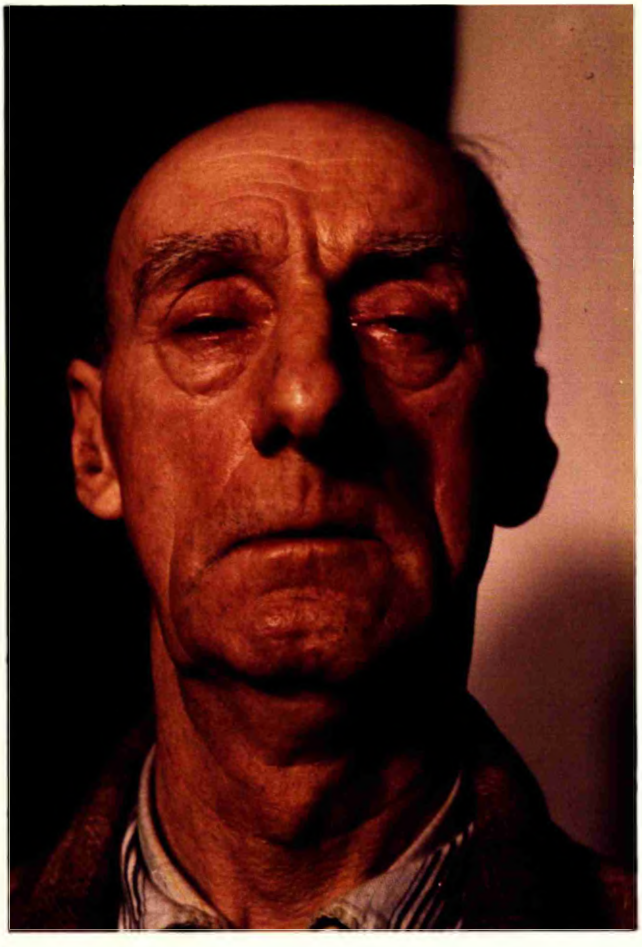
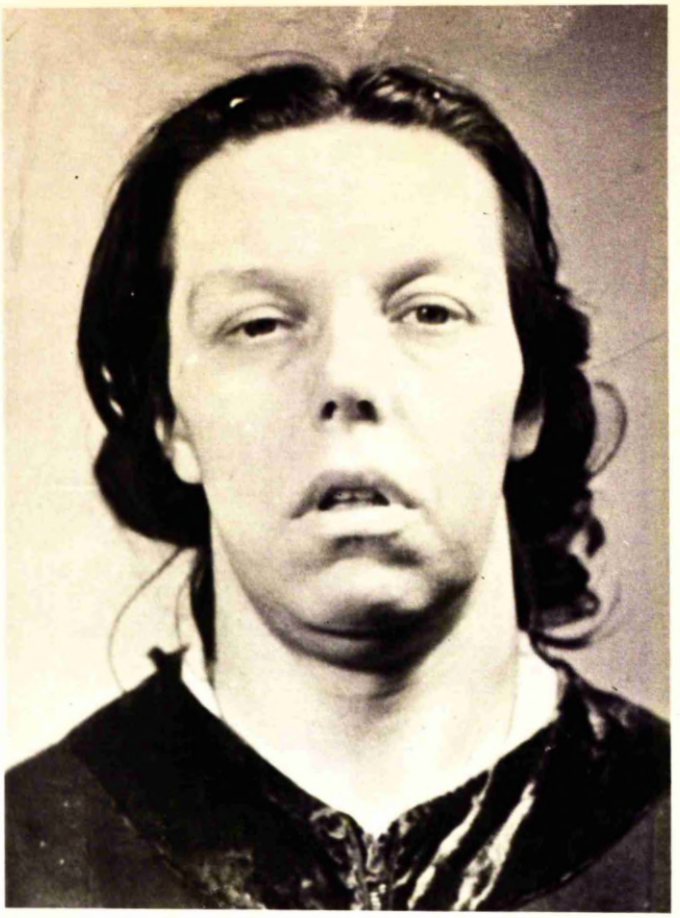
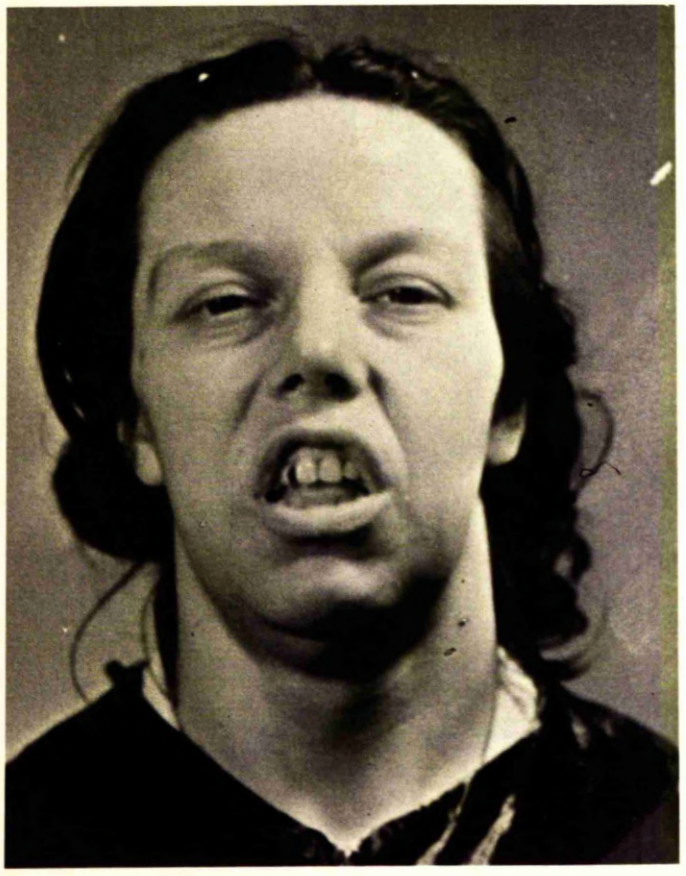


Fig. 3, 7.

Case MN 7779. Myasthenic facies in a middle-aged woman.

a) at rest
b) attempting to show her teeth
c) the same twenty minutes after subcutaneous injection of neostigmine.





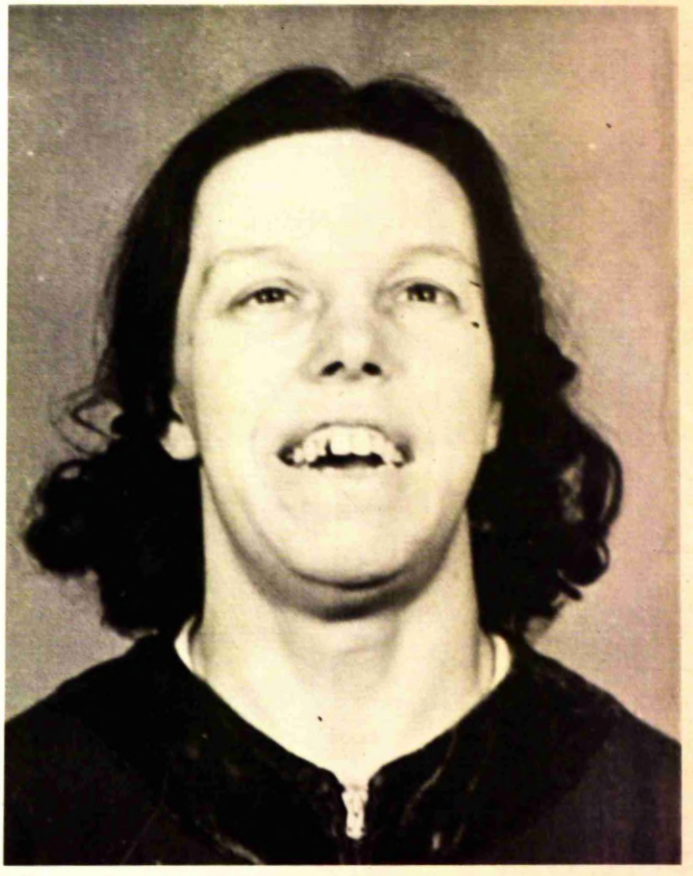


Fig. 3, 7.

d) Typical myasthenic facies at the characteristic age of onset. Note the bilateral ptosis, divergent strabismus and absence of facial expression.

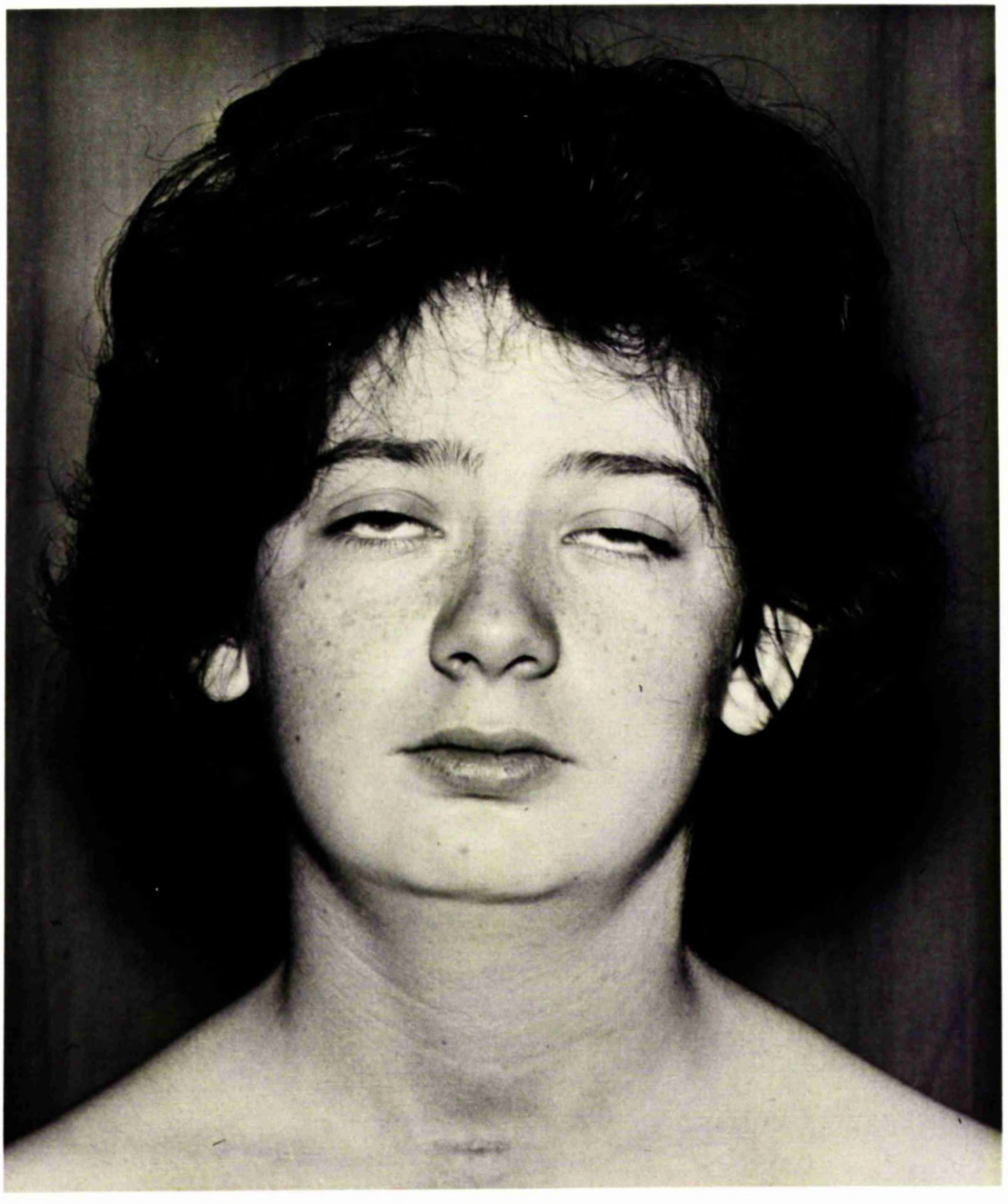


Fig. 4, 1.

Case MN 3126. Positive Harvey-Masland test in a patient with sensorimotor and reflex changes suggestive of peripheral neuritis. The later history was compatible with myasthenia gravis.

P. L. Post-Peripheral Neuritis Myasthenia

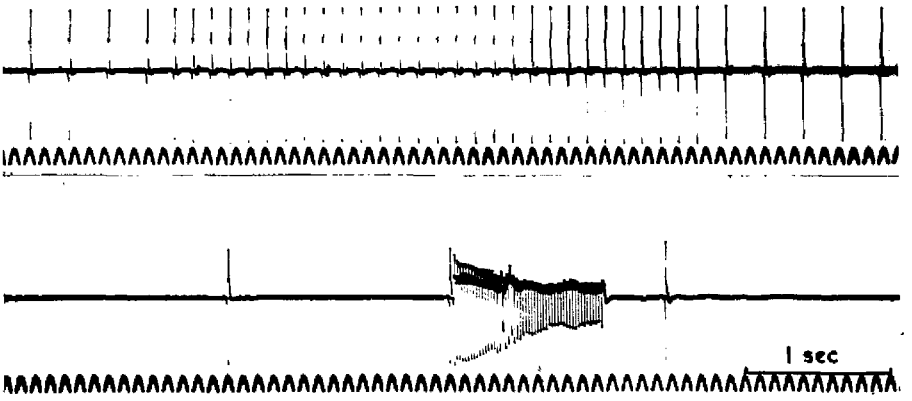


Fig. 4, 2.

Case MN 5095. Myasthenia gravis associated with a thymic tumour. He had sensory symptoms including temporary disturbance of taste sense. The illustration shows that the mucous membrane of the tongue was atrophic. He later developed megaloblastic and haemolytic anaemia.

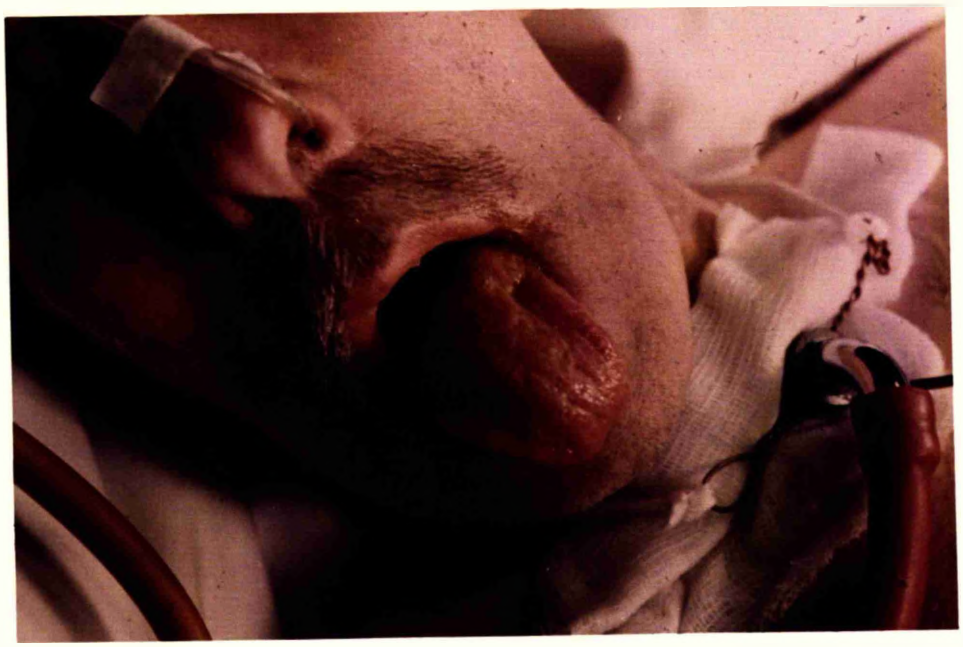
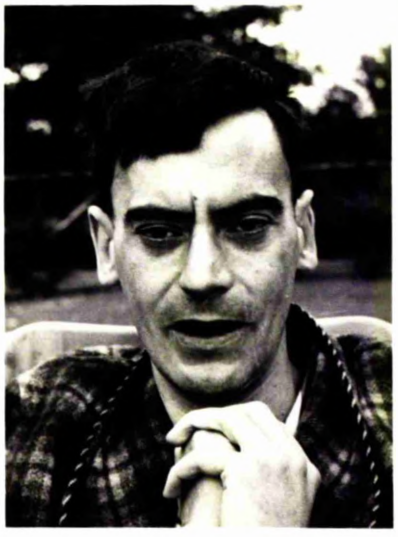


Fig. 5, 1.

Case MN 5652. Thyrotoxicosis in youth. Now euthyroid but exophthalmos is still present.



GK/DB		+		NH 31572		+	
				NH 36167	+		
				NE 39367		+	
GK/EC			+	NH 44225		?	
				NH 46967		+	
				NH 48570	+		
GK/DJ	+			NH 54016	+		
GK/CMcR	L⊕			NH 54248	+		
GK/AM	+			NH 61127	+		
GK/RP	+			NH 61423		+	
GK/LR	+			NH 61463	+		
GK/IES	myx.						
GK/JT	+						
GK/ET	+			NH 61495		+	
GK/MV	+			NH 61506			T.G.G. ⊗
NH/FW/MB	?			NH 62022		+	
NH/GH/AB		+		NH 62026		+	
NH/EC/GR	+			NH 62040			+
NH/DB/RC		+		NH 62049	+		
NH/EC/MC		+		MN 1906			+
NH/EC/EC	+			MN 2257	L⊕		
NH/FW/MD		+		MN 2327	L⊕		
NH/EC/FL		+		MN 3054		+	
NH/EC/PS		+		MN 3609			?
NH 537		+		MN 4536		?	
NH 3279		+		MN 4636			+
NH 4750	+			MN 4649		+	
NH 5658	+						
NH 5660	+			MN 4656			?
NH 7583	+			MN 4934		+	
NH 8191			+				
NH 12172		+		MN 5503	L⊕		
NH 12374			+	MN 5625	+		
NH 20233		+					
NH 21451	+						
MN 7543		+					
MN 7781		+					
MN 7855	+						
63	29	25	9				
(21%)	(9.7%)	(8.3%)	(3%)				

L⊕ = Lymphadenoid gland.

⊗ = T.G.G. = Thyroglossal cyst.

Table 5,2.

Clinical or autopsy abnormalities of thyroid gland.

Non-tumour cases (Male) (141).

Case.	Non-toxic goitre.	Thyrotoxicosis.	F.H. of goitre.
GK/WB		+	
GK/CC	+	+	
GK/SC	+		
GK/SJ	+		
NH/PM/AB		+	
NH/EC/WC		+	
NH/EC/VJ	+		
NH/GH/AP	+		
NH 5233		+	
NH 11102	+		
NH 61462		+	
MN 5652		+	
MN 7390	H(†)		
13	6	7	0
(9.2%)	(4.2%)	(5%)	

(†) Hashimoto's disease.

Table. 5.3.

Clinical or autopsy abnormalities of thyroid gland.

Cases with Thymoma.

Females (29).				Males (19).			
Case	Non-toxic goitre.	Thyrotoxicosis	P.H. of goitre.	Case	Non-toxic goitre.	Thyrotoxicosis	P.H. of goitre.
GK/CD		+		GK/GS			+
GK/BG	+			GK/FW	+		
GK/FG	+			MN 6476	? myx.		
GK/AT	+						
NH 11406		+					
NH 40934	+						
MN 2257	L (†)						
7	5	2	0	3	2	0	1
(24%)	(17%)	(7%)		(15.5%)	(10.5%)		(5%)

(†) L = Lymphadenoid gland.

Fig. 5, 2.

Case MN 4636. Thyrotoxicosis in earlier life but now euthyroid. Note supraorbital pads. Myasthenia gravis is now complicated by episodes of sudden loss of consciousness.

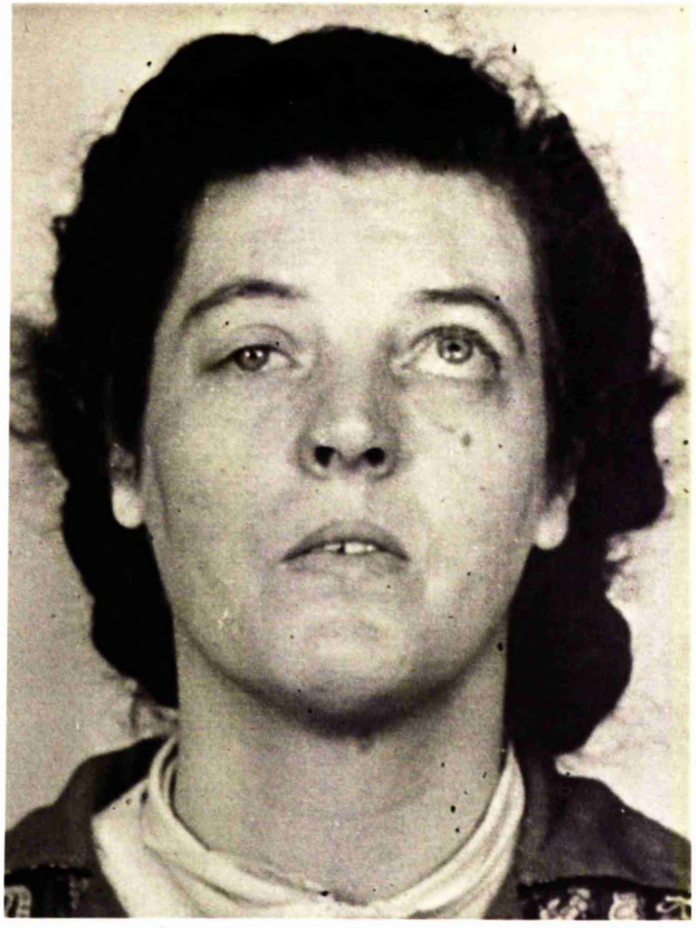
Fig. 5, 3.

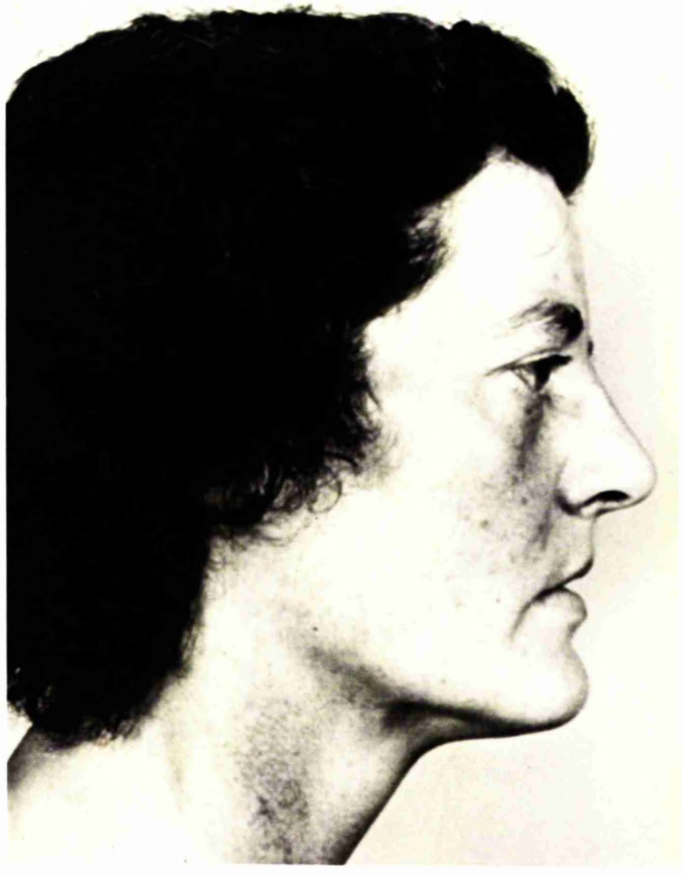
Case MN 4934. Thyrotoxicosis had been suspected years previously but not confirmed by investigation. When she developed myasthenia gravis she was euthyroid but had a slight goitre (a). Six months later, after thymectomy, the goitre was larger (b), and in another few months she had become thyrotoxic (c). She has had a remission of myasthenia since one year after thymectomy but requires carbimazole for thyrotoxicosis.

Fig. 5, 4.

Case MN 7781.

a) 1955. Myasthenia gravis. Normal thyroid function.
b) 1963. Thyrotoxicosis. Myasthenia gravis in remission but still has paresis of elevation of right eye.





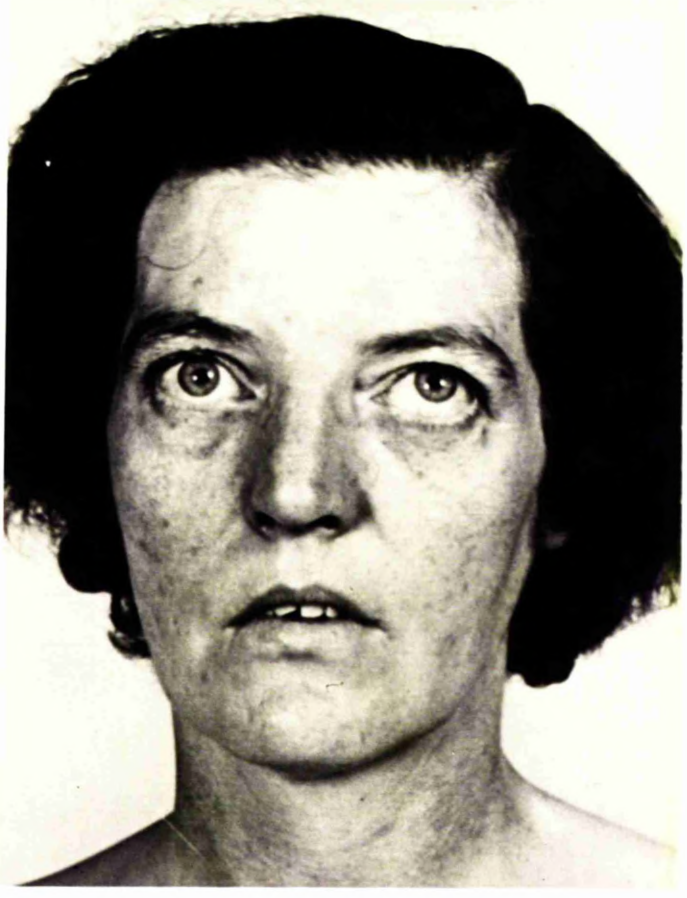


Table 5.4.

Family history of thyroid disorder.

Females.				Males.			
Case	Relation	Paternal/ Maternal	Disorder	Case	Relation	Paternal/ Maternal	Disorder
GK/MB	Mother	M	'Goitre'	NH 4648	Twin sister		Thyrotoxicosis
GK/CH	Mother	M	Thyrotoxicosis	NH 5786	Mother	M	Thyrotoxicosis
GK/NT	Sister •		'Goitre'	NH 61500	Cousin (♀)	P (?)	Thyrotoxicosis
NH 3279	Sister		Thyrotoxicosis	MN 6780	Daughter		Thyrotoxicosis
NH 61423	Sister		Thyrotoxicosis				
NH 61465	Sister		'Goitre'				
MN 3609	Father's aunt	P	'Goitre'				
MN 4536	Aunt	M	'Goitre'				
MN 4603	Grandmother	P	'Goitre'				
MN 4611	Aunt	P	Thyrotoxicosis				
MN 4650	Niece		Thyrotoxicosis				
MN 4656	Cousin (♀)	P	Thyrotoxicosis				
MN 5315	Uncle	M	'Goitre'				
MN 6481	Sister		'Goitre'				
MN 6998	Cousin (♀)	M	Thyrotoxicosis				
MN 7543	Aunt	M	Myxoedema				
MN 8092	Mother	M	Exophthalmic				
17 of 328 females (5%) *				4 of 160 males (2.5%) *			

* - Minimal incidence; family history not specifically enquired for in first 500 cases.

• - Thymoma.

TABLE 5. 5.

Effect of pregnancy on myasthenic status.

	1st trimester	2nd trimester	3rd trimester	post-partum 0-3 months.	post-partu 3-6 months
				MN 5683	
				MN 3451	
				NH 62039 (x2)	
				NH 62026 (x3)	
				NH 62025	
				NH 61494	
				NH 37065	
	MN 7587			NH 20233 (b)	
	MN 4186 (b)			NH 19400	
	NH 61430			NH 10829	
	NH 61127 (a)			NH 9175	
npne	NH 45067			NH 8191	
	NH 12172			NH 5343 (a)	
	NH 8191			NH 4388	
	NH 5556			NH 4384	
	NH 4749	MN 4636 abort.		NH/HH/CB	
	NH/PM/IM (a)	NH 39637 (a)		NH/EC/EC	
	GK/EA	NH 33942		NH/PM/IM (b)	MN 7779
	GK/CC	NH 16187 (b)		NH/GH/IR	NH 61498
	GK/SE	NH 4388 (a)	MN 3912	GK/LB (b)	NH 46967
	GK/CH	GK/LB (b)	NH 61127 (b)	GK/PB	NH 5343 (b,c)
	GK/EH	GK/PB	NH 20233 (a)	GK/SE	GK/LB (a)
	GK/LN	GK/DJ	GK/LR	GK/AM	GK/MG
	GK/SR (x3)	GK/MM abort.	GK/ST	GK/NP	GK/AW
	NH 4384	GK/CC abort.	GK/PB	NH 33942	
		GK/JD			
	NH 20233	GK/AM	GK/MM (b)		
		GK/FN			
	MN 32170	GK/AW	NH/EC/EC		
	NH 61494	NH/D-B/AH	NH/PM/IM (a) abort.		
	NH 62025	NH/GH/IR (x3)			
t		NH 2927			
		NH 4388 (b)			
		NH 5343 (x3)			
		NH 5433			
		NH 5556 abort.			
		NH 8191			
		NH 16187			
		NH 19400			
		NH 26672			
		NH 37065 (x2)			
		NH 39637 (b)			
		NH 45067abort.			
		NH 61465			
		NH 62022			
		NH 62026			
		MN 4186 (a)			

Table 6,1.

Serum Enzymes.

	Glutamic oxalacetic transaminase Units/ml. (1)	Glutamic pyruvic transaminase Units/ml. (1)	Creatine phospho-kinase Units/ml. (2)	Aldolase Units/ml. (3)
Normal	8-40	5-35	0-1.5	3-8
Cases				
MN 269		0		
MN 4301	22		0.5	6
MN 5095	14			
MN 5409		8		
MN 5503			0.6	11
MN 5652		27	1.8	0
MN 6476	14	8		
MN 6481	64†			
MN 6522		6		
MN 6807	3-40	14		
MN 7345		34		
MN 7550	4	0	0.2	9
MN 7587		5		76 ⊛
MN 7720	17	8	0.8	4
MN 7855	37	15		
MN 8088		19-26		12.5
MN 8092	37			
MN 8170	32	14	4.0	15-20

(1) Sigma Frankel units.
(2) Wróblenski units.
(3) Sibley Lehninger units.
(+) Estimated during hepatitis.
⊛ Unexplained, probably artefact.

Table 6,2.

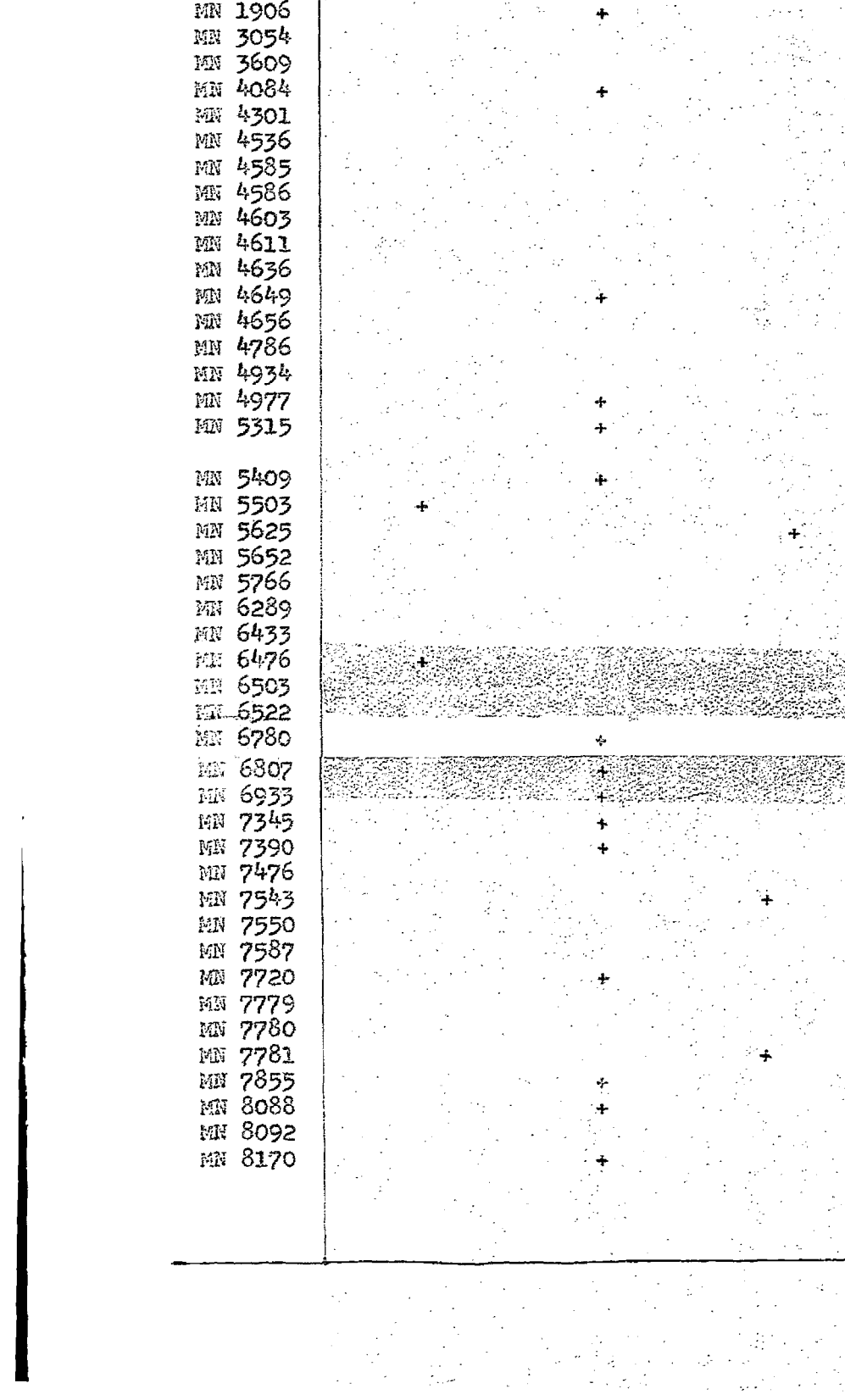
PLASMA PROTEINS.

CASE	TOTAL PROTEIN g/100g.plasma	ALB. g/100g.	GLOBULINS g/100g. α^1	α^2	β	γ	CEPH. CHOL. FLOCC.	THYMOL TURBIDITY	E.S.R. mm.1stHr.	ASSOC. DISORDERS
MN 294	6.75	3.5	0.15	0.6	0.8	1.7		5	18	'Rheumatoid' Arthritis
MN 2143	7.9	4.5	0.2	0.6	0.95	1.65	+(1)	5	15	
MN 2257	6.9	3.4	0.5	0.7	1.0	1.3			3	Thymoma; Hashimoto's D
MN 2327	8.4	4.0	0.4	1.1	0.9	2.0			28	Hashimoto's Disease.
MN 3054	7.0	5.1	0.2	0.3	0.65	0.75			15	Non-toxic goitre.
MN 3451	6.75	3.85	0.25	0.5	0.7	1.5				
MN 4084	6.5						-	2	20	
MN 4301	6.75	4.2			2.55		-	3-6	6	
MN 4536	6.75	4.8	0.4	0.4	0.1	1.05			2	
MN 4585	8.25	6.1	0.3	0.5	0.55	0.8			3	
MN 4586	7.75	6.0	0.3	0.4	0.45	0.6			10	
MN 4603	7.25	4.4	0.3	0.5	1.0	1.05	+(3)	4	22	Lymphadenopathy.
MN 4611	7.75	4.7	0.2	0.55	0.65	1.65		4	11	
MN 4636	8.25	4.6	0.45	0.6	0.9	1.7		3	31	Thyroid antibody in serum.
MN 4649	6.25	4.0	0.15	0.7	0.6	0.8		2	4	Raised C.S.F. protein.
MN 4656	7.75	4.4	0.2	0.8	1.25	1.1			15	
MN 4786	8.25	4.75	0.3	0.75	1.0	1.45	-	3	9	
MN 4977	6.75	3.25	0.25	0.65	1.0	1.6			5	
MN 5095	6.75	4.0	0.2	0.4	0.8	1.35	+(4)	4	75	Thymoma. Megaloblastic and haemolytic anaemia.
MN 5315	7.25	4.9	0.1	0.47	0.68	1.1			4	
MN 5409	7.25	5.45	0.1	0.4	0.65	0.65	-	2		Addison's disease.
MN 5503	6.75	5.3	0.1	0.2	0.6	0.55			26	Pernicious anaemia and Hashimoto's disease.
MN 5625	7.25	4.85	0.5	0.5	0.8	0.6			18	Goitre.
MN 5672	6.5	3.4	0.3	0.4	0.6	1.4	-	5	9	Previous thyrotoxicosis
MN 6289	5.7	3.55	0.2	0.4	0.7	0.85			12	
MN 6476	6.75	3.8	0.3	0.95	0.6	1.1			5	Thymoma.
MN 6481	5.5						2	5	10	Hepatitis, ANF+
MN 6503	6.25-8.0							2	4	ANF+
MN 6522	8.0	4.0	0.2	1.1	1.0	1.7				Thymoma.
MN 6780	8.0	4.3	0.4	0.6	1.0	1.7		3	2	
MN 6807	8.0	6.0	0.3	0.3	0.75	0.65				
MN 6933	7.1	5.2	0.3	0.4	0.8	0.4		3		
MN 7345	7.25	5.3	0.25	0.5	0.6	0.6	-	3		
MN 7390	8.2	3.3	0.2	0.5	1.4	2.8	+	5	72	Hashimoto's disease.
MN 7476	7.25	4.35	0.15	0.65	0.9	1.2			13	
MN 7543							+	4	3	Thyrotoxicosis, ANF+
MN 7550	8.75	3.45	0.5	0.9	1.1	2.8	-	4		
MN 7587	7.0	4.75	0.2	0.5	0.55	1.0	-	3	2	
MN 7720	6.75						-	6	3	ANF+
MN 7780	5.6	3.3	0.1	0.4	0.6	1.2			21	Pernicious anaemia.
MN 7781	8.75	5.4			3.35			2	17	Thyrotoxicosis later.
MN 8088	8.7						2	5	3	
MN 8092	8.5	3.7	0.5	1.25	1.25	1.8	-	1	3	
MN 8170	7.25	3.6	0.3	0.85	0.6	1.9	-	2	2	
MN 7788	9.1	4.4	0.6	1.0	1.0	2.1				

Table 6.3

CEREBROSPINAL FLUID.

CASE	PROTEIN. mg/100ml.	PANDY TEST.	LANGE CURVE.	OTHER DISORDERS.
NH/PS/JF	125	+	000000000	Acroparaesthesia.
NH/MC/AW	50	±	000000000	Raynaud's syndrome; Minor fits.
NH/PM/WB	80	+	000000000	Diabetes.
NH 61127	220			Non-toxic goitre; Guillain-Barré syndrome after 16 years myasthenia.
NH 61423	60	+	000000000	Thyrotoxicosis; nystagmus.
NH 61491	80	+	000112110	-
NH 62044	80	+	000000000	-
MN 675	55		000000000	Prominent eyes; arthropathy.
MN 4649	100		554421000	No C.N.S. disease, W.R. -ve.
MN 7778	56	-	000000000	-


MN 1906
MN 3054
MN 3609
MN 4084
MN 4301
MN 4536
MN 4585
MN 4586
MN 4603
MN 4611
MN 4636
MN 4649
MN 4656
MN 4786
MN 4934
MN 4977
MN 5315
MN 5409
MN 5503
MN 5625
MN 5652
MN 5766
MN 6289
MN 6433
MN 6476
MN 6503
MN 6522
MN 6780
MN 6807
MN 6933
MN 7345
MN 7390
MN 7476
MN 7543
MN 7550
MN 7587
MN 7720
MN 7779
MN 7780
MN 7781
MN 7855
MN 8088
MN 8092
MN 8170

	225	+11	
	316	+ 2	Goitre.
	268	- 2	Prominent eyes.
		- 4	
3.5			
		- 1	Prominent eyes.
	280	+ 9	
		- 3	Prominent eyes.
	280		
	235	- 1	F.H. of Thyrotoxicosis.
5.1			Previous Thyrotoxicosis
3.3	280	+ 4	Prominent eyes.
4.5	290	- 6	von Graefe's sign.
	265	- 6	
> 14.0			Thyrotoxicosis.
		-10	
		+ 1	Proptosis : F.H. of Thyrotoxicosis.
		+14	
2.4		- 8	Hashimoto's disease (PM)
	330		Goitre.
6.0			F.H. of Thyrotoxicosis.
?	225		
4.3			
5.6			
3.8			
	175		
3.6			
5.4			
5.7			
5.6		+ 2	
14.0			Hashimoto's disease.
3.7			Thyrotoxicosis.
5.3			
5.0			
	139		
	200		
7.7		+30	Thyrotoxicosis. Goitre.
4.7			F.H. of Thyrotoxicosis.
5.8			

Table 6, 5.

GLUCOSE TOLERANCE TEST (VENOUS).

Hours after 50mg. glucose orally.

CASE	FASTING mg/100ml.	½ mg/100ml.	1 mg/100ml.	1½ mg/100ml.	2 mg/100ml.	2½ mg/100ml.	GLYCO-SURIA	ASSOCIATED DISORDERS.
MN 3912	Reported normal tolerance							
MN 4301	75	93	125	105	64		++	Renal glycosuria F.H. diabetes.
MN 4536	88	134	166	155	100		+	? Thyrotoxicosis.
MN 4585	75	93	50	75	67	70		
MN 4611	87	150	153	153	143			F.H. diabetes.
MN 4636	80	127	147	160	117	87		Thyrotoxicosis.
MN 4649	83	167	177	183	113			F.H. diabetes.
MN 4786	67	83	117	60				
MN 5409	79	125	95	69	60	36		Addison's disease
MN 5503	107							
MN 5625	90	170	87	123	63			Non-toxic goitre.
MN 5652	73	150	122	108	82	67		Thyrotoxicosis.
MN 5766	83	117	97	87	83	87		
MN 6476	80	123	117	100	72	55		
MN 6503	100	213	152	120	102			F.H. diabetes.
MN 6522	87	138	98	87	75			
MN 6780	75	151	207	129	63	46		'lag storage'.
MN 6807	103	100	160	150	100			
MN 6933	80	100	108	93	92			
MN 7345	83	155	135	77	68	70		
MN 7390	80	145	140	125	78	59		Hashimoto's disea
MN 7476	90	130	123	113	90	90		
MN 7543	73	87	107	80	63	73		Thyrotoxicosis.
MN 7550	80	130	140	157	147	105		
MN 7587	89	110	104	104	107	72		
MN 7720	97	100	93	115	82			
MN 7779	87	167	154	150	129	116	+	
MN 8092	98		102	97	80			F.H. glycosuria.
MN 8170	100	147	170	155	95			
MN 8279	462						+++	Diabetes mellitus

Table 6, 6.

SERUM CALCIUM AND INORGANIC PHOSPHORUS.

CASE	CALCIUM mg/100ml.	INORGANIC P. mg/100ml.	CASE	CALCIUM mg/100ml.	INORGANIC P. mg/100ml.
MN 294	10.1	3.5			
MN 4084	9.7	-	MN 6476	10.8	2.8
MN 4301	8.8	4.8	MN 6503	12.0	3.5
MN 4536	9.3	4.2	MN 6522	9.4	3.0
MN 4585	10.2	4.7	MN 6780	9.6	3.0
MN 4611	9.6	3.9	MN 6807	10.4	3.0
MN 4636	10.4	2.4	MN 6933	10.1	-
MN 4649	9.0	1.9	MN 7345	10.4	4.3
MN 4786	10.9	2.8	MN 7390	10.6	3.0
MN 4977	9.6	2.8	MN 7476	9.1	2.3
MN 5095	9.6	-	MN 7543	9.4	2.3
MN 5409	9.9	3.0	MN 7550	9.4	3.0
MN 5494	9.1	-	MN 7587	10.0	4.0
MN 5503	8.5	3.6	MN 7720	10.8	1.8
MN 5625	10.4	2.5	MN 7776	9.4	4.6
MN 5652	11.0	3.0	MN 8088	9.7	-
MN 5766	9.2	3.5	MN 8092	10.6	4.1
MN 6433	10.8	3.3	MN 8170	10.0	3.3

Table 6, 7.

URINARY STEROIDS.

CASE	SEX	17-HYDROXYCORTICOSTEROIDS mg/24 hours.	17-KETOSTEROIDS. mg/24 hours.
MN 4301	M	3.8	2.0
MN 4536	F	9.1	-
MN 4585	F	4.7	4.3
MN 4611	F	11.8	-
MN 4636	F	10.0	8.0
MN 4649	F	12.0	-
MN 4656	F	4.2	-
MN 4786	F	4.1	-
MN 5409	M	+ 3.1-11.1	+ 1.3-5.0
MN 5503	F	3.8	2.6-3.8
MN 5652	M	11.2-22.0	4.9-10.6
MN 5766	F	10.5	6.7
MN 6433	F	* 1.2	* 0.2
MN 6476	M	8.2	12.3
MN 6503	M	2.4	1.6
MN 6522	F	5.1	11.5
MN 6780	M	2.9	2.5
MN 6807	M	8.1	8.1
MN 6933	F	6.0	13.0
MN 7345	M	9.1	5.0
MN 7390	M	4.8	3.2
MN 7476	F	17.8	5.9
MN 7543	F	11.1	6.2
MN 7550	M	17.2	8.6
MN 7587	F	8.7	6.4
MN 7720	F	12.7	8.6
MN 7776	F	-	5.1
MN 7779	F	-	7.8
MN 8088	F	3.0	4.7
MN 8170	M	4.0	11.5

\+ Terminal; clinical evidence of Addison's disease.

* Urinary specimens believed to be incomplete.

Fig. 7, 1.

Case NH 22715. Thymoma with aplastic anaemia. Effect of ACTH, thymectomy and splenectomy. (from Chalmers and Boheimer, 1954).

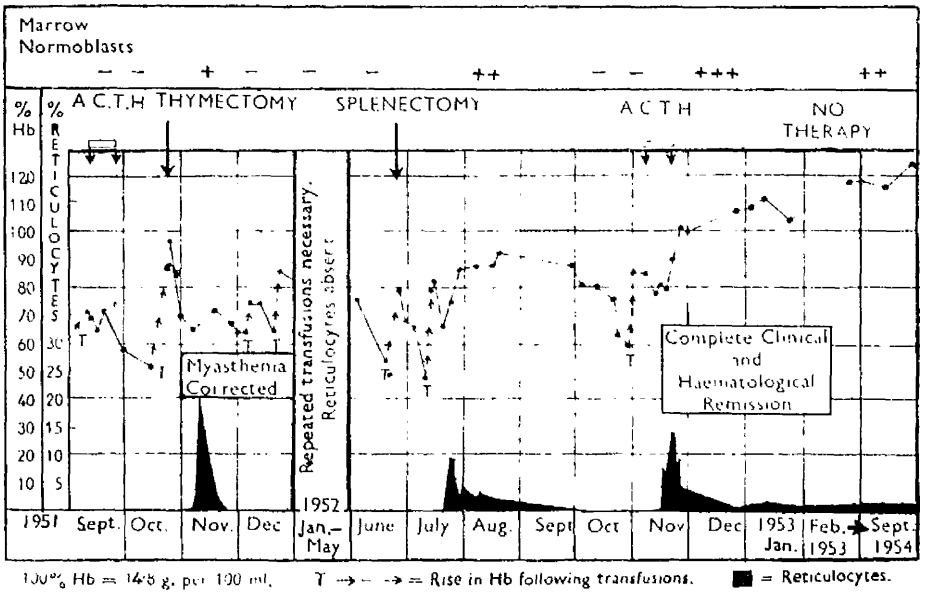
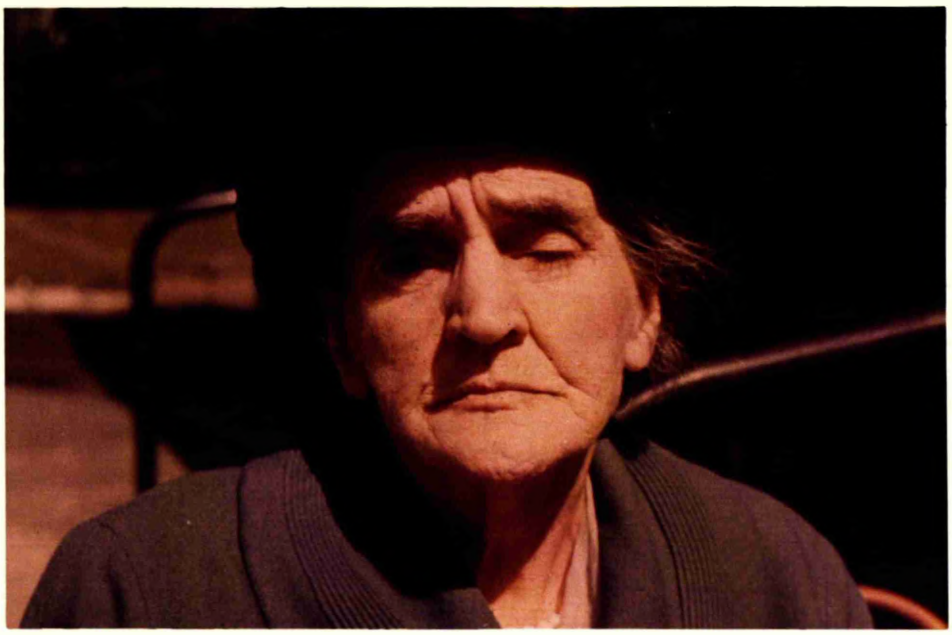
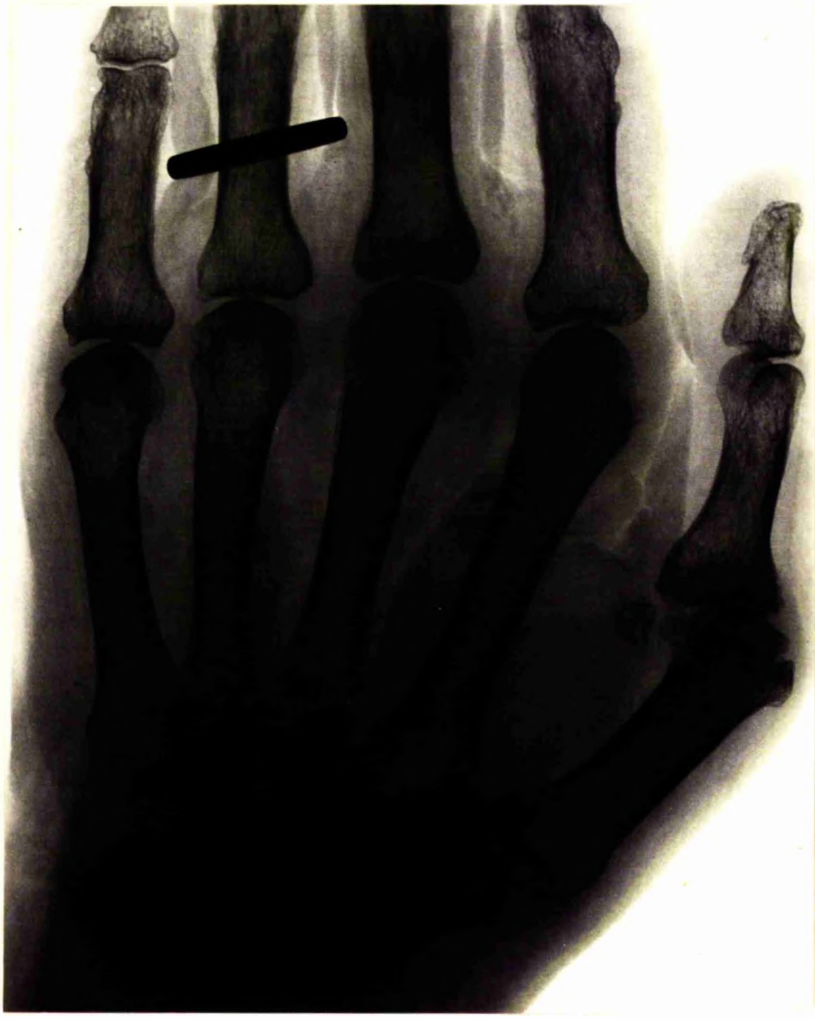


FIG. 1.—Case 1. Pure red-cell anaemia in a patient with myasthenia gravis and thymoma. Haematological and therapeutic data over a period of three years.

Fig. 7, 2.

Case MN 294. Myasthenia gravis with 'rheumatoid' arthritis of metacarpo-phalangeal joints of left hand.





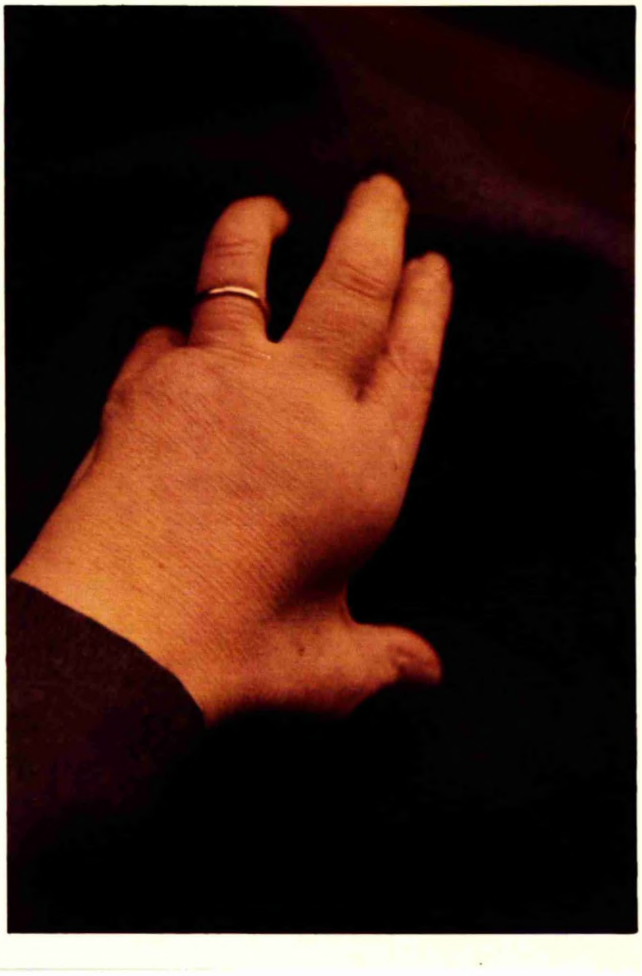
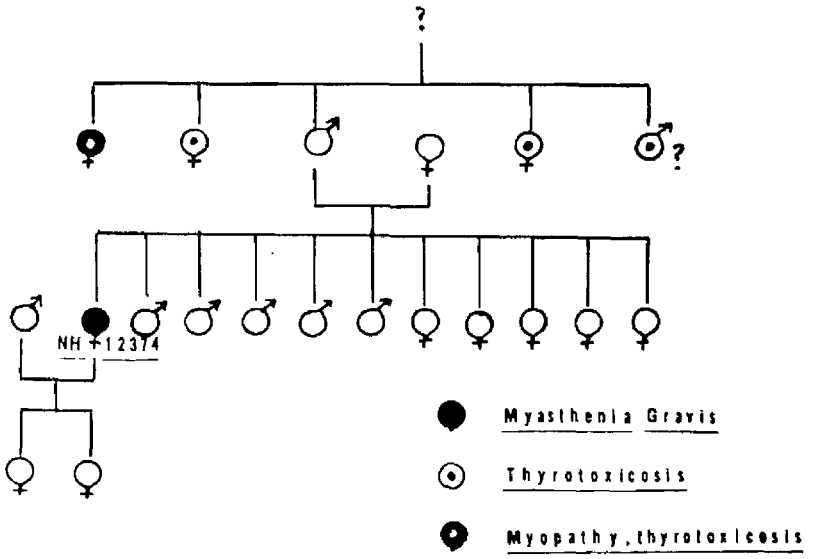


Fig. 8, 1.

a) Case NH 12374. Four cases of thyrotoxicosis in the previous generation (paternal side). One of these relatives also had muscular weakness and wasting.

b) Cases NH 29555 and NH 62033 were distantly related to each other. No details are known about other relatives.


?
NH 12374
Myasthenia Gravis
Thyrotoxicosis
Myopathy, thyrotoxicosis

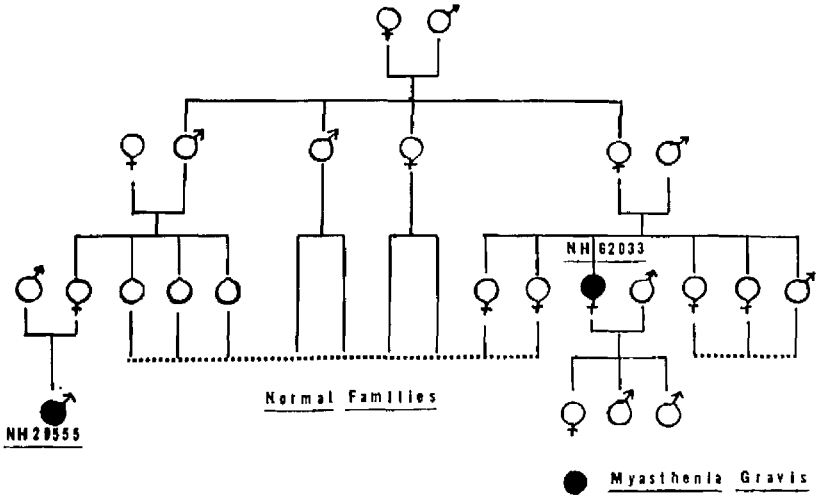

NH 62033
NH 29555
Normal Families
Myasthenia Gravis

Fig. 8, 2.

Case MN 4275. Typical myasthenia gravis with good response to neostigmine and to thymectomy. Her mother is said to have had neostigmine-responsive myasthenia gravis.

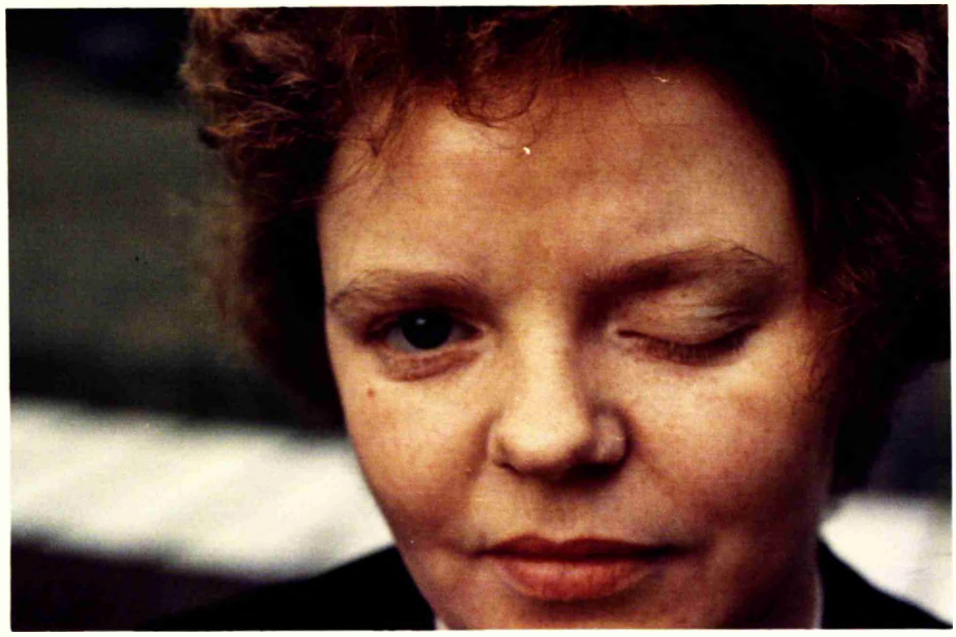
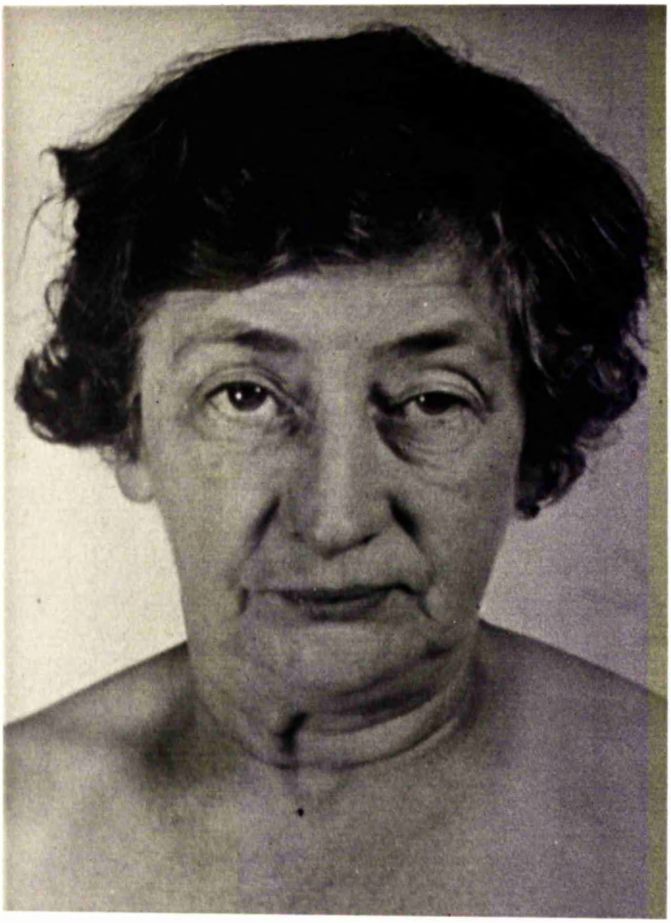


Fig. 8, 3.

a) Case MN 4650. Familial myasthenia gravis with a previous history of pernicious anaemia and transient 'rheumatoid' arthritis.

b) Sister of Case MN 4650. Typical history of myasthenia gravis. (Not examined personally owing to death).

See Fig. 8, 4 for family history.



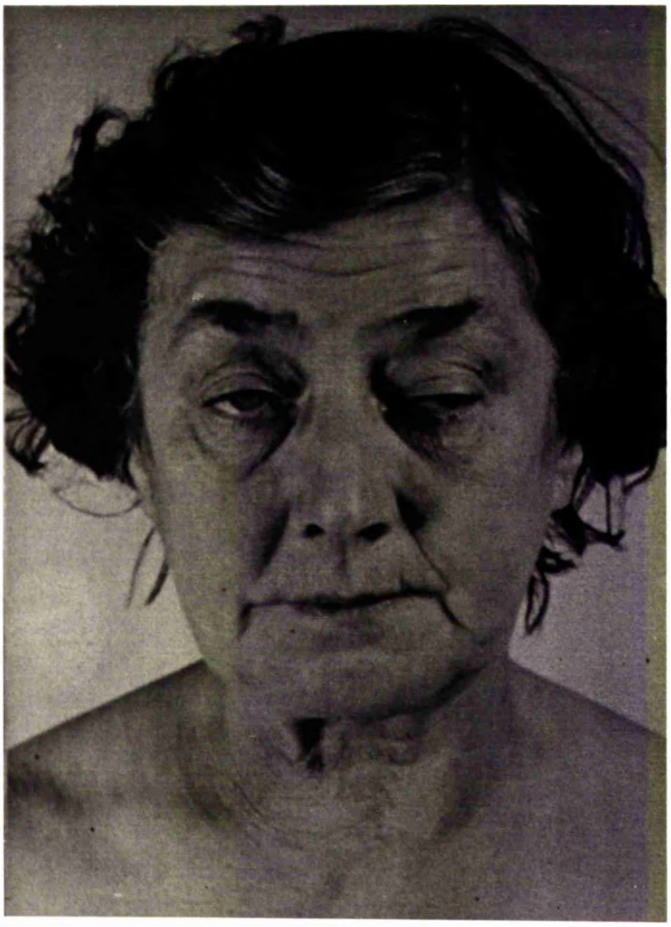


Fig. 8, 4. Family history of Case MN 4650. In addition to a sister with myasthenia gravis there is a history of ptosis and blindness (apparently inherited as an autosomal factor from her grandmother). A niece has thyrotoxicosis.

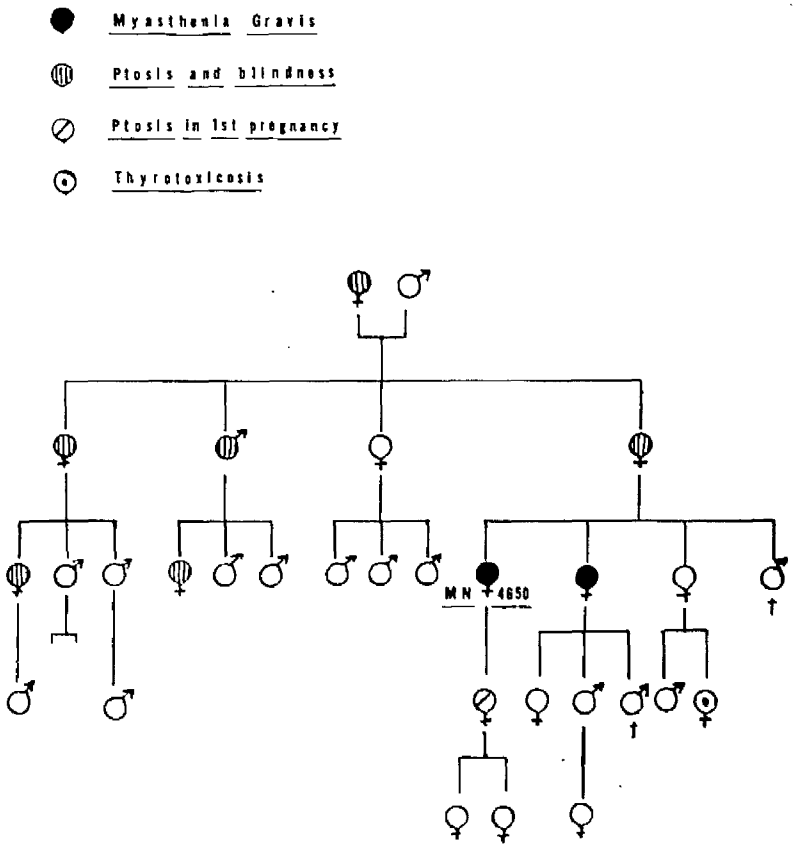

Myasthenia Gravis
Ptosis and blindness
Ptosis in 1st pregnancy
Thyrotoxicosis
M N 4650

Fig. 8, 5.

Case NH 31239, on right of figure has myasthenia gravis. Her twin sister is unaffected.

Fig. 8, 6.

Case MN 6140. Congenital myasthenia.

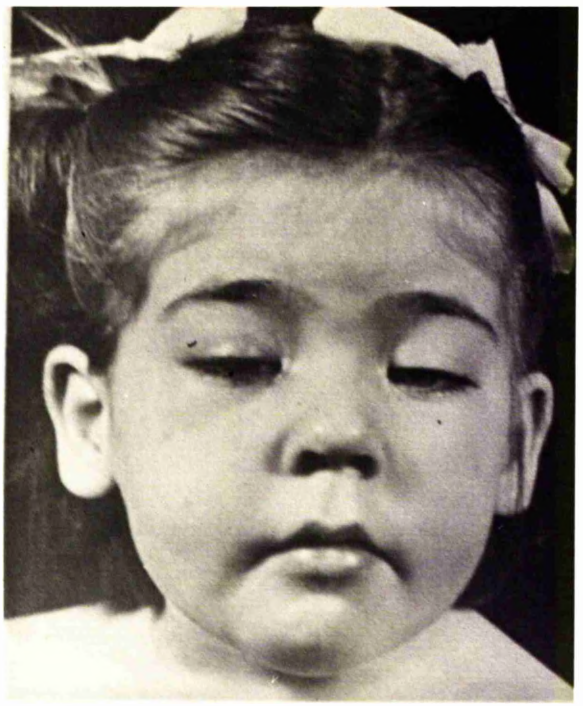
Fig. 8, 7.

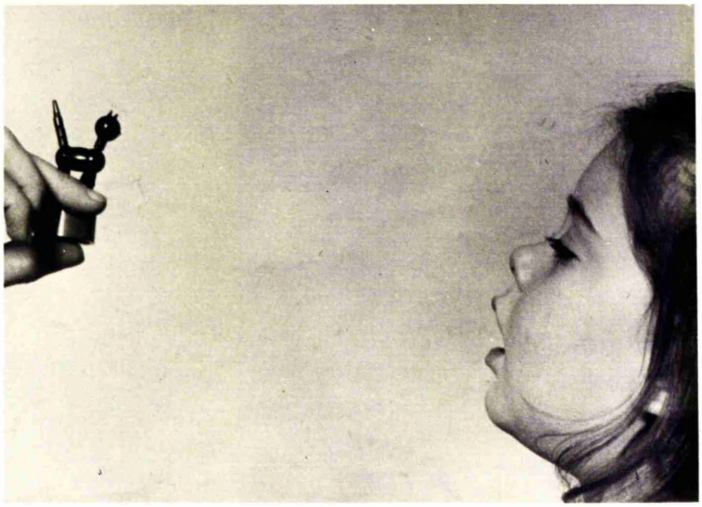
Case MN 6139. Congenital myasthenia, younger sister of the patient in Fig. 8, 6.

a) Before neostigmine.

b) After neostigmine - she is now able to look at the toy without holding her head back though there is little obvious decrease of ptosis.

(By courtesy of Prof. J. Hutchinson).





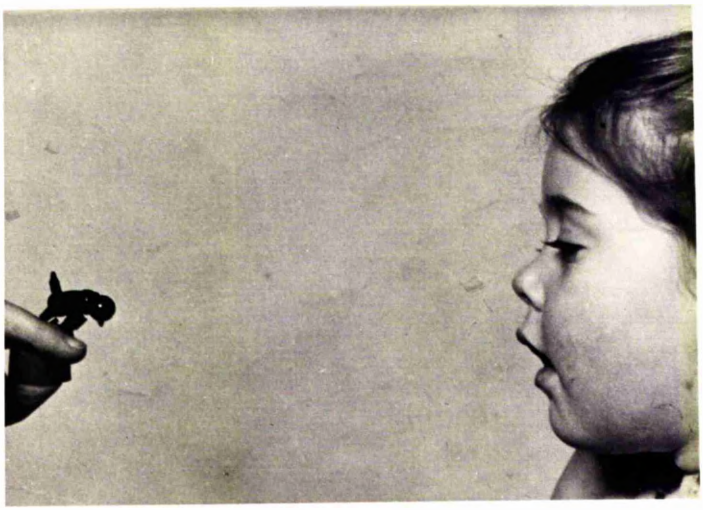


Fig. 8, 8. Resistance to decamethonium (C.10) in a case of benign congenital myopathy with myasthenic features (see Appendix B).

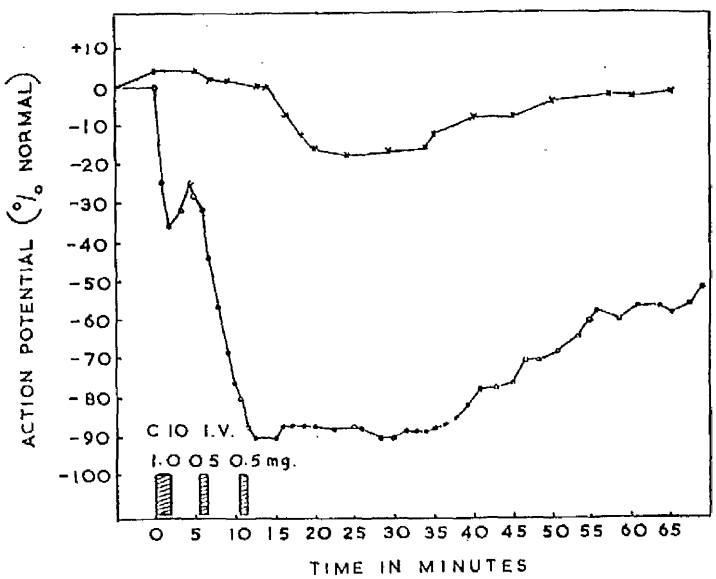
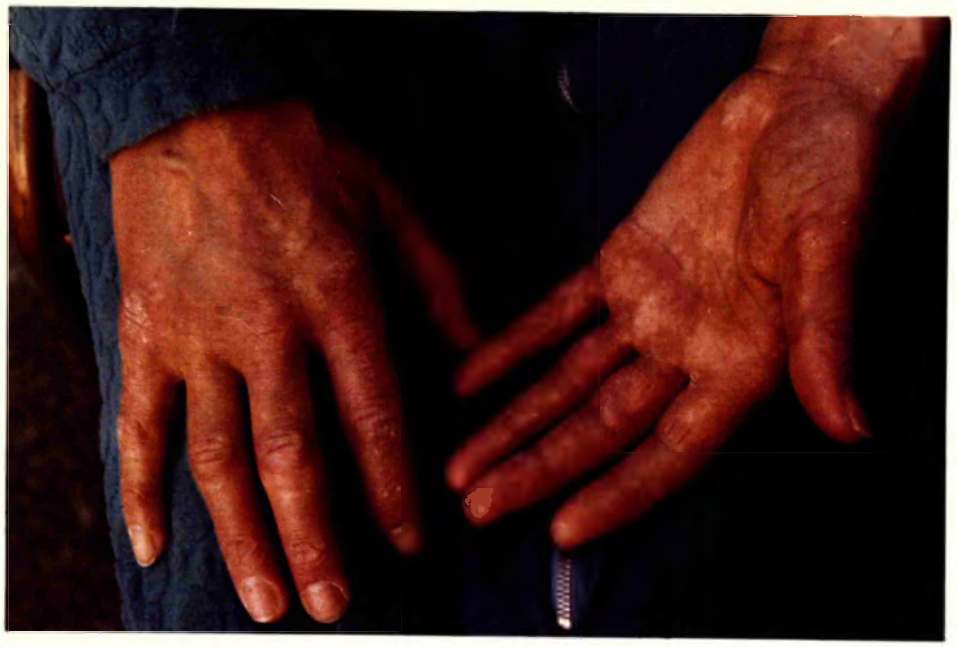

ACTION POTENTIAL (% NORMAL)
+10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
C 10 I.V.
1.0 0.5 0.5 mg.
0 5 10 15 20 25 30 35 40 45 50 55 60 65
TIME IN MINUTES

Fig. 9, 1.

a) Case MN 74. Neostigmine-resistant muscular weakness resembling myasthenia gravis (see also Fig. 9, 2). The hands show arthritis, erythema, and desquamation.

b) Case MN 74. Radiograph of right hand. Note localised erosions of metacarpophalangeal and proximal interphalangeal joints resembling rheumatoid arthritis.



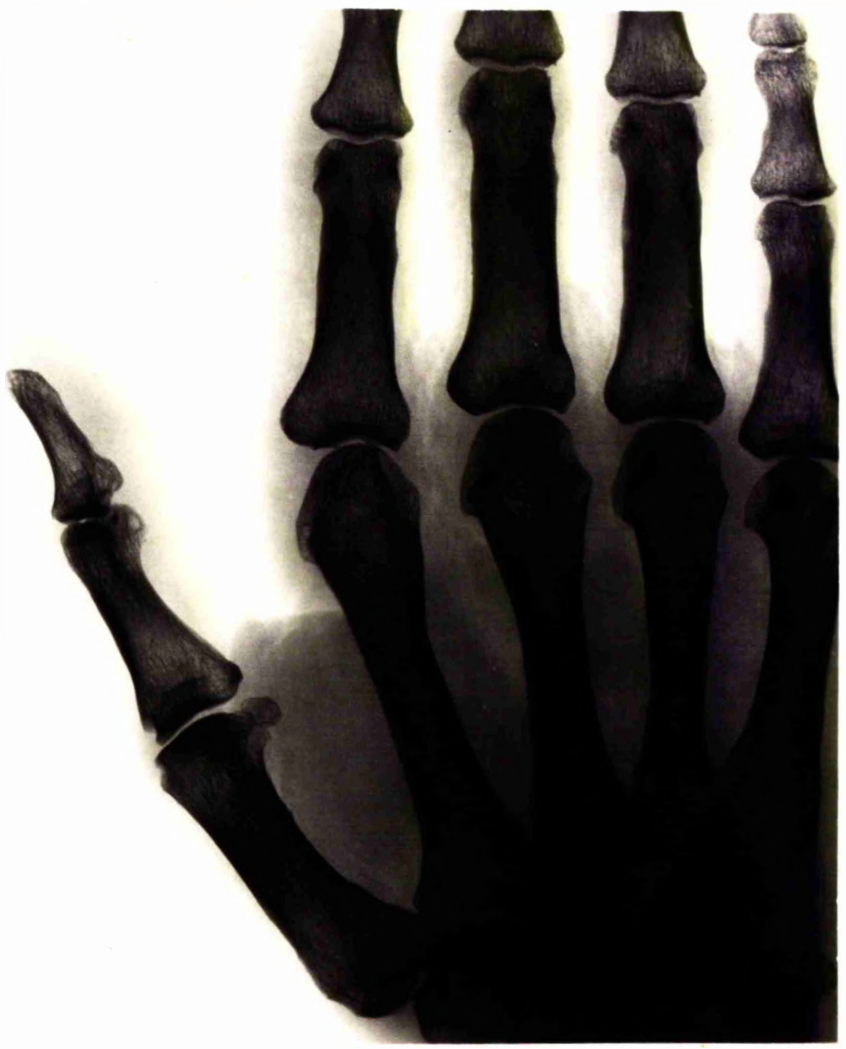


Fig. 9, 2.

Case MN 74. Facies resembles myasthenia gravis. She sits with a hand supporting her jaw and head. Power did not improve with anticholinesterase drugs.

Fig. 9, 3.

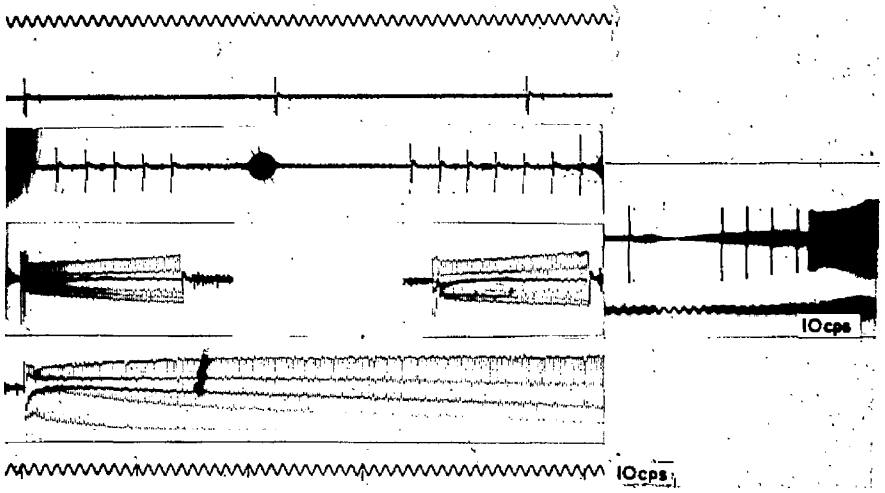
Case MN 74. Difficulty in raising arms and in sitting with head upright.

Fig. 9, 4.

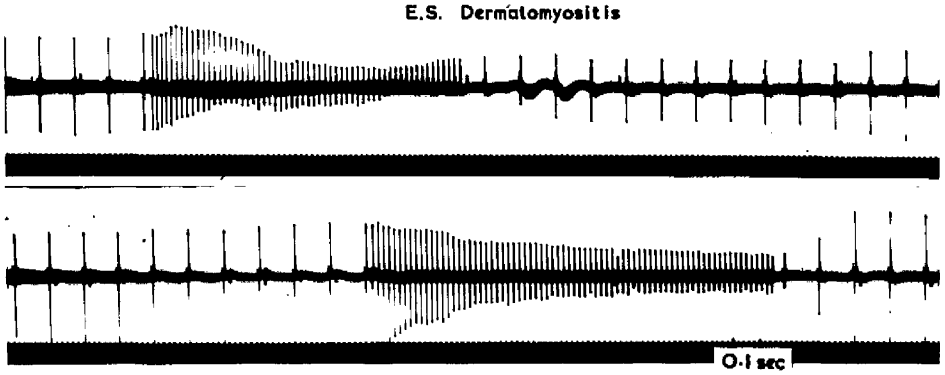
Case MN 1714. Neostigmine-resistant myasthenic syndrome with progressive improvement in voluntary contraction. Harvey-Masland test to show decrementing response to supramaximal neural stimulation at 0.5 and 4.0/sec. Stimulation at 50/sec. causes a decrementing response to the first five stimuli then a progressive increment of the muscular action-potential, associated with more powerful contraction as in the sustained voluntary contraction (Simpson and Lenman, 1959).

Fig. 9, 5.

a) A myasthenic reaction to the Harvey-Masland test in a case of dermatomyositis.
b) The myasthenic response is not significantly influenced by injection of edrophonium.



E.S. Dermatomyositis



Tension 10mg 1 V

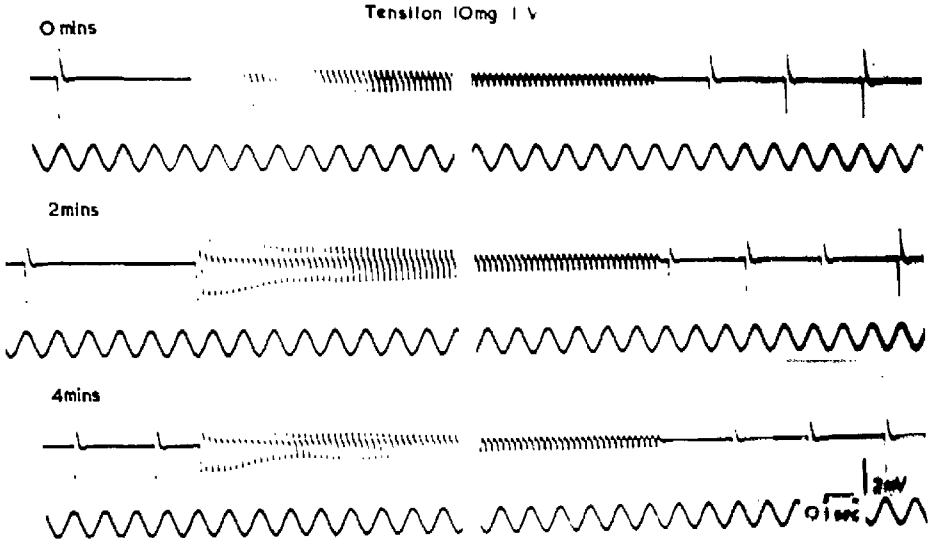


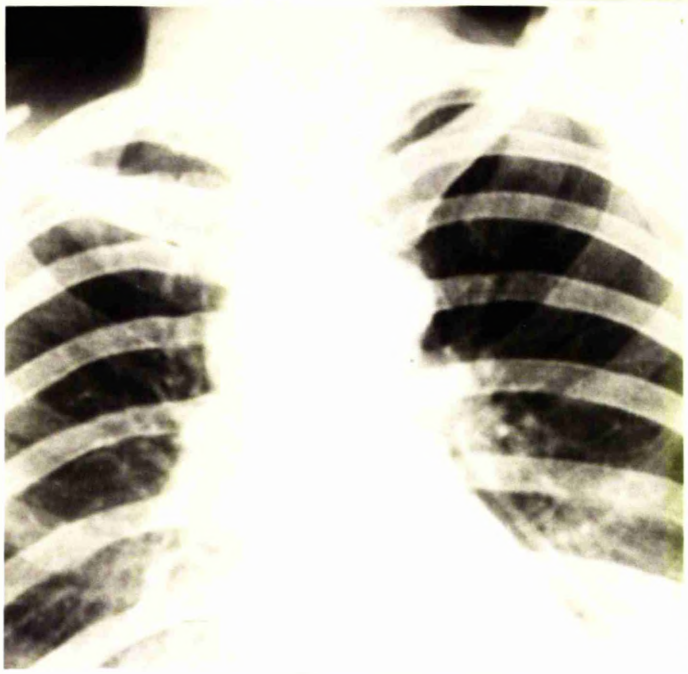
Fig. 9, 6.

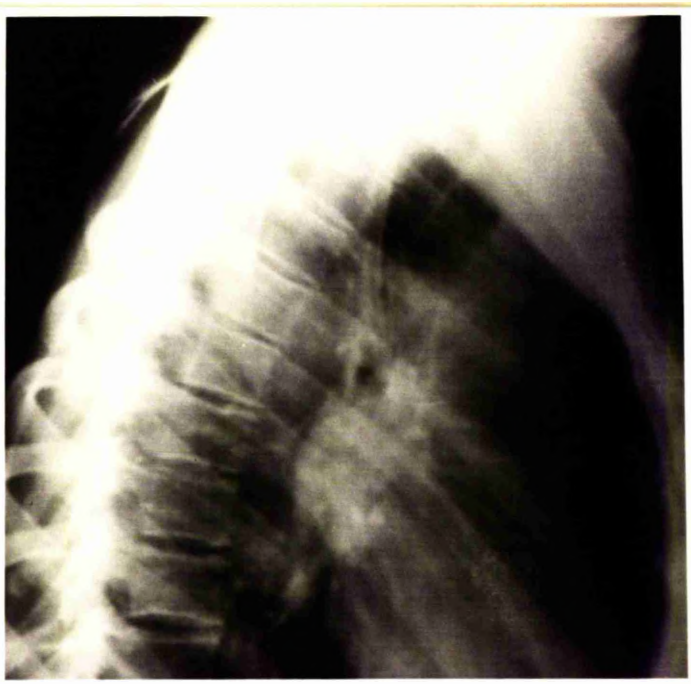
Case MN 7531. Carcinomatous myasthenia.

a) The postero-anterior radiograph of the chest was considered by the referring physician to show a thymoma.

b) A lateral view shows that the abnormal mass is related to the hilar region and does not encroach on the anterior mediastinum.

c) Tomography confirmed the peri-carinal localisation and showed encroachment on the right main bronchus (not visible on reduced reproduction).





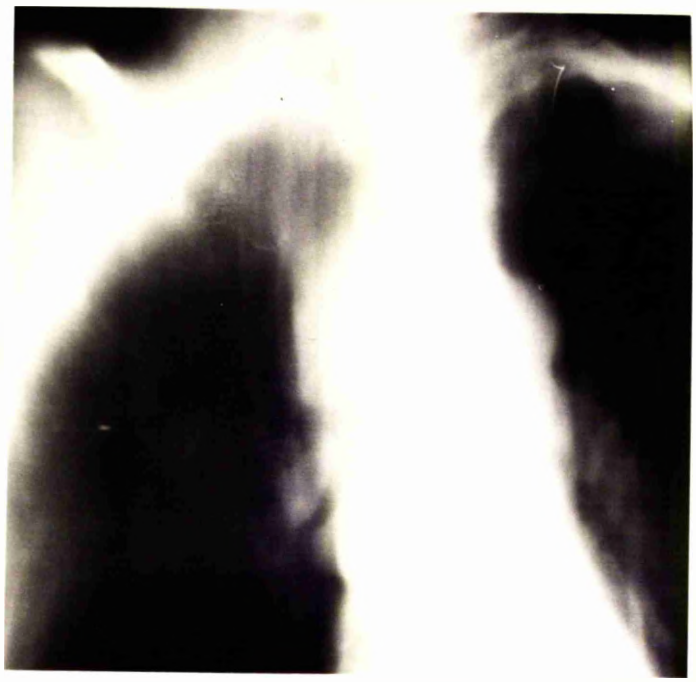


Fig. 9. 7.

Case MN 7024. Carcinomatous myasthenia.
Harvey-Masland test showing decrementing response of muscle to supramaximal neural stimulation at 2.5/sec. and incrementing response at 20/sec. Note prolonged period of post-tetanic potentiation.

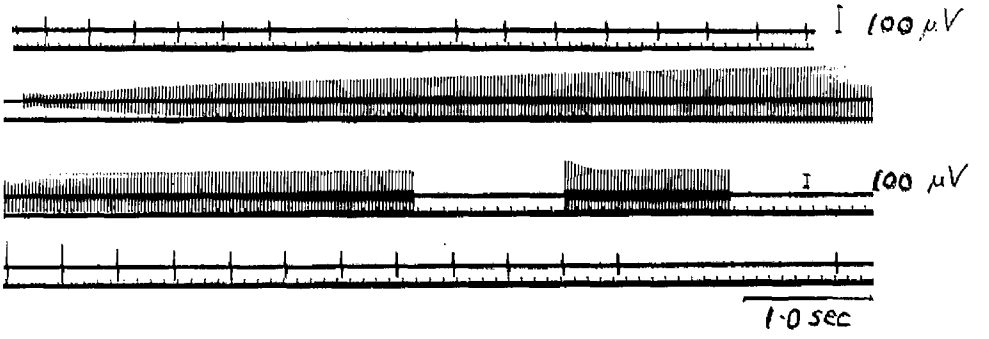

100 μV
100 μV
1·0 sec

Fig. 9, 8.

Case MN 7146. Pseudomyasthenia.

Fig. 9, 9.

Case MN 5765. Pseudomyasthenia.

Fig. 9, 10. Mrs. M.H. (73). Pseudomyasthenia.
This patient is not described in the text. She stated that her eyelids had always been heavy. For 3-4 years she had had definite ptosis, occasional double vision and slight weakness of her left hand. On examination she had bilateral ptosis, failure of upward gaze, fatiguable weakness of both deltoid muscles, right triceps, and the intrinsic muscles of the left hand. There was no response to edrophonium or neostigmine.
(Courtesy of Dr. J.K. Slater).

Note the striking similarity of the facies and history of these three patients.

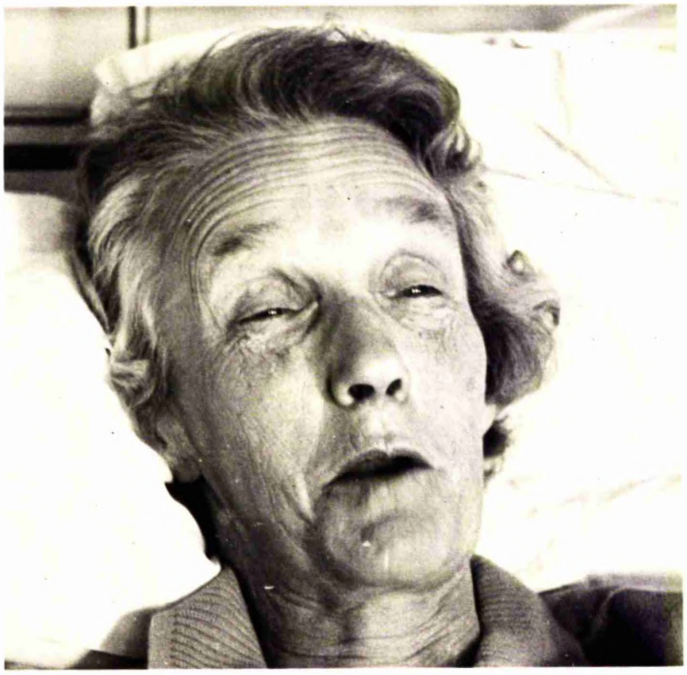


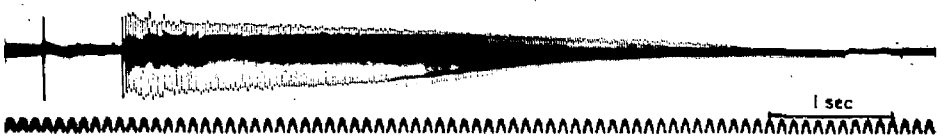
Fig. 9, 11. Positive Harvey-Masland test in diabetic neuritis without clinical evidence of myasthenia (Simpson, 1960b; 1962a).

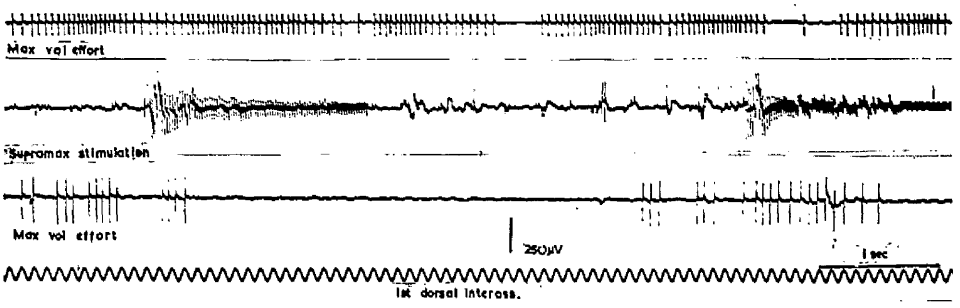
Fig. 9, 12. Myasthenic reaction in motor neurone disease (Simpson, 1960b).

a) Case 1. The co-axial needle electrode records only a single remaining motor unit in the 1st dorsal interosseous muscle. On maximum voluntary effort its amplitude decreases when the firing rate increases. There is a marked decrement on electrical stimulation at tetanic frequency. Subsequent voluntary contraction is restricted to brief bursts of innervation but the muscle potential no longer decrements.

b) Case 2. Marked decrement of single motor unit action potential on maximal voluntary effort (a) and supramaximal indirect tetanisation (b).

J.L. 7.5.58 Diabetic Neuritis





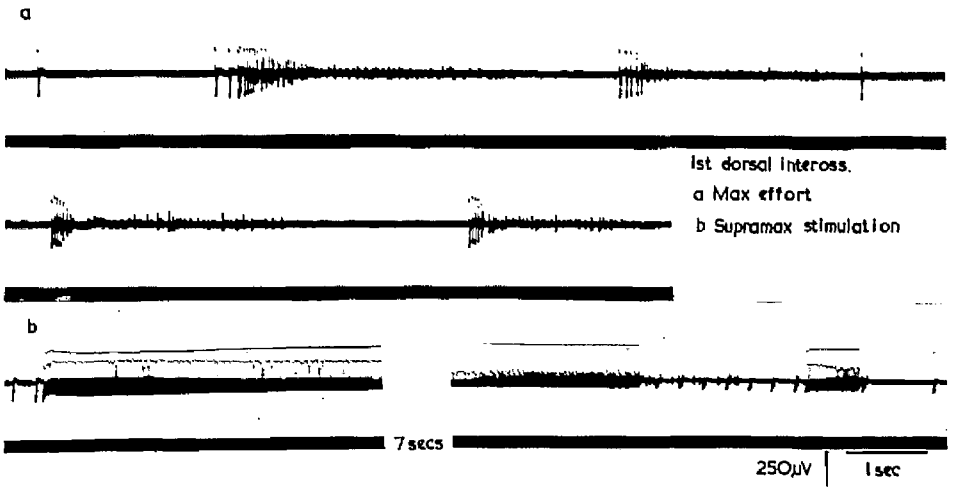


Table 10, 1. Change of status from datum point to time of follow-up in non-tumour patients, comparing operated with non-operated series. The diagram shows an increase in the proportions in categories A, B and C in the operated series, and a striking reduction in deaths caused by myasthenia (from Appendix C, Simpson, 1958).

TABLE V.—RESULTS—NON-TUMOUR

	Operated				*Not-operated*			
	F		*M*		*F*		*M*	
Category	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
A	40	22·0	15	19·7	9	15·3	7	17·5
B	24	13·2	8	10·5	3	5·1	2	5·0
C	42	23·1	18	23·7	9	15·3	3	7·5
D	32	17·6	15	19·7	8	13·5	10	25·0
Data incomplete	13	7·1	4	5·3	9	15·3	9	22·5
Myasth. deaths	14	7·7	9	11·8	17	28·8	8	20·0
Post.-op. deaths	14	7·7 } 17·0	6	7·9 } 21·0	—	} 35·6	—	} 22·5
Deaths, other	3	1·6	1	1·3	4	6·8	1	2·5
Total	182		76		59		40	

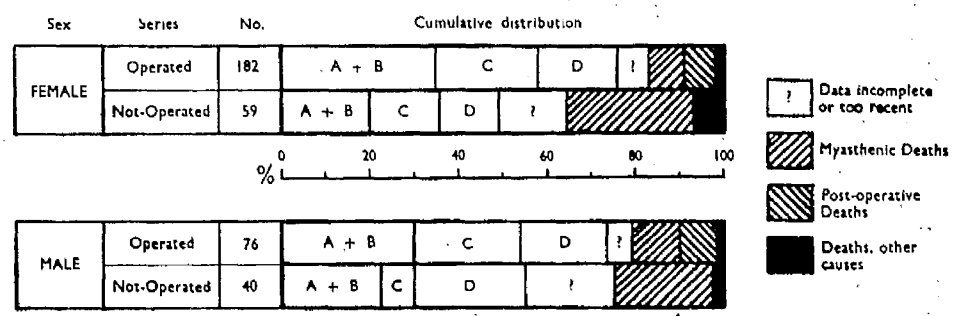


FIG. 2.—Comparison of series (non-tumour) to show cumulative difference.

Fig. 11, 1. Russell's type I lesion. Acute coagulative necrosis of muscle fibres with eosinophilic change, loss of cross striation, inflammatory cellular reaction and phagocytic removal of the fragmented muscle fibre.

H & E x 280.

Fig. 11, 2. Russell's type II lesion, the lymphorrhage, related to atrophy of a single muscle fibre with basophilia of the cytoplasm and loss of cross striation.

H & E x 210.

Fig. 11, 3. Russell's type III lesion. Focal muscle change with eosinophilia and swelling of the fibre but without loss of striation or inflammatory reaction.

H & E x 80.

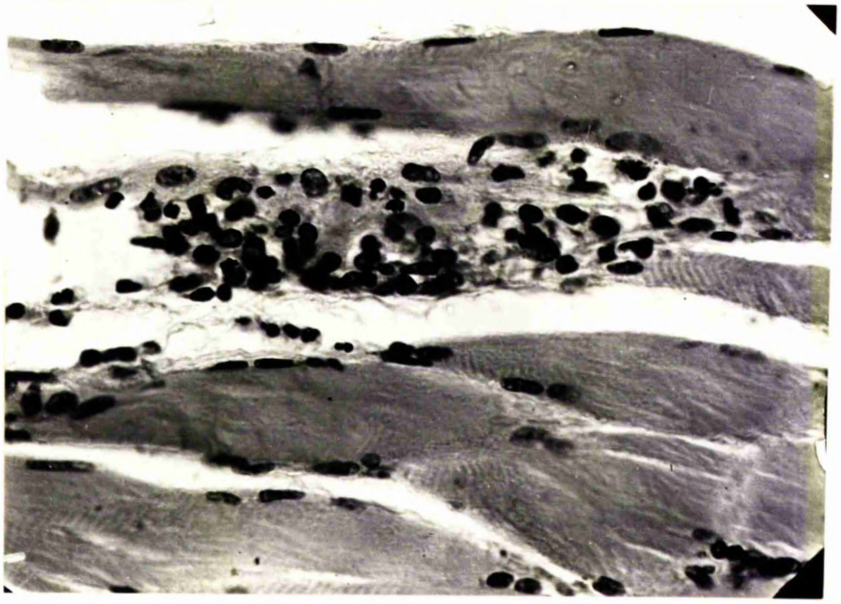
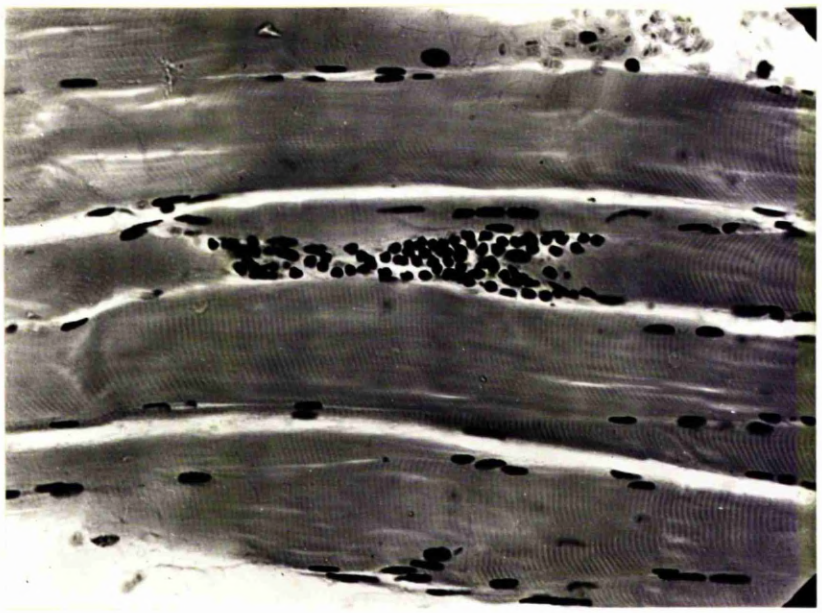


Fig. 11, 4.

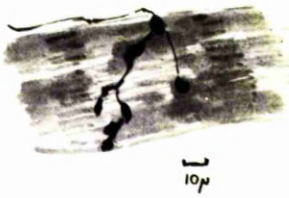
a) The lymphorrhage. The characteristic muscular lesion of myasthenia gravis.

H & E x 280.

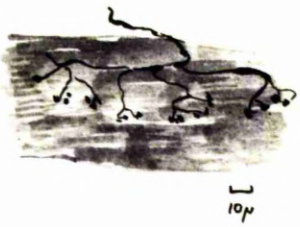
b) Types of motor nerve terminals found in myasthenia gravis. The dystrophic type is a reaction associated with muscular damage of various types; the dysplasic type is considered to be specific for myasthenia gravis. (Sketch based on the original paper by Coërs and Desmedt, 1959).



Normal



Dysplasic



Dystrophic

Fig. 12, 1. Photomicrograph of thymus from a patient with myasthenia gravis to show lymphoid follicular hyperplasia with Hassall's corpuscles grouped round a germinal centre.

H & E x 52.

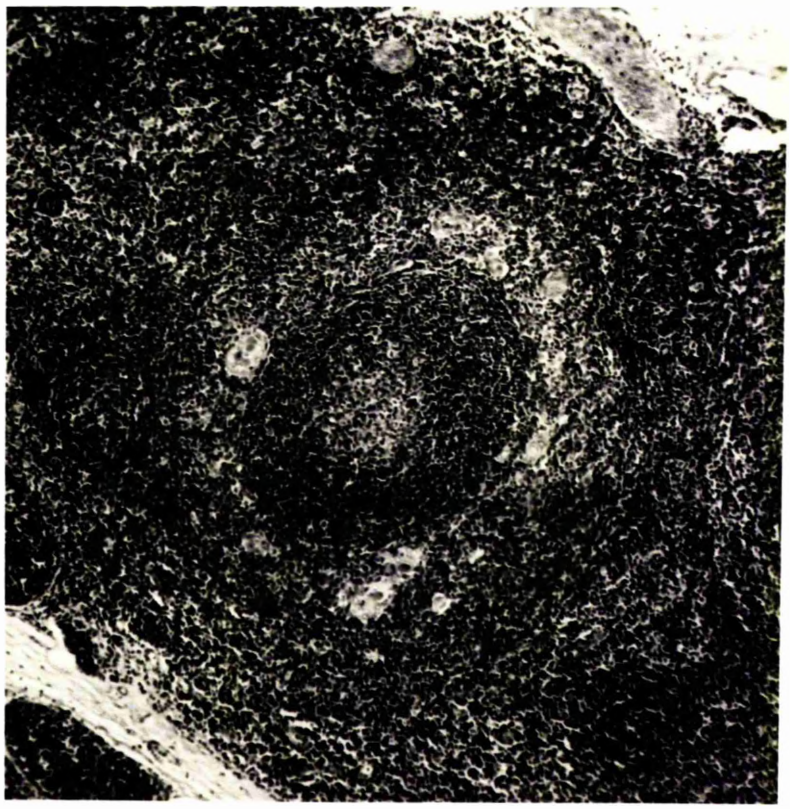
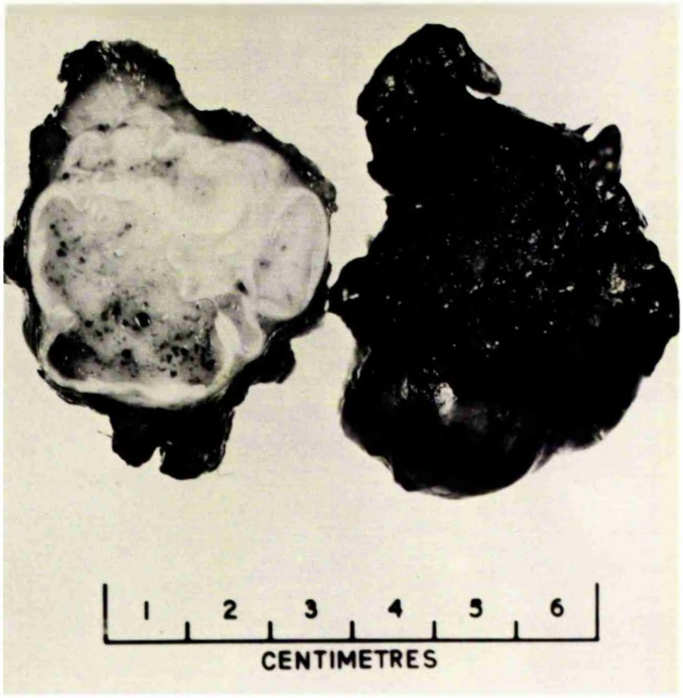


Fig. 12. 2.

a) Case MN 7784. Thymic tumour to show capsule.

b) Case MN 7788. Hyperplastic thymus. No tumour.


1 2 3 4 5 6
CENTIMETRES

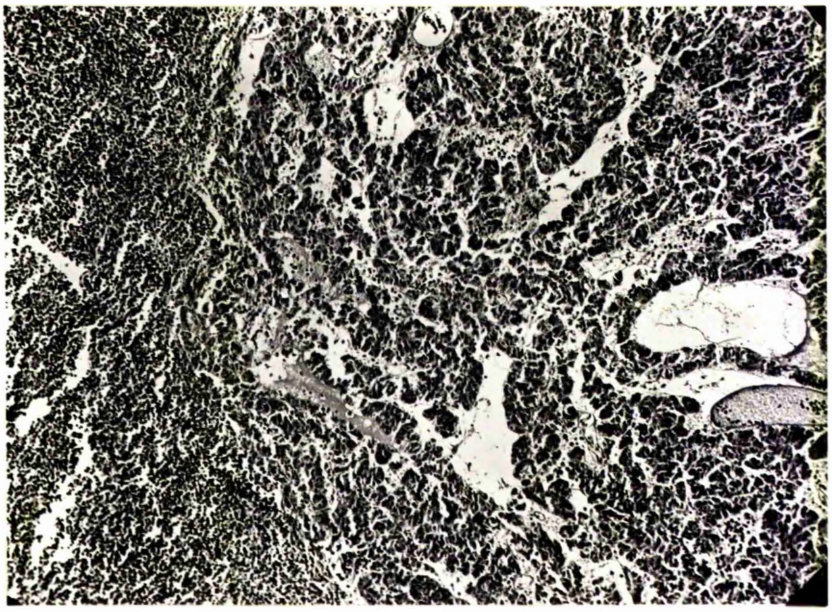

Cm 1 2 3 4 5 6

Fig. 12, 3. Photomicrograph of thymoma from a patient with myasthenia gravis. Note the tubular arrangement of epithelial-type cells. This is only one of several types of thymic tumour which may be associated with myasthenia gravis.

H & E x 42.

Fig. 12, 4. Germinal centres in the thymic tissue surrounding the tumour shown in Fig. 12, 3.

H & E x 52.



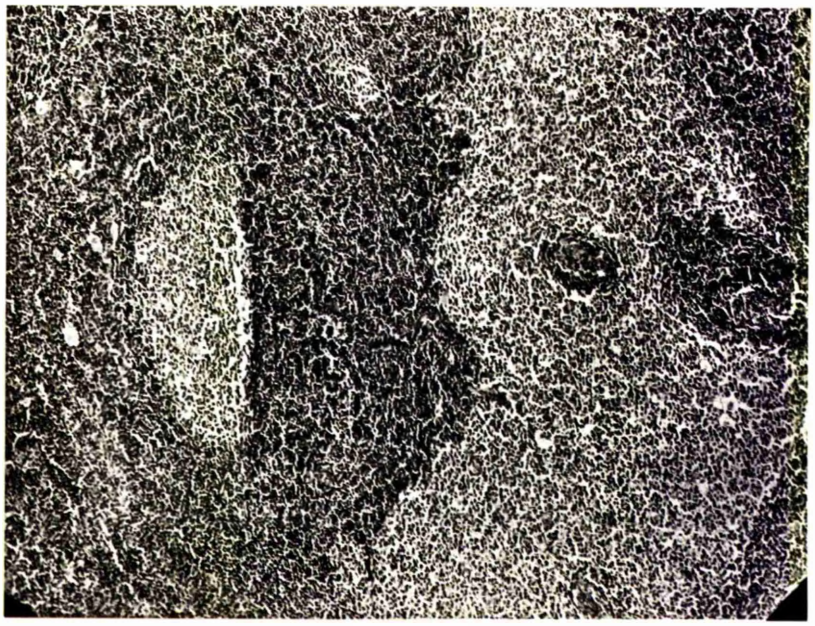
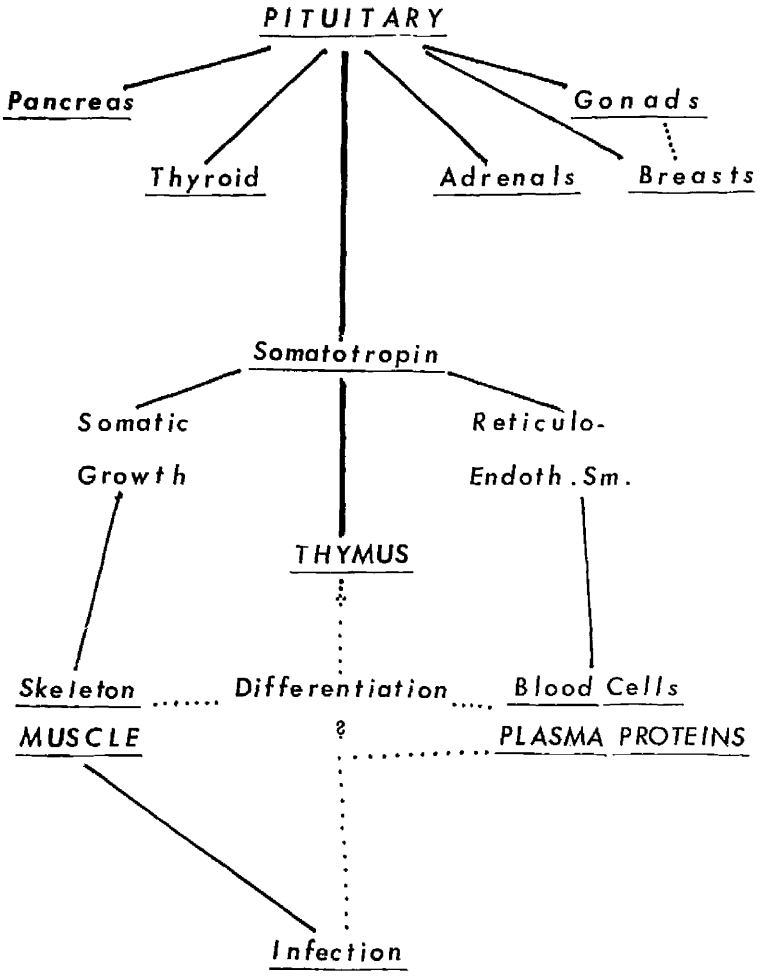


Fig. 12, 5. This figure is from Appendix D where it is more fully described. Prepared before the immunological nature of thymic function was established, it suggests a role for that organ in the differentiation of cells and plasma proteins, including immunologically competent cells and antibodies. It is now suggested that the hypothalamo-pituitary control shown may be a homeostatic influence required by some immunological theories. (Simpson, 1964a).


PITUITARY
Pancreas
Thyroid
Adrenals
Gonads
Breasts
Somatotropin
Somatic
Growth
Reticulo-
Endoth. Sm.
THYMUS
Skeleton
MUSCLE
Differentiation
?
Blood Cells
PLASMA PROTEINS
Infection

Case No.	Sex	Age	Thymoma	Thymectomy before tests	Antibodies Specific for the following Tissues. Thyroid T.C.H.	Thyroid C.F.T.	Gastric C.F.T.	Gastric Ic.	Liver C.F.T.	Muscle T.C.H.	Muscle Ic.	C.F.T.	ANF	S.S.C.T.	Associated Cond
MN 269	F	74	-										-	-	
MN 294	F	73	-		-	-	-	-	-	16	-		-	-	Arthritis
MN 3054	F	49	-		25	-	-	-	-	-	-		-		Previous thyro
MN 3231	F	48	-							-	-				
MN 3609	F	24	-	+						-	-				Previous thyro
MN 3912	F	32	-	+	250	32	32	+	-	-	-		-		? Previous thy
MN 4275	F	31	-	+	-	-	-	-							
MN 4301	M	55			-	-	-	-	-				-		Glycosuria
MN 4536	F	22	-	+	-	16	-	-	-				-	-	Slightly thyro glycosuria.
MN 4585	F	22	-	+	-	-	-	-	-				-		
MN 4586	F	13	-									-	-	-	? Thyrotoxic
MN 4603	F	8	-										-	-	Lymphadenopath
MN 4611	F	19	-									a.c.	-	-	
MN 4636	F	53			-	16	-	-	-						Previous thyro
MN 4649	F	48											-	-	Thyrotoxicosis glycosuria; re protein in C.S
MN 4656	F	30			5			-					-	-	? Previous thy
MN 4934	F	32	-	+	25	-	8	+	-				-		Severe thyroto
					5		16								previous mucus
MN 5315	F	27	-	+	-	-	-	-	-				-		Fits; Raunaud'
MN 5401	F	64											-		Fits
MN 5409	M	39			-	-	-	-	-	-	-	-	-		Raynaud's synd Addison's dise
MN 5494	F	78			-	-	-	-	-				-		Arthritis
MN 5503	F	72			250	-	16	++	-				-		Pernicious ana Hashimoto's di autopsy.
MN 5625	F	21			-	-	-	-	-				+		Slight thyroto
MN 5652	M	28	-	+	-	16	-	-	-				-	-	Epilepsy; prev
MN 5683	F	38			-	-	-	-	-				-		thyrotoxicosis
MN 5766	F	23		+	-	-	-	-	-			-	-		
MN 6289	M	39			250	-	-	-	-				-		? Previous thy
MN 6433	F	14	-		-	-	-	-	-				+		
MN 6476	M	50	+	+	-	-	-	-	-				+		Hyperthyroid;
MN 6481	F	41	-		-	-	-	-	-				++		Hepatitis
MN 6503	M	54			-	-	-	-	-				+		Glycosuria
MN 6522	F	57	+	+	250	-	-	-	-				++		
MN 6780	M	65			-	-	-	-	-				-		Glycosuria
MN 6792	F	22	-	+	-	-	-	-	-				-		Penicillin all
MN 6807	M	39	-		250	-	-	-	-				-		
MN 6811	M	54			-	-	-	-	-				-		Raynaud's synd
MN 6933	F	17	-		-	-	-	-	-				-		
MN 6998	F	52			-	-	-	-	-						
MN 7345	M	31			-	-	-	-	-				-		
MN 7390	M	36	-	+	25,000	16	-	-	-				-		Hashimoto's di
MN 7476	F	71			-	-	-	-	-				-		Arthritis
MN 7543	F	40	-		-	-	-	-	-				++		Raynaud's synd thyrotoxicosis
MN 7550	M	22	-	+	-	-	-	-	-				-		
MN 7587	F	31	-		-	-	-	-	-				-		
MN 7720	F	50			-	-	-	-					+		Asthma
MN 7780	F	75											-		Pernicious ana
MN 7781	F	40			-	-	-	-							Severe thyroto
MN 7855	F	17			-	-	-	-					-		Non-toxic goit
MN 8088	F	35			-	-		-					-		
MN 8092	F	14			-	-	-	-					-		
MN 8170	M	52	-		-	-		-					-		
RI.1	M	67			-	-	-	-	-						
RI.2	M	66			-	-	-	-	-						
Positive			2			12	3		0		1		8	0	
Total			53			44	44		36		9		45	9	

Table 13, 1. Serum Antibodies.

		A.N.F.	R.F. †	Muscle	Thyroid	Stomach	Liver
Present Series	Positive	8	0	1	10	3	0
	Total	40	8	10	38	37	35
White & Marshall (1962)	Positive	6	2		1		
	Total	15*	15		15		
Van der Geld et al (1963)	Positive	11	5	38	36		
	Total	111	111	98	111		

Table 13, 2. Antibodies detected in sera from patients with myasthenia gravis.

* One case of carcinomatous myasthenia excluded.

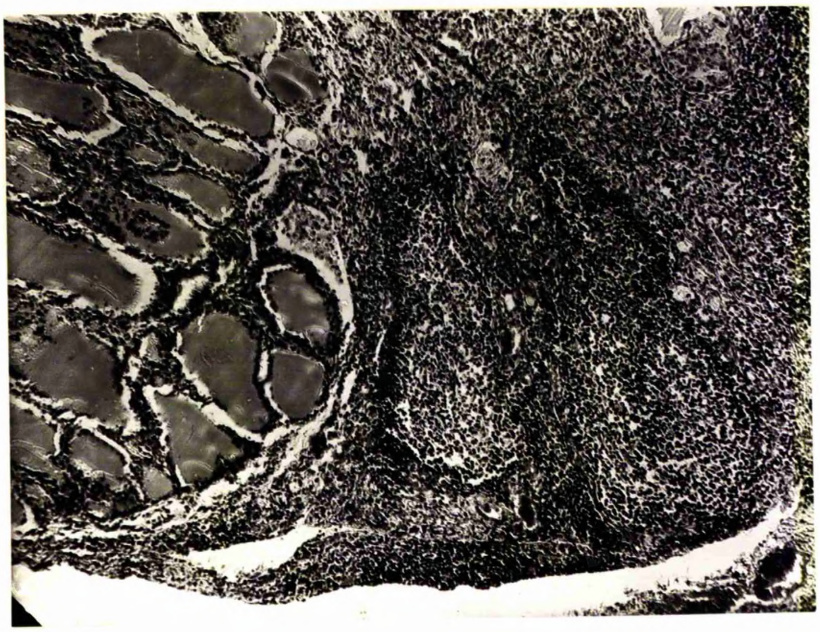
† Rheumatoid factor - S.S.C.T. in present series, latex test in others.

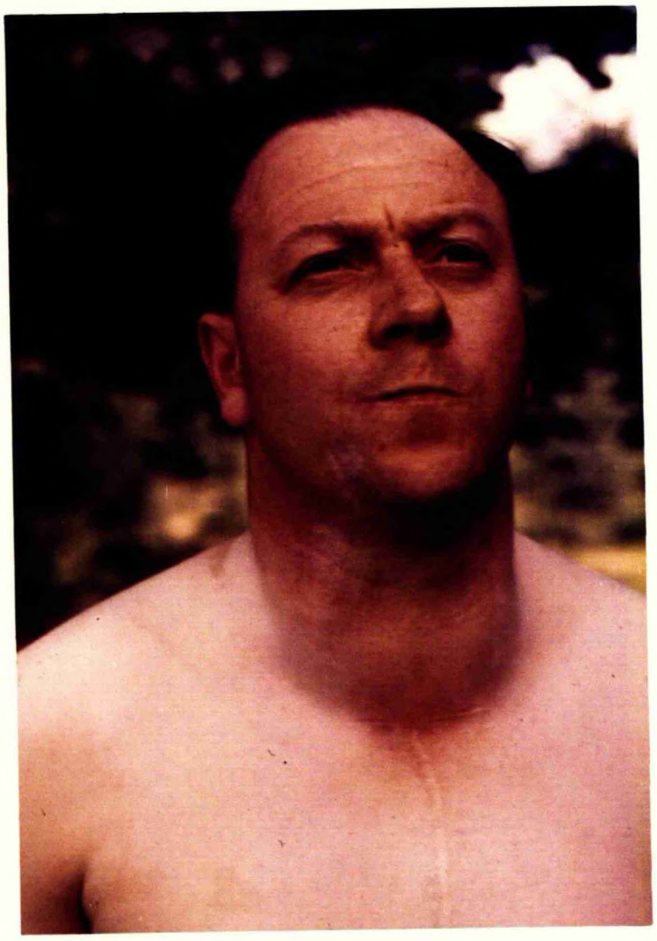
Fig. 13, 1.

Case 7290. Hashimoto's disease developing after thymectomy for myasthenia gravis.

a) Photomicrograph of thyroid gland.
H & E x 42.

b) Diffuse goitre, pigmentation of head and neck, and vitiligo.





	Present Series° London	Present Series° Scotland	Osserman (1958)	Storm-Mathisen (1962)	White & Marshall (1962)	Oosterhuis (1963) ‡
Thyroid (all types)	67	19	17	5	3	15
Diabetes & glycosuria	9	7	8		1	6
'Rheumatoid' arthritis	12	6	15	3	2	6
Systemic L.E.	1				1	
Cutaneous L.E.					1	
Sarcoidosis	1					
Red cell aplasia	1					2
Pernicious anaemia	1	8				1
Haemolytic anaemia		2 †		1		
Hepatitis		2 †	2			2
Nephritis	2		1	1 (?)		
Raynaud's syndrome	10	6				7
Epilepsy and 'blackouts'	5	6	2			1
Psychosis	9	1	14	4		3
Patients	407	84	325	90	15	154

Table 13, 3. Disorders associated with myasthenia gravis.

° The series reported by Simpson (1960) includes all the London cases and the first 33 from Scotland.

* Includes one case of Hashimoto's disease and two of lymphadenoid thyroid at autopsy.

† Considered to be caused by medication.

‡ Includes series previously reported by Van der Geld et al (1963).

Fig. 15, 1. Diagram of motor nerve termination and neuromuscular junction.

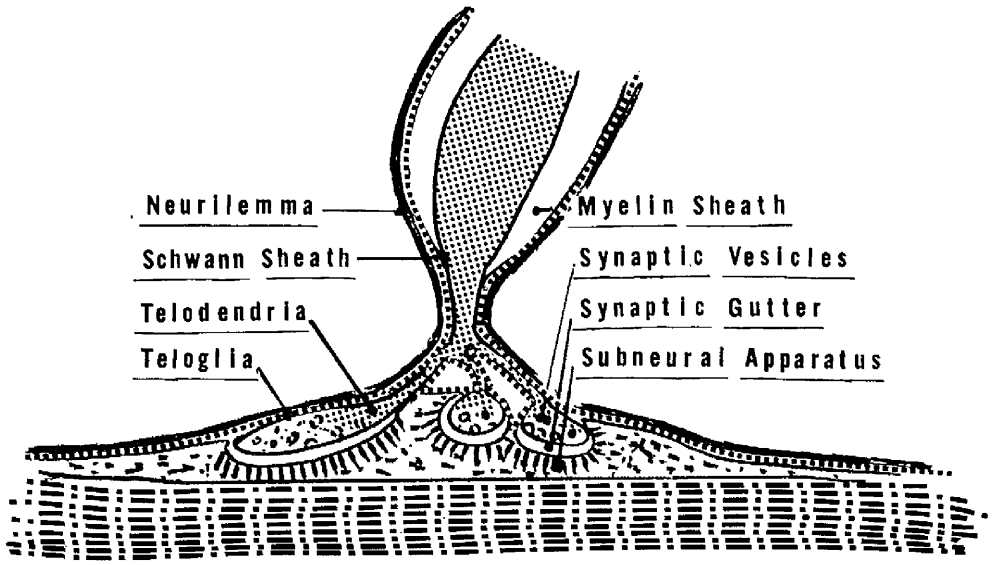

Neurilemma
Schwann Sheath
Telodendria
Teloglia
Myelin Sheath
Synaptic Vesicles
Synaptic Gutter
Subneural Apparatus

Fig. 15, 2. Case MN 5401.

a) Electromyograph of sustained voluntary contraction of right deltoid muscle recorded by a co-axial needle electrode. The film has been stopped at three points but the record is otherwise continuous. Note the progressive decrement and simplification of the record as 'myasthenic fatigue' occurs but the single units, recognizable towards the end of the contraction, stop firing suddenly without further decrement. There is temporary post-tetanic facilitation after a brief 'rest'.

b) The same muscle to show marked insertion activity and spontaneous fibrillation at rest.

Fig. 15, 3. Myopathic motor units in myasthenia gravis.

a) Case MN 3054, myopathic unit at slight contraction.
b) Same case, stronger contraction.
c) Case NH 980, myopathic units at slight contraction.
d) Same case, full interference pattern at maximal effort.
e) Case NH 5233, spontaneous single fibre potentials (fibrillation).

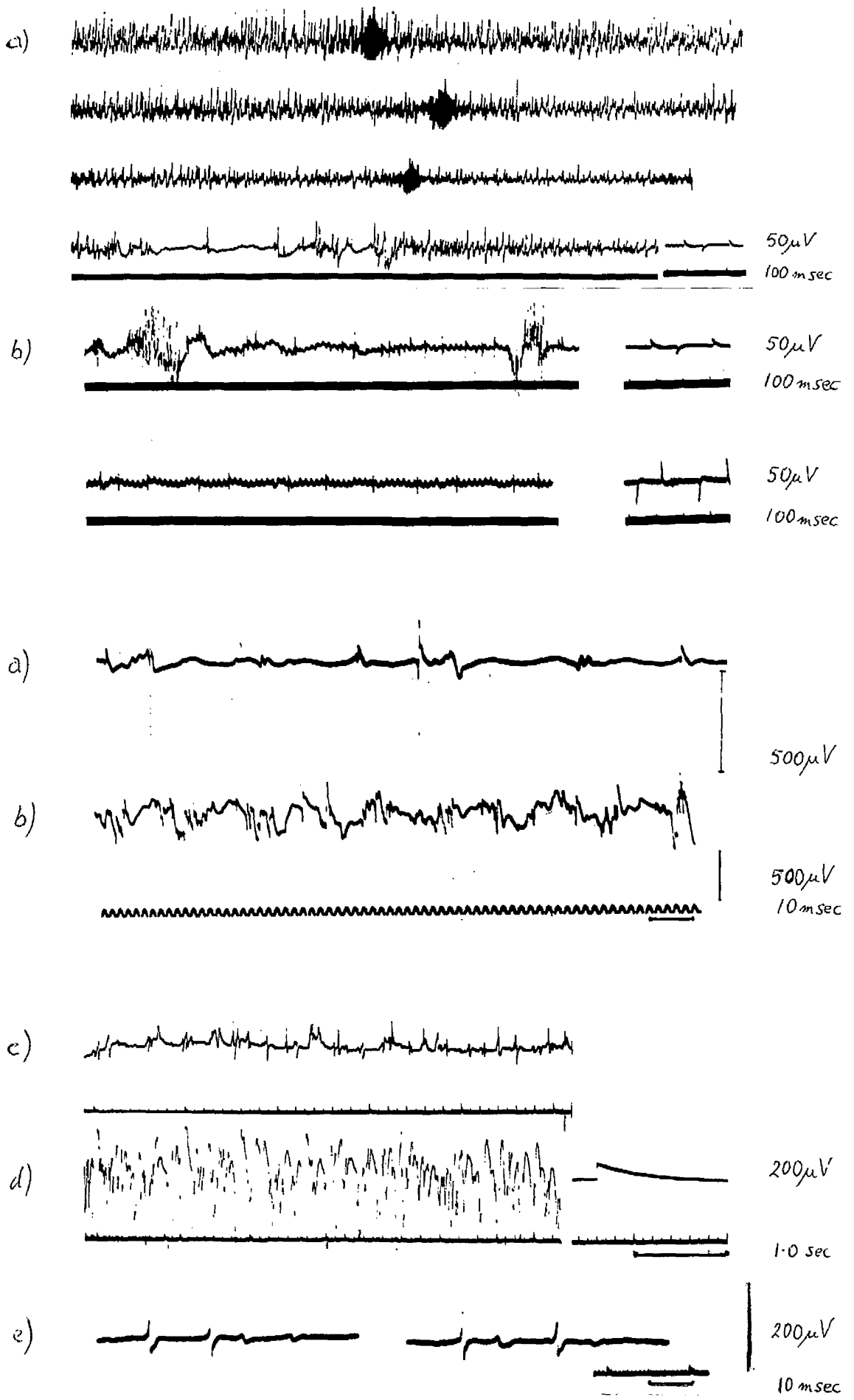

a)
50μV
100 msec
b)
50μV
100 msec
50μV
100 msec
a)
500μV
b)
500μV
10 msec
c)
d)
200μV
1·0 sec
e)
200μV
10 msec

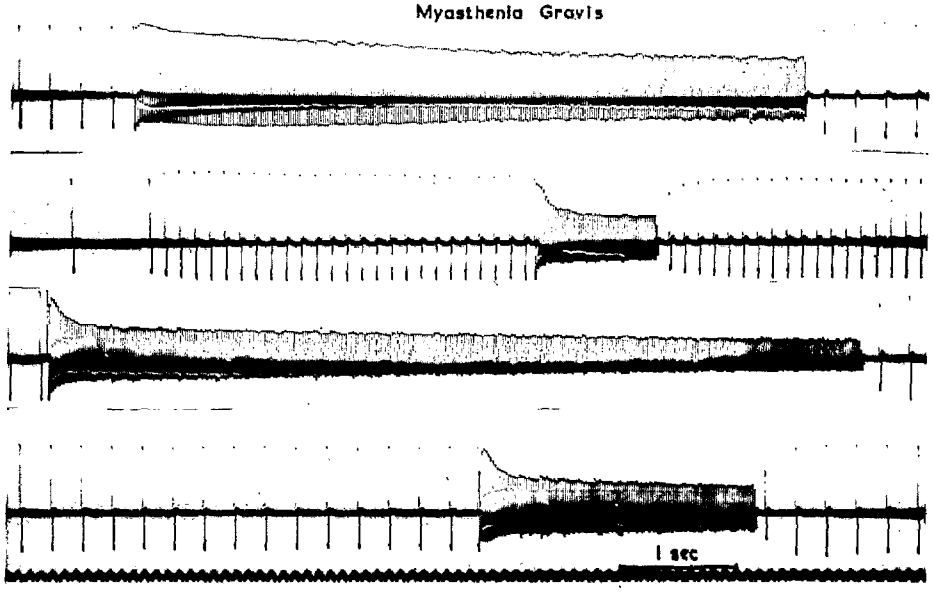
Fig. 15, 4.

Case MN 294. Positive Harvey-Masland test with decremental response to stimulation at 50/sec. but not at 10/sec. or slower. There is slight post-tetanic potentiation.

Fig. 15, 5.

Case MN 382. Decremental response in right abductor digiti minimi. Immediate decremental followed by prolonged facilitation and then delayed decrement in left triceps muscle.

Myasthenia Gravis



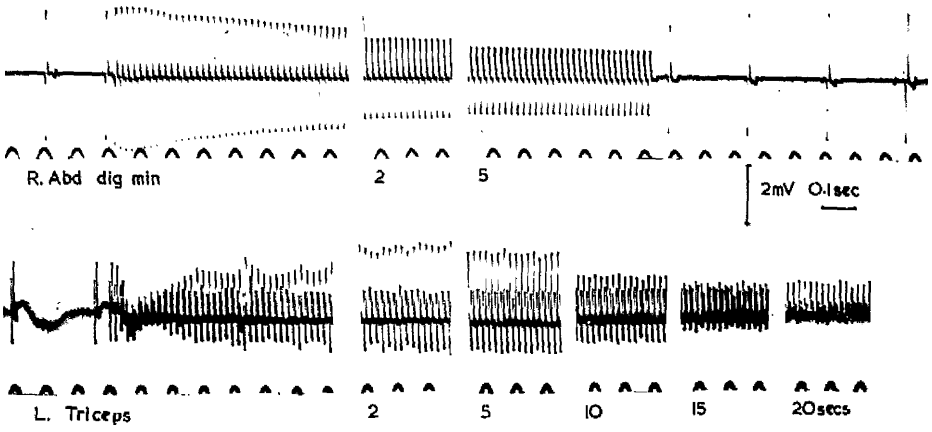


Fig. 15, 6. Early and sustained facilitation response to supramaximal neural stimulation.

a) Case MN 3609. Stimulation at 10/sec.
b) Case MN 4084. Stimulation at 16/sec.

Fig. 15, 7. Post-tetanic facilitation.

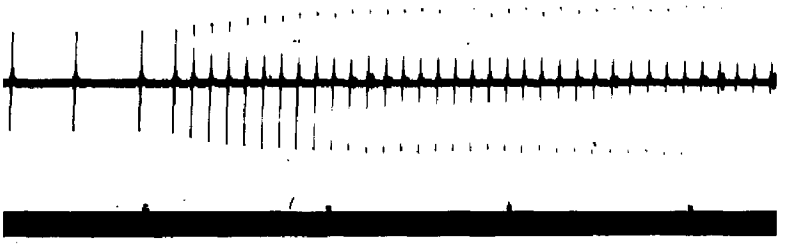
a) Case MN 3054. (The fourth line shows the improved maintenance of the muscular action potential after Hexadistigmin I.V.)
b) Case MN 5652.

Fig. 15, 8.

Case MN 2914. Decremental response to stimulation at 10/sec. but incremental response at 50/sec.

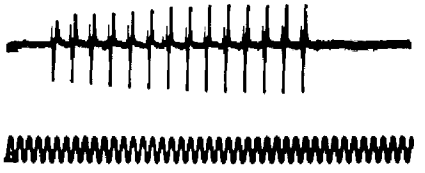
15,6

a)



1·0 sec

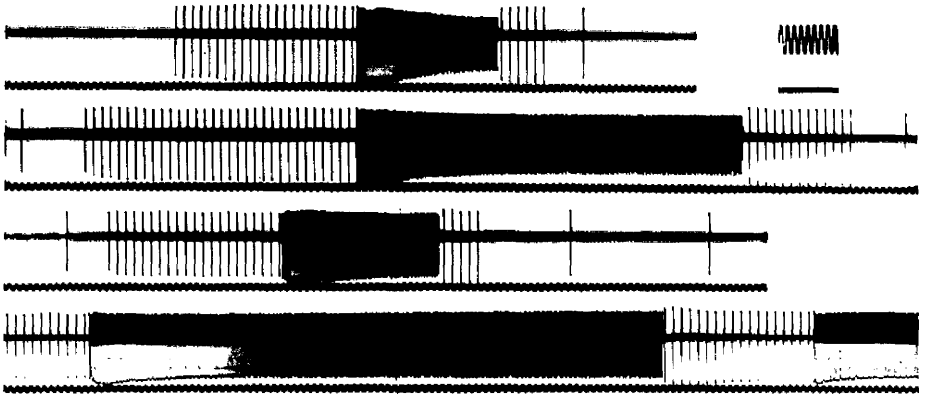
b)



50 c/s.

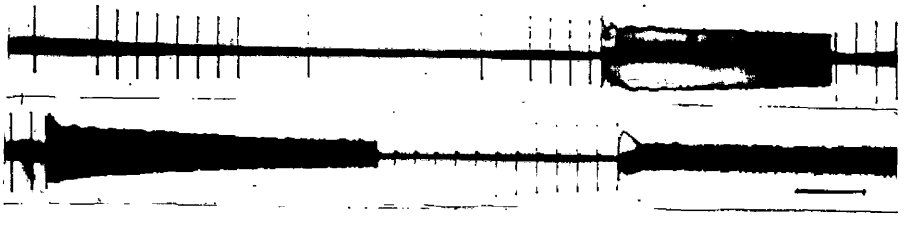
15,7

a)



5 mV
10 c/s

b)



1·0 sec

15,8

10 c/s

Fig. 15, 9.

Case MN 2143. The records read continuously. Gaps in the recording are indicated (3", etc.) but stimulation was not interrupted. The Harvey-Masland test appeared to be negative until the fifth burst of stimulation at 50/sec.

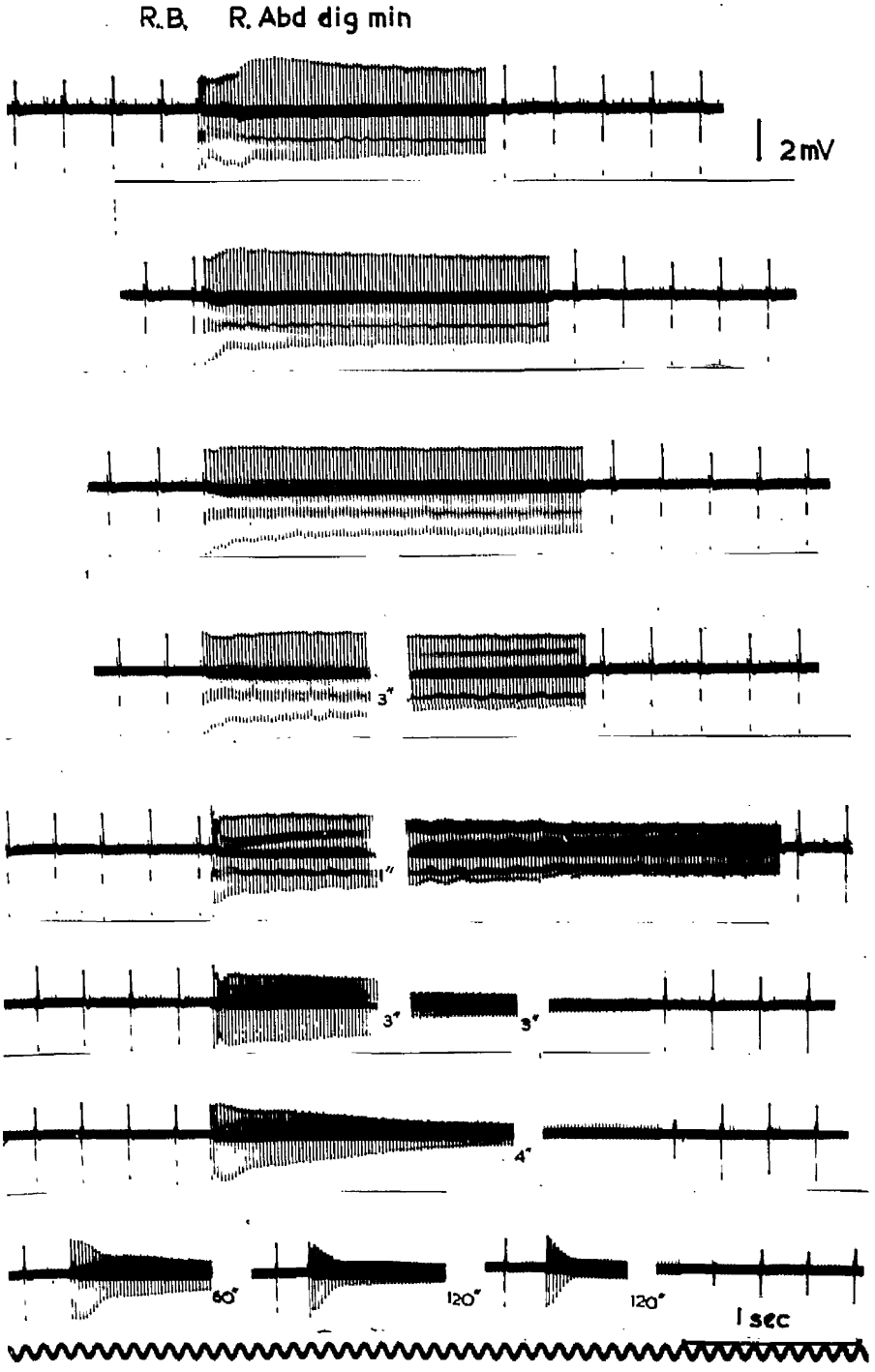

R.B. R. Abd dig min
2mV
3"
1"
3"
3"
4"
60"
120"
120"
1 sec

Fig. 16, 1. Personal theory of nature of drug action at the neuromuscular junction (from Simpson, 1960a).

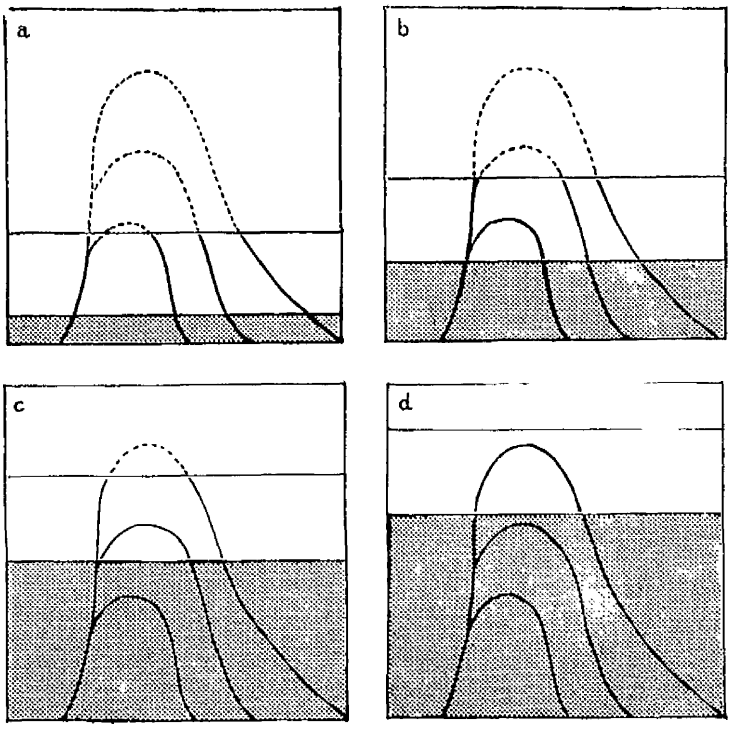


Fig. 15. Time course (diagrammatic) of rise and fall of charge-density at motor end-plate of muscle for three doses of a depolarizing substance such as decamethonium to show the differing effects due to dose level, particularly in the recovery stages. The shaded area indicates the zone of competition with acetylcholine, increased from *a* to *d* by a hypothetical competitive substance. If the charge-density rises to the value between the horizontal lines (constant in each diagram), propagated action potentials occur. If the charge-density rises rapidly above this zone (dotted part of curves), the resulting twitch is brief and the muscle is then paralysed by depolarization block. As the drug is dispersed, the charge-density falls through the critical zone but 'desensitization' prevents further response. If the dose is sufficiently high the prolonged effect may cause facilitation of test stimuli. When there is a substance competing for end-plate receptors (*b*—*d*), only the biggest doses causes depolarization block, and this is succeeded by competitive block (mixed responses)'. A lower dose, sufficient to block the normal end-plate, causes only stimulation—'decamethonium resistance'. (Compare lower two curves in *a* and *c*.)

Fig. 17, 1. Ptosis in a case of myxoedema. No response to edrophonium. The upper photograph shows the patient before she became myxoedematous.

Fig. 17, 2. Decamethonium test. There is a clear difference in the ability of this drug to block neuromuscular transmission in the myasthenic patients. The two patients with 'pseudo-myasthenia' (Chapter 9) show initial resistance followed by a degree of block which is intermediate between true myasthenics and normal subjects.

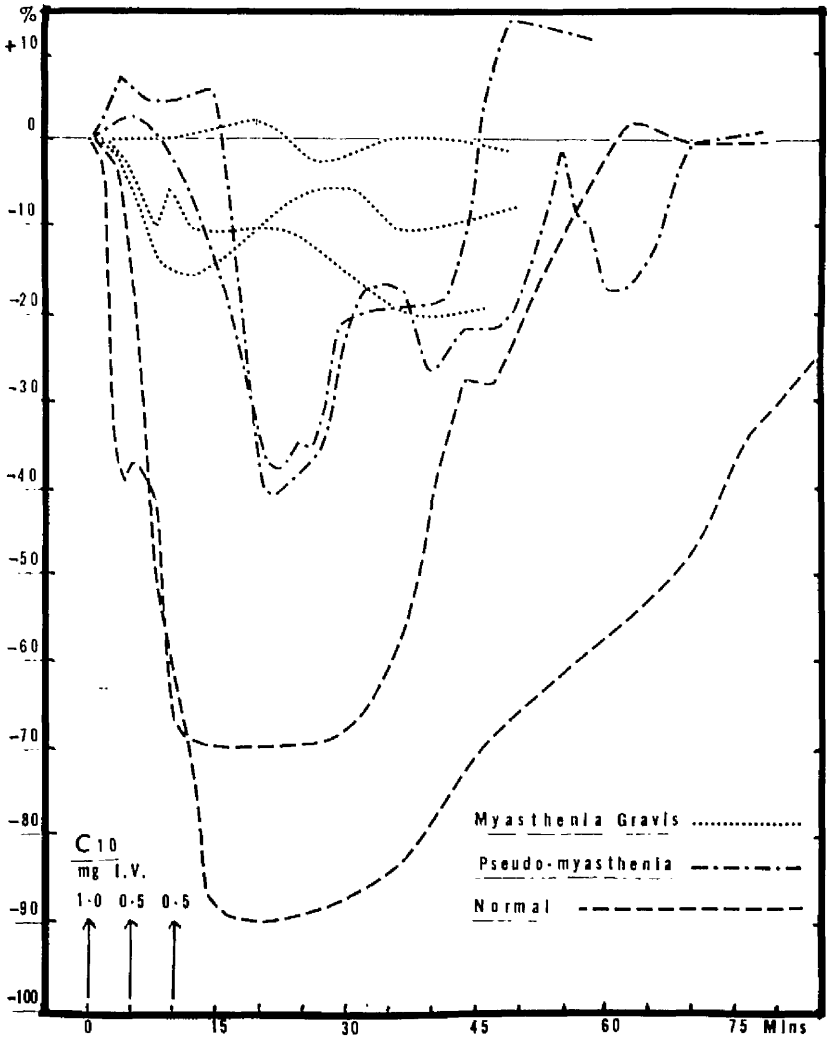
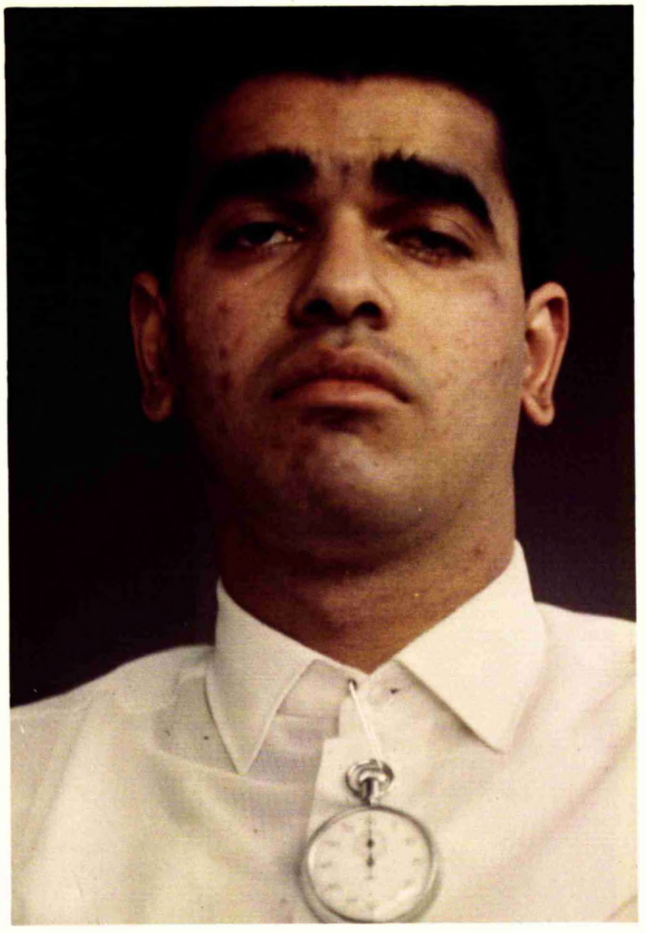

%
+10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
0
15
30
45
60
75 Mins
C10
mg I.V.
1·0 0·5 0·5
Myasthenia Gravis
Pseudo-myasthenia
Normal

Fig. 17, 3. Edrophonium test. The stopwatch was started when 10mg. had been injected into the vein. Ptosis is relieved in 45 seconds.



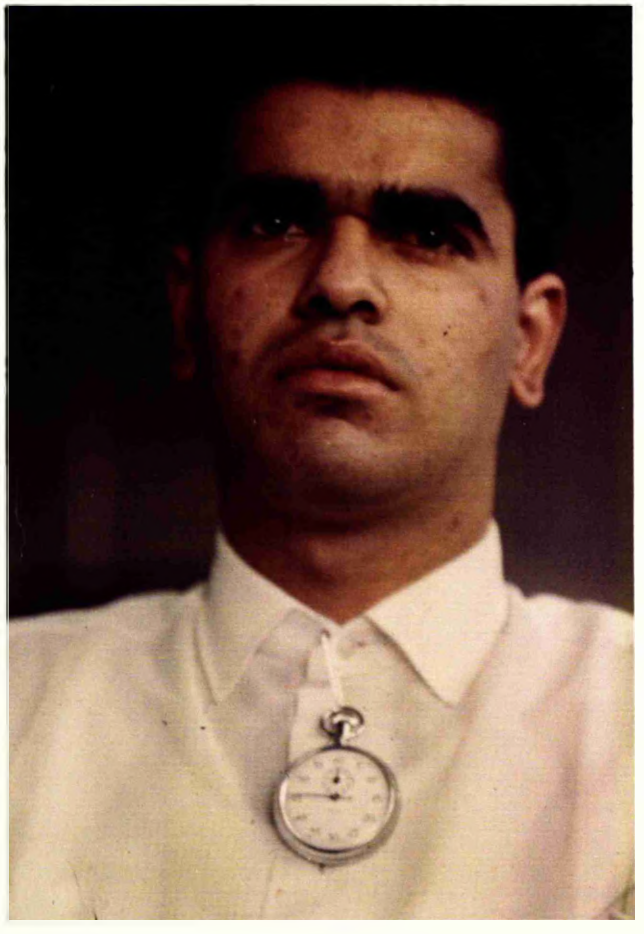
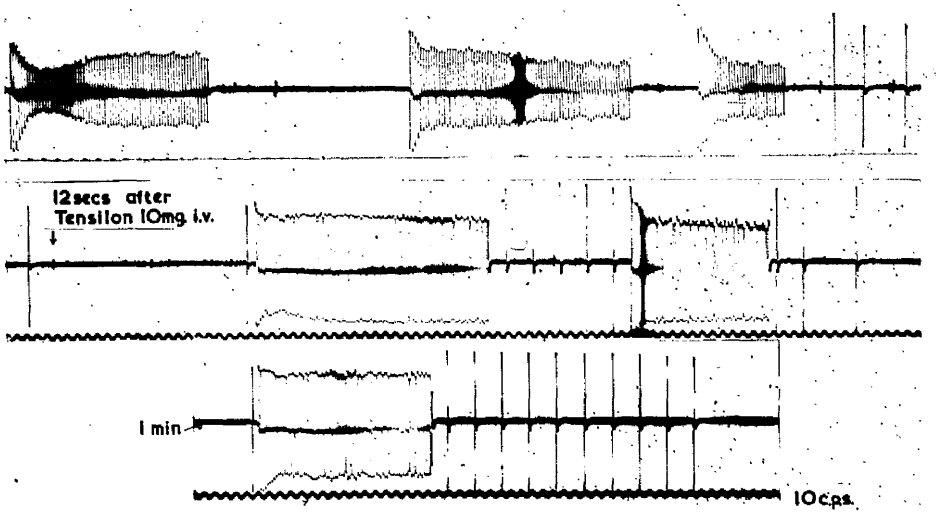


Fig. 17. 4.

Case MN 1714. Edrophonium test. A tetanus is well maintained 12-60 seconds after intravenous injection of 10mg. The post-tetanic facilitation shows that the response is not maximal.

Fig. 17. 5.

Case MN 3054. Edrophonium test. Positive response.


12secs after
Tension 10mg i.v.
1 min
10cps.

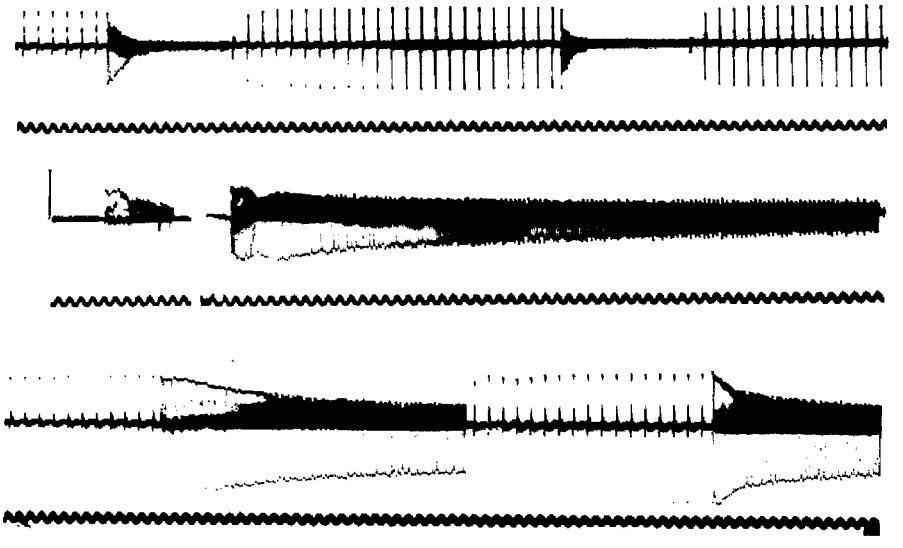
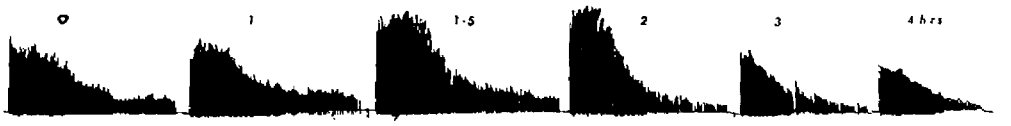

200μV
10 c/s

Fig. 18, 1.

a) Ergographic recording of repeated flexion of right index finger against a spring load at intervals after a dose of pyridostigmine. Note that the patient is capable of stronger contraction while the drug is active but the rate of fatigue is greater so that there is little difference at the end of each series of contractions.

b) Diagram of duration of effective action of three anticholinesterase drugs to show the necessity for suitable timing of dosage.


0
1
1-5
2
3
4 hrs

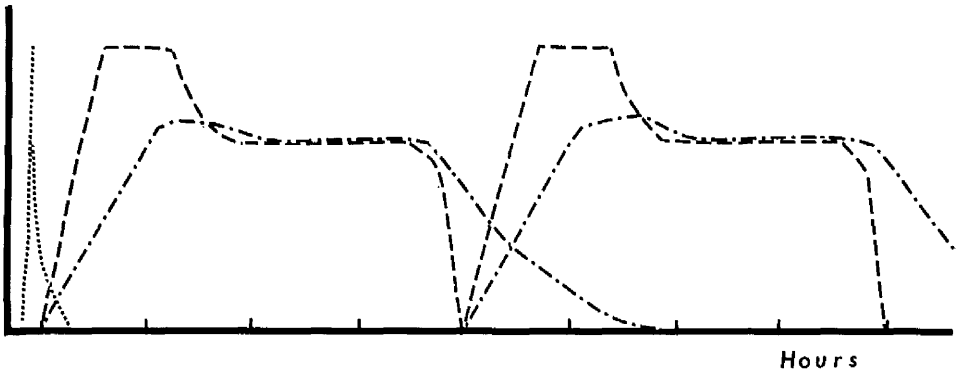

Hours
Edrophonium
Neostigmine
Pyridostigmine

Fig. 18, 2. Trial of Hexadistigmin 0.3mg. intravenously (Case MN 294). Ptosis was decreased from 4-8 minutes and borborygmi occurred at six minutes. A tetanus was better sustained from 10-18 minutes after the injection but the Harvey-Masland test shows that the response was sub-optimal.

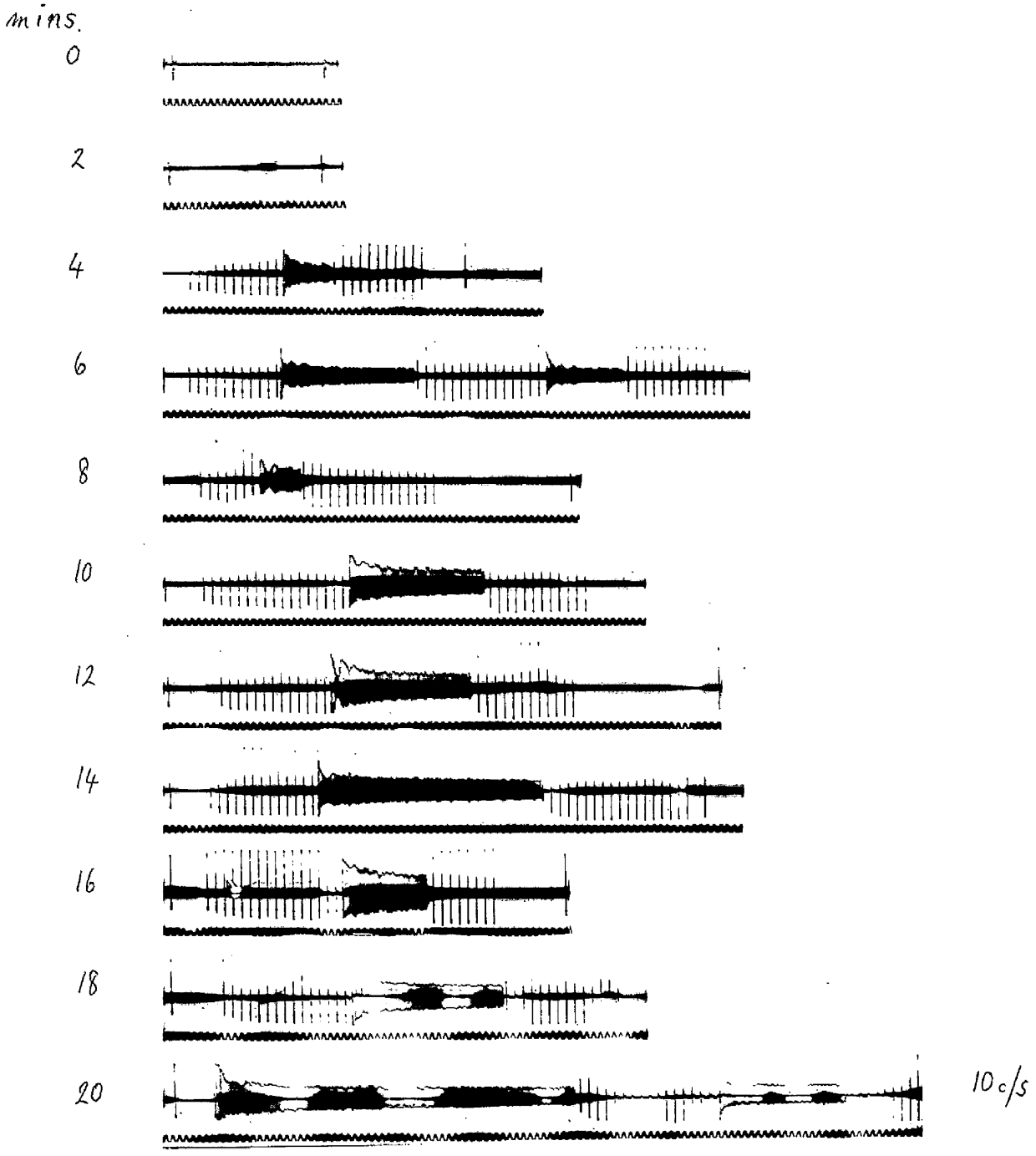
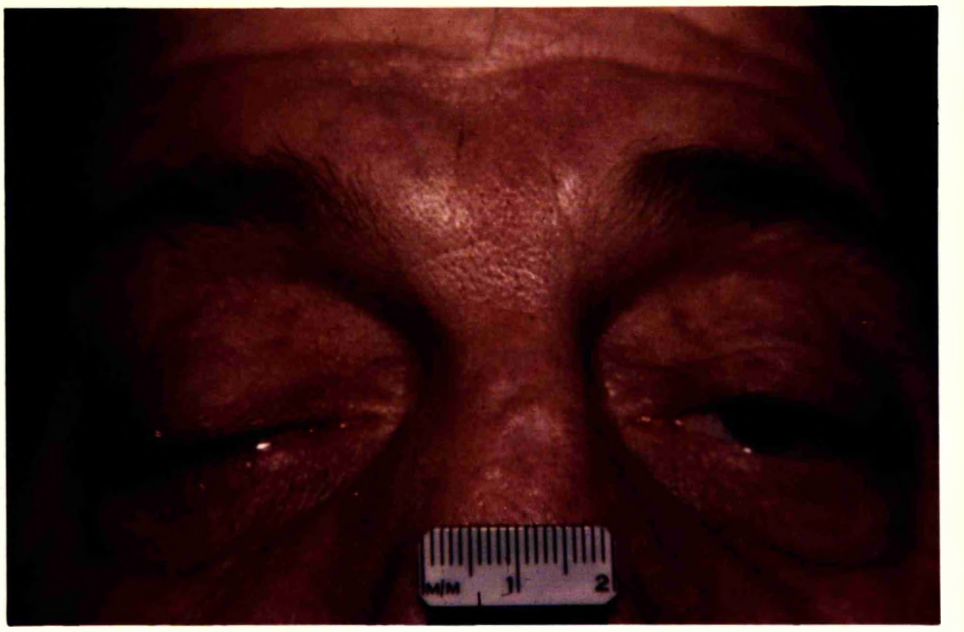

mins.
0
2
4
6
8
10
12
14
16
18
20
10 c/s

Fig. 18, 3.

Case MN 6289. Severe ptosis which no longer responds to neostigmine, partially corrected by plastic surgery.


M/M
1
2

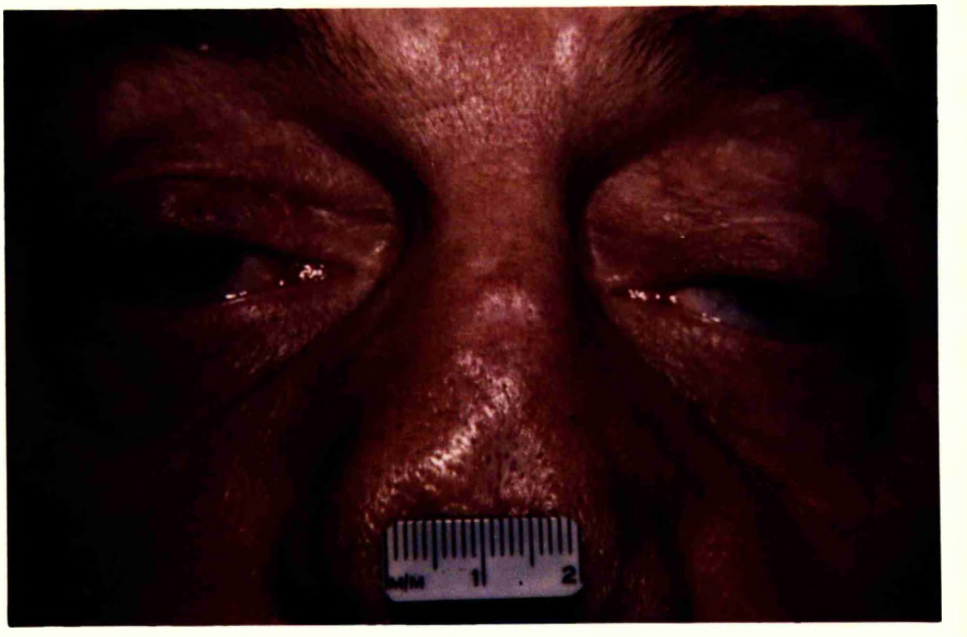

M/M
1
2

Fig. 18, 4.

Case MN 5095. Tracheostomy with positive-pressure respiration and feeding by nasal tube or by gastrostomy may be life-saving. The air pumped from the ventilator passes over a humidifier and is led by a lagged tube to a flutter valve. A pressure gauge is connected between the flutter valve and the connection to the cuffed tracheostomy tube.

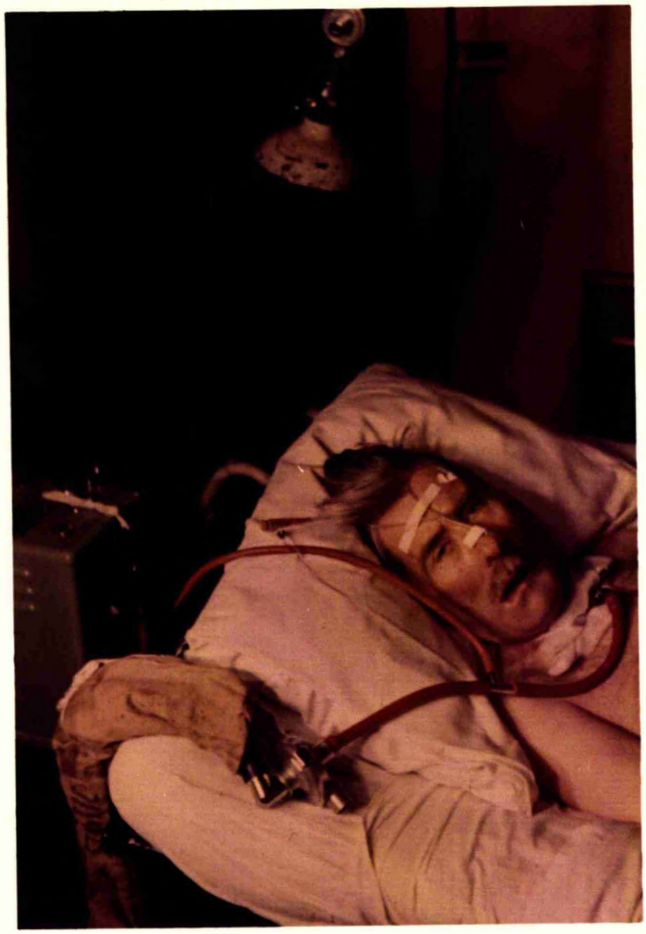
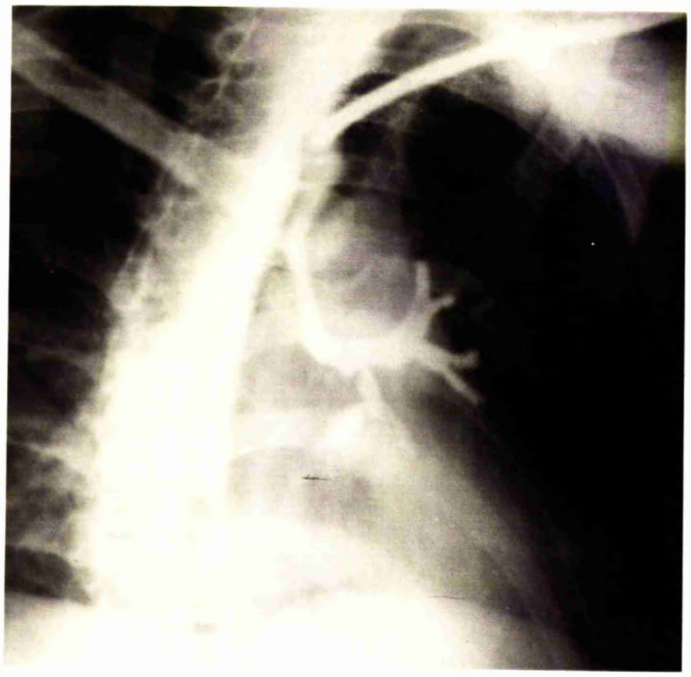


Fig. 18, 5.

Case MN 5652. Even with a cuffed tracheostomy tube, pharyngeal contents may enter the lungs. Lipiodol placed in the mouth is shown to enter the left main bronchus, having passed the inflated cuff.



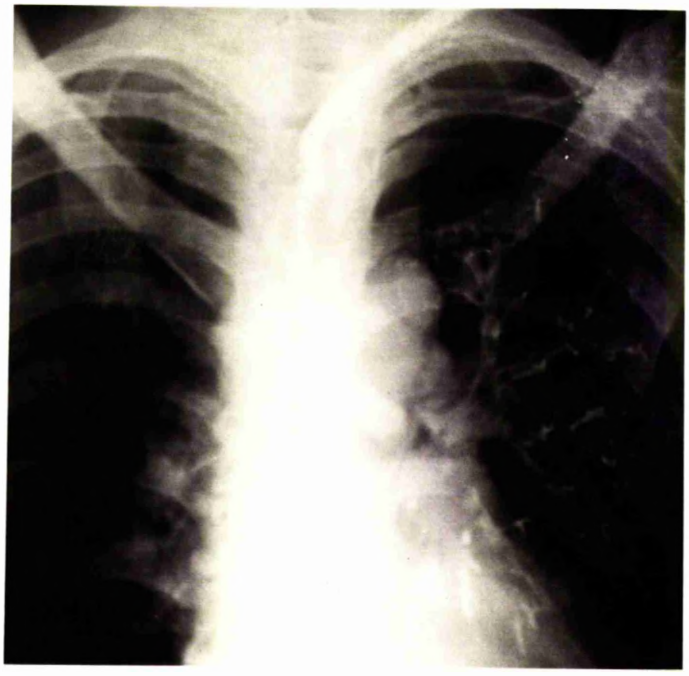


Fig. 19, 1. Ergograph used to record response to edrophonium two hours after oral dose of an anticholinesterase drug. The response shows that the patient is underdosed.

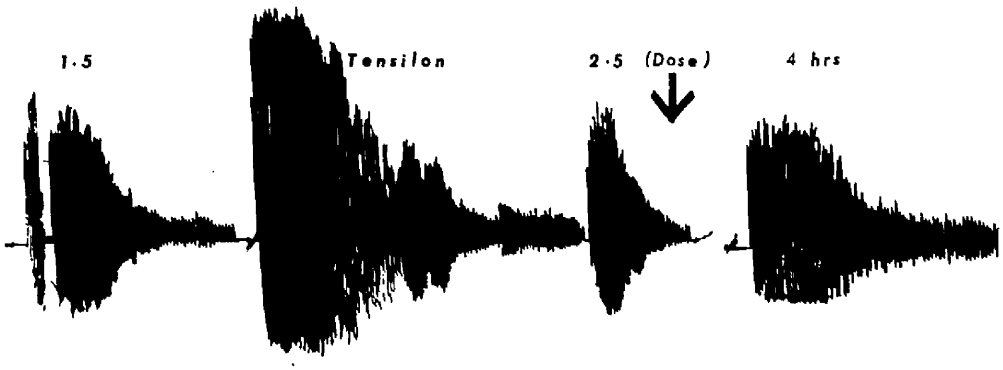

1·5
Tensilon
2·5 (Dose)
4 hrs

Fig. 19, 2. Intravenous infusion of neostigmine may decrease the power of some muscles while increasing the power of those more severely affected by myasthenia gravis. (Fig. 3 of Rowland et al, 1955).

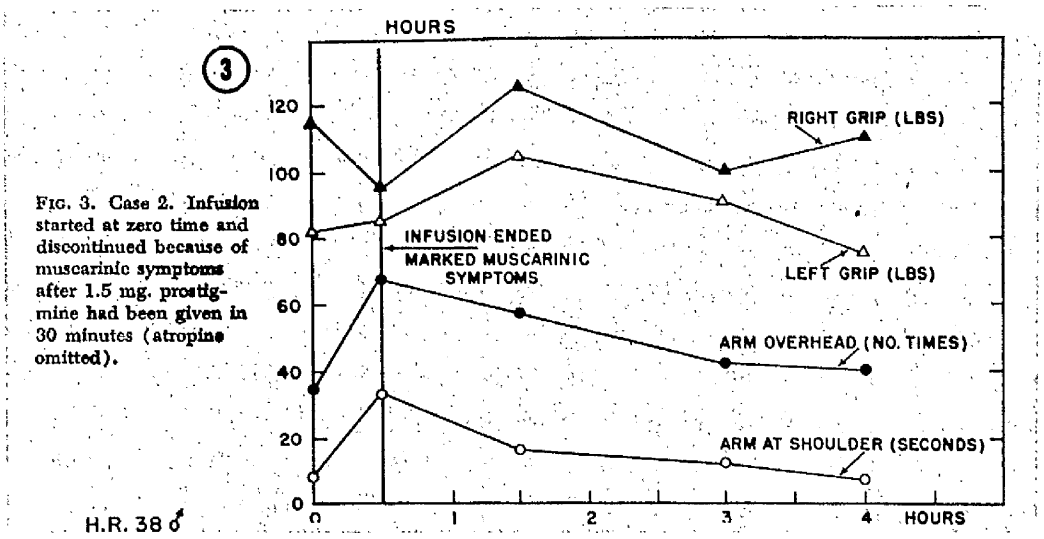


FIG. 3. Case 2. Infusion started at zero time and discontinued because of muscarinic symptoms after 1.5 mg. prostigmine had been given in 30 minutes (atropine omitted).

Fig. 19, 3.

Case MN 5095. Stage 1.
Gradual onset of cholinergic weakness, increasing fasciculation, miosis and sweating. Equivocal results of edrophonium testing based on subjective response. The neostigmine injected intramuscularly is charted on an equivalence of 1mg. to 10mg. by mouth. Unsatisfactory response to P.A.M. 500mg. I.V.
Hypotension soon after injection of P.A.M. Haemolysis and oliguria three days later but power improved and less fasciculation.

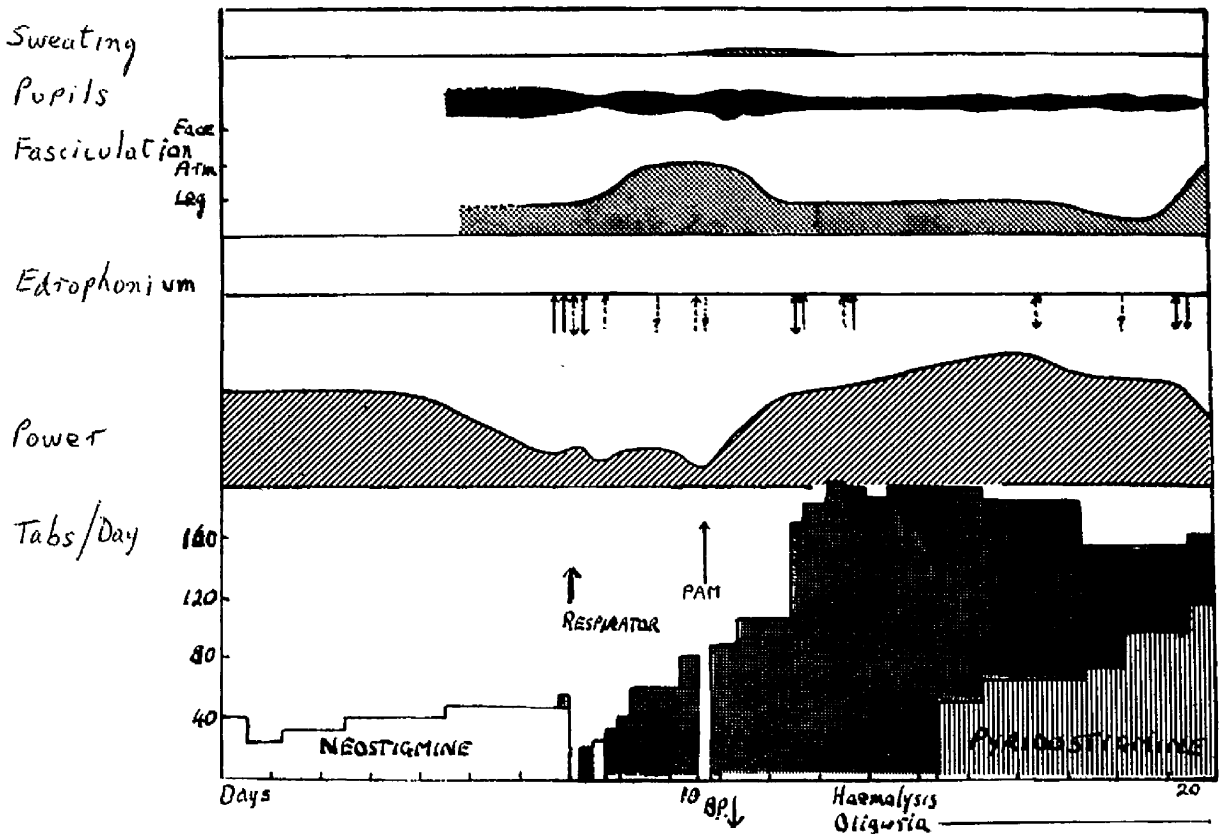
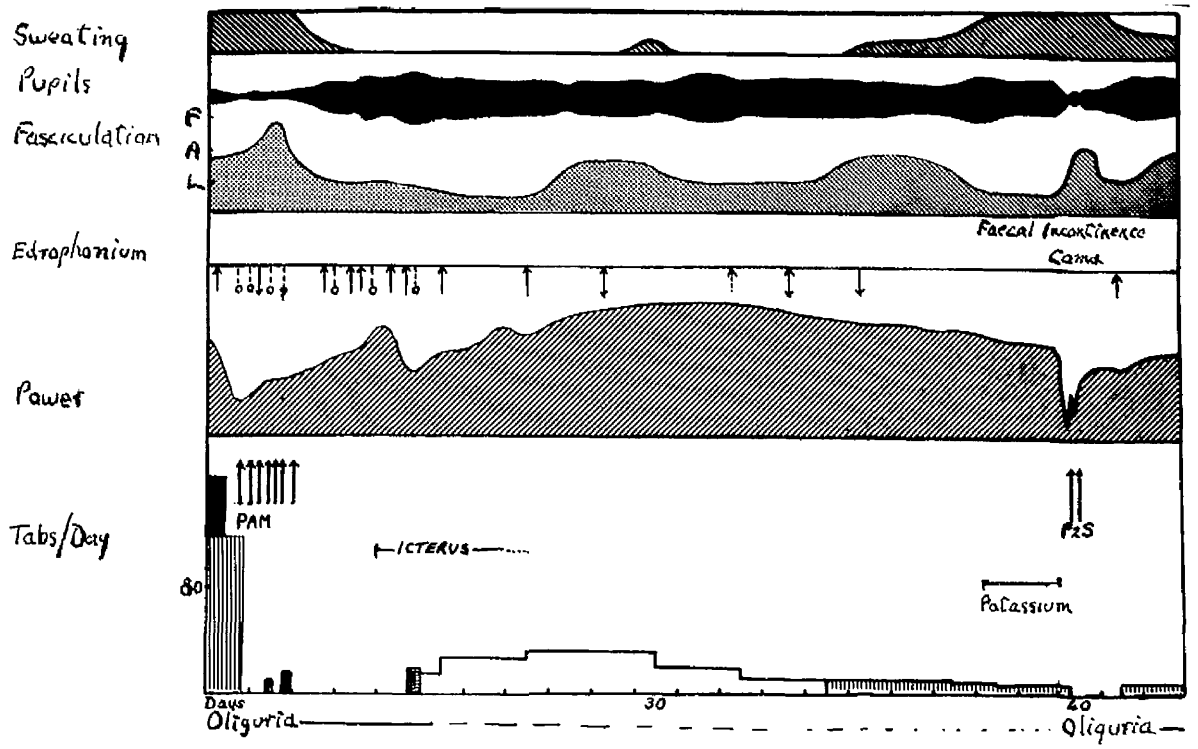

Sweating
Pupils
Fasciculation
Face
Arm
Leg
Edrophonium
Power
Tabs/Day
160
120
80
40
RESPIRATOR
PAM
NEOSTIGMINE
PYRIDOSTIGMINE
Days
10
BP
Haemolysis
Oliguria
20

Fig. 19, 4. Stages 2 and 3.

Continuation of Fig. 19, 3 showing onset of renewed cholinergic crisis, delayed response to P.A.M., icterus three days later. Neostigmine by injection resumed on day 24 and pyridostigmine on day 34. The latter was associated with gradual return of cholinergic signs. Sudden crisis on day 40 treated with P_2S.

Fig. 19, 5. Stage 2 - enlarged scale.

Poor response of second cholinergic crisis (Stage 2) to repeated injections of P.A.M. Temporary increase of slight hypotension


Sweating
Pupils
Fasciculation
F
A
L
Edrophonium
Faecal Incontinence
Coma
Power
Tabs/Day
PAM
ICTERUS
80
PzS
Potassium
Days
30
40
Oliguria
Oliguria

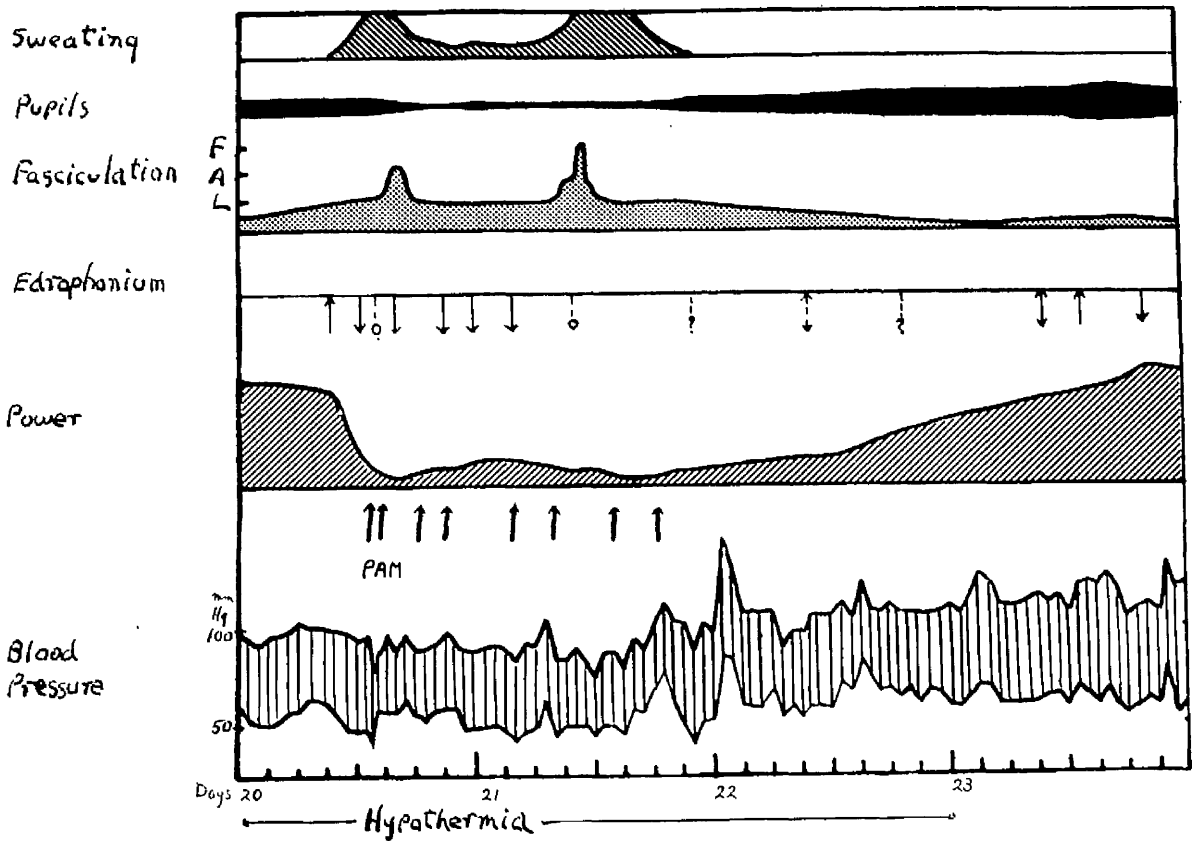
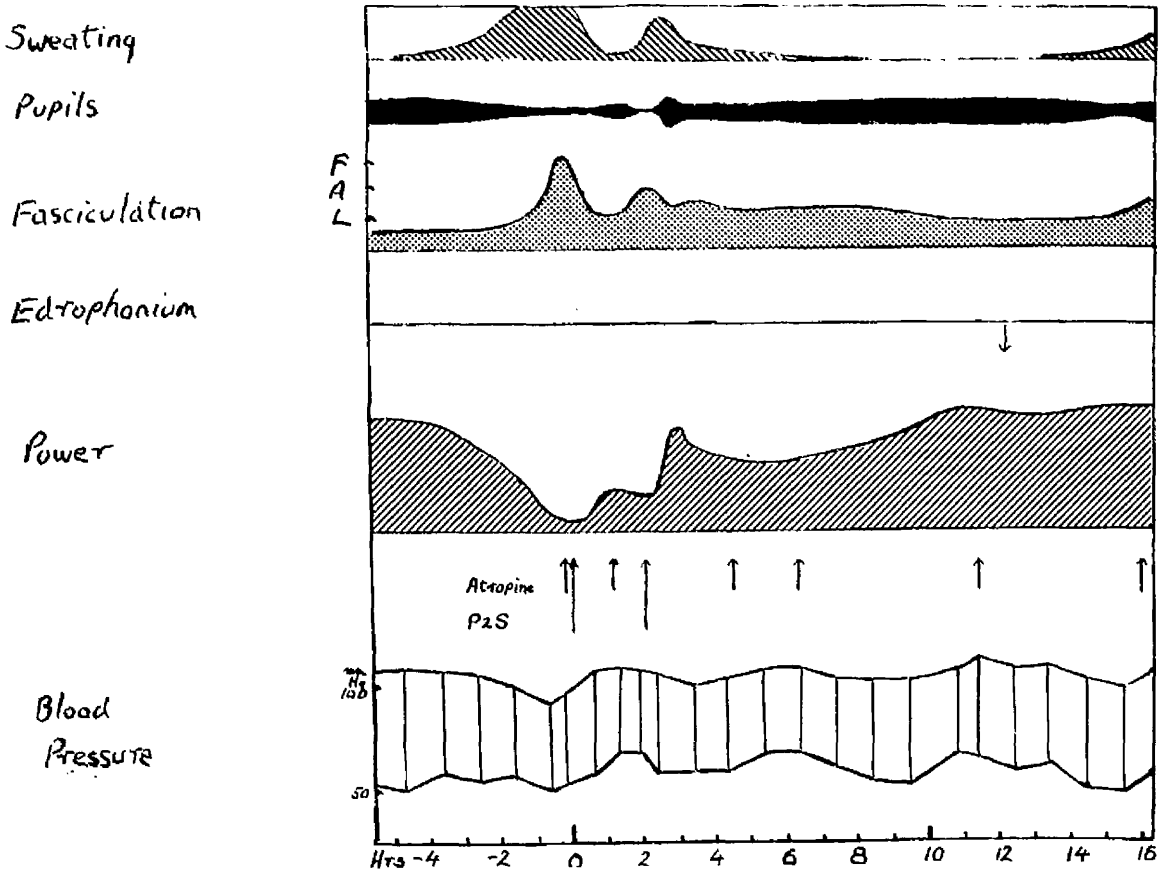

Sweating
Pupils
Fasciculation
F
A
L
Edrophonium
Power
PAM
Blood Pressure
mm Hg
100
50
Days 20
21
22
23
Hypothermia

Fig. 19, 6. Stage 3 - enlarged scale.

Response to P_2S in one hour but pupils relatively unaffected.

Fig. 19, 7. Stage 4.

Relatively smooth control on a small dose of pyridostigmine (360mg/day). Sweating and fasciculation persist, especially when potassium added, but pupils not constricted. Gradual deterioration starting at day 58 despite absence of muscarinic signs.


Sweating
Pupils
Fasciculation
F
A
L
Edrophonium
Power
Atropine
P2S
Blood Pressure
mm Hg
100
50
Hrs -4 -2 0 2 4 6 8 10 12 14 16

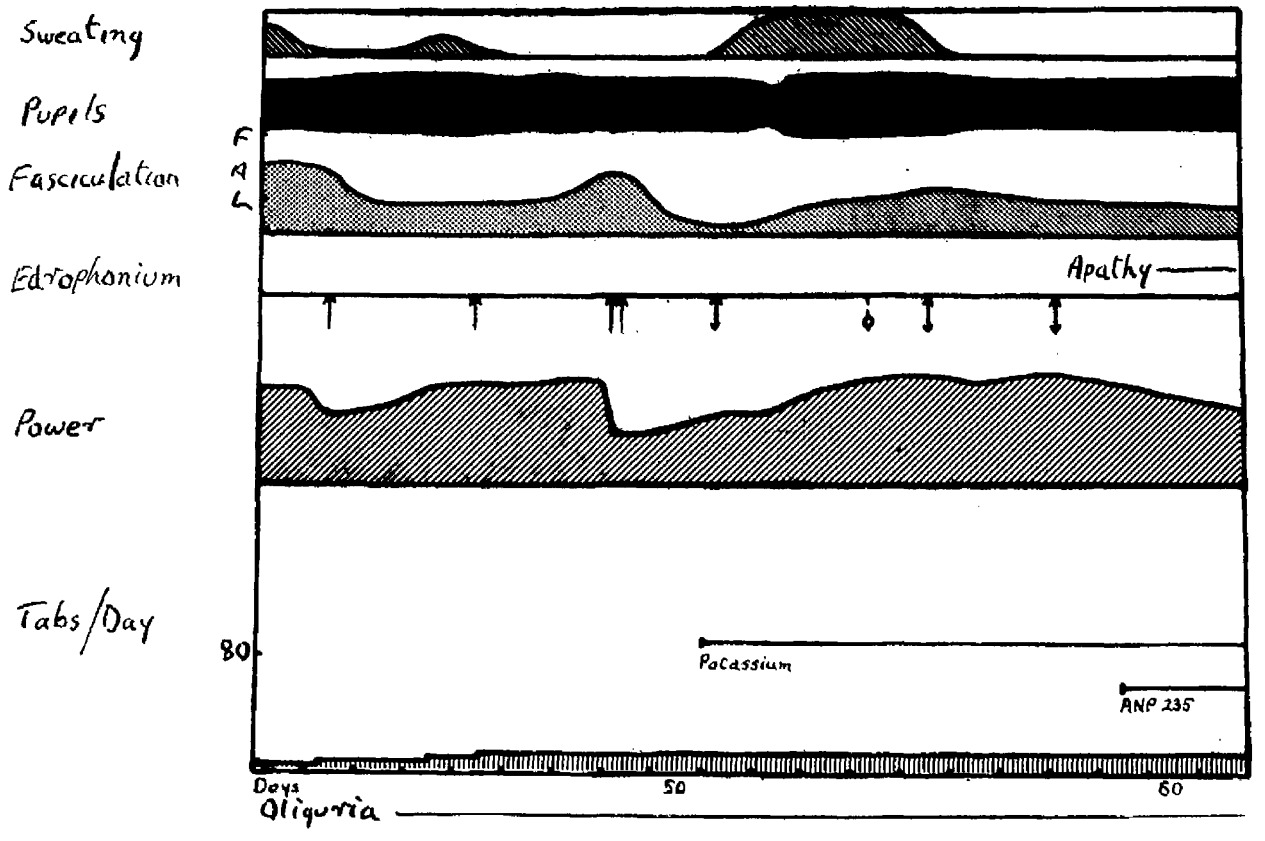
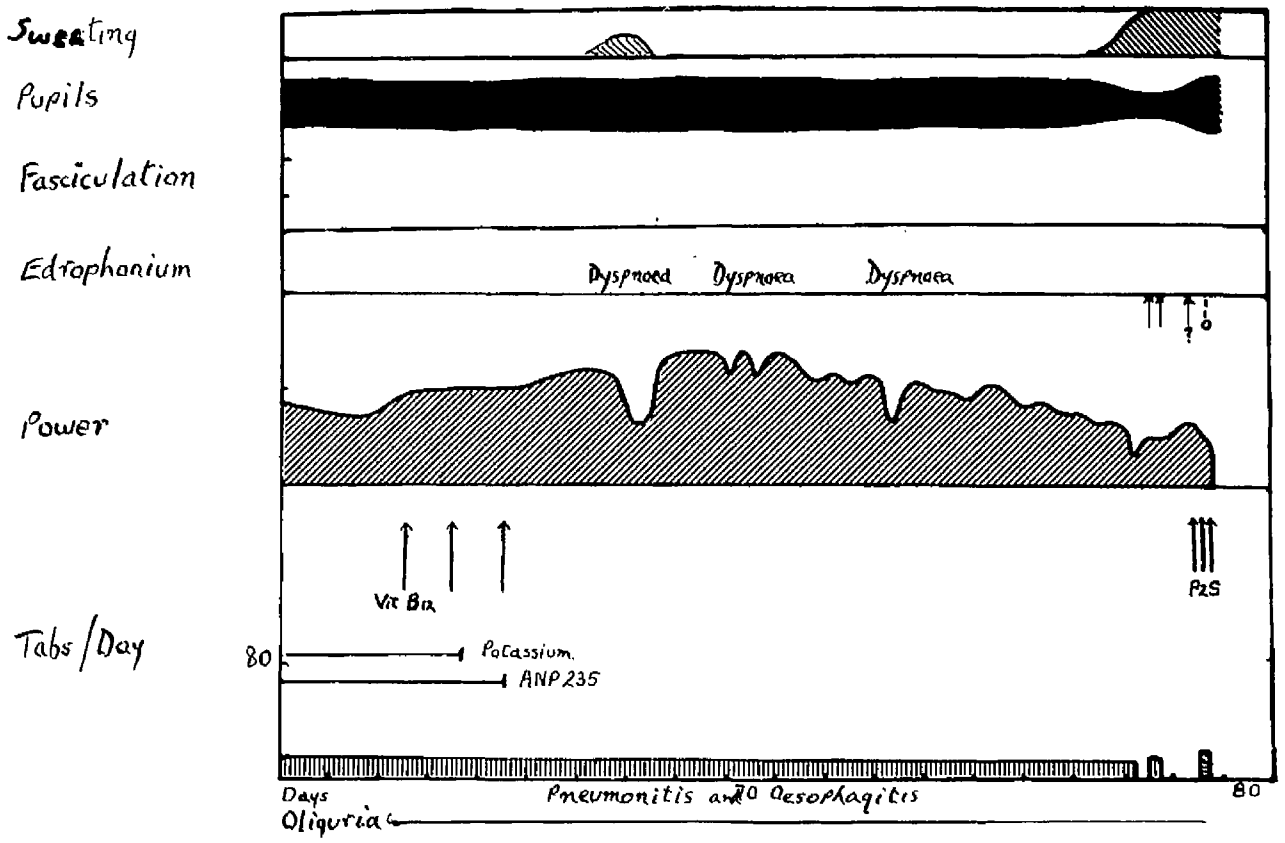

Sweating
Pupils
Fasciculation
F
A
L
Edrophonium
Apathy
Power
Tabs/Day
80
Pacassium
ANP 235
Days
50
60
Oliguria

Fig. 19, 8. Stage 5.

Continuing oliguria. General deterioration with aregenerative anaemia, pneumonitis, oesophagitis, and attacks of dyspnoea. Terminal deterioration with hypoxic signs resembling the muscarinic signs of the cholinergic state.

Fig. 19, 9. Stage 5 - enlarged scale.

Terminal pseudo-cholinergic state not improved by injection of P_2S and atropine.


Sweating
Pupils
Fasciculation
Edrophonium
Dyspnoea
Dyspnoea
Dyspnoea
Power
Vit B12
P2S
Tabs/Day
80
Potassium
ANP235
Days
80
Pneumonitis and Oesophagitis
Oliguria

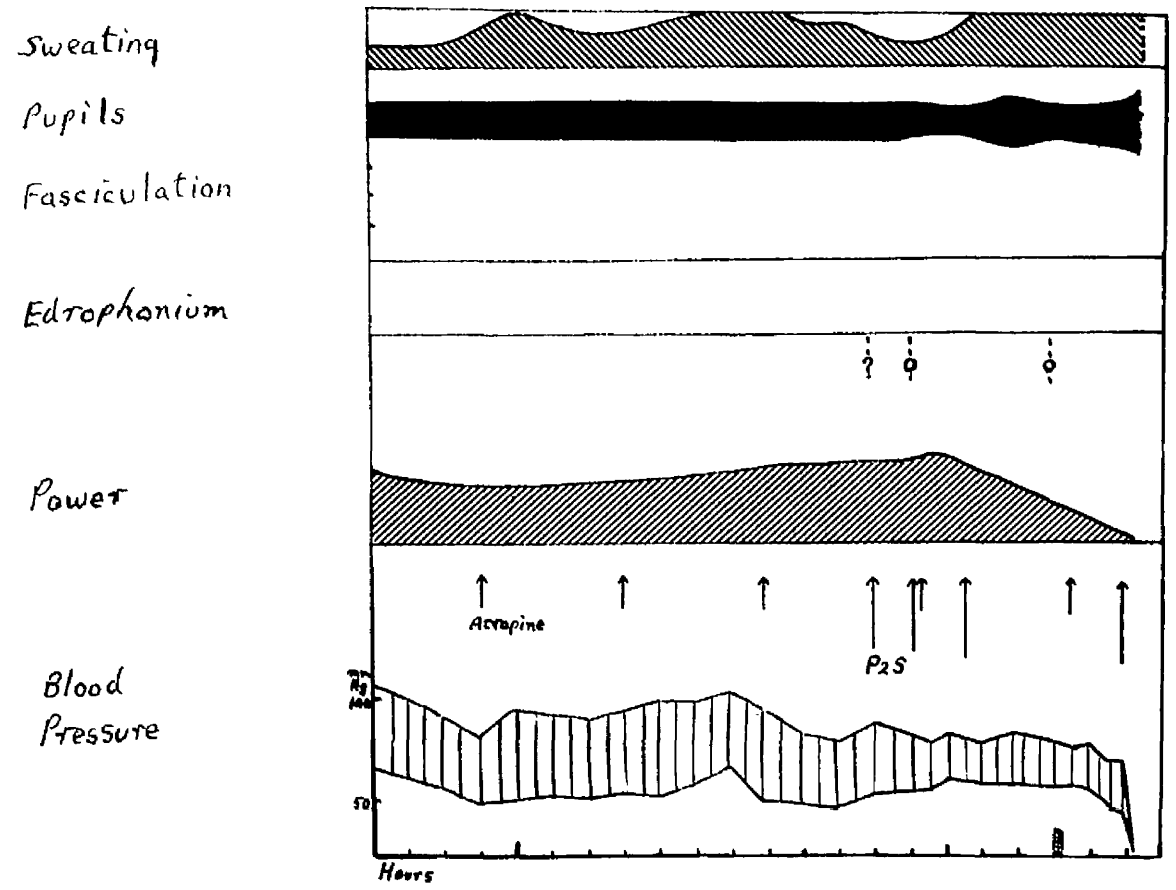

Sweating
Pupils
Fasciculation
Edrophonium
Power
Atropine
P2S
Blood Pressure
Hours

Table. 19, 8

Comparison of symptoms of ventilatory failure in neuromuscular disease (Simpson, 1964e).

		Under-Ventilation	Over-Ventilation	Myasthenic Crisis	Cholinergic Crisis
Central	Air hunger	+	+	+	+
	Dizziness	+	+	?	?
	Confusion	Restless	Apathetic	Restless	Restless
	Convulsions	+	+	?	++
	Coma	+	+	?	+
Muscarinic	Headache	+	* sl.	-	+
	Blood pressure	↑——↓	* ↑——↓	-	-
	Pulse	↑——↓	↑	↑	↓↑
	Skin	Flush	Pallor	Pallor	Pallor
	Sweating	+	-	-	+
	Salivation	+	-	+	++
	Bronchorrhoea	+	-	+	++
	Bronchospasm	+	-	-	+
	Miosis	+	-	-	+
Nicotinic or Tetanic	Twitching	+	+ Tetany	-	+
	Paralysis	-	-	+	+
	Paraesthesia	-	+	?	-

* High thoracic spinal transection.

APPENDIX A.

Results of a clinical trial of apparently identical sugar-coated tablets (A and B) whose nature was unknown until the end of the trial, and comparison with BC 40 and BC 51.

Each tablet was given for a minimum period of three days except where shown as 'random' when the tablets were given randomly for one day at a time.

The number of tablets in each dose was equivalent to that required in a preliminary trial with standard neostigmine tablets. The timing of each dose was determined by the patient's awareness of returning myasthenic weakness. Each patient charted the time of dosage, degree of recovery of muscular power and presence of nicotinic or muscarinic side effects. None knew when A and B were substituted.

Case.	Order of Drugs.	Awareness that tablet had been changed.	Preference.	Duration of action (hrs) A.	Duration of action (hrs) B.	Side Effects A.	Side Effects B.
ME 4384	A,B	-	B	5	5	-	+
MH 8162	B,A,A,B	+	A	?	?	+	++
ME 33152	A,B,A,B	+	B	2	2	+	-
MH 47889	A,B,A,B	+	B	3	4	-	+
MH 57596	B,A,B,A,A	+	B	2-3	2	+	-
MN 277	B,A,B,A,B,A,B	+	B	3-4	6	-	-
MN 294	BC51, B,A,B,A,B	+	B	2	4	+	+
MN 382	BC51, A,A,B	-	equal	3	3	-	-
MN 1906	B,A,B,A,A,B,A,B,A	+	B	5-6	6	+	+
MH 2016	B.A.B, random	-	equal	3-4	4-6	+	+
MH 2143	Random	+	B	5	5	-	-
MH 2257	B,A,B,A,B,B,A,B,A	+	B	2	2	+	+
MH 2327	A,B,A,B, random	-	equal	3-4	4-5	-	-
MH 3054	BC40, BC51, A,B	+	B	5-6	5-6	+	+
MH 3451	A,B	-	B	3-4	5-6	+	-
MH 3912	B,A,A,B,BC40, BC51	+	B	4	4	-	-
MH 4084	A,B,A	-	equal	3-4	6-7	+	+
MH 4275	A,B,A,B	-	B	1-3	2-3	+	+
MH 4301	A,B,B,A	+	B	4	6-8	-	+
MH 4585	B,B,A,B,BC40, BC51	+	B	2-3	2-4	-	-
MH 4586	B,B,A,B,B	-	equal	?	?	-	-
MH 4611	BC51,BC40,B,A,B	-	equal	3	3	-	-
MH 7788	B,A,B,A,B,A,B	-	equal	6	6	++	+

Preference for B - 15 cases
Preference for A - 1 case
No preference - 7 cases.

Side effects A - 11, B - 11

the manufacturer (Messrs. Roche Products Ltd.) revealed that tablet A contained neostigmine 15mg. and tablet B contained pyridostigmine, 60mg.

Appendix B

BENIGN CONGENITAL MYOPATHY WITH MYASTHENIC FEATURES

BY
JOHN N. WALTON, NORMAN GESCHWIND, and J. A. SIMPSON

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LONDON
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TAVISTOCK SQUARE, W.C.1

J. Neurol. Neurosurg. Psychiat., 1956, **19**, 224.

BENIGN CONGENITAL MYOPATHY WITH MYASTHENIC FEATURES

BY

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It has been increasingly apparent in recent years that in addition to cases which fall into recognizable categories of muscle disease, a number of less common disorders occur from time to time which do not correspond to the accepted descriptions. Some of these appear to be metabolic in origin and can be elucidated, at least in part, by modern methods of investigation (McArdle, 1951) while others seem to fall into a borderland of either myopathy or myasthenia gravis. A case of the latter type is described and discussed below.

Case History

R. M. (N. H. case 4838), a female telephonist, was born in 1919; her mother was well during pregnancy, labour was normal, and the baby thrived well during the neonatal period. She seemed normally active and lively and sat up at 7 months; at 9 months she tipped over her pram by jumping vigorously and sustained a cut chin but no other injury. Shortly after this episode her mother noticed that the limbs and body tended to flop limply when she was lifted and the head lolled as if she were totally unable to support it. The limbs were unusually flexible, like those of a rag doll, and she lay in her pram almost immobile, without kicking her legs or waving her arms. Nevertheless, at the age of a year she was able to crawl a short distance when put on the floor; her crawling improved steadily, although her limbs remained rather loose and "floppy". However, this was her only means of locomotion until she reached the age of 5 years, when she began to pull herself up with her arms and to walk around the furniture. When she was 5½ years old she was able to walk a few paces unaided and the limbs, though somewhat weak, were not so loose. The patient's mother suggested that at this age she was very little stronger but had learned to overcome her weakness. At the age of 7 she was able to go to a school for disabled children and could walk about 20 yards, but would then have to rest for about a minute in order to regain her strength. She always tended to tire throughout the day and was much weaker in the evening than on waking. She had particular difficulty in climbing stairs or in rising from a low chair and showed a considerable tendency to trip and fall, after which she would find it difficult to get up again. Apart from her muscular disability the patient developed normally; the menarche occurred at 13 years and she had menstruated normally since.

As the patient grew older she was gradually able to extend her activities, although her muscular weakness was virtually unchanged. She attempted numerous occupations and finally worked (from 1948) for two years as a telephonist, but was compelled to give up this post because of her muscular disability; since 1950 she had helped her mother in the home. The patient had two sisters, one older and one younger than herself, both of whom were well, and there was no history of muscular disease in the family.

The patient was first admitted to the National Hospital in 1941 under the care of Dr. E. A. Carmichael, when generalized muscular hypotonia of moderate degree and diffuse atrophy of proximal limb muscles were discovered. She showed an accentuated lumbar lordosis and tended to waddle when she walked. There was also bilateral ptosis and weakness of the upper facial musculature. A diagnosis of atypical amyotonia congenita was made. She was readmitted on several occasions during the ensuing years, when her symptoms and physical signs were virtually unchanged. In 1944 she was seen by Dr. Gordon Holmes, who suggested that she was suffering from an unidentified defect of muscle metabolism. In 1948 Sir Charles Symonds could demonstrate no myasthenic tiring of the eyelids, although there was pathological fatiguability of the deltoids; he agreed that the patient was suffering from an unusual metabolic disorder of muscle. On at least three occasions the effect of an intramuscular injection of 1·5 mg. prostigmine was tested. Each time the drug made the patient feel "queer" and dizzy, but nevertheless it produced some subjective improvement in muscular power, though there was little objective change. Twice the improvement in strength appeared to persist for two or three days after the injection and the drug was given by mouth in a dosage of up to 90 mg. daily. On each occasion there was a marked subjective improvement which, however, passed off after between one and two weeks and the treatment was discontinued. A similar improvement appeared to follow ephedrine, gr. ½, three times daily; the effect of

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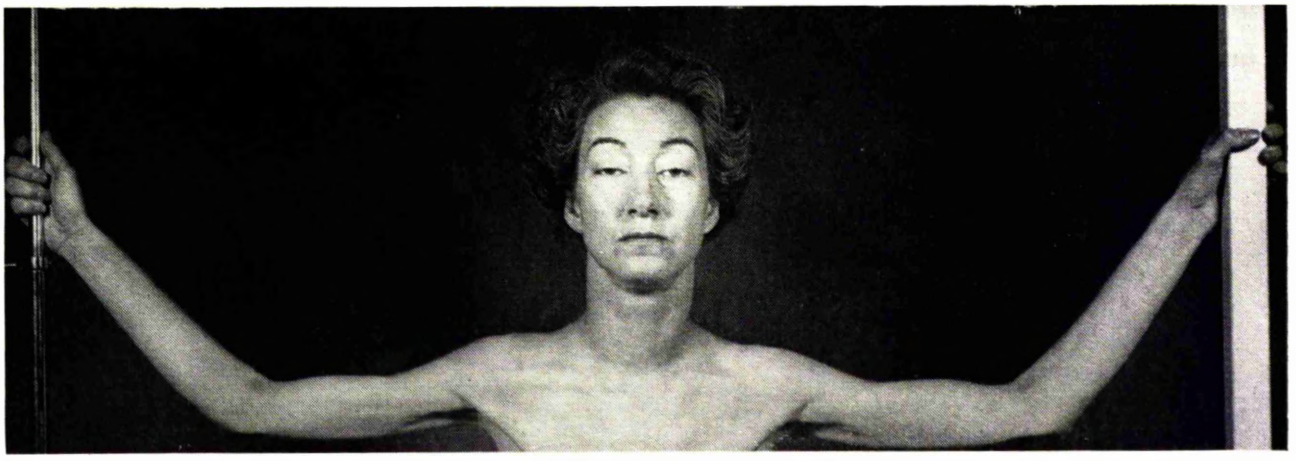

FIG. 1.—The bilateral ptosis and moderate atrophy of the shoulder girdle and arm muscles (particularly on the right side) are seen.

this drug was, in the patient's view, sustained, and she had been taking it continuously for several years. In 1952 the patient was admitted to the Clinical Research Unit at Guy's Hospital and was investigated by Dr. B. McArdle; the results of these studies are given below. At that time she seemed to show doubtful improvement on treatment with oral potassium (dosage 1 g. KCl t.d.s.) and had continued to take this remedy, as well as ephedrine, until she returned to the National Hospital in 1955. Assessment of therapeutic results in this patient was always difficult as she was a suggestible, nervous individual, who suffered numerous episodes of emotional instability, exaggerated by periods of conflict with her mother.

On readmission under the care of Dr. Carmichael on May 6, 1955, the patient's symptoms were virtually unchanged from those she had expressed on her previous admissions, save for the fact that she had experienced occasional dysphagia when tired. However, she was still able to do housework and to walk considerable distances (with many rest periods). She felt that the muscles of her legs seemed to " let her down " less often than they had done some years before, but there had been no striking change in the condition of the limbs for many years.

On examination (Fig. 1) the patient was thin and slightly built and walked with a distinct waddle and with a considerable increase in the lumbar lordosis. There was bilateral ptosis, with impaired ocular movement upwards, but not laterally or downwards; the ocular axes were parallel throughout and there was no diplopia. Both orbiculares oculi were strikingly weak, but the lower facial muscles, masseters, and temporales were strong. Palatal and pharyngeal movements were normal and the tongue showed no atrophy or fasciculation. The patient had a curiously long " swan-like " neck, but the sternomastoids were large and powerful as were the posterior cervical muscles; because of the ptosis she tended to hold her head backwards. There was undoubtedly atrophy of the sacrospinalis and other posterior spinal muscles, but those of the abdominal wall were good. The limbs were generally thin, particularly proximally, and there seemed to be a general moderate atrophy, with considerable weakness, of all girdle and proximal muscles in the upper and lower limbs. The extensors of the wrist and fingers were also weak; the finger flexors were stronger but, nevertheless, considerably weaker than would have been expected in a normal individual of the patient's age. In the lower limbs the anterior tibial and peroneal groups showed the same atrophy and weakness as the proximal muscles, although the calf muscles were more powerful. All deep tendon reflexes were present, though depressed, and direct muscle excitability was normal; the abdominal reflexes were brisk, the plantar responses flexor. The secondary sexual characteristics were normally developed and there was no abnormality to be detected on examination of the chest, abdomen, and cardiovascular system.

Electrodiagnosis.—In 1948, an intensity-duration curve from the right deltoid was normal; Dr. W. A. Cobb recorded an electromyogram from the same muscle, using a concentric needle electrode. He reported that there was no spontaneous activity and on voluntary contraction the motor unit action potentials were normal in amplitude and duration. In June, 1948, Dr. P. Merton found no decrement in the amplitude of a muscle action potential recorded with a surface electrode on the hypothenar eminence, on supra-maximal stimulation of the ulnar nerve at 3 per second.

Muscle Biopsy.—A specimen of muscle was removed from the right deltoid in 1950. There was no increase in perimysial connective tissue nor was there any accumulation of fat between the fibres. Some of the muscle fibres were slightly enlarged, measuring 85μ in diameter, while very occasional atrophic fibres were seen. In a few fibres sarcolemmal nuclei had migrated into the substance of the fibre and one or two short chains of nuclei, subsarcolemmal in position, were seen. No segmental necrosis of fibres was evident and there was no cellular infiltration or evidence of muscle fibre regeneration. A number of nerve filaments were present in the section and appeared to be normal; two muscle spindles of normal appearance were also observed. Hence the histological changes were minimal. Although perhaps compatible with a mild myopathic disorder they were

much less than would have been expected considering the length of history and the comparative severity of the patient's weakness.

Dr. J. N. Cumings reported that the potassium content of the muscle was 1·1 g. % by dry weight, a normal figure.

Metabolic Studies.—Studies carried out in June, 1948, by Dr. J. N. Cumings yielded the following results:—

CREATINE AND CREATININE EXCRETION

Day	Urinary Volume (ml.)	Creatinine (g.)	Creatine (g.)	Inorganic Phosphate (g.)
1	900	0·73	0·18	0·51
2	820	0·84	0·27	0·53
3	940	0·86	0·12	0·41
4	763	0·79	0·16	0·40
5	570	0·75	0·04	0·51
6	940	0·87	0·08	0·56

Ephedrine medication and all other medicinal treatment was discontinued from the third day of this test; a creatine tolerance test was performed on the fourth day and gave results as follows :—

Creatine Tolerance Test.—Urinary and blood estimations were carried out at the stated times before and after the oral ingestion of 1 g. of creatine.

RESULTS IN URINE

Time	Volume (ml.)	Creatinine (g.)	Creatine (g.)	Inorganic Phosphate (g.)
Fasting	35	0·07	0·01	0·03
1 hour	57	0·05	0·05	0·02
2½ hours	121	0·10	0·04	0·03

RESULTS IN BLOOD

Time	Creatinine (mg. %)	Creatine (mg. %)	Inorganic Phosphate (mg. %)	Potassium (mg. %)
Fasting	1·0	0·38	4·3	19·4
1 hour	1·12	1·63	4·7	20·0
2½ hours	1·25	0·87	4·7	22·5

Response to Insulin and Glucose.—The patient was given 100 g. glucose by mouth and 25 units of insulin subcutaneously. Before the experiment was begun the serum potassium level was 20·0 mg./100 ml., the serum inorganic phosphate level 4·5 mg./100 ml., and the blood sugar level 100 mg./100 ml. Thirty minutes after the injection, the serum potassium level was 18·3 mg./100ml., the inorganic phosphate level was unchanged, and the blood sugar level was 168 mg./100 ml.

Dr. Cumings remarked that the urinary creatine was low and almost absent when the patient was taking no drugs, while the creatine tolerance and the potassium response to insulin and glucose were all normal.

Metabolic Activity of Forearm Muscles.—In January, 1952, the following studies were carried out by Dr. B. McArdle in the Clinical Research Unit at Guy's Hospital, London. The patient had received no drugs for about a week before the test. Blood was taken from the left antecubital vein before the test and again following the release of an occluding cuff after a period of ischaemic work by the forearm muscles. The work consisted in raising and lowering (56 pulls) a 5 kg. weight by means of a gripping movement on an ergometer. A wrist cuff inflated to 200 mm. Hg ensured that blood taken from the antecubital vein came only from the forearm muscles. The results of this test were as follows :—

Time	Blood Pyruvate (mg. %)	Blood Lactate (mg. %)	Serum Potassium (mg. %)	Serum Sodium (mg. %)	Serum Magnesium (mg. %)	Serum Inorganic Phosphate (mg. %)
Before	0·63	6·0	15·2	325	2·23	3·57
30 sec. after release of cuff	1·26	31·3	16·4	340	2·50	3·67
2 min. after release of cuff	0·91	29·4	15·6	—	—	—
6 min. after release of cuff	1·13	24·2	14·8	328	—	3·28
10 min. after release of cuff	1·01	16·3	14·7	330	—	—
20 min. after release of cuff	0·86	12·7	14·5	329	—	3·18

Dr. McArdle remarked that all of these results were within normal limits.

Other Investigations.—Haemoglobin was 100% (14·8 g./100 ml.); W. B. C. 4,000/c.mm. (63% polymorphonuclears, 31% lymphocytes).

The E. S. R. was 8 mm. in one hour (Westergren). The Wassermann and Kahn reactions were negative.

The serum protein-bound iodine was 3γ %. The total serum proteins were 7·9 g./100 ml. (albumin 4·4, globulin 3·5).

A radiograph of the chest showed a slight dorsal scoliosis, convex to the right. The lung fields and heart were normal and the thymus did not appear to be enlarged. An electrocardiogram was normal, and a basal metabolic rate was minus 11%. The urinary 17-ketosteroid excretion was 4·9 mg. in 24 hours.

Discussion and Experiments

It was clear from the information recorded that this patient fitted no clearly recognizable form of muscle disease as previously described. The non-progressive nature of the disease and the diffuse rather than selective distribution of muscular wasting and weakness made it apparent that she was not suffering from any of the common categories of muscular dystrophy. Furthermore, the pathological changes in the muscle were far less than would have been expected in a long-standing muscular dystrophy or polymyositis. She showed many characteristics reminiscent of the benign congenital myopathy or myopathic form of amyotonia congenita as described by Batten (1910) and by Aldren Turner (1940, 1949). Because of the general reduction in size of the skeletal muscles, the resemblance to Krabbe's (1946) "congenital universal muscular hypoplasia" was even more striking, since in Turner's cases the muscular wasting and weakness affected selectively the proximal muscles of the limbs and the face was not

involved. Despite these discrepancies, the results of a recent follow-up of cases of amyotonia congenita by one of us (Walton, 1956) have suggested that the disorders described by Krabbe and Turner may be the same. However, in this case there were additional unusual features: the variability of her weakness, the fatiguability, which had been a consistent feature, and the apparent response to ephedrine, suggested that there might be some defect in neuromuscular transmission akin to that seen in myasthenia gravis. It was evident that the patient was not suffering from the latter disease, in view of the diffuse muscular wasting and the failure to show a sustained response to prostigmine therapy. Rowland (1955) has recently described a number of patients who appeared to be suffering from myasthenia gravis but who showed either a very variable response to prostigmine or none at all. However, from his descriptions it seems likely that some of his cases were examples of polymyositis, a condition which may show temporary improvement with this drug (Eaton, 1954). It is clear from the clinical and pathological findings that our case was not suffering from polymyositis. An alternative possibility seemed to be that she was suffering from an unidentified disorder of muscle metabolism, although Dr. McArdle's results indicated that there was no serious defect in carbohydrate breakdown and utilization in the muscle.

In view of the apparent improvement which the patient had shown on potassium therapy it was decided to investigate the effect upon her muscular power of alterations in the serum potassium level. It was recognized that her symptoms were not like those of familial periodic paralysis, nor were they characteristic of those noted in chronic potassium deficiency (as in potassium-losing nephritis). It was also appreciated that the serum potassium level does not necessarily give a faithful indication of the intramuscular concentration of this ion. Nevertheless, since potassium is recognized to be one of the most freely diffusible ions, it was felt that if the patient's condition were due to a deficiency of intramuscular potassium, she would become significantly weaker if the serum potassium level were lowered. Another possibility seemed to be that she might have some anomaly whereby her muscles required a higher than normal concentration of potassium in order to function properly. In this case, too, a fall in extracellular potassium would increase her weakness.

It was also decided to repeat the electromyogram and to study the effects upon the muscle action potential of repetitive nerve stimulation, first under normal conditions and secondly after increasing doses of intravenous decamethonium iodide. Harvey and Masland (1941) found that in patients with myasthenia gravis, if the muscle action potential was recorded from the skin overlying a weak muscle during repetitive supramaximal stimulation of its nerve of supply at a rate of 3 per second, the potential often showed a rapid decrease in amplitude. This was suggested as a diagnostic test, and it has been conventional to take the recording from the hypothenar eminence during stimulation of the ulnar nerve at the elbow. If this muscle group is not clinically affected, however, another must be chosen. Recently, Churchill-Davidson and Richardson (1952) have shown that in the normal individual an intravenous injection of 2 mg. of decamethonium iodide will give a significant fall in amplitude of the motor unit potential recorded from the hypothenar eminence during stimulation of the ulnar nerve at a frequency of 10 per second. Patients with myasthenia gravis, however, in whom the hypothenar muscles were not weakened by the disease, were remarkably resistant to this drug and could often take 3 mg. or more without a significant decrement in the action potential.

Clearly it also seemed important in this patient to assess, under the conditions of a controlled experiment, the effect of ephedrine, prostigmine, tensilon, and potassium upon the muscular weakness. It was decided in addition to study the effects of intravenous caffeine and of calcium, in view of the direct stimulant effect which these substances appear to have upon the muscle fibre.

Before carrying out these experiments all treatment was stopped and the patient's muscular power was assessed three times daily by one of us, at 9.30 a.m., 1 p.m., and 5 p.m., in order to see whether there was any significant variation depending upon the time of day. The power of individual muscle groups was assessed clinically and strength of grip was measured with a spring dynamometer, the value recorded being taken as the average of three maximal grips with each of the two hands. It was discovered that the latter test gave a satisfactory indication of general muscular power. Another useful test was to measure the time for which both arms could be held out horizontally in front of the body with the patient sitting in bed; the end-point was taken at the time when one hand touched the bed-clothes. Using these methods it was found that after five days in hospital, with approximately the same amount of activity carried out each day, consistent values for strength of grip and for holding out the arms were obtained from day to day. Each day there was a consistent slight decrease in these readings as the day advanced; for this reason it

was decided to carry out all experiments at approximately the same time in the mornings. All chemical estimations were carried out by one of us (N. G.) using a standard technique. The assessments of muscular power were made by J. N. W. and electrodiagnostic tests were carried out by J. A. S.

Experiment I: Lowering of Serum Potassium Level.—On May 20, 1955, the patient was starved and 5 ml. of blood was taken from the right antecubital vein at 9 a.m.: the serum potassium level, as estimated with a flame photometer, was 4·4 mEq./litre (17·2 mg./100ml.). At 9.5 a.m. the patient was given 150 g. glucose orally and at 9.25 a.m. 25 units of insulin were given subcutaneously. At 10 a.m. muscular power was unaltered, but the serum potassium level was 4·1 mEq./litre (16·0 mg./100 ml.). Hence the fall in serum potassium level produced by this technique was inadequate.

On May 23, 1955, after a large breakfast, the serum potassium level was estimated at 9.10 a.m. to be 4·0 mEq./litre (15·6 mg./100 ml.). At 9.20 a.m., and again at 9.35 a.m. and 9.50 a.m. the patient was given 15 g. sodium bicarbonate in 2 oz. water. At 10.30 a.m. the patient felt somewhat tired and nauseated but there was no objective change in muscle power. At 1.15 p.m. the serum potassium level was 3·12 mEq./litre (12·2 mg./100 ml.) and 1 ml. of 1 in 1,000 adrenaline was administered subcutaneously. At 2 p.m. the serum potassium level had fallen to 3·0 mEq./litre (11·7 mg./100 ml.) but there was still no significant change in muscular power. This technique for lowering the serum potassium level will be reported in detail by one of us (N. G.) in a subsequent communication.

Experiment II: Electromyography and Effect of Intravenous Tensilon and Ephedrine.—On May 24, 1955, the electromyogram from the right deltoid muscle was recorded at 9.30 a.m., using a concentric needle electrode. There was no spontaneous activity; on voluntary contraction the interference pattern was sustained but contained an undoubted excess of polyphasic and short-duration potentials. After sustained abduction of the arm for 90 seconds, with the needle *in situ*, the proportion of short-duration and polyphasic potentials showed a significant increase. After assessment of voluntary power, 20 mg. " tensilon " was injected intravenously at 10 a.m. The patient immediately felt faint and dizzy and there was no increase in voluntary power, while the electromyogram was unchanged. At 10.50 a.m. ephedrine hydrochloride, gr. ½, was given intravenously; the patient immediately felt stronger, and voluntary power, as assessed with the dynamometer and by holding out the arms, increased to a level higher than any recorded since admission to hospital. The electromyogram now showed fewer polyphasic and short-duration potentials. The patient was unaware of the constitution of any of the injections she received.

Experiment III: Supramaximal Stimulation of Ulnar Nerve before and after Injection of Decamethonium Iodide.—On June 4, 1955, a surface electrode was applied to the left hypothenar eminence (with the indifferent electrode on the fifth finger), and at 10 a.m. recording of the action potential produced by supramaximal stimulation of the left ulnar nerve at the elbow was begun. With a stimulation frequency of 2 per second there was no significant decrease in amplitude of the motor unit potential over a 10-minute period. Stimulation was then discontinued but was restarted at 10.20 a.m. At 10.38 a.m. 1 mg. decamethonium iodide was injected over a two-minute period. Immediately the patient felt faint and dizzy (as after " tensilon "); her ptosis increased considerably and she developed diplopia, but the action potential of the hypothenar muscles was unchanged. At 10.44 a.m. and at 10.49 a.m. two further injections, each of 0·5 mg., were given; the patient felt subjectively weaker but there was no change in the action potential. A further injection of 0·5 mg. was given at 10.54 a.m. (total 2·5 mg.); at 10.59 the action potential showed a 13% decrease in amplitude; the patient felt weaker, was apprehensive, and refused to have further injections. The original amplitude of the action potential was restored by 11.25 a.m. With this dose of decamethonium, the action potential of a normal subject would decrease in amplitude by more than 50%. The results of this experiment are recorded graphically in Fig. 2, using the same ordinates as those utilized by Churchill-Davidson and Richardson (1952).

Experiment IV: Therapeutic Trials.—Five substances

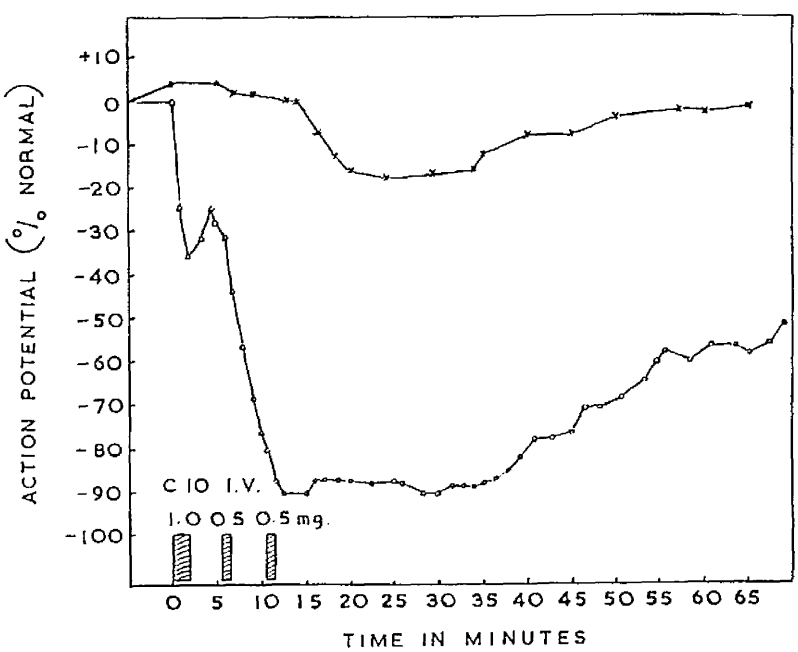

FIG. 2.—Effect of decamethonium on the action potential of abductor digiti minimi during supramaximal ulnar nerve stimulation in R.M. (upper curve) and in a control subject (lower curve).

were used, namely, ephedrine, calcium, potassium, caffeine, and prostigmine.

Ephedrine.—For a period of seven days from May 25, 1955, the patient was given tablets four times daily; for a part of this time the tablets were ephedrine hydrochloride (gr. ½), and for the remainder nicotinamide 25 mg. (which looked identical). This trial was designed by J. A. S. so that neither the observer testing muscular power (J. N. W.), the patient, nor the ward nurses were aware which tablet was being given at any one time, nor when the treatment was changed. At the end of this period it was clear that during the three-day period of treatment with ephedrine the patient was both subjectively and objectively stronger than when she was receiving nicotinamide.

Calcium.—On successive days the patient received an intravenous infusion of 500 ml. of fluid over a two-hour period. One of these infusions consisted of 500 mg. of calcium (as the gluconate) in normal saline while the other was saline alone. The observer concerned with the measurement of the patient's muscular power was not aware which infusion was being administered. After each infusion the patient claimed to be considerably stronger and showed a moderate increase in power as recorded dynamometrically and by holding the arms outstretched.

Potassium.—Over a seven-day period, from June 5, 1955, the patient was given four times a day 1 oz. of an orange-flavoured preparation. For a part of this time the preparation contained 2 g. potassium citrate in each ounce and for the remainder sodium citrate. As with the trial of ephedrine neither the patient nor the observer was aware which remedy was being given at any one time nor when the change-over occurred. Throughout this period the patient's condition remained unchanged; neither substance produced a significant change in muscular power.

Caffeine.—On June 12, 1955, the patient received three intravenous injections of comparable volume and appearance at intervals of one hour. One was caffeine sodium benzoate, 0·5 g., another ephedrine hydrochloride, gr. ½, and the other sterile saline. The injections were given by J. A. S. and neither the patient nor the clinical examiner (J. N. W.) was aware which injection was being given. It was discovered that the injection of saline had no effect, but both the ephedrine and the caffeine produced a distinct subjective and objective improvement in muscular strength of comparable degree.

Prostigmine.—On June 13, 1955, it was decided to study the effects of long-term oral prostigmine therapy, despite the fact that this treatment had proved ineffective in the past. Accordingly therapy with 15 mg. tablets of prostigmine four times daily was instituted, but was changed, at a time unknown to the patient and observer, to an inert tablet of identical appearance. This trial was continued over a five-day period. There was no doubt that both subjectively and objectively the patient was considerably stronger while on prostigmine. Indeed, she recorded higher dynamometer readings and was able to hold out her arms longer than at any time since her admission to hospital. During the next five days prostigmine therapy was alternated with pyridostigmine in equivalent dosage, but there was little difference in the effect of the two remedies, although overall improvement was maintained.

Subsequent Progress.—As a result of the findings in the experiments outlined above it was decided to give the patient combined treatment with prostigmine, one tablet of 15 mg., four times daily, and ephedrine, one tablet of gr. ½, also four times a day. For three days the improvement in the patient's strength was sustained: she moved about the ward more easily, could lift objects of considerable weight, and climbed three flights of stairs relatively briskly. Unfortunately she then developed follicular tonsillitis with a high fever and was compelled to take to her bed. This infection resolved within a few days but left the patient depressed, tearful and weak, though no weaker than she had been on admission. She asked to be discharged, feeling that she would pick up more quickly at home; she therefore left hospital, taking both ephedrine and prostigmine, on June 23, 1955. On discharge, physical examination revealed no significant change from her state on admission.

The patient was readmitted to hospital on August 9, 1955. After returning home she had improved quickly and soon felt that her strength had returned to what it was after beginning combined prostigmine and ephedrine therapy in hospital. This improvement continued for three weeks but then she began to feel unaccountably weaker. Although she had experienced some fluctuation in her muscular strength as a result of emotional disturbances, the present deterioration was quite different, being steadily progressive. In addition, she became short of breath and could no longer lie down in bed at night, or walk more than a few paces because of dyspnoea. On examination on admission the patient was unable to walk more than a few paces with considerable effort and she was quite unable to negotiate stairs. Her resting pulse rate was 120 per minute, but the heart and chest showed no abnormality on examination. She was severely breathless, with very poor abdominal and thoracic movement and striking activity of the accessory muscles of respiration, including the sternomastoids and scaleni. Her ptosis and facial weakness had not increased since her previous admission but her strength of grip was strikingly weak and she was quite unable to lift her arms from the bed. Her vital capacity could not be measured as she said she was unable to blow into the machine. An electrocardiogram was normal but for the tachycardia. Although an accurate assessment of her physical state was made difficult by emotional factors, there was no doubt that she showed persistent tachycardia and severe weakness of limb, trunk, and respiratory muscles, like that seen in severe myasthenia gravis. Intravenous tensilon and intramuscular prostigmine therapy produced no improvement in her condition; indeed, she insisted that these remedies made her worse. After each, some muscular fasciculation was seen but there were no abdominal symptoms. Accordingly, all therapy was

discontinued and over the next two weeks there was a gradual improvement in her respiration and in the power of the limbs; her pulse rate returned to 80 per minute. The patient was finally discharged from hospital on September 16, 1955, receiving only ephedrine gr. ½ four times daily. Her condition was virtually the same as when she was first admitted in May, 1955.

Conclusions

There seems to be little doubt whatever that this patient was suffering from a relatively benign, probably congenital, non-progressive myopathy, showing certain features reminiscent of myasthenia gravis. Dr. McArdle's investigations revealed no apparent defect in carbohydrate metabolism, while we were unable to produce any evidence to indicate that alterations in serum potassium affected her muscular condition. Save for the " myasthenic " features, her condition corresponds closely to the " benign congenital myopathy " or myopathic form of amyotonia congenita described by Batten (1910) and Aldren Turner (1940, 1949). However, Turner did not describe any fatiguability or apparent response to ephedrine or prostigmine therapy in his cases, nor were these features seen in the other cases of this type which were reviewed recently by one of us (Walton, 1956). On the other hand, it is evident that this patient was not suffering from true myasthenia gravis, in view of the failure to respond to tensilon, as well as the atypical clinical picture. Nevertheless, it must be admitted that she showed a considerable resistance to decamethonium iodide, while the sustained improvement on ephedrine therapy and the temporary response to prostigmine were suggestive of the latter disease. The apparent increase in strength following an injection of caffeine sodium benzoate was of doubtful significance.

Of great interest was the striking increase in weakness, particularly of the respiratory muscles, after prostigmine therapy had been in progress for some weeks. The associated tachycardia was suggestive of vagal inhibition but it is difficult to see how moderate dosage of prostigmine, which would be expected to give a bradycardia, could produce this effect. It seems most probable that the weakness could be attributed to this drug, despite the absence of other side-effects, and that the temporary improvement, perhaps due to its anti-cholinesterase effect, was subsequently overcome by a persistent depolarizing effect which appeared to be cumulative. It is well recognized that even patients with myasthenia gravis may become weak as a result of excessive dosage of this drug (Rowland, Korengold, Jaffe, Berg, and Shy, 1955), but the dosage administered to our patient was only 60 mg. daily which could not be expected to produce such an effect in an individual with true myasthenia. It is also difficult to understand the action of ephedrine in this case. Unlike adrenaline, this drug does not cause glycogen breakdown, hyperglycaemia, or a fall in the serum potassium level. We may ask whether its effect is unrelated to the energy metabolism of muscle and whether it may have a direct effect upon the muscle membrane or perhaps at the motor end-plate. We have no evidence which could help in deciding this problem.

The paradoxical responses which this patient showed to ephedrine, prostigmine, decamethonium, and " tensilon " suggest that in her case there may be some hitherto unrecognized defect in the muscle fibre and/or its end-plate or membrane. We can think of no better description for her condition than " benign congenital myopathy with myasthenic features " while recognizing that we do not understand the essential nature of her disorder.

Although this patient, so far as we are aware, shows features which are unique, there is no doubt that other cases showing a resemblance to this clinical picture are seen from time to time. One of us (J. N. W.) in a previous communication (Walton and Nattrass, 1954) has referred to a number of cases of " myasthenic myopathy ". This term is probably unsatisfactory, as it could be taken to refer to the irreversible muscular weakness and atrophy which may develop in the limb or ocular muscles of certain long-standing cases of myasthenia gravis. One of us (J. A. S.) in a recent study of a large series of cases of the latter condition has come to feel that such changes occur in a not insignificant proportion of cases and may follow a recognizable pattern, particularly in the limb muscles. However, the three cases briefly referred to by Walton and Nattrass (1954) were not of this type; rather, they were individuals with a long-standing weakness and atrophy of girdle and limb muscles who yet showed a somewhat phasic course and a definite, though sometimes temporary, response to ephedrine and/or prostigmine. Similar patients with a clinical picture like a combination of muscular dystrophy and myasthenia gravis have been reported by Laruelle and Massion-Verniory (1937), by Jezkova and Sachs (1939) and by Hosotte (1951). Hosotte's case, however, may have been one of true myasthenia gravis with eventual amyotrophy. In none of the cases mentioned by Walton and Nattrass did the condition begin so soon after birth as in the patient described in the present report. It is of considerable interest that one of these patients, shortly to be reported by Griffin, Nattrass, and Pask (1956), was given increasing doses of prostigmine with apparent improvement in the power of the limbs, but

with eventual respiratory paralysis, necessitating management with intermittent positive-pressure respiration. He was subsequently subjected to thymectomy with dramatic improvement.

It must be concluded that there exist a number of obscure disorders falling into the borderland of both myopathy and myasthenia gravis, of which the present case is a striking example. We have at present, however, no information to indicate the the nature of the basic muscular defect in such individuals.

Summary

The case is reported of a woman who developed muscular weakness and hypotonia in the first year of life; she has shown subsequently persistent though non-progressive weakness, with moderate diffuse atrophy of the upper facial, trunk, and limb muscles. Her weakness has always become worse after exertion and she has had slight dysphagia but no diplopia.

Extensive metabolic, electrophysiological, and therapeutic experiments have revealed no defect in carbohydrate utilization or in potassium metabolism. She is more resistant to decamethonium iodide than the normal individual and shows improvement on ephedrine therapy but none following tensilon. Prostigmine produces definite improvement in muscular power, but if continued indefinitely in moderate dosage it appears to produce an increase in weakness, particularly of the respiratory muscles. A muscle biopsy revealed only slight, indefinite changes compatible with a myopathic disorder.

It is suggested that this condition falls into a borderland of myopathy and myasthenia and that it should be styled " benign congenital myopathy with myasthenic features ". It was not possible to determine the nature of the biochemical or other defect in the muscle fibre and/or its end-plate or membrane which was responsible for this patient's condition.

We wish to thank Dr. E. A. Carmichael for permission to report this case and for his encouragement and advice. We are also grateful to Dr. J. N. Cumings, Dr. B. McArdle, Dr. W. A. Cobb, and Dr. P. A. Merton for permission to quote their findings. Fig. 1 was prepared in the Department of Photography, the National Hospital, Queen Square, Fig. 2 in the Gardiner Institute of Medicine, University of Glasgow.

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Appendix C

AN EVALUATION OF THYMECTOMY IN MYASTHENIA GRAVIS

BY

JOHN A. SIMPSON

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1958

AN EVALUATION OF THYMECTOMY IN MYASTHENIA GRAVIS

BY

JOHN A. SIMPSON[1]

(From The Neurological Research Unit of the Medical Research Council, The National Hospital, Queen Square, London)

FEW diseases have been more satisfying to the teacher of medicine than myasthenia gravis for no better meeting ground exists for clinician, physiologist and pharmacologist. Ten years ago the standard teaching was that the myasthenic response must indicate one of three possible "chemical lesions" at the neuromuscular junction: (i) insufficiency of acetylcholine, (ii) excess of cholinesterase, or (iii) a "curariform" block of transmission, presumably due to a substance carried in the blood. More recently the logical fourth possibility of an abnormality of the motor end-plates of muscle has been postulated. It seemed only a matter of time and of refinement of physiological and pharmacological techniques before the true lesion would be demonstrated. In that same period knowledge of the physiology of the neuromuscular junction has made its greatest advances, yet the solution of the problem of myasthenia evades us despite renewed and world-wide interest as evinced by two recent symposia (*Acta neurol. psychiat. belg.*, 1955; *Amer. J. Med.*, 1955).

Fundamental to any satisfactory theory is an explanation of the role of the thymus gland. It is not the purpose of this paper to reconsider the evidence that the thymus gland is implicated in myasthenia gravis; this has been admirably reviewed by McEachern (1943) and by Eaton, Clagett and Bastron (1953). The association of thymic pathology with myasthenia gravis has been recognized for more than fifty years and is not in question, but mere association is less important than the concept that it may be causally related to the transmission defect in muscle. It is difficult to implicate the thymus in any "chemical pathology" of myasthenia gravis with the possible exception of the neuromuscular block theory, and it is significant that the exponents of the other theories make no serious efforts to solve the dilemma. The evidence for causal relationship is of two types, (*a*) thymic extracts may have neuromuscular blocking properties, and (*b*) operative removal or radiotherapeutic destruction of the gland is followed

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by significant improvement in patients suffering from myasthenia gravis. Evidence of the first type and its antithesis has been reviewed recently by Wilson and Wilson (1955); the present paper is designed to review the evidence of the second type and to present the results of an independent survey of the largest series yet reported. A preliminary account has been presented (Simpson, 1956).

Material and Methods

The records of all patients diagnosed as myasthenia gravis at the National Hospital for Nervous Diseases since 1934 were scrutinized and an attempt made to trace survivors and to determine the fate of those who had died. Most of the cases seen after 1941 were subjected to thymectomy, the majority by Sir Geoffrey Keynes. The survey was extended by kind invitation of Sir Geoffrey to include his full series operated on at Saint Bartholomew's and New End Hospitals.

Criteria for inclusion of cases in the survey were:

(*a*) A firm diagnosis of myasthenia gravis by a consultant neurologist to one of these hospitals.

(*b*) A convincing case history of loss of muscle power after exercise, relieved by rest.

(*c*) Documented evidence of improvement with neostigmine (even if only a test injection).

(*d*) Absence of evidence of central neurological disease.

A total of 404 cases was available for study. Where death was not known to have occurred the patients were invited to attend the National Hospital for examination. All were traced except 12 operated and 18 not-operated patients. Doctors and hospital records were consulted for evidence of the cause of death in non-survivors. Where this was impossible the certified cause of death was ascertained. Of the 245 known survivors who could be traced, 181 were examined personally and 64 patients who were unable to attend the hospital (mainly due to residence abroad) were asked to complete a detailed questionnaire with the assistance of their family doctor.

The operated cases were classified in the following categories in which the essential feature is a comparison of the state at the time of follow-up with the state before operation with respect to (i) presence of signs and symptoms of myasthenia, (ii) exercise tolerance, (iii) drug requirements.

Category A: Full working life with no restriction. No neostigmine required. No subjective weakness. A small degree of permanent objective weakness, unrelieved by neostigmine, is permitted. The present state must represent a marked improvement from the original.

Category B: Able to lead a full life with only minor myasthenic symptoms, requiring no neostigmine or controlled by not more than 4 tablets (60 mg.) daily. A significant improvement is required.

Category C: Full life with few restrictions but (*a*) demonstrable myasthenia not requiring neostigmine, or (*b*) still requiring neostigmine but at least 40 per cent less than before and with improved response.

Category D: (*a*) Improved, but neostigmine requirements unchanged or increased, (*b*) unimproved, irrespective of neostigmine dosage, (*c*) worse.

Post-operative death.—Death occurring within three weeks of operation.

Myasthenic death.—Death occurring at a later date where the history suggested asphyxial death or death not explicable by other causes.

Death from other causes.—Death directly attributable to significant disease where the history suggested that myasthenia was not a major factor (e.g. cerebral hæmorrhage).

Patients who had not been treated by thymectomy were assessed by the same criteria with reference to the condition on first admission to hospital. The essential feature is an assessment of *change of status*, hence a patient with little disability (e.g. ocular myasthenia) does not qualify for a high category if this state is not significantly better than at the datum point. In case of doubt a patient was assigned to the lower category.

The data were analysed statistically with respect to sex, age at onset, duration of symptoms before the datum point, and length of follow-up to determine whether the two series ("operated" and "not-operated") could be accepted as representative samples of the population of myasthenics. Cases known to have a thymoma were considered separately. These analyses will be presented before comparing the natural history of the two series.

PART I

Comparison of "Operated" and "Not-operated" Series

The *sex distribution* and the *frequency of thymic tumours* in the two series is shown in Table I. It is, of course, possible that some thymic tumours

TABLE I.—DISTRIBUTION OF THYMIC TUMOURS

	Operated			*Not-operated*			
Sex	*Non-tumour*	*Thymoma*	*%*	*Non-tumour*	*Thymoma*	*%*	*All cases*
Female ..	182	23	11·4	59	6	9·2	270
Male ..	76	13	14·6	40	5	11·1	134
Both ..	258	36	12·3	99	11	10·0	404

have not been diagnosed in the not-operated patients, but the close resemblance of the two series suggests that this is not so. Table I does, however, show a difference in the sex distribution. This is further analysed for non-tumour cases in Tables II and III and in fig. 1.

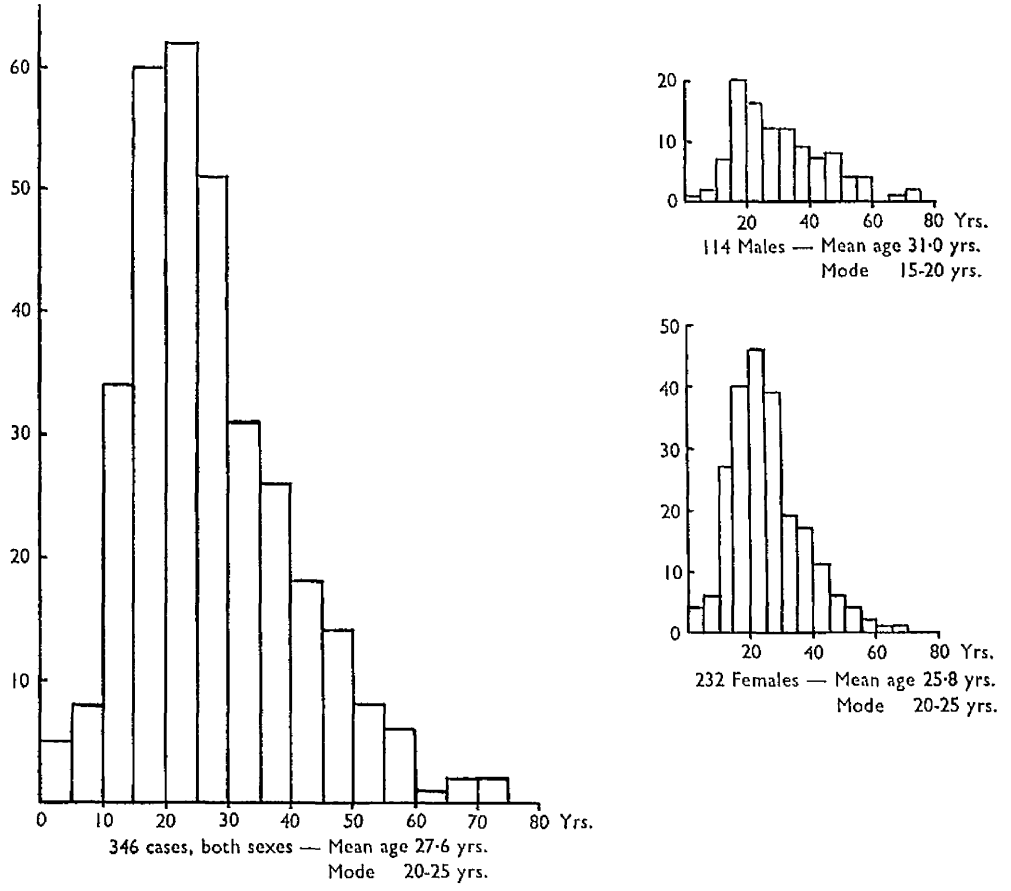

FIG. 1.—Distribution of age at onset of myasthenia (non-tumour).

TABLE II.—SEX DISTRIBUTION (NON-TUMOUR CASES)

	Operated			*Not-operated*		
Age at onset Years	*F*	*M*	*Ratio*	*F*	*M*	*Ratio*
0–10	9	2	4·5 : 1	1	1	1 : 1
11–20	62	20	3·1 : 1	8	8	1 : 1
21–30	67	24	2·8 : 1	21	8	2·6 : 1
31–40	23	17	1·4 : 1	16	6	2·7 : 1
41–50	11	10	1·1 : 1	6	6	1 : 1
51–60	2	1	(2 : 1)	4	8	1 : 2
61–70				2	1	2 : 1
71–80					2	
Unknown	8	2		1		
Total	182	76	2·4 : 1	59	40	1·5 : 1
Mean (years)	23·7	27·9		32·3	36·9	

Table II and\fig. 1 showing the *age at onset*, reveal marked differences between the two series. Inspection of the histograms of fig. 1 suggests that there is an incidence of age-at-onset which has a skew distribution about a modal value of 20 years (approx.) and that this does not differ greatly with sex, although the males have relatively more cases in the older age groups (causing a higher average age). This difference could be due to the small numbers of males, and might disappear in a larger series, but the same trend was reported by Grob and Harvey (1953). The regularity of the distribution curves in the operated series alone and in the total series suggests that they must closely represent the true population of myasthenic subjects if the age of onset is not randomly distributed. There is a preponderance of females of 4·5–1 in the first decade which steadily decreases to unity in the fifth decade (numbers are too small to attribute any significance to the possible reversal of sex incidence in later age groups). On this interpretation the "not-operated" series is gravely deficient in females under the age of 20 and contains relatively more males over 50 (hence the higher mean age for both sexes) (Table II). The series are closely similar for the age period from 16 to 35 which contains two-thirds of the operated series, though only half of the not-operated series (Table III). It will be necessary to make all comparisons in this section of the case

TABLE III.—THE AGE-GROUP 16–35

Age at onset Years	*Operated*		*Not-operated*	
	F	*M*	*F*	*M*
16–20	36	15	6	6
21–25	37	13	12	5
26–30	30	10	9	3
31–35	13	11	8	2
Total	116	49	35	16
Ratio	2·3	1	2·2	1

material before accepting conclusions derived from comparison of the whole of both series, since the value of thymectomy has been stated to be most evident in women who develop myasthenia at an early age.

The *length of survival* from the onset of myasthenic symptoms (to April 1956) is shown in Table XV. It will be more convenient to discuss the breakdown into categories later. The mean survival is closely similar in the two series, indeed despite the longer time at risk in the not-operated series it is slightly lower than in the operated series, due to the long-duration survivors being matched by a higher proportion of deaths within a few years of the onset.

Associated phenomena of myasthenia gravis occurred with equal frequency in both series (non-tumour) (Table IV). "Myopathy" represents

TABLE IV.—ASSOCIATED PHENOMENA (NON-TUMOUR SERIES)

		Operated		*Not-operated*	
		F %	*M* %	*F* %	*M* %
Ocular	Myasthenia	1·6	5·3	1·2	20·0
	Myopathy	9·3	22·4	10·2	15·0
	Goitre ..	18·0	9·0	8·5	2·5

permanently weak wasted muscles not improved by neostigmine. "Goitre" includes simple non-toxic enlargement of the thyroid and thyrotoxicosis. "Ocular myasthenia" indicates the proportion of cases in which the myasthenia remained confined to the extra-ocular muscles (including orbicularis oculi) for the duration of the survey.

PART II

Results

The classification of both series in April 1956 is shown in Table V and in percentage form in fig. 2. There are three questions to be answered by this survey: (i) Is there any significant difference in prognosis between the two groups? (ii) If there is any benefit to be gained from thymectomy, is it obtained by both sexes? (iii) Are there any other factors which affect the response to operation?

TABLE V.—RESULTS—NON-TUMOUR

	Operated				*Not-operated*			
	F		*M*		*F*		*M*	
Category	*No.*	%	*No.*	%	*No.*	%	*No.*	%
A	40	22·0	15	19·7	9	15·3	7	17·5
B	24	13·2	8	10·5	3	5·1	2	5·0
C	42	23·1	18	23·7	9	15·3	3	7·5
D	32	17·6	15	19·7	8	13·5	10	25·0
Data incomplete	13	7·1	4	5·3	9	15·3	9	22·5
Myasth. deaths	14	7·7	9	11·8	17	28·8	8	20·0
Post.-op. deaths	14	7·7 } 17·0	6	7·9 } 21·0	—	} 35·6	—	} 22·5
Deaths, other	3	1·6	1	1·3	4	6·8	1	2·5
Total	182		76		59		40	

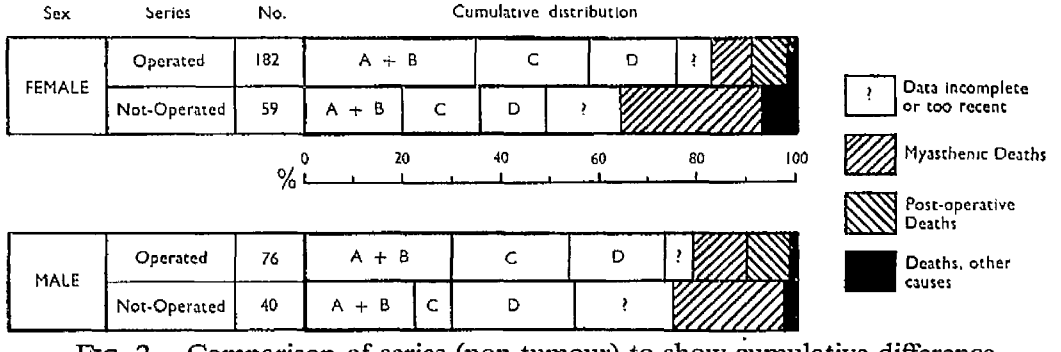

FIG. 2.—Comparison of series (non-tumour) to show cumulative difference.

TABLE VI.—COMPARISON OF TREATMENTS FOR EACH SEX

	Female		*Male*	
Category	*Difference**	*S.E. of diff.*	*Difference**	*S.E. of diff.*
A+B	+14·8†	6·3	+ 7·7	8·4
C	+ 6·8	5·6	+16·2†	6·4
D	+ 4·1	5·3	− 5·3	8·2
Myasth. deaths	−21·1†	6·2	− 8·2	7·3
All deaths	−18·6†	6·8	− 1·5	8·1

*Per cent in operated series minus per cent in not-operated series.
†Unlikely to occur by chance.

TABLE VII.—SEX-DIFFERENCE IN EACH SERIES

	Operated		*Not-operated*	
Category	*Difference**	*S.E. of diff.*	*Difference**	*S.E. of diff.*
A+B	+5·0	6·3	− 2·1	8·4
C	−0·6	5·8	+ 7·8	6·2
D	−2·1	5·4	−11·5	8·1
Myasth. deaths	−4·1	8·2	+ 8·8	8·6
All deaths	−4·0	5·4	+13·1	9·0

*Per cent females minus per cent males in each series. There is no significant difference.

The first two questions may be investigated concurrently.

Comparison of results. Sex differences.—For further statistical analysis, Categories A and B will be considered together as the distinction between them is a fine one of doubtful validity. All cases in these categories are for practical purposes without any disability due to myasthenia.

In Table VI the percentages in each category are compared separately for each sex. The difference is expressed as +ve if the proportion is greater in the operated series than in the not-operated, and −ve if otherwise. If a difference in percentage exceeds twice the standard error of the difference the odds are more than 20 : 1 against the difference being due to chance; such a difference is accepted as statistically significant. In Table VII a similar comparison is made between male and female in each series.

This analysis answers the first two questions. The operated series contains a higher proportion of females in Category A and B than would be likely to occur by chance (at the 5 per cent level), and the death-rate from myasthenia is very significantly reduced (Table VI). Even when the operative hazard is added, the total mortality rate is significantly lower than in the not-operated series. Males show a similar trend though the difference is not statistically significant except in Category C. Table VII suggests a possible explanation. Neither series shows a significant difference between the sexes. In the not-operated series there is a higher female mortality and fewer women than men reach Categories A and B, in the operated series this trend is completely reversed. It may be that thymectomy reverses an unfavourable prognosis for women, but any

conclusions must be tentative as the analysis does not exclude the possibility of the sex difference in either series having occurred by chance. As the benefit in favour of operation for women is unlikely to be due to chance it is possible that a larger series would show that the similar trend for males is equally significant. It is also possible that differences in composition of the series may be important. The following tables are of the same type as Tables V–VII for the age group 16–35.

TABLE VIII.—RESULTS IN AGE-GROUP 16–35

	Operated				*Not-operated*			
	F		*M*		*F*		*M*	
Category	*No.*	—	*No.*	%	*No.*	%	*No.*	%
A	24	20·7	11	22·5	6	17·1	2	12·5
B	17	14·6	7	14·3	1	2·9	1	6·3
C	31	26·7	12	24·5	4	11·4	1	6·3
D	21	18·1	8	16·3	6	17·1	4	25·0
Data incomplete	4	3·4	1	2·0	7	20·0	5	31·2
Myasth. deaths	9	7·7	7	14·3	10	28·6	2	12·5
Post-op. deaths	8	6·9	2	4·1	—	—	—	—
Deaths, other	2	1·7	1	2·0	1	2·9	1	6·3
Total	116		49		35		16	

TABLE IX.—COMPARISON OF TREATMENTS FOR EACH SEX (AGE 16–35)

	Female		*Male*	
Category	*Difference**	*S.E. of diff.*	*Difference**	*S.E. of diff.*
A+B	+15·3	16·8	+18·0	25·2
C	+15·3	17·7	+18·2	27·2
D	+ 1·0	17·5	− 8·7	21·9
Myasth. deaths	−20·9	16·8	+ 1·8	26·8
All deaths	−15·2	16·3	+ 1·6	25·9

*Per cent in operated series minus per cent in not-operated series. There is no significant difference.

TABLE X.—SEX-DIFFERENCE IN EACH SERIES (AGE 16–35)

	Operated		*Not-operated*	
Category	*Difference**	*S.E. of diff.*	*Difference**	*S.E. of diff.*
A+B	−1·5	13·6	+ 1·2	27·1
C	+2·2	14·7	+ 5·1	29·0
D	+1·8	15·5	− 7·9	23·4
Myasth. deaths	−6·6	15·9	+16·1	27·4
All deaths	−4·1	15·3	+12·7	26·5

*Per cent females minus per cent males in each series. There is no significant difference.

Table VIII shows no essential difference from Table V except that the male mortality rate is not apparently improved by thymectomy. This may be due to the high proportion of unoperated patients whose fate is not

known. If only the known cases are considered the deaths from myasthenia form 18 per cent of the total, which is comparable with the figure obtained in the full series. The poorer prognosis for women and its reversal by operation are again suggested by this limited series but unfortunately none of the figures are significant in the statistical sense (Tables IX and X). This is largely due to the small statistical population. The proportion of not-operated patients in the "insufficient data" category is unfortunately high, but recalculation of the figures in terms of known results only does not make enough difference to satisfy statistical criteria. Failure to satisfy these criteria shows that the results could have occurred by chance but, of course, does not indicate that they need have done so. The close resemblance to the figures calculated from cases of all ages (Table V) suggests that the trends disclosed are not chance ones and that a larger series, by lowering the sampling errors, would confirm the validity of the trends.

Factors affecting response to operation.—The third question to be answered refers to the possibility that the response to operation may be influenced by the patient's age at the time of onset of myasthenia or at the time of operation; by the duration of illness prior to operation; or by the severity of the myasthenia.

TABLE XI.—AGE AT ONSET OF MYASTHENIA

	Sex	*Cases No.*		A+B *yrs.*	*C yrs.*	*D yrs.*	*Myasth. deaths yrs.*	*Group yrs.*
Operated	F	182	Mean	22·8	23·7	25·2	24·0	23·7
			(s.e.)	(1·2)	(1·2)	(1·8)	(2·8)	(0·5)
			S.D.	9·6	7·6	10·4	10·7	6·5
			P.*	0·1–0·05	1·0	0·01–0·001	> 0·1	
	M	76	Mean	26·2	27·7	31·0	22·3	27·9
			(s.e.)	(1·8)	(2·1)	(3·4)	(2·9)	(1·3)
			S.D.	8·9	8·7	13·8	8·7	10·9
			P.*	> 0·1	> 0·1	0·05–0·02	0·01–0·001	
Not-operated	F	59	Mean	33·0	36·7	30·4	32·0	32·3
			(s.e.)	(3·4)	(4·0)	(3·2)	(3·1)	(1·7)
			S.D.	11·9	11·9	11·4	12·9	12·6
			P.*	> 0·1	0·05–0·02	> 0·1	> 0·1	
	M	40	Mean	36·7	40·6	36·4	44·0	36·9
			(s.e.)	(6·7)	(9·1)	(4·1)	(8·7)	(2·9)
			S.D.	20·2	15·7	12·9	24·6	18·2
			P.*	> 0·1	> 0·1	> 0·1	0·05–0·02	

*Probability, calculated by Student's t test, that the mean age of the category is the same as the mean age of the whole group.

Age at onset.—It has been suggested that onset at an early age gives a better chance of good operative results in contrast with a poor prognosis without operation (Schwab and Leland, 1953; Eaton, Clagett and Bastron (1953), Table XIX). This factor is examined in Table XI for the present series. The average age of the operated series is nine years younger than the not-operated series owing to the larger representation of young people already shown in Table II but in each series the mean age of the female patients is four years younger than the male average at the onset of myasthenic symptoms. Examination of the breakdown into categories shows that of the surviving groups of not-operated patients only C-female differs significantly from the mean age of the whole series. In the operated series, group D is significantly older than the overall mean age in both sexes. There is also a trend of increasing age from A and B through C to D though the difference may not be significant. This analysis provides slender evidence for the suggestion quoted that the earlier the onset the better the response to operation. The suggested converse trend for not-operated patients is not confirmed. The age difference is clearly too small to be of practical value in selection of cases for operation. If the question asked is "in what respect do all other categories differ from Category D (which is that of 'no change') with respect to age of onset? the answer is that none differs significantly. The age of onset of male patients who died of myasthenia after operation was significantly younger than the mean for the series or Category D, whereas myasthenic deaths in the unoperated males occurred in patients whose average age at onset was significantly older than the group mean or Category D. The very high mean age at onset of the unoperated males who died of myasthenia has too high a standard deviation to justify further discussion. The discrepancy is not present in the 16–35 age group so it may be due to the many older cases in the full series. Because the restricted group is specially selected for age this factor has not been tabulated, but it may be stated that within that group no effect of age at onset on the final result could be demonstrated. This question is discussed more fully in Part IV.

Pre-operative duration.—The possibility that the final state is inversely proportional to the duration of myasthenia before operation is investigated in Table XII. The female Category A+B has a mean pre-operative duration which is very significantly less than the mean of all the female patients subjected to operation and significantly less than that of categories C and D. Categories C and D have a significantly longer history than the group mean. (Category C does not differ significantly from Category D.) A similar trend is disclosed by the males, though chance differences cannot be excluded. The mean pre-operative duration of those who subsequently died a myasthenic death despite operation was closely similar to the mean for the group, and in fact was not significantly different from the A+B categories. There is thus no indication that those who die of myasthenia

TABLE XII.—PRE-OPERATIVE DURATION OF MYASTHENIA

	Females					*Males*				
	Group	*A+B*	*C*	*D*	*Myasth. deaths*	*Group*	*A+B*	*C*	*D*	*Myasth. deaths*
	yrs.	*yrs.*	*yrs.*	*yrs.*	*yrs.*	*yrs.*	*yrs.*	*yrs.*	*yrs.*	*yrs.*
Cases	179	64	42	32	14	74	23	18	15	9
Mean duration	5·8	3·4	7·8	8·5	4·3	5·2	4·0	4·8	8·4	5·5
(s.e. of mean)	(0·44)	(0·5)	(0·91)	(1·2)	(1·4)	(0·8)	(0·8)	(1·2)	(2·8)	(2·6)
S.D.	5·9	4·0	5·9	7·0	5·5	6·7	3·8	5·2	10·9	7·8
s.e. of difference of D. from other cats.	1·2	1·3	1·5	—	1·8	2·5	2·5	3·0	—	3·8
s.e. of difference of cat. from group mean	—	0·6	1·0	1·2	1·5	—	1·1	1·2	2·5	2·7
P.*		<0·001	0·05	0·05–0·02	>0·1		>0·1	>0·1	>0·1	>0·1

*Probability, calculated by Student's t test, that the mean pre-operative duration of myasthenia of the category is the same as the mean of the whole Group.

TABLE XIII.—AGE AT OPERATION

	Females					*Males*				
	Group	*A+B*	*C*	*D*	*Myasth. deaths*	*Group*	*A+B*	*C*	*D*	*Myasth. deaths*
	yrs.	*yrs.*	*yrs.*	*yrs.*	*yrs.*	*yrs.*	*yrs.*	*yrs.*	*yrs.*	*yrs.*
Cases	164†	62	39	32	14	71†	23	18	15	9
Mean age	29·7	26·3	31·5	33·7	28·3	32·7	30·1	32·5	39·4	27·8
(s.e. of mean)	(0·85)	(1·4)	(1·75)	(1·9)	(2·9)	(1·4)	(2·5)	(2·9)	(3·2)	(4·1)
S.D.	10·9	10·3	7·3	10·6	14·0	12·2	10·0	10·3	14·5	10·0
s.e. of difference from Category D	2·1	2·3	2·6	—	3·4	3·5	4·7	4·3	—	5·2
s.e. of difference from sex mean	—	1·6	2·0	2·1	3·0	—	2·8	3·2	3·5	4·3
P.*		0·02	>0·1	0·05–0·02	>0·1		>0·1	1·0	>0·05	>0·1

*Probability, calculated by Student's t test, that the mean age at operation of the category is the same as the mean of the whole Group.

†Age at operation not recorded in 15 female and 3 male cases.

despite thymectomy differ in the length of history from those who survive. This point will be returned to in a later section.

Age at operation.—The age at the time of operation may be more important than the previous duration of illness. The analysis (Table XIII) for females shows that A+B are younger and D older than average, to a highly significant extent and that A+B are significantly younger than D at the time of operation. In the males, group D is also older than the group average though this is barely significant (at the 5 per cent level) and although A+B is not much younger than the group average the difference from D approaches the same order of significance. Those who subsequently died of myasthenia were a little younger than the group average and considerably younger than D (the "unchanged" survivors) and this difference is significant for males. Again the two sexes show the same trends.

It is not possible to say whether pre-operative duration or the age at the time of operation is the more important factor. Obviously they are interrelated. Formal analysis would require a series of cases aged less than 30 at the time of operation who had been myasthenic for, say five to ten years, for comparison with a series of older patients with myasthenia of recent onset. Individual patients of the present material could be quoted with good or bad results in both these categories so that the analysis would have no relevance in the assessment of a particular patient when operation is under consideration.

Neostigmine requirements.—A major difficulty in an investigation involving the comparison of large numbers of patients over a period of many years is the classification of patients according to severity. Even if it were possible for a single clinician to establish and maintain accurate standards for twenty years, it would be impossible for a later examiner to make such a decision, especially in a disease of widely varying manifestations, treated by numerous physicians during a period in which therapy was changing. The amount of neostigmine required by the patient before operation is a reasonably objective index of severity. The sexes do not differ greatly in this respect (Table XIV) and those patients who have done well after operation required little less neostigmine before operation than those who did not benefit. Those who eventually died a myasthenic

TABLE XIV.—NEOSTIGMINE REQUIREMENTS

	Sex	A tabs.*	B tabs.	C tabs.	D tabs.	Myasth. deaths tabs.	Group tabs.
Operated ..	F	10·0	12·6	19·3	12·4	14·3	13·6
	M	8·0	12·6	19·2	10·5	17·5	
Not-operated	F	5·1	10·0	7·2	10·0	13·2	8·7
	M	4·9	4·5	8·0	6·8	9·0	

*15 mg. tablets. Where parenteral injection was used the equivalent oral dose has been calculated on the basis of 0·5 mg. I.M. = 15·0 mg. oral.

death required more neostigmine than the survivors. The considerably higher requirements in Category C cannot be explained. Ross (1952) records the same trend but had too few cases in Category D to note the anomaly. It is not found in the corresponding not-operated group. The possibility must be considered that Category C is an artificial one and not truly different from Category D in which the "improvement" due to operation could be explained if many had been given more neostigmine than necessary before operation, but subsequently resumed their true requirements. No patients have been included in Category C who did not give a history suggestive of genuine improvement despite the decreased dosage of neostigmine. Apart from this discrepancy the not-operated series shows a trend similar to the operated series though the general dosage level was lower (lower dosage of neostigmine was then customary).

It is concluded that there is no clear evidence that the severity of myasthenia materially affected the final state in survivors.

Survival.—A final question must be considered before the comparative figures of Table V can be accepted. Is the follow-up period comparable for all categories? This must be known to exclude the possibility that immediate good results lapse with passage of time, or conversely, that if an unoperated patient survives long enough there is a progressive tendency to improve. Relapses do occur after operation, but in a minority of cases. The author was, on many occasions, surprised to note how closely his estimate agreed with that of Ross (1952) where the latter's note was avail-

TABLE XV.—SURVIVAL FROM ONSET

	Sex		*All known survivors* *yrs.*	*A+B* *yrs.*	*C* *yrs.*	*D* *yrs.*	*Myasth. deaths* *yrs.*
Operated ..	F	Mean	13·0	10·9	14·2	15·8	6·7
		(s.e.)	(0·6)	(0·7)	(1·1)	(1·4)	(1·5)
		S.D.	7·1	5·2	7·7	7·9	5·8
		P.*		0·01–0·001	>0·1	>0·05	0·001
	M	Mean	12·5	12·1	10·9	15·1	6·6
		(s.e.)	(1·0)	(0·9)	(1·1)	(3·7)	(2·7)
		S.D.	7·4	4·3	4·8	11·8	8·0
		P.*		>0·1	0·05–0·02	>0·1	>0·05
Not-operated	F	Mean	14·7	16·6	14·1	12·6	5·2
		(s.e.)	(1·2)	(2·5)	(2·7)	(2·7)	(1·2)
		S.D.	6·9	7·1	8·0	7·7	5·1
		P.*		>0·1	>0·1	>0·1	>0·001
	M	Mean	12·4	9·4	15·2	14·5	4·0
		(s.e.)	(2·1)	(2·3)	(1·0)	(3·8)	(1·2)
		S.D.	9·9	6·8	1·4	12·3	3·3
		P.*		>0·1	>0·1	>0·1	<0·001

*Probability, calculated by Student's t test, that the mean duration of survival from the onset is the same as the mean for all known survivors.

TABLE XVI.—POST-OPERATIVE SURVIVAL

Sex	*All known survivors* yrs.	*A+B* yrs.	*C* yrs.	*D* yrs.	*Myasthenic deaths* yrs.
F	7·2	7·5	6·7	7·3	2·4
M	7·1	8·1	6·1	6·7	1·0

able in the case record. (Unfortunately, this was not always present making an accurate review of the identical series impossible.)

Table XV shows the mean survival times from the onset of myasthenia in both series and the survival after operation in the operated series (to April 1956) is in Table XVI. The apparent shorter survival from onset of operated group A+B must be taken along with the figures for post-operative survival (Table XVI) which shows a longer post-operative follow-up than the other categories, thus the lower figure in Table XV merely reflects the fact that A+B tends to have a shorter pre-operative history.

There is nothing to indicate that the longer the series is followed the more cases will move from Category A+B to C or D, confirming the clinical impression. The further question regarding the possibility of improvement with time in not-operated patients is not answered unequivocally since the sexes differ and no category differs significantly from the mean for all survivors (Table XV). An interesting point emerges from Table XV. Those patients who eventually died of myasthenia gravis did so on average four to seven years after the onset of the disease whether thymectomy was carried out or not. Deaths from myasthenia gravis *per se* rarely occurred more than ten years after the onset of symptoms.

Conclusions.—Fewer women die of myasthenia gravis if their thymus is removed than would be expected if they were treated with neostigmine only, and a higher proportion of operated cases is very greatly improved ten or more years after the onset of the illness. This difference is unlikely to have occurred by chance. The greatest improvement tends to occur in a group with myasthenia starting rather younger than average and with a shorter pre-operative course than the less successful cases but the differences are not sufficiently marked to discount chance effects. The pre-operative severity is probably not a significant factor. Similar trends are noted in male cases. Though, considered in isolation, none of the differences noted in the operated male series are of such magnitude as to exclude the possibility that they result from chance, the fact that all trends after operation are in the same direction as in the female cases and that a direct comparison between the sexes shows no significant difference suggests that males do benefit in the same way as females. There is some evidence (Tables VI and VII) that the greater benefit obtained by thymectomy in women is due to the change from a prognosis slightly poorer than the male to one better than the male. Though the sex difference is not significant (in the statistical sense) in either series the swing is sufficiently great to be beyond chance (Table VI).

PART III

Thymomas

The number of patients in whom thymoma was known to be present was not great (29 women and 18 men); the numbers are too small to make the results statistically significant, but it is apparent from the breakdown shown in Table XVII that the mortality rate is not strikingly lowered by

TABLE XVII.—RESULTS—THYMOMAS

	Operated				*Not-operated*			
	F		*M*		*F*		*M*	
Category	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
A	1	4·3	3	23·0	0	0	1	20·0
B	0	0	0	0	1	16·7	0	0
C	4	17·4	1	7·7	1	16·7	0	0
D	3	13·0	1	7·7	1	16·7	0	0
Myasth. deaths	7	30·4	5	38·5	3	50·0	4	80·0
Post-op. deaths	7	30·4	2	15·4	—	—	—	—
Deaths, others	1	4·3	1	7·7	0	0	0	0
Total	23		13		6		5	

operation. It is very much higher in both series than in myasthenia unaccompanied by thymoma whatever form of treatment was used (Table V). Of the 9 post-operative deaths, only 2 had been shown to have thymoma by previous radiography and each of these had been operated on after a course of deep radiotherapy. In the other 7 the X-ray studies had not revealed the tumour. The deaths recorded on the line for "other causes" were a patient, described elsewhere by Chalmers and Boheimer (1954), who died of hæmosiderosis without recurrence of myasthenia gravis three and a half years after operation, and another who died of acute mania complicated by bronchopneumonia. The circumstances of the other deaths were investigated as fully as possible by retrospective inquiry. In all cases the nature of the terminal illness was consistent with death due to myasthenia gravis. In at least 7 of these patients the immediate effects of operation were comparable with the non-tumour patients and indeed three of them had long periods (two and a half, six and seven years) of complete remission from myasthenia before the relapse which led to death in a short period.

Age at onset.—The mean age at onset of myasthenic symptoms was higher than in comparable non-tumour groups but the small number of cases and the wide scatter of ages make this of doubtful significance (Table XVIII). This information was not available in two male patients who have been omitted from the table.

The mean age at onset of myasthenia for all known cases of thymoma was 40·8 years for females and 39·3 years for males. The earliest onset was in a woman of 24 (died) and the oldest a woman aged 64 who at the age of 70 was in excellent health (Category A) five years after removal of

TABLE XVIII.—AGE AT ONSET OF MYASTHENIA (THYMOMAS)

		Operated		*Not-operated*	
		F	*M*	*F*	*M*
Cases	No.	23	12*	6	4*
Mean age	Yrs.	42·5	39·3	35·8	39·3
(s.e. of mean)	Yrs.	(6·3)	(2·5)	(4·5)	(4·1)
S.D.	Yrs.	30·1	8·5	11·1	8·2

*Age at onset unknown in one male of each group.

TABLE XIX.—SURVIVAL FROM ONSET OF MYASTHENIA (THYMOMAS)

	Sex	*Cases No.*	*All survivors yrs.*	*A yrs.*	*B yrs.*	*C yrs.*	*D yrs.*	*Myasth. deaths yrs.*
Operated ..	F	23	9·6	8·3	—	7·5	12·7	5·6
	M	13	7·4	5·3	—	11·6	9·5	3·1
Not-operated	F	6	9·3	—	9	9·6	?	6·4
	M	5	4·8	4·8	—	—	—	2·3

TABLE XX.—POST-OPERATIVE SURVIVAL—THYMOMAS

	Sex	*Cases No.*	*All survivors yrs.*	*A yrs.*	*B yrs.*	*C yrs.*	*D yrs.*	*Myasth. deaths yrs.*
Operated ..	F	15	5·3	5·8	—	3·9	6·9	2·6
	M	10	5·5	4·6	—	9·3	4·5	2·1

a thymoma (with only post-operative radiotherapy). It does not appear as if the patient's age when myasthenia first manifests itself is of much assistance in diagnosis or in prognosis but Keynes (1955) has remarked on the absence of cases under 20 and the low incidence under 30 (4 per cent).

Survival.—It has been thought advisable to show the survival figure of this group, though the numbers are too small for proper comparison with the non-tumour series, as there is a common tendency to give a poorer prognosis than is justified by the facts. The high mortality of this group has been discussed above, but many years of survival in a high category are possible (Table XIX). The post-operative survival is also shown for comparison with Table XVI (Table XX).

The follow-up period is of the same order as in the non-tumour cases. Furthermore Tables XIX and XX show that although myasthenic death is more likely to occur in the presence of a thymic tumour, this event tends to occur at much the same time from the onset or after operation, whether tumour is present or not. In other ways, too, the patients with a thymoma showed no obvious clinical difference from the others. The incidence of myopathic change and of goitre was the same (compare Table XXI with Table IV).

TABLE XXI.—ASSOCIATED PHENOMENA (THYMOMAS)

	Operated		*Not-operated*	
	F	*M*	*F*	*M*
	%	%	%	%
Ocular myasthenia*	0	0	0	0
Myopathy* ..	8·7	23·0	16·7	20·0
Goitre	21·0	8·0	16·7	0

*As defined for Table IV.

Keynes (1955) thought that the tumour cases were nearly always associated with severe symptoms which were difficult to control. The average neostigmine requirements of the thymoma group was about 25–50 per cent higher than the non-tumour series (Tables XXII and XIV) and neostigmine resistance was more common. There is a marked discrepancy in this index of severity when Category A is examined (Table XXII). In

TABLE XXII.—NEOSTIGMINE REQUIREMENTS (THYMOMAS)

	Sex	*A tabs.**	*B tabs.*	*C tabs.*	*D tabs.*	*Myasth. deaths tabs.*	*Group tabs.*
Operated ..	F	30	—	23	13	10·4	17·0
	M	26	—	8+	1	17·6	
Not-operated	F	—	24	10	10	40+	20·0
	M	27	—	—	—	5†	

*15 mg. tablets. Parenteral dosage equated as before.

†Not known in 2 cases.

the non-tumour series this category had a slightly lower than average pre-operative requirement for neostigmine, but in the tumour group the mean dosage was much higher than average. Too much stress should not be placed on this unexpected finding as the whole group includes only 4 cases, nevertheless, this observation once again underlines the fact that excellent recovery may follow removal of a thymoma in a severely myasthenic patient. The 3 male patients in Category A had pre-operative radiotherapy (which caused increased weakness). The female patient did not have radiotherapy until after operation. Keynes (1955) stresses the desirability of pre-operative radiation but records successful results in the absence of this precaution. Of 20 patients with thymoma treated with deep X-ray therapy followed by operation between 1948 and 1953, only 4 (20 per cent) had died at the time of his report (1953, published 1955).

PART IV

Comparison with Published Series

Comparison of one published series with another cannot be made with great accuracy. The most important reason for this is the failure to differentiate the cases associated with a thymic tumour from those in

which no tumour can be demonstrated. The numbers involved in most of the series are small and their selection varies. Sir Geoffrey Keynes has operated on almost every patient referred to him. (I have only found 3 patients who were rejected as "bad risks" so their inclusion in the not-operated series does not introduce a significantly adverse factor.) The number of patients who were not referred to a surgeon is not known, but is believed to be small. In his series of papers from 1946 to 1955 Keynes has reported the cumulative results of his experience. In the present paper (Table XXIII) his figures have been recalculated in terms of the total material instead of percentage survivors as reported. Ross (1952), reporting an independent assessment of Keynes' patients, examined "100 consecutive patients" from the latter author's series. It seems implicit that this means "100 consecutive patients who survived thymectomy." To this extent the series is not representative of the total case material now included. Keynes and Ross did not publish separate statistics for each sex, nor did Viets (1945, 1950), Harvey (1948) and Eaton and Clagett (1950), reporting the early results from Boston, Baltimore and the Mayo Clinic. Furthermore, the American reports of that period included tumour and non-tumour cases in the one analysis. Indeed some of these centres considered that the presence of a thymoma was the main indication for operation (Eaton and Clagett, 1950) and in other ways their series were more "selected" than the London series. Viets (1950), for instance, states that he had "deliberately avoided operating upon mild cases, or those fully maintained under oral medication" and excluded most patients under 40. He considered that less than half of 300 patients he had seen since 1935 were proper candidates for thymectomy. Schwab and Passouant (1952) and Schwab and Leland (1953) correlated the findings with sex and age, but still included cases with thymoma. In the last report from Boston (Schwab and Leland, 1953) 22 per cent of 78 patients subjected to thymectomy had thymomas. As tumours were present in 32 per cent of their male cases against 17 per cent of their females it is apparent that their conclusion that males received no evident benefit from the operation requires further examination. The method of selection of patients for thymectomy by Schwab and Leland (1953) "depended partly on chance, economic reasons and random persuasion in different periods by a number of different physicians, with a large number of variables. There has been, however, a trend towards selection of younger patients." A like number of patients was selected from a group of 250 myasthenia gravis patients as controls "that matched the thymectomy patients by sex, age of onset (within five years), severity of disease and presence or absence of thymoma." The intention is most laudable, but considering the "method of selection" of cases for operation and the virtual impossibility (to the writer) of matching many cases from such a small population, the "control" must be considered dubious.

The Baltimore series, starting with the famous paper of Blalock (1941), was reported briefly by Harvey (1948) and more fully by Grob (1953) who discusses the sex difference, but unfortunately there is no report of this series in which the tumour material is separated from the non-tumour. (20 per cent of 44 operated cases had thymomas; 40 per cent of the deaths in the operated series had tumours as compared with 10 per cent of the deaths in the not-operated cases.) The criteria for selection for operation are not reported but "the average severity of disease at the time of operation was slightly greater than in the other patients with myasthenia who were hospitalized but who did not have thymectomy or irradiation." The incidence of ocular myasthenia was 4·5 per cent in the thymectomy series and 29·7 per cent in the remainder.

The failure to separate thymoma from non-tumour cases was also the cause of confusion in the first reports from the Mayo Clinic by Eaton and Clagett and their collaborators (1949, 1950). The sexes were not considered separately. It appears that "some patients were too ill or too old for major surgical procedures to be recommended." On the other hand many cases of mild myasthenia gravis were included in the control group. These authors also attempted the case-matching type of control in their later papers (1950, 1953, 1955), nevertheless in 1950 Eaton and Clagett concluded that "at present thymectomy in the treatment of myasthenia gravis is recommended by us because of the potentially malignant character of the thymomas and not because of anticipated improvement in the myasthenia gravis. Thymectomy is seldom recommended except when the following conditions prevail: (1) A thymic tumour can be demonstrated roentgenologically. (2) The condition of the patient is such that the risk of operation is not considered excessive. (3) There is no roentgenological or clinical evidence of inoperability of the tumour." When their material was redeployed to take account of presence or absence of tumour, Eaton, Clagett and Bastron (1953) expressed surprise on finding statistically significant benefit from operation in the non-tumour cases. The fullest discussion of the Mayo Clinic series including the sex factor, is made by Eaton and Clagett (1955). This is the only American paper which breaks down the material in such a way as to allow comparison with the London series. It is apparent that the earlier views were based on a surgical series in which 42 per cent of patients had thymomas against 7 per cent of non-surgical cases. The criteria for operation after this recognition was made are not reported, though it appears that the risk of operation was accepted in more severely ill patients "on the basis that thymectomy might prove to be lifesaving." In view of the very marked differences between patients selected for operation and those not so treated, Eaton and Clagett (1953, 1955) use the match-control method criticised above.

This detailed study of the constitution of the major series in the literature

is not made in any critical sense. The writer is well aware of the deficiencies and lack of planned control in the present series, but the literature has been so long bedevilled by conflicting claims it seems essential to examine the basis of these claims with care before a comparison is made. It is also necessary to examine the method of classification of results used in the different centres. This has been done in Table XXV. Where the authors define their criteria they have been quoted and this has been amplified from internal evidence in the text or tabulated data. The classifications differ widely, particularly in the large group in which improvement short of complete remission is recognized. It is not always made clear that the grading represents a *change* of status from some datum point such as the pre-operative period rather than a classification of physical status at the time of follow-up. Under the first system, used in this paper, a mild case of ocular myasthenia showing no spread but no significant improvement would be classed in Group D. In the alternative scheme it would be in Group B. Table XXIII shows the apparent relationship between the different reports and the further comparisons are based on this assumption. Eaton and Clagett (1955) state that their criteria for "complete remission" are stricter than those of Keynes. If a minor degree of myasthenia gravis persists these authors classify the result as "considerably improved." The definition of Group A used in the present report is restricted in the same way, but it has been considered justifiable, following Keynes (1954), to permit "myopathic" weakness (wasting, and weakness not related to effort nor reversible by neostigmine). This point is not discussed by the other authors, but since it cannot be expected that thymectomy could reverse a myopathic lesion, such a concession seems permissible. On the other hand my criteria for C and probably B are stricter. The combined A and B groups are believed to conform to the criteria of Keynes and Ross.

Table XXIV shows the relation between successive reports from London, but it should be remembered that Keynes did not operate on a small number of the present operated series which accordingly includes the "first steps" mortality of several surgical units. It is evident that the present author's assessment is similar to that made by Keynes in 1949 although the proportion not included in the improved categories is some 10 per cent higher. This is certainly attributable to the very rigid criteria adopted, for instance Group D (a) were undoubtedly improved, and might well have been in Group C in Keynes' classification, but they have been kept in the lower group because the neostigmine dosage was not decreased. This decision is certainly open to argument, but the writer's aim is to present the operative results in the least favourable light so that any result will not be open to accusation of special pleading. The discrepancy with Ross's results (which Keynes has described as "better than I have ever claimed myself") is not understood. Though it is apparent that the criteria for

TABLE XXIII.—

Simpson, 1956	Keynes (1946, 1949, 1954)	Ross (1952)
A. Full working life with no restrictions. No neostigmine No subjective weakness. (Small degree of permanent objective weakness permitted.) Markedly different from pre-operative state	A. Quite well. No symptoms. No neostigmine	A. Quite well. No symptoms or treatment
B. Full life. Minor symptoms, not requiring neostigmine or controlled by not more than 60 mg. Significantly better	B. Virtually well. Minimal symptoms. Small dose of neostigmine	B. Symptoms inconstant and minor e.g. only present at menses. The patient is able to carry on with full scale of activities. Treatment minimal; significantly less (mean post-op. dose 6·8 tabs. S.D.4·8)
C. Full life with few restrictrictions: (*a*) demonstrable myasth. but not requiring neostigmine		
(*b*) Still requiring drug but at least 40 per cent less than before and with improved response	C. Some improvement, often considerable. Neostigmine still necessary but less than before	C. Considerable improvement. Fewer or less severe signs and symptoms, and responds to signif. smaller dose of neostigmine
D. (*a*) Improved, but on same or greater dose of neostigmine		
(*b*) Unimproved, irrespective of dosage (even if in good health e.g. ocular myasthenia).	D. No change	D. Unchanged or worse
(*c*) Worse		
DIED (*a*) Death due to myasthenia after three weeks	DIED (*a*) Later myasthenia	DIED Later myasthenia
(*b*) Post-op. within three weeks	(*b*) Post-operative	—
(*c*) Death due to other causes	(*c*) Other causes	Other causes

COMPARISON OF CRITERIA

Eaton *et al.* (1953)	Schwab and Leland (1953)	Grob (1953)
+4 Complete remission No symptoms. No neostigmine	A. Complete remission. No longer required any medication and had no symptoms	In a complete or nearly complete remission
+3 Considerable improvement (1) Subjectively well. Examination discloses (*a*) min. weakness due to myasthenia (*b*) Unequivocal sensitivity to curare (2) Marked subjective improvement. Verified by increased work and activity, plus great reduction in amount of neostigmine required	B. Significantly and objectively improved, took less medicament and had fewer symptoms. Medical referees would all agree as to the presence of improvement	
		Improved to a moderate degree
+2 Moderate improvement (2) Same work and activity accomplished with signif. reduction of neostigmine		
(1) Greater work and activity accomplished with use of same amount of neostigmine	C. Various degrees of slight to mod. improvement which was subjective oftener than objective. Difficult to evaluate quantitatively and would not convince referees	
+No essential change −2 Worse	D. Unchanged or worse	Unchanged. Worse
−4 DIED, Myasthenia gravis	E. All deaths	DIED (all cases)
−4 Surgical death		

Category B are less rigid (cf. neostigmine requirements) and Ross agrees with Keynes in B. C. D. there is a difference between the proportions in Category A which can only be attributed to fortuitous selection. The apparent selection of survivors of the operation has already been pointed out. Certainly the writer was frequently able to check his own assessment with that made on the same case a few years earlier by Ross and there was rarely disagreement; and 54 per cent of the patients Ross had assessed as A made up 56 per cent of these classified as A by Keynes in 1949 (Ross, 1952). This strongly suggests that the difference is a genuine one due to examination of a consecutive series of cases which was not a true sample of the whole operated population—a well-known risk in surveys of this type. The present assessment in which no sampling is involved, should, therefore, be taken as an expression of the writer's opinion of the latest state of the whole London series when looked at in the most critical light. This can now be compared with the other major series, bearing in mind the differences in composition and in the criteria of assessment which have been presented above. The figures tabulated (Table XXV) are those most recently reported.

The closest agreement with the results of the present survey is the much smaller series of Schwab and Leland (1953). Unfortunately, 9 of the 53 females (17·0 per cent) and 8 of the 25 males (32 per cent) in the operated series had thymomas and the published data are insufficient to permit computation of the non-tumour results though it is stated that exclusion of the thymomas raised the A or B remission (A+B+C of the present classification) to 68 per cent for females, but left the rate unchanged for males (24 per cent). On the other hand, exclusion of the tumours lowered the mortality rate for males from 32 per cent to 18 per cent (though not stated it is assumed that the female mortality rate is little affected by the adjustment). These authors, then, agree closely with the London results except for the poor improvement rate in males. Their control series closely resembles the present one in all respects except for the larger number of females considered unchanged or worse. It should be remembered that the control series was selected to contain the same incidence of tumour as the operated series.

Eaton and Clagett (1953) also report results of the same order as the present ones in their operated series, but agree with Schwab and Leland (1953) in finding more females improved and more males unchanged or worse. The figures for their control series, however, are so markedly different from all the other series (which are consistent with each other) as to raise doubts about the validity of their matching technique. They report the following assessment of 142 unselected controls: A 7·7 per cent, B 9·9 per cent, C 10·6 per cent, D 49·3 per cent, Died 22·5 per cent, but 9 per cent of this series were previously reported to be cases with tumour (Eaton and Clagett, 1950). Nevertheless, the mortality rate is more consistent with that in the other not-operated series.

TABLE XXIV.—PROGRESSIVE ASSESSMENT OF LONDON SERIES (NON-TUMOUR)

	Keynes (1946)		*Keynes* (1949)		*Ross* (1952)		*Simpson* (1956)	
	No.	%*	*No.*	%	*No.*	%	*No.*†	%
A	9	27·3	39	28·4	41	41	55	21·3
B	11	33·3	40	29·2	26	26	32	12·4
C	8	24·2	31	22·6	20	20	60	23·3
D	5	15·2	10	7·3	6	6	47	18·2
Data incomplete ..	—		7	5·1	0	0	17	6·6
Myasth. deaths ..	—		0	0	1	1	23	9·0
Post-op. deaths ..	—		10	7·3	0	0	20	7·7
Deaths, others ..	—		0	0	6	6	4	1·5
Total	33		137		100		258	

*Per cent of survivors only.
†Both sexes combined.

TABLE XXV.—COMPARISON OF NON-TUMOUR CASES WITH OTHER SERIES

		Operated				*Not-operated*			
*Series**		*London* %		*Mayo* %	*Boston* %	*Baltimore* %	*London* %		*Mayo* %	*Boston* %	*Baltimore* %
A	F	22·0		16·7	20·7	12·0	15·3		5·6	13·0	14·0
B		13·2		36·7	41·5	36·0	5·1		14·8	20·7	22·0
C		23·1		20·0			15·3		14·8		
D		17·6		16·7	22·6	24·0	13·5		57·4	37·7	34·0
Data incomplete		7·1		—	—	—	15·3		—	—	—
Myasth. deaths		7·7		6·6	7·6		28·8		7·4	28·3	30·0
Post-op. deaths		7·7	17·0	6·3	7·5	28·0	—	35·6	—	—	—
Deaths, other		1·6		—	—		6·8		—	—	
Total cases		182		30	53	25	59		54	53	77
A	M	19·7		17·7	8·0	22·0	17·5		13·0	16·0	17·0
B		10·5		17·7	16·0	16·0	5·0		17·4	10·0	12·0
C		23·7		17·7			7·5		17·4		
D		19·7		35·3	44·0	21·0	25·0		43·5	24·0	27·0
Data incomplete		5·3		—	—	—	22·5		—	—	—
Myasth. deaths		11·8		0	8·0		20·0		8·7	20·0	
Post-op. deaths		7·9	21·0	11·8	24·0	42·0	—	22·5	—	—	44·0
Deaths, others		1·3		—	—		2·5		—	—	
Total cases		76		17	25	19	40		23	25	41

*London—present series. Mayo Clinic—Eaton and Clagett (1955). Boston—Schwab and Leland (1953). Baltimore—Grob (1953).

Grob (1953) agrees with the present author in his grouping of male cases with or without operation except for the considerably higher mortality rate. Considering the numbers involved the female series are in reasonable agreement, but the mortality rate of the operated series is much

higher. Unfortunately, no details are given to show how much of this represents operative risk, but the high proportion of thymomas may be responsible. 9 of the 44 operated patients (sex not distinguished) had thymomas and 6 of these "died of myasthenia gravis." Removal of these would lower the combined sex mortality from 34 per cent to 10 per cent. On the contrary, only 4 of the 41 not-operated deaths were thymomas (and 2 surviving tumours were known) giving a corrected combined-sex mortality rate of 33 per cent (37 of 112). These figures are again similar to those reported here.

To summarize, there is general agreement on the mortality rate and extent of remission in operated and not-operated series and that differences in assessment of the remainder can be attributed to differences in methods of classification or to errors of sampling in small series. All four centres agree that thymectomy results in a worth-while improvement in prognosis for women, particularly in the reduced mortality rate, but the three American centres do not consider that males are significantly benefited by operation. On first glance at Table XXV this conclusion would appear justified, but close inspection suggests that the conclusion may be premature since the male mortality in the operated series of Eaton and Clagett (1955) is entirely an operative mortality and in Schwab and Leland's (1953) it is predominantly so. It will further be recollected that 32 per cent of the operated males in the latter series had thymomas (double the incidence in females). Grob (1953) does not detail the distribution of the thymomas which formed 20 per cent of his entire operated series and contributed 60 per cent of the deaths. In the light of these considerations, the American position cannot be sustained until analyses of their non-tumour series are provided. Their conclusions are in line with those in Part II of this study and all four series show identical trends (in favour of operation) though no single series reaches statistical certainty. The identical trends in all series are unlikely to be fortuitous. With regard to the influence of age, Eaton and Clagett (1955) since removing thymomas from their series, now agree with Keynes and Ross (1952) and return to their opinion (of 1950), that the age at onset does not significantly affect the response to thymectomy, though earlier (Eaton, Clagett and Bastron, 1953) they had agreed with Schwab and Leland (1953) that the younger the patient at onset, the better the response to thymectomy. The latter authors, however, state that "the high proportion of thymomas in older females (in their series) probably explains their poorer result." The present study now provides further evidence that the non-tumour patients who show the poorest response are a little older than the average, although a direct comparison between the good results and the failures shows no difference sufficient to be of practical value.

An unexpected finding is that the myasthenic deaths occurring despite operation do so in a group whose characteristic age of onset, age at

operation and duration of symptoms before operation are substantially similar to those of the group deriving most benefit. From Table XV it appears that the crucial period is four to seven years from the onset, whether operation is carried out or not, and it is possible that these patients are more difficult to control by neostigmine (Table XIV). The available data do not suggest any method of selecting this unfavourable group.

The beneficial effect of shorter pre-operative duration demonstrated in this paper confirms the findings of Keynes (1946 and 1949) and Ross (1952). Schwab and Leland (1953) agree so far as females are concerned, but not for males. The high incidence of tumours again invalidates their findings. The Mayo Clinic and Baltimore groups have not commented on the influence of pre-operative duration of myasthenia. Eaton and Clagett (1950) also agree that the pre-operative duration is, on average, slightly shorter in those showing marked post-operative improvement (without distinction of sex). Nevertheless, the inference that the incidence of deaths due to myasthenia despite thymectomy would be reduced by selecting young patients with a short pre-operative history is not borne out by the present survey since the average age at onset and at operation and the average pre-operative duration in these patients is actually lower than in the unimproved (D) patients, and sometimes lower than the average of the whole group or even of Group A+B. One would expect that the response to any form of therapy would be a function of the severity of the illness at the time treatment was started, that is to say that the final category would bear some simple relation to the initial severity of myasthenia. The method of assessment used in this and in the other surveys reviewed does not permit deductions of such a nature since the factor of change of status selected for analysis takes no cognizance of the severity of the disease from which that change occurred. The necessity for this approach has been discussed already, but it is worth re-emphasizing that the bald classification of a case as Category C or even B according to the rigid definitions used does not convey how truly dramatic the change may be. Some measure of the severity of myasthenia at the datum point is given by the neostigmine requirements of the patient at that time. It was found (in agreement with Ross, 1952) that the requirements in those ultimately achieving Category A were little lower than the remainder, but certain possible fallacies (discussed in Part II) make this conclusion only tentative. None of the American series allows direct comparison. Eaton, Clagett and Bastron (1950) give criteria for classification of severity, but do not state how it correlates with the final outcome. It is, however, relevant to note that the re-analysis of their non-tumour material which forced them to acknowledge the value of thymectomy was based on cases selected as being of "average severity." Indeed a method of classification based on extent of change in state is likely to be biased against the mild

case in which any change can only be of small amount. This limitation was accepted in the present study as it was thought desirable that any bias introduced should be against thymectomy on the grounds that the onus of proof rests on the proponents of radical forms of treatment. The "devil's advocate" has nevertheless confirmed their claims that a significant saving of life results from removing the non-malignant thymus gland of patients with myasthenia gravis and that the survivors have a better chance of complete and lasting remission or of great improvement in myasthenic symptoms, particularly if operation is performed within four years of the onset of symptoms. It is perhaps not out of place to add that the extent of this improvement may be very great. It is usually permanent, though a few relapses have been noted, and it is common for improvement to be progressive for several years after operation. For the present purposes Category D has not been subdivided, but physicians considering subjecting patients to operation should know that most of the patients in this category were "unchanged," very few became worse after operation. Unfortunately, apart from duration of symptoms, this study (and parallel unpublished observations) has not shown criteria which would allow one to predict the effect of thymectomy in the individual case, but this writer is satisfied that although the chances of significant improvement, or arrest, are not overwhelmingly superior to those of non-surgical treatment, they are sufficiently great and the extent of the improvement so potentially spectacular that the operation should be seriously considered in all cases in which myasthenia is not confined to the ocular muscles. This qualification seems necessary in view of the report of Ferguson, Hutchinson, and Liversedge (1955). These workers put forward the view that the prognosis of myasthenia gravis is not unduly poor with medical management. They traced 69 of 75 cases seen over a period of twenty-two years and only 9 of these had died (2 with thymomas). Of the 60 survivors 42 were well controlled with medical treatment. They pointed out that in 27 of these (36 per cent of the total material) the myasthenia had remained confined to the ocular muscles. It is apparent that they have seen a much higher proportion of ocular myasthenia than occurs in the practice of the National Hospital (Tables IV and XXI).

Discussion

Seventeen years have passed since Blalock (1941) reawakened interest in the role of thymectomy in myasthenia gravis, yet the value of the operation is still debated. The apparent lack of agreement between the few centres with wide experience of thymectomy has caused those looking for guidance to assume that the evidence was too equivocal to carry conviction (*Lancet*, 1954). Keynes has pointed out on numerous occasions that the apparently poor results in some of the American reports were due to the failure to separate those patients with thymic tumours from the

remainder. Where such differentiation has been made (Eaton and Clagett, 1955), the favourable results reported by Keynes have been confirmed.

Criticism has been made of the method used in this and the earlier surveys. The deficiences of the method are clear and are freely acknowledged. It is obvious that in a disease of protean manifestations without measurable characteristics any assessment of disability on an absolute scale would be misleading if not impossible. Nor would it be possible for even a single observer to maintain rigid standards of severity for a disease of rare occurrence. It is, however, comparatively easy by the normal means of clinical investigation for any physician to decide whether or not a patient has improved significantly from a given point in time and, if the criteria are rigidly defined and the categories are not too narrow, any experienced observer can assess the degree of improvement. Two difficulties do arise. Firstly, there must be reasonable certainty that the original diagnosis was correct. In the present study this was assumed if the diagnosis was confirmed by an experienced neurologist and a record fulfilling certain criteria was available for study. The second difficulty is more serious: Since the basis of classification is a change in clinical status it is obvious that the extent of this change may be little or great, depending on the severity of the disease at the time used as reference point. A little consideration will show that this factor cannot influence Category A and probably would not materially affect Category D, but may substantially affect the relative distribution between Categories B and C. As this effect is a random one it should not be a serious matter in a large series, but it may well explain some of the anomalies in the smaller series.

Further criticism encountered during this work has been the time-honoured "you can't reduce a complex disease in a living subject to a number." This has been answered in an admirable way by Herdan (1955) who writes:

"Some clinicians are not sympathetic to methods tending to condense the information on a patient's hospital record by disregarding certain details, in order to make the material amenable to statistical methods. They consider this inferior to working with the complete picture of the case. But such a view rests upon the illusion that our intellect is capable of integrating all the data on a patient's card or even on a number of such cards, into one clear-cut conclusion without neglecting any details. Unfortunately, our mind is not made that way. Combination of observations—and without it no conclusion can claim the slightest degree of generality—implies neglect of details. Since no two cases are completely alike they can for the purpose of combination be made alike only by dropping unnecessary detail. What statistics offer in this respect is a legitimate method free from arbitrariness, by which to replace the highly subjective method of the man who labours under the illusion that he never

neglects a detail." No other way of assessment is open. It is not sufficient to quote a case of spectacular cure of myasthenia gravis or one in which no benefit resulted without adding the (statistical) statement that such a result may be expected to occur in a certain proportion of trials. Nor would the statement be complete without the addition of the further information of the extent to which such a result differed from that to be expected from other modes of treatment.

The last statement raises the question of "controls." For the present purposes a series of patients treated medically by the same group of physicians was, *faute de mieux*, regarded as an index of the expected outcome of myasthenia gravis when treated without thymectomy, but in all other respects in the same manner. In the event, it became clear that this comparison could not be sustained since there were marked dissimilarities in the composition of the two series ("operated" and "not-operated"). This has been countered by demonstrating that the statistics of the total material are substantially the same as those of a selected sample of each group in which age and sex were comparable. It was not, however, possible to ensure that previous medical treatment was the same in both groups as the majority of the not-operated series were patients treated between 1934 and 1941 when neostigmine was customarily prescribed in lower dosage than is now practised. Two of the American series have attempted to obtain a control series of "not-operated" cases by selecting for their unoperated group a case believed to match in every respect each one in the "operated" series. The principle is good and it is probably the best method where numbers are high and operation has been advised for all cases without conscious selection. The writer does not believe that the method is at all reliable where numbers are small, operation has been selective, and the disease is so variable as to make matching in every respect a virtual impossibility. Furthermore, the "control" series is already selected by the fact of survival. It does not seem likely that if two subjects had similar clinical manifestations, but one died at one year from the onset of myasthenia, while the other survived to two years, the former would be chosen to pair a third "identical" subject operated on at nine months from the onset and still surviving at two years. Yet there would seem no reason why at the relevant time—nine months—the second patient should be considered a better match than the first. Without first-hand evidence no more can be said, but it may well be that considerations of this nature explain the very low mortality rate of Eaton and Clagett's (1955) "controls" which differs so strikingly from that reported from the other centres. These authors readily concede the tentative nature of their results in view of the small size of their series. The only satisfactory method in a disease with so many variable factors (e.g. do two paralysed limbs equal one paralysed palate?) is to allocate cases randomly to one or other series and to continue each series until it is sufficiently large for all the variables

to occur without statistically significant difference and thereafter until sequential analysis shows that one series differs significantly in its natural history from the other. Unfortunately this was not done in the present instance. The physicians treating myasthenia gravis in London were sufficiently impressed by the results of the early cases which they had submitted to Keynes for thymectomy to wish to carry on in the belief that it was in the interests of their patients to do so (*Proc. Roy. Soc. Med.*, 1946). No controlled trial was instituted at that time and it is doubtful if such a measure would now be ethically justifiable. Though not scientifically elegant the results reported here show that (in a series sufficiently large to reduce the effect of random variations) there is a great saving of life in patients subjected to thymectomy even when the hazards of operation are included, and further that a greater proportion is greatly improved at the end of a comparable period than is the case where the non-tumour thymus is not removed. This difference has been shown to be greater than can be attributed to chance in the female sex and the trend in males is the same, although the level of statistical significance is not reached. No marked sex difference could be established in either series. Slightly more women than men were in Categories A and B after operation and fewer died of myasthenia. Analysis shows that this could have occurred by chance and so does not conflict with the impression of Keynes (personal communication) that the results are equally good in both sexes. On the other hand though the sexes were again very similar in the not-operated series the trend was quite different since women had a slightly poorer prognosis than men. The change in prognosis for women when thymectomy is performed is greater than can be explained by chance. This conclusion agrees with Schwab and Leland (1953) and Eaton and Clagett (1955), thus reconciling theirs with Keynes' apparently conflicting point of view. The inclusion of tumour cases in the Boston and Baltimore series and the small size of the Mayo Clinic series have been shown to introduce fallacies which make more direct comparison impossible, but it should be remembered that two of these series agree with the writer that the benefit from thymectomy may be shown by males though statistical analysis does not exclude the possibility of chance. It would seem worth while appealing to other centres to reclassify the small numbers involved according to the criteria stated in this paper (since no others have been defined) in order that a unified body of data might be available to test those points where statistical confirmation is lacking because of shortage of cases.

Summary

A long term follow-up survey of 404 patients with myasthenia gravis is reported and the value of thymectomy compared with medical treatment alone. The 47 patients with thymic tumour are considered separately. The cases were classified according to definite criteria with respect to

change of status from the pre-operative period or the time of first entering hospital in the not-operated series.

In Part I the "operated" and "not-operated" series are compared with respect to sex distribution, age incidence at onset of myasthenia, length of survival from onset of symptoms, and incidence of "myopathy," "goitre," and "ocular myasthenia" (as defined).

Part II analyses the assessment of non-tumour cases. It is concluded that significantly fewer women die of myasthenia gravis if their thymus is removed than would be expected if they were treated with neostigmine only. The number of women very greatly improved ten or more years after the onset of the illness is significantly greater. Similar trends are noted in men but the benefit in favour of operation is not so clear. It is suggested that without operation women have a poorer prognosis than men but after thymectomy they have a better outlook and that the extent of this change explains the more obvious advantage of thymectomy in women.

No clinical indication of the type of cases likely to be helped by operation is noted. It is confirmed that the best results are found in a group of cases with younger mean age at onset, shorter pre-operative duration of myasthenia, and younger mean age when operation was carried out. The age differences were not sufficiently marked to be of clinical value. There is strong evidence that a good result is most probable if the myasthenia has been present for less than five years at the time of operation though some excellent results were noted where the duration was much longer. On the other hand, the pre-operative duration of those who subsequently died of myasthenia (after the post-operative period) was no different from the average. The age-at-onset and at operation was average in women who died but lower than average in men. The female myasthenic deaths were also of average age-at-onset in the unoperated group but the corresponding males were significantly older than average, due to a relative excess of older men in the unoperated group. Death from myasthenia tended to occur four to seven years from the onset in each series. During life these patients required more neostigmine than those who survived but there is no clear evidence that the severity of myasthenia materially affects the final state of survivors.

The duration of follow-up of both series was the same and did not influence the category. There was no indication that a good response was temporary (though a few relapses after early improvement were noted). The main conclusions were confirmed in part of the series omitting the extremes of age in which the case material was more homogeneous.

The effect of thymic tumour is presented in Part III. Myasthenia gravis in the presence of thymoma differed from the non-tumour group in the later age of onset (average 40 years) and the severity of symptoms which were difficult to control with neostigmine. The incidence of myopathy and

thyroid disease was the same but myasthenia never remained confined to the ocular muscles. The operative death-rate was high and combined with a subsequent mortality from myasthenia to give a poor prognosis which was little better than that obtained without operation. Nevertheless attention is drawn to the possibility of excellent response with long survival (even without radiotherapy though Keynes (1955) stresses the desirability of it). The total survival of those who died of myasthenia was closely similar to the non-tumour group.

In Part IV the other major series in the literature are analysed because of apparent discrepancies. It is submitted that the differences are due to (1) failure of other workers to report thymoma cases separately; (2) different criteria for classification; (3) methods of selection for operation; (4) selection of unoperated cases for "controls." A tabulated comparison of series is made with the original reports adjusted to match the criteria of this paper as closely as possible. It is shown that the results of all series are then similar, allowing for the sampling errors of small series.

Conclusions

(1) There is a substantial chance of improvement after thymectomy in all cases. This is most evident, and the saving in life is greatest, when the duration is less than five years and no thymoma is present.

(2) After seven years from the onset considerable improvement after operation is less likely though it may still occur, but the risk of death from myasthenia is less whether operated or not.

(3) Improvement occurs in both sexes and the ultimate distribution of categories is the same but the extent of improvement is most significant in women as they would otherwise have a poorer prognosis than men.

(4) The prognosis for life remains poor if a thymoma is present, though pre-operative radiotherapy may be beneficial. Only one case in three survives but the improvement in myasthenia may then be as great as in non-tumour cases.

(5) The maximum improvement occurs in patients who first show symptoms at an earlier age and who have their operation younger than the average but the difference is insufficient to influence the selection of cases for operation. Death from myasthenia is more probable in cases requiring large doses of neostigmine but if they survive the ultimate category after operation is not influenced by the pre-operative severity.

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Appendix D

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Myasthenia gravis : a new hypothesis

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MYASTHENIA GRAVIS: A NEW HYPOTHESIS*

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In a part of the world which has now adopted more sophisticated methods of brain washing, it was once the custom to expose those with unorthodox ideas to a trial by ordeal which consisted of the chewing of the Calabar bean. Today I wish to present you with some unorthodox ideas so let me start by asking you to throw away the Calabar bean, or at least to keep its active constituent, physostigmine, out of sight, for I believe that this magic bean, or its synthetic competitors may have blurred our vision of the true nature of myasthenia gravis.

First let me pay tribute to Mrs Honyman-Gillespie who has made these lectures possible and the Post-Graduate Committee who invited me to contribute to this famous series. The first lecture was given by Edwin Bramwell (1938) on the contributions of the Edinburgh school to the study of the reactions of the pupil of the eye. From him I learned that the mydriatic action of the Calabar bean was discovered by Sir Thomas Fraser in 1863 when he was professor of materia medica in Edinburgh and a physician to the Royal Infirmary, and introduced to ophthalmological practice in the same year by the young Argyll Robertson in a paper read before the Medico-Chirurgical Society of Edinburgh.

Collier (1930) attributed the first British *recognition* of myasthenia gravis to this same Edwin Bramwell when he was starting his illustrious neurological career as a house-physician at Queen Square. Though first described by the Englishman Thomas Willis in 1672, the syndrome was unrecognized until the magnificent papers of Erb (1879) and Goldflam (1893). Indeed, Bramwell's father, Byrom Bramwell, gives an excellent description of a case in his famous *Atlas* (1892*a*) but could not name it, and the illustration reproduced in Figure 1 is almost certainly a myasthenic child. Edwin Bramwell with Campbell reviewed the known cases in 1900 (Campbell & Bramwell, 1900) and recognition became more common from that time on. If some of the facts I shall present are unfamiliar it is humbling to record that almost all are present in that instructive review or in the interesting paper by their colleague Buzzard (1905). They have been ignored, and many later observations discarded because they are difficult to reconcile with views which have been current since attention was focussed on the phenomena of neuromuscular transmission which is presumed to be disturbed in myasthenia gravis.

I would like you to forget all that you have been taught or presumed with regard to myasthenia and look with me at the symptoms and signs present in a series of 440 cases which I have been privileged to examine through the kindness of colleagues in Edinburgh, London and Glasgow. Let us not decide what is 'relevant' until the whole picture is before us. I shall draw some novel conclusions from this analysis, leading to a new hypothesis. This will probably require modification in detail but has the double merit of incorporating all the clinical phenomena without exception, and of suggesting completely new lines of inquiry. In the closing part of the lecture a necessarily brief account of the pathophysiology and pharmacology of myasthenia will be given to demonstrate that the hypothesis is compatible with the known facts.

*A Honyman-Gillespie Lecture delivered on 28th April 1960.

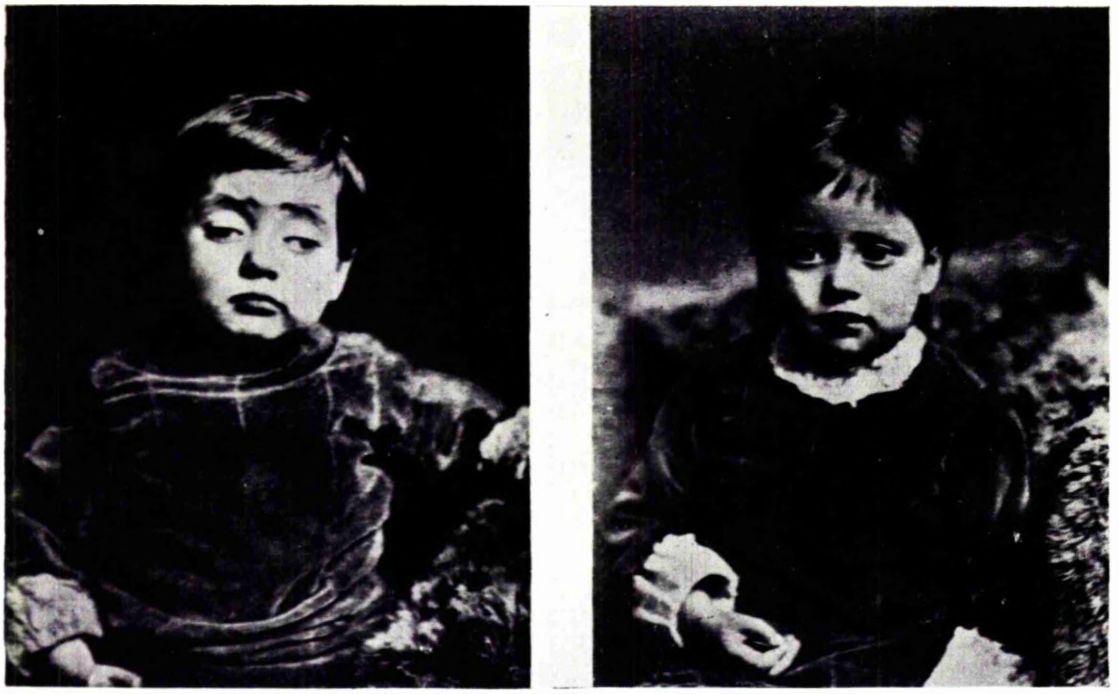


Fig. 1. Remittent ophthalmoplegia of uncertain aetiology, attributed to syphilis. Note the bilateral ptosis and drooping of the mouth (Bramwell, 1892*b*). (*Reproduced by kind permission of Edinburgh University Press*).

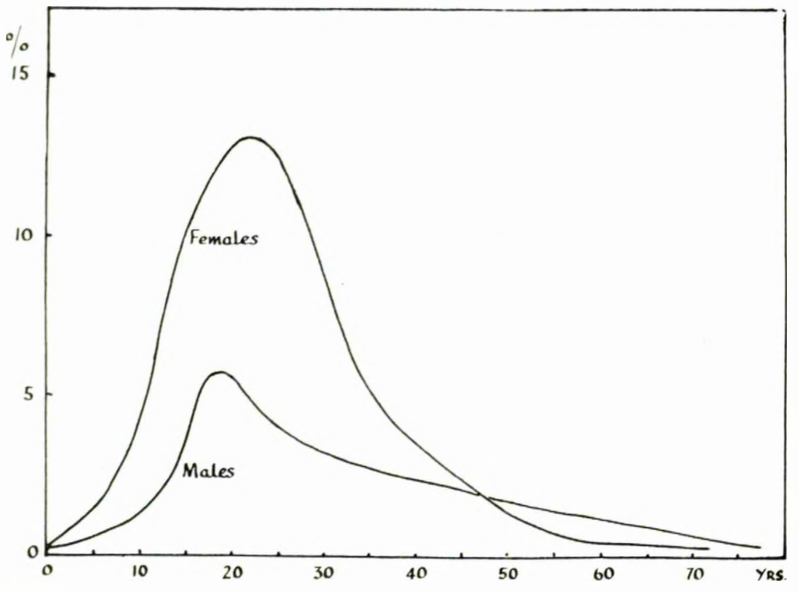


Fig. 2. Distribution of age at first myasthenic symptom.

NATURAL HISTORY

Myasthenia gravis is twice as common in women as in men. The ratio is higher in the first three decades and reverses in the sixth decade, being more common in males in the later part of life, so that the mean age at onset of the disease is slightly less in women (26 yr.) than in men (31 yr.), but the modal age is about 20 years for both sexes (Simpson, 1958). The smoothness of the age distribution curve (Fig. 2) does not suggest that we are dealing with a miscellany of diseases with myasthenic fatiguability as a common symptom.

The picture of generalized myasthenia is well known (Fig. 3). There is ptosis (often asymmetrical), diplopia, facial weakness with a typical vertical 'snarl' on showing the teeth. Weakness of the jaw and neck muscles cause

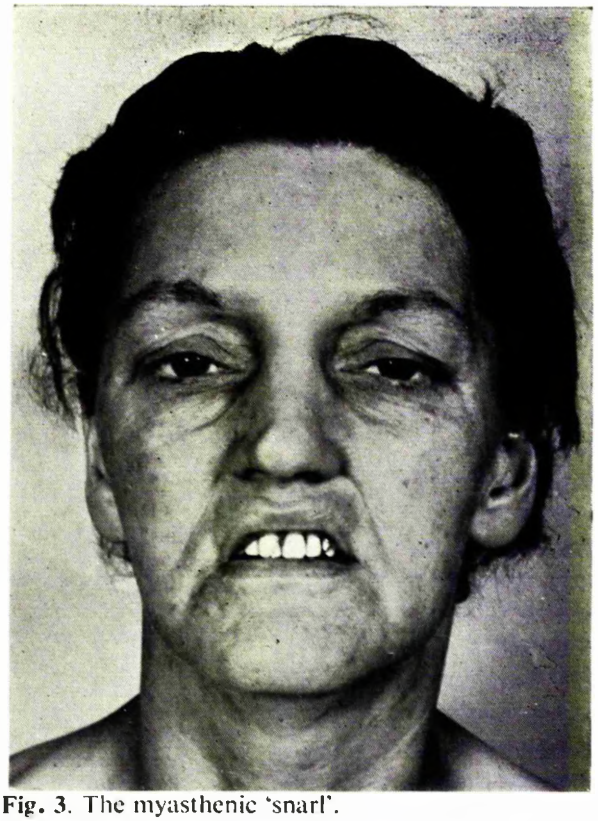


Fig. 3. The myasthenic 'snarl'.

the characteristic posture of the myasthenic, sitting supporting head and jaw with her hand. The limb and trunk muscles may be weak. Weakness of the tongue and laryngeal muscles causes dysarthria. Involvement of skeletal muscle of the upper pharynx and oesophagus causes dysphagia. Vocal cord and respiratory paresis cause the voice to fade and breathlessness to interfere with speech and other activities.

Those areas shaded most heavily in Figure 4 are usually first to be involved. They are also the most frequently affected altogether, and usually the most severely involved when myasthenia is generalized. Thus, though the distribution is apparently random and usually asymmetrical in the individual case, a distinct pattern emerges when a large series is analyzed. The most frequently involved are the extra-ocular muscles (including orbicularis oculi) and then the muscles of the neck, shoulder girdle and hip flexors. The proximal limb muscles are more severely affected than the distal. Extensor muscles are more involved

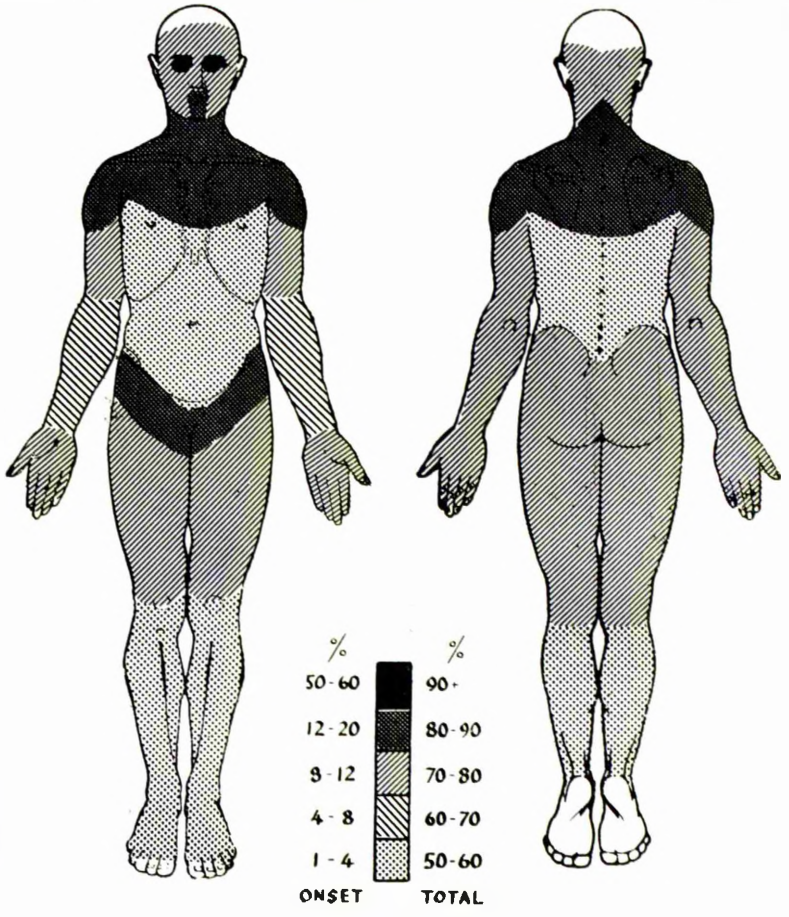


Fig. 4. Percentage of cases in which various muscle groups are affected at the onset (left of key) and at some time during the illness (right of key).

than flexors in the upper limbs, but flexors more than extensors in the lower limbs which are usually less severely affected than the upper. Trunk muscles, other than erector spinae, are least affected. Fortunately few patients show the generalized distribution. It is much more common for the disorder to involve a group of muscles, a single muscle, or even part of a compound muscle (*e.g.* extensor digitorum longus) and the initial weakness may affect any muscle. Seven patients had unilateral facial palsy which was considered to be Bell's palsy for several months until further weakness developed. Four patients had sudden severe inspiratory dyspnoea as the first symptom. Commonly the complaint is related to a muscle fatigued by a particular movement required by the patient's work. Systematic examination may reveal unsuspected weakness or fatiguability of other muscles but examination must be thorough and include contraction maintained against resistance for an adequate period. If this rule is strictly followed I believe that myasthenia is less frequently confined entirely to the extra-ocular muscles than other writers have claimed. Certainly the present series gives but scanty support to the statement that myasthenia is commonly confined to these muscles. Grob (1953) states that if weakness has not spread from the extra-ocular muscles to others in 2 years it is unlikely to do so.

Weakness increases with repeated use of a muscle or with long-maintained contraction. If the patient is asked to gaze upwards the eyelids gradually droop. Eventually she blinks and immediately the ptosis lessens and may disappear. But it again reappears on refixing the gaze, and each time this happens the fatigue appears more rapidly until finally no improvement occurs. Exactly the same happens to the outstretched arms. The slow drooping followed by the cycles of sudden drop and renewed effort until fatigue is complete, looks like a hysterical manifestation to the inexperienced. Electromyography shows that the patient is taking advantage of post-tetanic facilitation accumulating during a brief rest to restore full activity temporarily. A similar phenomenon in the extra-ocular muscles causes coarse nystagmus which may be monocular. The patient, if observant, will state that the object she is looking at 'suddenly slips'. The reflexes are often unusually brisk (indeed ankle clonus is sometimes observed) but may be fatigued if elicited repeatedly.

This short-term fatiguability is highly characteristic of myasthenia. It is not surprising that facilitative compensation should become less effective after the day's activities, and most patients do complain of increased weakness towards evening, but this is not so invariable as is often believed. Indeed one of the major difficulties in treatment is due to the fact that the patient is often extremely weak on first waking in the morning. This is not confined to those requiring frequent dosage who might be deprived of their drug during the night, as it occurs before treatment is started. Indeed I have had ten patients (eight of whom were males) who have noticed that they improved as the day advanced, and two actually used exercise as a means of increasing their strength. This is probably associated with the 'de-curarization' phenomenon which will be described later (Simpson & Lenman, 1959).

Permanent weakness, not responding to neostigmine, and atrophy of muscle are much commoner than generally believed (10% in this series, [Simpson, 1958]). This is the so-called 'myasthenic myopathy'. It may affect any muscle. The triple-furrowed tongue, named after Kinnier Wilson though previously described by Erb (1879) and Buzzard (1905), was only found in six cases (Fig. 5). The extra-ocular muscles quite frequently become unresponsive to neostigmine, and the triceps brachii and ilio-psoas next most commonly. Electromyographic and histological changes in these 'myopathic' muscles are indistinguishable from polymyositis.

The onset is often insidious and progress slow or rapid, but in some it has a very sudden beginning. It commonly follows a febrile disease, usually an upper respiratory infection. Only a little less common is precipitation by an emotional upset and this can be most dramatic. One patient, thrown to the ground by blast in the blitz, was unable to rise again, Another developed ptosis and diplopia the day after an accident at work, in which he was unharmed but was certain he was about to be killed. Two women had ptosis for the first

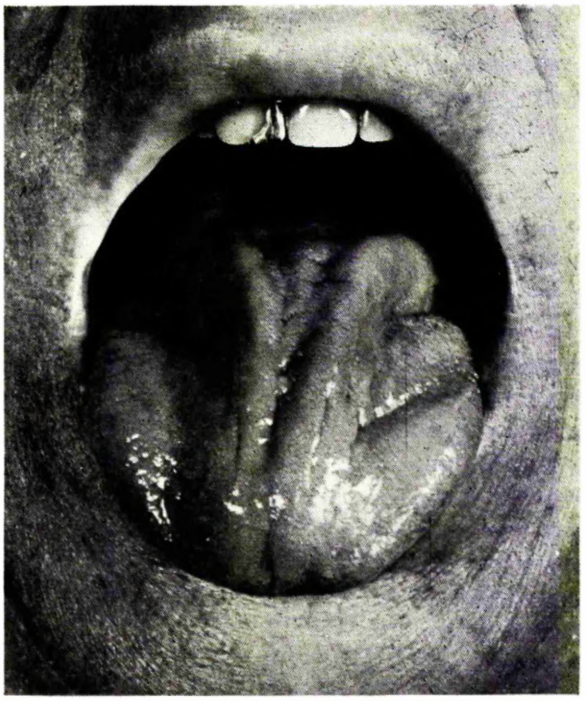


Fig. 5. The triple furrowed tongue of myasthenia (same patient as Fig. 3).

time at their wedding, and one when she found evidence of her husband's infidelity. Very many attributed the onset to anger, quarrels, worry *etc.* with details too circumstantial to discount. All had myasthenia from then on, (as one woman ruefully remarked 'girls with myasthenia shouldn't fall in love'). A few women first had symptoms during pregnancy, and four cases were detected by abnormal response to relaxant drugs used by anaesthetists.

Later relapses were attributed to the same factors, but other causes were the pre-menstrual period, cold, warmth (especially a hot bath) and allergy to shell fish (two cases) and one case followed soon after inoculation. Sunlight often caused ptosis and blurred vision, and a few patients asserted that it also caused generalized weakness.

There can be quite surprising variation from day to day and even hour to hour. Physical exertion is certainly a factor, but I believe that the emotional state is more important. This raises the question of remissions. Remissions are generally considered so characteristic of myasthenia as to cause difficulty in evaluating therapy. It is quite true that sudden improvement can occur, but complete remission lasting for more than a month is seen in less than half of the patients, and more than one long remission is very rare. Furthermore, most of the 'worthwhile' remissions occur during the first 3 years, though there are notable exceptions to this rule. This is the period which sees most of the deaths from myasthenia (especially the first year of the disease) and thymectomy, to be beneficial, is best done during the first 5 years (Simpson, 1958). The impression I have is that the 'active' stage of the disease is limited to this period and the subsequent course depends on the extent of the damage occurring then. This is not to say that the patient is out of all danger if he survives for 5 years. On the contrary I am impressed with the 'brittleness' of the remissions and the delicate balance which takes place. Sudden death may occur from apparently trivial respiratory obstruction, and many examples could be quoted. Nevertheless these catastrophes are due to the precariousness of an adaptation which is sufficient for normal existence without permitting mobilization of reserve muscular power in emergency. They are not, in my opinion, usually due to sudden relapses or to a progressive disease process, though second waves of renewed activity do occur sometimes, particularly after upper respiratory infection or renewed emotional stress.

Pain is quite common in weak muscles, usually an ache which is presumably due to the extra effort required to maintain posture. This often causes headache, pain round the eyes, backache *etc.* Sometimes the muscles are actually tender, and pain has been noted to persist even while resting in bed. One is irresistably reminded of polymyositis. A few patients have complained of mid-sternal pain, often on stooping, which is sometimes associated with palpitations. Other sensory symptoms are rare but cannot be ignored as they have been present in other series (Harvey, 1948). Most often there is tingling of the hands, thighs, or face, sometimes unilaterally. I have usually considered that there was a mechanical explanation, as from shoulder-girdle drop, or a misinterpretation by the patient of muscle 'stiffness'. Deafness, often variable, sometimes occurs, from Eustachian block in pharyngeal paresis or an unusual

deafness for low frequencies which may be caused by paralysis of the tensor tympani. If the stapedius muscle is weak the patient has hyperacusis. Some authors describe objective sensory changes including a few cases of loss of taste or altered olfactory sensation which are difficult to explain (Alajouanine *et al.*, 1957). Epilepsy was present in two of my cases and unexplained blackouts in another three. These were thought to be coincidental, but Hoefer *et al.* (1958) found an unusually high incidence of epilepsy associated with myasthenia. Raised protein in the cerebro-spinal fluid was present in nine cases, but the fluid was only rarely examined. There is a substantial collection of similar cases in the literature.

Tables I and II list some disorders which were present in these cases, but it should be observed that they were noted in their case records by various observers or by myself when studying the value of thymectomy and no systematic attempt was made to record the true incidence of conditions to which I then attached no significance. For this reason no attempt was made to express the figures as percentages.

Table I. Associated conditions in 440 patients with myasthenia gravis.

Association	Number of patients
Carcinoma (present at onset of myasthenia)	3
Diffuse lupus erythematosus	1
Sarcoidosis	1
'Rheumatoid' arthritis	16
Acrocyanosis	12
Nephritis	2
Allergy (precipitating myasthenia)	3
Sensory phenomena, other than pain	11
Epilepsy and recurrent blackouts	5
Psychosis	3
Cerebrospinal fluid protein raised	9

If one defines myasthenia gravis as a disorder of neuromuscular transmission it is obligatory to consider these phenomena as irrelevant coincidences, especially as the frequency of any one is too low to be statistically significant. But it may be more profitable to consider the possiblity that the various phenomena are related to the muscular disorder.

Table II. Disorders of blood and reticulo-endothelial system in 440 patients with myasthenia gravis.

Disorder	Number of patients
Pure red-cell aplasia	1
Normocytic anaemia	3
Microcytic anaemia	3
Macrocytic anaemia*	4
Generalized lymphadenopathy	1
Splenomegaly (autopsy)	3
Lymphosarcoma	1
Hyperglobulinaemia	4

* No marrow smear but clinical diagnosis of pernicious anaemia based on peripheral blood, achlorhydria and therapeutic response.

It is interesting to note that all the disorders listed in Table I and many of those in Table II were noted as manifestations of diffuse lupus erythematosus by Harvey *et al.* (1954). Indeed the precipitating factors and the age and sex distribution already discussed are exactly those found in that disease by these authors. It may then be significant to note that Rowland (1955) found lupus erythematosus cells in a case presenting as myasthenia gravis while Harvey *et al.* (1954) found myasthenic symptoms in three cases of diffuse lupus erythematosus. A list of cases is rapidly accumulating of myasthenic symptoms in other connective tissue-muscular disorders such as dermatomyositis, sarcoid and carcinomatous neuropathy. One patient in the present series had sarcoid at the onset, one had diffuse lupus erythematosus and three patients had neoplasm present or diagnosed soon after the onset of myasthenia. Can it be that myasthenia is a local manifestation of a disorder of the same type as diffuse lupus erythematosus, in which other tissues may sometimes be involved?

Myasthenic phenomena have occurred after prolonged dietary deficiency (in the Japanese 'Kubisagari' and in prisoners-of-war [Denny-Brown, 1947]). An outbreak in France was attributed to the chewing of tobacco infected by *Clostridium perfringens* (Coulonjou & Salaun, 1952). This organism

usually causes severe myositis (gas gangrene) but is related to *Clostridium botulinum*. Myasthenic features in anterior horn cell, peripheral nerve and muscular disorders have been discussed by Simpson and Lenman (1959).

The evidence that myasthenia gravis is a local manifestation of a disorder of variable aetiology, but often allergic, which may occasionally affect other tissues is too scanty to be dogmatic, but an interpretation of this type would satisfactorily account for all the clinical features so far discussed. Red cell aplasia (Table II) is in a slightly different category. This has been noted in patients with thymic tumour even if unaccompanied by myasthenia though more often with it than without. The first case with myasthenia was described by Wintrobe (1946) and the present one was reported in detail by Chalmers and Boheimer (1954). Some patients with thymoma have depression of other marrow elements and agammaglobulinaemia (Lambie *et al.*, 1957).

The erythrocyte sedimentation rate is usually normal in myasthenia, and total serum proteins are within the normal range. Lowered albumin and raised γ-globulin may be demonstrated by electrophoresis (Lowenthal & van Sande, 1956), but there is some technical argument about the validity of the observation. Some of my cases have had slight elevation of γ-globulin. Blood chemistry is otherwise normal, though some authors describe abnormal glucose tolerance. I found ten patients with glycosuria. Many of these, and others with normal glucose tolerance, had a family history of diabetes.

There have been many papers devoted to the relationship between myasthenia and thyrotoxicosis. This has obscured the fact that most of the early reports stressed the presence of non-toxic nodular goitre, and the histological appearance of lymphadenoid goitre. My material has a higher incidence of thyroid disorders than usually reported (females 18%; males 10%) but most of these were either non-toxic at all times, or had a very brief spell of toxicity, lasting only a few weeks or months, but often leaving traces of exophthalmos, with thick puffy eyelids. Some patients have the ocular changes usually associated with thyrotoxicosis but without goitre or abnormal basal metabolic rate at any time. There are cases reported with myasthenia gravis and myxoedema who had never had a thyrotoxic phase.

When toxic goitre does occur in myasthenics its appearance seems quite unrelated in time. They may coincide, but either may precede the other by many years and indeed antithyroid treatment may make myasthenia worse. These facts make it unthinkable that thyroxine can cause the myasthenia, but would strongly favour a pituitary factor, since all these thyroid states, toxic or otherwise, could be associated with excess pituitary secretion. I have already commented on the fact that a family history of diabetes is not uncommon, but this is a common disorder. An observation which I believe to be new is that there is a high incidence of thyrotoxicosis in close relatives of myasthenics, even those without thyroid disorders. This relationship appears to be mainly, but not exclusively, on the maternal side. It is not, perhaps, well known that there is quite substantial evidence for a genetic factor in exophthalmic goitre. It would be reasonable to suspect that this acts by a pituitary hormone and perhaps it may express itself in other ways such as myasthenia gravis. I do not say 'thyrotrophin' since there is some evidence of a separate factor related to it which acts on muscles, especially the extra-ocular ones. It might be a growth hormone. Such a hypothesis would account for the reports of myasthenia gravis associated with acromegaly, diabetes, Addison's disease, and perhaps for the effects of pregnancy, menstruation, and of the emotions acting *via* the hypothalamus.

Pregnancy has some sort of influence on myasthenia, but it is quite unpredictable. In general, remissions occur in the first trimester and relapses at the time of birth or during the puerperium, but some patients are worse during pregnancy and remit afterwards. Successive pregnancies may have different effects. If a hormonal influence is present it must be only one of the factors involved. Schrire (1959) has recently reported low pregnandiol excretion in myasthenia, which is corrected by thymectomy. As the recovery of pregnandiol in the urine after injection of progesterone was also low it is difficult to attribute

the low levels to a decreased progesterone secretion. Preliminary results of similar investigations being carried out in my patients by Dr K. Fotherby do not appear to confirm Schire's findings.

Interestingly enough the endocrine disorders referred to above are, like myasthenia, associated with lymphoid hyperplasia of the thymus. Comsa (1958) has confirmed that growth hormone causes enlargement of the thymus and suggests that it may be a necessary target organ through which the pituitary acts in controlling growth. Everything points towards the pituitary, but, despite a few reports of eosinophil changes or adenomas in that organ, most pathologists find it without abnormality.

If a genetic factor is involved—even if only for setting the stage for a myositic reaction—one would expect occasional evidence of familial myasthenia and this is indeed the case. I have seen three such families. One of these had the syndrome termed 'congenital myasthenia' in which there is a high incidence of ptosis and ophthalmoplegia but rare involvement of other muscles. Classical myasthenia rarely occurs in more than one person in a family, though I have examined two families with cousin and aunt involvement. On the other hand, one myasthenic girl in this series had an identical twin who is normal. Other workers have had the same experience.

These familial cases, like myasthenia occurring in young people, show no special tendency to remit.

The position is completely different in 'neonatal myasthenia', which is the name given to the myasthenia which sometimes affects the baby of a myasthenic mother. It may be serious and cause death if unrecognized as a cause of weakness, but if the child survives, with or without treatment, the weakness clears up within 6 to 7 weeks and never recurs. The suggestion of transplacental passage of a toxic substance is irresistable.

PATHOLOGY

The lymphocyte infiltrations of muscle described by Weigert (1901) were termed lymphorrhages by Buzzard (1905) to emphasize his belief that they originated from small blood vessels. He showed, and others have confirmed, that they are usually present if a search is sufficiently thorough, though they may decrease in number and size as time passes (Fig. 6). Buzzard's demonstration of similar foci in other organs, including the adrenals and pancreas, is repeatedly confirmed in the literature and in my own material but dismissed by most pathologists as 'non-specific'. So too, the associated degenerative changes of muscle fibre described by Buzzard (1905) and recently re-investigated and classified by Russell (1953) are considered by the latter to be non-specific.

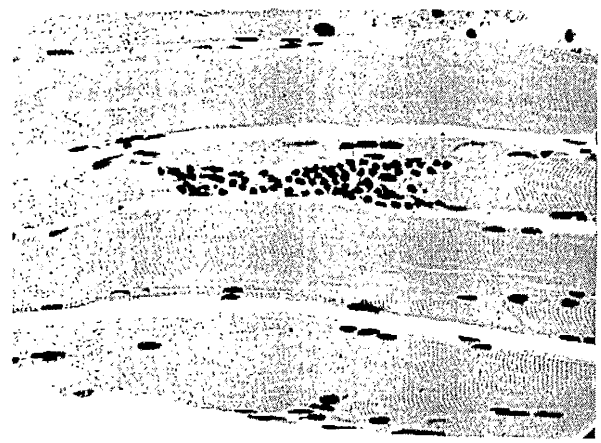


Fig. 6. Photomicrograph of skeletal muscle from patient with myasthenia gravis: lymphorrhage. Haematoxylin & eosin ×210

Professor Russell described three types of muscle change. Type I (Fig. 7) is an acute coagulative necrosis of the muscle fibre with eosinophilic change, loss of cross striation, and inflammatory cellular reaction leading to phagocytic removal of the fragmented muscle

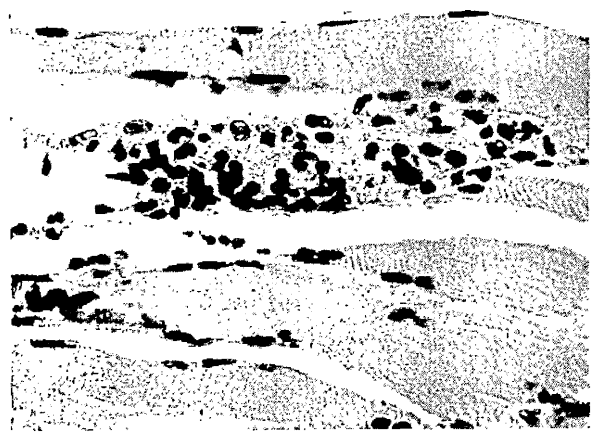


Fig. 7. Photomicrograph of skeletal muscle from patient with myasthenia gravis: Russell's type I lesion H. & E. ×280

fibre. This process may be limited to one fibre or so widespread as to cause naked-eye changes in the muscle. Type II (Fig. 8) is the lymphorrhage, which the author considers to be secondary to solitary muscle fibre atrophy with basophilia of the cytoplasm and loss of cross striation. Type III (Fig. 9) she considered to be the least specific, being a simple focal muscle change with eosinophilia and swelling but without loss of striation or inflammatory reaction. Similar changes occurred in the myocardium, but never in true smooth muscle. It is quite true that similar lesions are seen in other conditions, notably the rheumatic disorders, connective tissue disease, chronic infections, myositis and endocrine myopathies. The lymphorrhage is found in many of these besides being the characteristic lesion of allergic reactions. Querido (1929) was impressed with a vasculitis which he found associated with lymphorrhages. 'Non-specific' they may

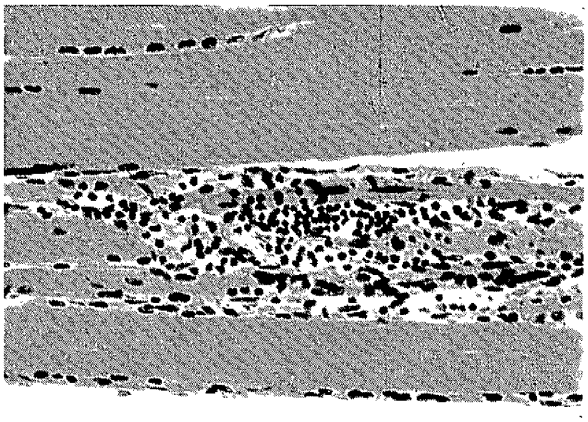


Fig. 8. Photomicrograph of skeletal muscle from patient with myasthenia gravis: Russell's type II lesion and lymphorrhage related to atrophic muscle fibre. H. & E. × 180

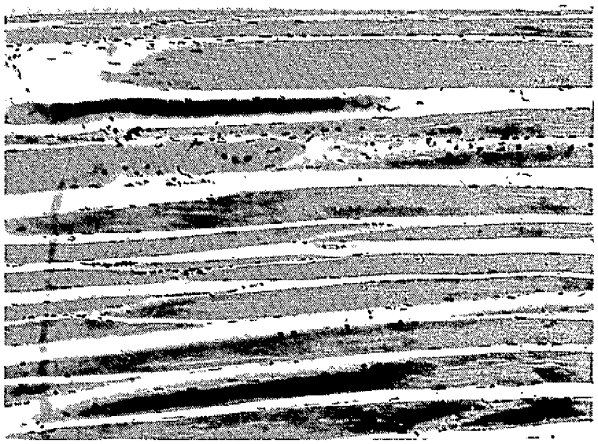


Fig. 9. Photomicrograph of skeletal muscle from patient with myasthenia gravis: Russell's type III lesion. H. & E. × 80

be, but in this list one notes many of the conditions already discussed under the clinical aspects. Again one can choose to consider the muscle reactions as 'non-specific' or to look for a common factor.

Special staining techniques applied to the motor nerve endings by Coërs and Desmedt (1959) have shown that the neuromuscular junctions may often be abnormal in myasthenia gravis. These authors describe two changes in the terminal arborization of motor nerves (Fig. 10). In one, the 'dystrophic' type, there is increased branching and the terminal knobs are distributed over a wider area of the muscle fibre than usual. This type is probably reactive as the related muscle fibre is usually abnormal and the same type of end-plate has been found in other neuromuscular disorders. In the other type, the 'dysplasic', there are few terminal knobs and these are arranged serially along a scanty number of terminal branches ending on a long end-plate

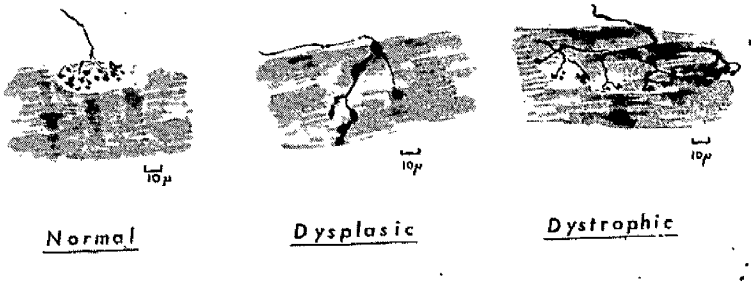
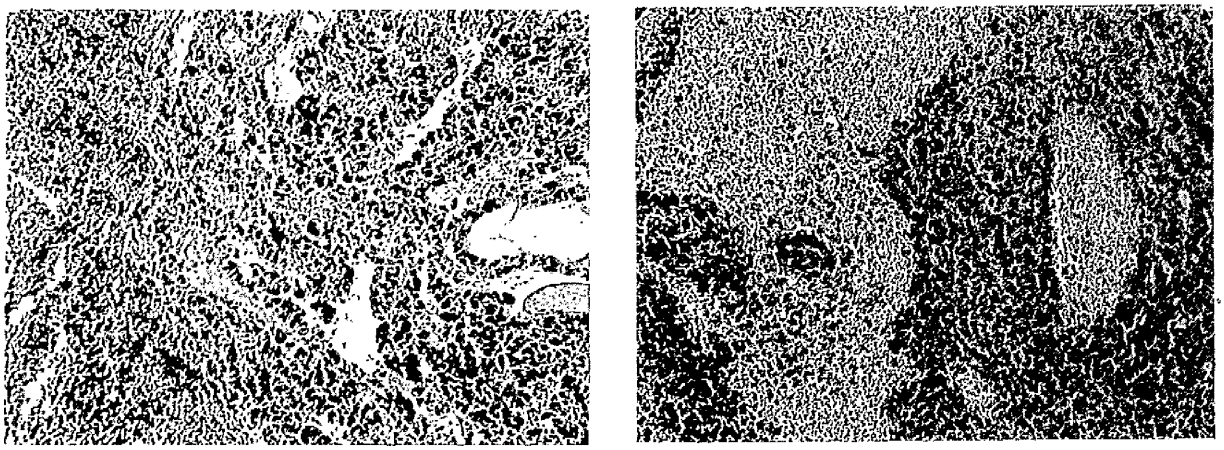


Fig. 10. Types of motor nerve terminals found in myasthenia gravis (Sketch based on the original paper by Coërs & Desmedt, 1959).

region. In their limited experience the authors have not found this type in any other disease. Further work is required to confirm their results for, like the muscle fibre changes already described, they bear no direct relationship to the severity of the loss of function. Nevertheless, the evidence for structural changes in nerve and muscle is convincing and no 'chemical' theory of myasthenia is acceptable which does not take account of them.

Now what of the thymus gland? Weigert (1901) thought that the lymphorrhages of muscle were metastases from a thymic tumour but Buzzard (1905) soon disproved this. Nevertheless, the incidence of thymoma is remarkably high (15—20%) and most cases show some thymic pathology. There has been a great deal of misunderstanding about this. Some textbooks describe 'thymic hypertrophy', and others 'failure of atrophy' such as a normal thymus is assumed to undergo. Both descriptions are wrong. Some thymus glands removed from myasthenic patients are undoubtedly larger than normal limits but the majority are not, and those with wide experience agree that normal thymic regression may occur with age (Sloan, 1943). But whether large or small, the organ shows increased content of lymphocytes (or thymocytes) in cortex and medulla and there is evidence of active formation of lymphocytes in the presence of 'germinal centres' (Fig. 11) This finding is very characteristic (Castleman & Norris, 1949). The epithelial cells of the thymus are not proliferated unless there is a tumour but in thymomas they may be arranged in cords or tubes, giving the appearance of a secretory tissue. Even then the surrounding non-tumour gland shows the typical 'germinal centres' (Fig. 12). It is interesting then to note the occasional presence (usually in young patients) of hyperplasia of lymph nodes and of lymphoid tissue in the spleen. One patient in the present series died of lymphosarcoma (Table II). Disorders of blood formation and of the plasma proteins have already been referred to. Each of these conditons is rare, but the total picture suggests that the thymus

Fig. 11. Photomicrograph of thymus from patient with myasthenia gravis: lymphoid follicular hyperplasia with Hassall's corpuscles grouped round a germinal centre. H. & E. ×42



(*a*) H. & E. ×42 (*b*) H. & E. ×52

Fig. 12 Photomicrographs of thymus from patient with myasthenia gravis:
(*a*) Thymoma, with tubular arrangement of epithelial-type cells.
(*b*) Germinal centres in thymic tissue surrounding a thymoma.

is participating in an activity of reticulo-endothelial type rather than a glandular one in the conventional sense and certainly no evidence of glandular activity can be seen.

Myasthenia has occurred after a thymoma has been removed. A small thymoma associated with severe myasthenia may continue to grow while the myasthenia remits. Operative removal of a thymoma does not usually affect the course of the disease but occasionally does so. Removal of the non-tumour gland, on the other hand, definitely improves the prognosis and saves may lives, but in general only if it is removed within the first 5 to 7 years of the myasthenia and even then the results are unpredictable for the individual and improvement may be immediate or delayed (Simpson, 1958). I have seen patients improve immediately and others not till months later, but improvement may continue for 3 years or more. Why should this be? Why too should improvement be most marked in young women, to the extent of changing their prognosis from one which is poorer than men to one which is better? (Simpson, 1958). Men may improve too, although the statistics are equivocal and their gain is less obvious.

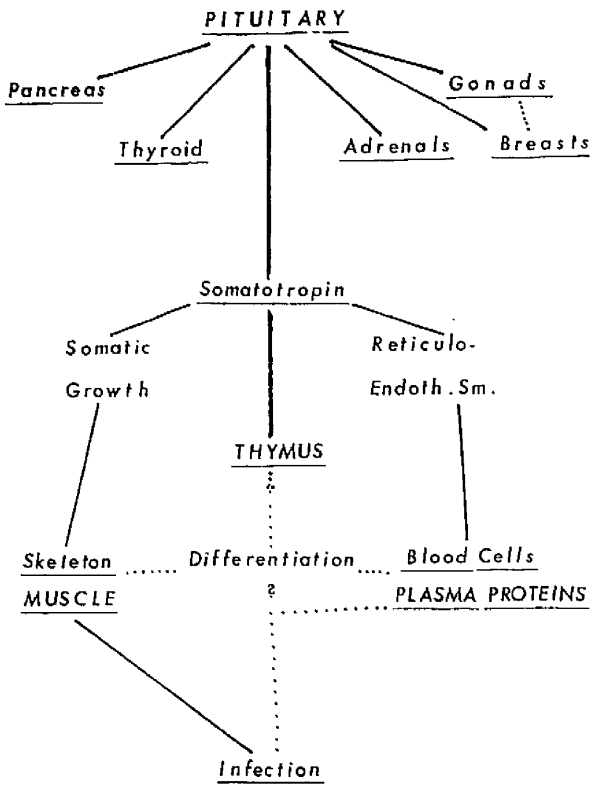


Fig. 13. Suggested role of pituitary and thymus in controlling growth and differentiation. Differentiation of blood cells and production of protein antibodies may be a surviving remnant of these functions in the adult. In myasthenia the thymus may produce an antibody against normal muscle, especially after upper respiratory infection.

A HYPOTHESIS

These facts do not suggest that the thymus is the source of a toxic substance or an endocrine gland with some necessary function. Rather it may act as an accessory organ in some mechanism, perhaps as a storage organ or possibly (as suggested by Comsa [1958] in another context) as a target gland of pituitary growth hormone which might atrophy in later life. The thymic-inhibitory effect of the thyroid and adrenal described by that author could be manifestations of the well-known pituitary feedback inhibition. Unfortunately, we know too little about the thymus to do more than speculate. Certainly the organ does not impress one as an endocrine gland, but more as a reticulo-endothelial organ. Metcalf of Sir F. Macfarlane Burnet's laboratory in Melbourne has recently isolated a factor secreted by the epithelial cells of thymus (in tissue culture) which appears in the blood plasma as a 'lymphocyte stimulating factor' (Metcalf, 1956). Though the main source of globulin antibodies is believed to be the plasma cells, the lymphocytes do seem to have some rôle in immunity reactions.

It is interesting to speculate on the possibility that a genetically-determined pituitary hormone acting on muscles might do so *via* a thymic secretion which releases an antibody carried by lymphocytes (Fig. 13) or alternatively that the thymus reacts 'allergically' to the breakdown products of muscle cells damaged by abnormal pituitary secretion or by a delayed-type allergy caused by infection. During the last 5 years Dr John Anderson of Glasgow and Dr Roland Alexander of Edinburgh have collaborated with me in a search for muscle antibodies in myasthenia gravis, but without success, perhaps because the substance sought is intracellular. We were encouraged to search for better methods on reading the recent report of Nastuk *et al.* (1959). Searching for a neuromuscular blocking substance, these authors found that blood from myasthenic patients (and a few control

subjects in lesser degree) caused lysis of frog muscle cells. Following up this surprising observation they found that the serum complement activity was within the normal range in most myasthenic patients, but was above or far below the normal range in a few cases and this tended to correlate with remissions and exacerbations respectively.

Last year Smithers (1959), studying the rôle of the thymus and lymphocytes in disease, concluded that they were implicated in auto-immunity and that the thymus changes of myasthenia gravis were strongly suggestive of an auto-immune process. Perhaps, too, the occasional benefit to myasthenics from corticotrophin or cortisone is further evidence of this. The muscle protein may be rendered antigenically 'foreign' by the same type of association with upper respiratory infection as is believed to occur in the rheumatic disorders and in acute nephritis. The postulated pituitary factor might predispose to this by disturbing cell membrane integrity and indeed if protein which is normally confined within the muscle cell were allowed to escape, the auto-immune process would be initiated. It is possible that we have here an example of the influence of the endocrine glands upon immune and allergic responses to bacterial infection demonstrated by Long (1955). Perhaps the place of the thymus in growth is as a regulator of cell-differentiation, a function which becomes unnecessary in the adult except for the formation of blood cells and plasma proteins. This action would include the recognition of 'foreign' proteins, and the reactions appropriate to them, that is the function of the reticulo-endothelial system. One can only speculate where knowledge is incomplete, but I do so without apology because the purpose of this lecture is to suggest new ideas for research on myasthenia gravis.

PATHO-PHYSIOLOGY

I have taken you a long way from the current ideas on myasthenia, but not far from those of the earlier workers who knew nothing about neuromuscular transmission or auto-immunity, and little about endocrinology. For my unorthodox ideas I must undergo the ordeal of the Calabar bean. How does the notion of an endocrine or auto-immune disorder combine with the patho-physiology and pharmacology of the disease?

The resemblance of myasthenia to curare poisoning had occurred to Oppenheim (1887) and to Jolly (1895) but it was Mary Walker's (1934) demonstration of the dramatic relief afforded by physostigmine coinciding with Dale and Feldberg's (1934) confirmation of the rôle of acetylcholine in neuromuscular transmission which turned all thinking towards transmission block. The effect of physostigmine and a variety of related synthetic compounds with anti-cholinesterase properties, suggested that a defect of acetylcholine transmission from nerve ending to muscle end-plate was present and would account for the weakness. Jolly (1895) had shown that the fatiguability could be reproduced by faradic stimulation of a motor nerve while the 'fatigued' muscle would still respond fully to locally applied galvanism. Modern electromyography shows that the loss of power is accompanied by a decrement of the evoked action potential of the muscle (Fig. 14). This seemed explicable by three hypotheses:

(1) diminished acetylcholine synthesis or release; (2) increased acetylcholine destruction by cholinesterase; (3) competition for receptors by a curare-like substance.

Before discussing these I must describe the finding of the opposite effect—an incremental response to tetanic stimulation —which is not uncommon in myasthenia (Fig. 14) and in polymyositis (Simpson & Lenman, 1959). Both effects may occur in the same patient. One is reminded of the decurarizing effect of tetanic stimulation when the dose of curare is low. The phenomenon is most simply explained if neuromuscular block in myasthenia is competitive in type. Post-tetanic facilitation, which is characteristic of true myasthenia gravis though not always present, is also strongly suggestive of a curare-type block.

It may be that one or more of the other mechanisms is responsible for the 'symptomatic myasthenias' found in motor neurone disease, polyneuritis, and polymyositis (Simpson & Lenman, 1959).

Perhaps more than one abnormality is present in myasthenia gravis, for instance the histological findings might suggest that both nerve and muscle are abnormal. Normal

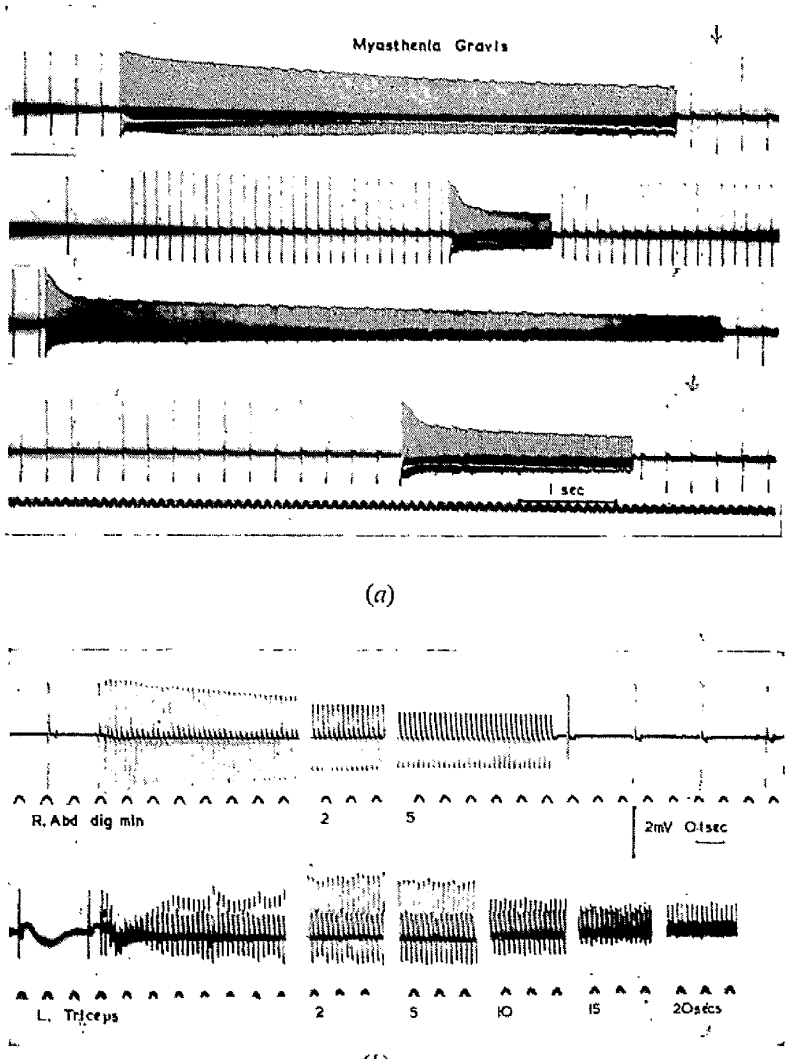


Fig. 14. Electromyograms from patients with myasthenia gravis: (*a*) Ulnar nerve at wrist stimulated with supramaximal electric shocks repeated 4, 8 and 50 times per second. Action potential recorded from abductor digiti minimi muscle by surface electrodes shows decrement ('fatigue') with fast tetanization only. Note post-tetanic facilitation at arrows.

(*b*) The classical response from abductor digiti minimi but the triceps shows a temporary incremental response.

physiology does not help one to predict the effects which would then occur, but it is desirable to attempt an explanation of the findings in disease in terms of the known normal mechanism. Pharmacological studies have recently added a new body of evidence which has first to be considered.

It has been recognized for some time that the myasthenic patient can be paralysed by an unusually small dose of *d*-tubocurarine or quinine, but Churchill-Davidson and Richardson (1952) showed that myasthenic muscle was extraordinarily resistant to the depolarizing blocking drug decamethonium (C10). A small dose might facilitate, or sometimes a depolarizing type of block might change to a competitive type with response to neostigmine (a 'mixed block'). Grob *et al.* (1956) showed a similar alteration of the response to choline—one of the breakdown products of acetylcholine. Zaimis *et al.* (1952) believe that these facts indicate an alteration in the motor endplate, which is one possible interpretation. Arguments about whether the myasthenic muscle is hypersensitive or hyposensitive to intra-arterially injected acetylcholine have

been shown to be due to usage of massive test doses (Engback, 1951). With suitable dosage there is no doubt that the myasthenic muscle has a raised threshold. This, too, makes the acetylcholine deficiency theory unacceptable. The pharmacological results, often seemingly conflicting, are difficult to summarize, but can be harmonized by the following hypothesis (Fig. 15).

It is proposed that the effective condition for depolarization of the end-plate membrane may be the *density* of ionic charges attached to the postulated receptor substance. Thus an applied substance will be effective only if (1) its ionic charge is adequate (Riker, 1953) and (2) there is an adequate charge per unit of receptor area. If this limiting charge density is not reached no depolarization occurs and the attached charges merely block receptors If an adequate charge density appears (probably with certain time factors) the membrane permeability is altered and a 'local response' causes depolarization. If this reaches a 'critical level' it becomes self-completing, an action potential propagates and the muscle twitches. If the charge density rises too high, or the stimulating chemical is resistant to hydrolysis by cholinesterase, depolarization persists causing neuromuscular block of a type which is made worse by anticholinesterase compounds or by the addition of acetylcholine ('depolarization block'). As the concentration of depolarizing substance falls, charge is lost from the end-plate which repolarizes. Inexcitability of the membrane due to 'desensitization' prevents further stimulation (Axelsson & Thes-

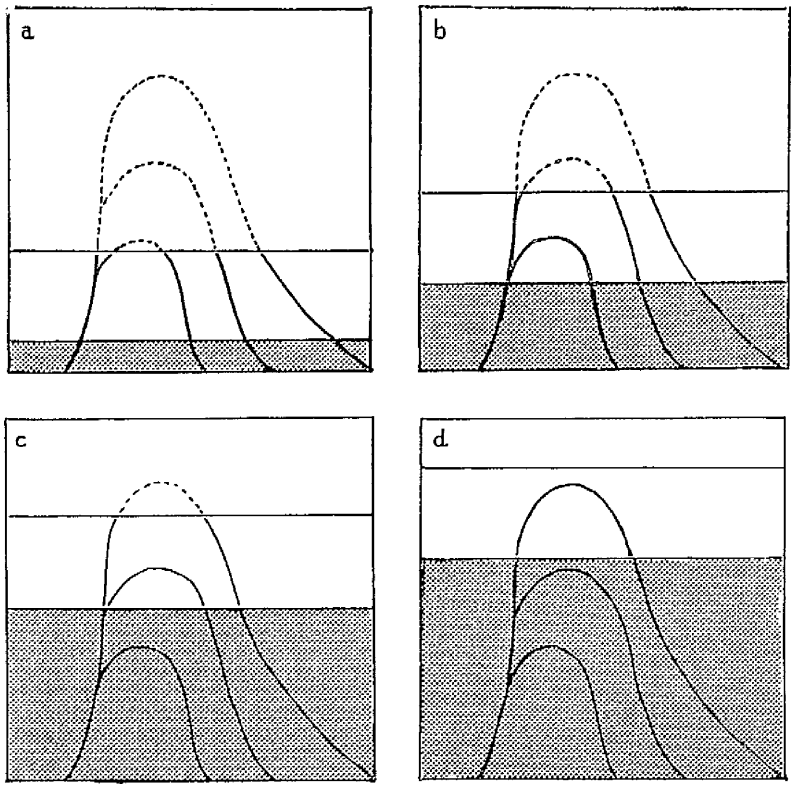


Fig. 15. Time course (diagrammatic) of rise and fall of charge-density at motor end-plate of muscle for three doses of a depolarizing substance such as decamethonium to show the differing effects due to dose level, particularly in the recovery stages. The shaded area indicates the zone of competition with acetylcholine, increased from *a* to *d* by a hypothetical competitive substance. If the charge-density rises to the value between the horizontal lines (constant in each diagram), propagated action potentials occur. If the charge-density rises rapidly above this zone (dotted part of curves), the resulting twitch is brief and the muscle is then paralysed by depolarization block. As the drug is dispersed, the charge-density falls through the critical zone but 'desensitization' prevents further response. If the dose is sufficiently high the prolonged effect may cause facilitation of test stimuli. When there is a substance competing for end-plate receptors (*b*—*d*), only the biggest doses causes depolarization block, and this is succeeded by competitive block (mixed responses)'. A lower dose, sufficient to block the normal end-plate, causes only stimulation—'decamethonium resistance'. (Compare lower two curves in *a* and *c*.)

leff, 1958), but if the ionic charge remains within the 'critical zone' sufficiently long it may facilitate neuromuscular transmission for a brief spell (Grob *et al.*, 1956) until the charge-density falls too low and it enters the zone of 'competitive block' where it will tend to inhibit response to indirect stimulation or to application of further depolarizing chemicals until the 'sticky molecules' (Zaimis *et al.*, 1952) become slowly detached. The two latter phases would be more prominent with large doses and with compounds resistant to hydrolysis. This hypothesis would explain all the phenomena described.

If now, ionic charge-density (note *not* necessarily the *total* charge) is decreased, the 'critical 'level is raised. The competitive zone is passed too quickly at first to cause clinical signs, stimulation occurs at a higher dose level, 'depolarization block' only occurs with the bigger doses and is soon followed by a prolonged 'competitive block' (the 'mixed response' of Zaimis). Smaller doses merely stimulate and drop rapidly through the competitive zone ('C10 resistance' *etc.*). Time factors will differ with different drugs and animal species, but all the reported phenomena can be fitted into the scheme. What light does it throw on the alternative hypotheses?

(1) Diminished acetylcholine production is unlikely unless the charge is dispersed spatially. Coërs and Desmedt's (1959) histological findings would be compatible with this.

(2) Increased cholinesterase would decrease the rate of rise, lower the crest and steepen the falling phase of the curve. The observed results do not suggest that this occurs, and of course increased cholinesterase has never been demonstrated (in muscle or in circulation).

The remaining theories (i) alteration of the end-plate's properties so that it requires a greater charge density and (ii) occupation of some receptor sites by molecules with a negligible charge, would both fit the observations. The first is the 'end-plate abnormality' theory, the second the 'curare-substance' theory. The pharmacological results are compatible with each, or with dispersed acetylcholine receptors. Further studies of this type are unlikely to settle the matter if the physics of the situation are those postulated. Selection between the alternatives must depend on other factors. It may be that more than one factor is present, but when the decurarization effect, the post-tetanic phenomena, the natural history of the disease, and above all the probability of placental transmission of the disorder are taken into account the only satisfactory single theory is the 'competitive-blocking' substance (Table III). This substance must have the unusual property of persistence in the myasthenic baby for several weeks.

Despite claims to the contrary—especially Strüpplers (1954) recent work—there is no satisfactory evidence that serum from myasthenic patients will cause block of normal neuromuscular junctions. Cross transfusion to normal subjects has no effect. Wilson and his colleagues in Liverpool have tried for years to isolate such a substance from the thymus (Wilson *et al.*, 1953). Their early

Table III. The ability of theories of causation of myasthenia gravis to explain the known phenonema of the disease.

Theory	'Indirect' tetanus		Post-tetanic		Pharmacology	Remissions	Placental transfer
	Decrementing ('fatigued')	Augmenting ('decurarized')	Depression	Facilitation	A.Ch.; C10.; choline		
Acetylcholine deficiency	+	?	+	?	0	+	0
Cholinesterase excess	+	0	+	0	0	?	0
End-plate change	+	0	?	0	+	0	0
Competitive block	+	+	+	+	+	+	+

results with extracts of glands removed from myasthenic patients were most promising but have been criticized as being attributable to potassium in the extract. They have recently isolated a series of substances from the thymus of whale foetuses but they seem to block by depolarization (Nowell *et al.*, 1959). In view of the warning I have given of the different effects occurring with varying dose levels of quaternary onium compounds it would be unwise to dismiss these extracts from further consideration, but they do not seem to have the desired properties. (For instance a sudden relapse should cause spontaneous twitching or a depolarization block and be aggravated by anticholinesterase compounds).

Where, then, are we to look for a blocking substance which must be of competitive type, transmissible through the placenta, with persistence in the child for a few weeks only, but not transmissible to another adult? If one looks at the mechanism of attachment of acetylcholine to receptor protein (Fig. 16) one is immediately reminded of the Ehrlich theory of antibody action. Let us suppose that antibody was developed against the 'receptor

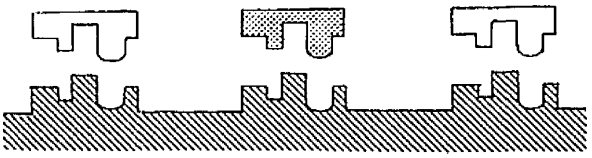


Fig. 16. Two molecules of acetylcholine and one of antibody have similar configuration, based on end-plate receptor 'templates'. They will compete for receptor sites.

substance' of the end-plate protein. Would not this substance have exactly the properties described? All that is required of it is that it should be detachable and should only occasionally lead to lysis of the muscle cell. That is, it should have the properties of an incomplete antibody (odd that the alternative name of 'blocking antibody' should have been coined by the haematologists!). Perhaps a 'complete' antibody, or one modelled to the rest of the muscle membrane gives rise to 'polymyositis'.

SUMMARY AND CONCLUSIONS

In summary then, my suggestion is that myasthenia is an 'auto-immune' response of muscle in which an antibody to end-plate protein may be formed. This would have the properties of an acetylcholine-competitive-blocking substance, specific to the individual, and occasionally to the foetus of a myasthenic mother. Nerve endings, muscle fibres, and on occasion the central nervous system might sometimes be involved, in close analogy with diffuse lupus erythematosus and dermatomyositis. Myasthenia gravis is, therefore, a restricted form of myositis. It may be the result of an auto-immune response to an infection, usually of the upper respiratory tract, or the reticulo-endothelial system, specifically the thymus, may react to muscle end-plate protein as if it were 'foreign' in disorders of the thymus. The latter is probably under the influence of the pituitary gland, probably by a growth hormone, and this may be a necessary condition for the allergic response to infection. A familial incidence of thyrotoxicosis or diabetes is reported for the first time.

These conclusions have been reached from a detailed analysis of 440 cases and of the literature. No other theory of myasthenia gravis attempts to explain all the phenomena, clinical and experimental. The present attempt is speculative, but I hope it is justified by the many new lines of research immediately suggested by it. Let me close by quoting Hughlings Jackson (Taylor, 1958):

'The use of hypotheses is the method of science. To suppose we can make discoveries by the Baconian method is a delusion. A hypothesis or supposition is not a conclusion; it is only a starting point for methodical observation and experiment, the endeavour being not only to prove it, but to disprove it'.

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