

### *Appearances in Cases with Tumour Formation*

In one case in which there appeared to be a small tumour approximately 1 cm in diameter lying anteriorly in the left lobe, there was a corresponding large vein which had a uniform curve but no extra fine vessels. A similar curve, but in a much smaller vessel, was noted towards the apex of the left lobe in another patient; this, however, proved to correspond only to the more bulbous end of a thymic gland of the larger type seen in young adults.

An obvious left-sided tumour was examined by venography and it was found that the more proximal part of this tumour had a very vascular pattern forming a network (Fig 3), whereas the distal portion was markedly avascular, causing only displacement of the veins.

A calcified left-sided thymic tumour showed that the extent of the tumour on venography was much greater than the calcification itself or than the soft-tissue shadowing as seen on fluoroscopy or tomography. The venous network pattern extended both above and below the calcified area.

In one case a marked fine network pattern was demonstrated in the right lobe whereas the left lobe was quite normal. This area was approximately  $1.5 \times 1.5 \times 1$  cm in size. This was seen both on the oblique frontal view and on the lateral view. The last injection of the series produced a localized blush area. In this case there is no confirmation that this corresponds to a tumour.

With retrograde venography as compared to arteriography the injection of contrast medium must be extremely gentle. Frequently the first test picture is by far the best, and to obtain adequate filling the Valsalva manoeuvre is of particular value. It is easy to produce perivenular extravasation which is accompanied by pain, but no other untoward reaction. Once this extravasation has occurred, the procedure should be abandoned as venous filling will no longer be possible.

In conclusion, therefore, one can say that by radiological means it is now possible to obtain visualization of even small thymomas. The value and necessity of this, however, must be dependent on the results obtained by surgery and radiotherapy in this condition.

#### REFERENCES

- Caffey J (1961) *Pediatric X-ray Diagnosis*, 4th ed. Chicago; p 413  
 Harper R A K & Guyer P B (1965) *Clin. Radiol.* 16, 97  
 Kreef L (1965) *Proc. XI Int. Congr. Radiol.* p 555  
 (1967) *Brit. med. J.* i, 406  
 Kreef L, Blendis L M & Piercy J E (1964) *Clin. Radiol.* 15, 219  
 Kreef L & James V (1965) *Radiography* 31, 133

### **Professor John A Simpson<sup>1</sup>**

(*Institute of Neurological Sciences, Glasgow; Department of Neurology, Glasgow University*)

### **Myasthenia Gravis: Clinical Aspects**

The first time I addressed this Society on the subject of myasthenia gravis was to give a preliminary report on an evaluation of thymectomy (Simpson 1956). That work gave me the chance to examine more than 400 patients with myasthenia in a comparatively short period of time. This provided a golden opportunity to study the natural history of the disease and its rarer manifestations. Some curious facts appeared which led me to propose that the neuromuscular disorder was only part of a multisystem disorder, probably based on a breakdown of immunological tolerance (Simpson 1960).

Time does not permit a review of all the evidence which led to this hypothesis and I shall only summarize some parts which seem to be relevant to the interests of this Section.

#### *Natural History*

Myasthenia gravis occurs at all ages but the modal age of onset is about 20 years, with a secondary peak for males in the fifth decade. Below that age females outnumber males 4.5:1, but in later life males predominate. The onset may be insidious or sudden. It is often precipitated by an emotional upset, and this fact accounts for the common failure to make the diagnosis in the first years, as the dramatic but reversible weakness is readily mistaken for hysteria. Infections or pregnancy are also precipitating factors—rarely physical exercise. A tendency to have remissions is well known, but prolonged complete remissions are in fact not common and rarely repeated. Most of the 'useful' remissions occur during the first seven years. Conversely most of the deaths due to progressive myasthenia also occur in the same period. The highest mortality is in the first year, with a second danger period from four to seven years after the onset (Simpson 1958). Most of the beneficial response to thymectomy is seen in patients operated on during this same period, which appears to be an active and labile stage of the disease. After that period remissions are less complete, thymectomy is less valuable, and there may be less response to anticholinesterase drugs. On the other hand, deterioration is less rapid or stops and deaths are fewer (though risk of asphyxia from aspiration may persist). One has the strong

<sup>1</sup>*in absentia* read by Dr J Dow

impression that about the 5–7 year point the active disease process subsides, leaving more or less permanent sequelæ.

I will not discuss the well-known symptoms of neuromuscular disease, but only draw attention to the distribution of weakness when a large population is studied. Certain muscle groups are more likely to show the earliest signs and the ranking order is the same if one lists the total incidence of involvement – extraocular, bulbar, neck, limb girdles, distal limbs and trunk. I draw attention to this because it is quite different from the distribution of a peripheral neuropathy of axonal type and much closer to the distribution of a myopathy. A clinical observation of this type must be kept in mind when deciding between prejunctional and postjunctional mechanisms.

#### *Associated Disorders*

Most people are aware that there is some connexion between myasthenia gravis and thyrotoxicosis. Studies of small numbers of cases have led to false conclusions such as a presumed ‘see-saw’ relationship between the two. In fact in my series of 510 cases it is obvious that all one can conclude is that both diseases may occur at some time or another in the same individual, with no obligatory temporal relationship. Furthermore, thyroid disease appears more often than one would expect in close relatives of myasthenic patients (Simpson 1960). Interestingly enough, if the earlier literature is reviewed it will be seen that there are more reports of ‘lymphadenoid’ goitre than of thyrotoxicosis (Ringertz 1951). In my experience nontoxic goitre and myxœdema occur quite commonly, giving a total incidence of thyroid disease of 9% in males and 18% in females suffering from myasthenia gravis (Simpson 1958). Radioiodine studies show that the majority of myasthenic patients have normal thyroid function and there are as many subthyroid as hyperthyroid among those without clinical manifestations of thyroid disorder (Simpson 1966*b*). Clinical or latent Hashimoto’s thyroiditis is not uncommon and may develop after thymectomy (Simpson 1964).

The role of the other endocrine glands is less certain. Glycosuria or diabetes mellitus appear to be a little more common than expected. Premenstrual exacerbation of symptoms is common, and pregnancy has a definite though variable effect. Exacerbation usually occurs during the first trimester with later remission followed by relapse in the puerperium (Fraser & Turner 1953), but the course may be different in successive pregnancies.

My study of the patients in the thymectomy series first drew attention to a relationship between myasthenia gravis and other disorders, notably an arthropathy resembling rheumatoid

arthritis, pernicious anæmia, and other disorders now recognized as being associated with disordered immunological mechanisms (Simpson 1960). These findings have been confirmed by other workers (Downes *et al.* 1966). In postulating an immunological basis for the syndrome I was influenced by seven facts:

- (1) The age and sex incidence, the remitting course and the observed precipitating factors bore a marked resemblance to systemic lupus erythematosus (Harvey *et al.* 1954).
- (2) My observations suggested a multi-organ disorder.
- (3) The characteristic muscular pathology – the lymphorrhage – suggested an ‘allergic’ reaction. It had previously been discounted as ‘nonspecific’ because lymphorrhages were found in other conditions but all of these were disorders in which current theory was implicating ‘autoimmune’ disturbances.
- (4) It appeared to me that the thymus was more like an active lymphoid organ than an endocrine gland as it was then considered, and this conviction was enhanced by Smithers’ (1959) paper.
- (5) Cortisone may cause remission after temporary relapse.
- (6) The infant born to a myasthenic mother may have myasthenic weakness. It does not occur in every pregnancy and the child is only affected for 4–8 weeks. Despite this, nobody has ever succeeded in making another adult myasthenic by transfusion of blood from a myasthenic patient. Obviously this could be accounted for if the ‘toxin’ presumed to cross the placental barrier was an antibody, and the duration of the neonatal disorder fitted rather well with this concept.
- (7) While my findings were being prepared for publication Nastuk *et al.* (1959) reported that myasthenic serum appeared to lyse frog muscle cells and this appeared to be a complement-fixing reaction.

From 1956 my colleagues in immunology had searched unsuccessfully for antimuscle antibodies, and we had failed to produce autoimmune muscle disease in mice. Working independently from the cytolytic effect Strauss *et al.* (1960) were able to demonstrate antimuscle antibodies in myasthenic serum. The volume of supporting work is now too great to review here (cf. *Ann N. Y. Acad. Sci.* 1966, 135, Art. 1). The multi-organ involvement is confirmed by the increased incidence of antibody against thyroid and stomach (Simpson 1966*a*). There is a significant incidence of hypergammaglobulinæmia which tends to correlate with a thymoma, rheumatoid arthritis, Hashimoto’s disease or pernicious anæmia (Simpson 1966*b*).

For the first time a logical connexion between the thymus and muscle has been established. It has been known for nearly sixty years that the thymus is usually abnormal in myasthenia gravis and that 10–15% of cases have a thymic tumour, the latter cases being clinically more severe. Now it has been shown that the titre of antimuscle antibody is greatest in the presence of a thymoma but that it need not necessarily be associated with clinical or latent myasthenia (Strauss *et al.* 1966).

Thus the present position is that there is no doubt that disordered immunological tolerance is common in myasthenia gravis but no evidence as to whether it is primary or secondary. When in 1960 I proposed this hypothesis Miller had not yet published his work establishing the immunological role of the thymus so it was necessary to suggest a possible mechanism for the neuromuscular disorder. At that time I favoured the idea that antibody against the receptor substance of the muscle endplate acted as a curare-like competitive blocking substance. At present there is no evidence to support this, and the nature of the defect remains obscure.

#### *Neuromuscular Transmission*

I cannot review here the mass of information on the functional disorder of neuromuscular transmission and abnormal responses to drugs acting at the endplate of muscle. I have recently analysed the data (Simpson 1968) and concluded that all can be accounted for by the structural changes demonstrated by Coërs & Woolf (1959). These are presumably the result of a substance elaborated by the thymus and capable of passing the placental barrier. In my opinion it is a globulin of the antibody type.

#### *Thymectomy*

The first thymectomy for myasthenia gravis was performed by Sauerbruck in 1912 but there was little interest in the operation until Blalock *et al.* (1941) reported a series. Later American reports were discouraging although Keynes (1946, 1955) found it a valuable procedure. An independent study by Simpson (1958) confirmed the claims of Keynes that the operation was valuable if no thymoma was present, and review of the various American statistics showed that they were consistent with this. The operation was most effective if performed during the 'active' stage of disease and women gained most benefit. Other methods of destroying the thymus (radiotherapy, steroids, carotid sinus denervation) are less direct and hence inferior since the operation is so safe in skilled hands. Working closely with Mr Andrew Logan in Edinburgh and Mr Kenneth Fraser in Glasgow during the last twelve years there have been no post-operative deaths in

patients under my care. For this reason I continue to rely on thymectomy, but it must be observed that in the last ten years there have been great improvements in medical management, notably in the wider use of pyridostigmine, better recognition of the difference between myasthenic and cholinergic crisis, greater familiarity with the use of edrophonium to evaluate the cause of weakness, and tremendous advance in the management of ventilatory failure. It might well be that these advances have restored the balance in favour of drug therapy.

#### REFERENCES

- Blalock A, Harvey A M, Ford F R & Lilienthal J L (1941) *J. Amer. med. Ass.* 117, 1529  
 Coërs C & Woolf A L (1959) The Innervation of Muscle: A Biopsy Study, Oxford  
 Downes J M, Greenwood B M & Wray S H (1966) *Quart. J. Med.* 35, 85  
 Fraser D & Turner J W A (1953) *Lancet* ii, 417  
 Harvey A M, Shulman L E, Tumulty P A, Conley C L & Schoenrich E H (1954) *Medicine (Baltimore)* 33, 291  
 Keynes G (1946) *Brit. J. Surg.* 33, 201  
 (1955) *Brit. J. Surg.* 42, 449  
 Nastuk W L, Strauss A J L & Osserman K E (1959) *Amer. J. Med.* 26, 394  
 Ringertz N (1951) *Acta path. microbiol. scand.* 29, 9  
 Simpson J A (1956) *Proc. roy. Soc. Med.* 49, 795  
 (1958) *Brain* 81, 112  
 (1960) *Scot. med. J.* 5, 419  
 (1964) *J. Neurol. Neurosurg. Psychiat.* 27, 485  
 (1966a) *Ann. N.Y. Acad. Sci.* 135, 506  
 (1966b) In: *Symposion über progressive Muskeldystrophie - Myotonie - Myasthenie*, Ed. E Kuhn, Berlin; p 339  
 (1968) In: *The Biological Basis of Medicine*, Ed. R A Farrand, London; 3 (in press)  
 Smithers D W (1959) *J. Fac. Radiol. (Lond.)* 10, 3  
 Strauss A J L, Seegal B C, Hsu K C, Burkholder P M, Nastuk W L & Osserman K E (1960) *Proc. Soc. exp. Biol. (N.Y.)* 105, 184  
 Strauss A J L, Smith C W, Cage G W, van der Geld H W R, McFarlin D E & Barlow M (1966) *Ann. N.Y. Acad. Sci.* 135, 557

Dr M H Llesof

(Guy's Hospital, London)

#### Immunological Aspects of Myasthenia Gravis

The recognition of the thymus as a central organizer of immunological function explains the occasional association of thymic disease with such immunological disturbances as agammaglobulinæmia, hæmolytic anæmia, Sjögren's syndrome, systemic lupus erythematosus and myasthenia gravis.

In the myasthenic the thymus is often abnormal histologically. It may contain many more germinal centres than are seen in health. The similarity of the histological picture to that of the thyroid in Hashimoto's disease led Smithers (1959) to suggest that myasthenia gravis was an autoimmune disease, and Professor Simpson (1960) has taken a similar view. Even in the 10–20% of cases in which a thymoma is present there are usually many germinal centres in the 'normal' thymic tissue which is adjacent to the tumour