people of Ontario. This has naturally led to an emotional discussion on whether everybody in Ontario is getting too much surgery, or whether the patients within the clinic are getting too little, and rational solution is unlikely. But the overall cost figures cannot be lightly exorcised. It would appear that the fee-for-item payment, even before the tax rip-off, is a cheaper way of paying for doctors' services. The Canadian taxpayer at the present time would appear to be getting good value for his tax money.

And this makes me wonder. As a burnt out negotiator for the profession, was I taken in by a deep Machiavellian plot?

Would we all have been better off on salary? And as I sit at my desk and write out the monthly cheques for my staff, and for my overheads, I contemplate the happiness of hierarchy for a few heretical moments. But not for long. Individual and professional freedoms are progressively conditional—and conditions always cost.

Reference

¹ Korcok, M, *Canadian Medical Association Journal*, 1974, 111, 1347.

Today's Treatment

Diseases of the central nervous system

Myasthenia gravis

C W H HAVARD

British Medical Journal, 1975, 4, 152-153

Myasthenia gravis is a disorder of neuromuscular function due to a defect in synthesis or storage of acetylcholine at the nerve ending. The muscle weakness is characteristically worse after effort and improved by rest. The patient starts to comb her hair and is unable to finish, or halfway through a meal finds that she can chew no longer. Myasthenia gravis occurs at all ages but the modal age of onset is about 20 years. There is a tendency to early remission but complete remissions are not prolonged. The muscle weakness has a characteristic distribution, the extraocular, bulbar, and neck muscles, limb girdles, distal limbs, and trunk muscles being affected in that order. The myasthenia responds to cholinesterase inhibitors, which enhance the effects of the limited supply of acetylcholine at a neuromuscular junction, and the quick-acting anticholinesterase edrophonium (Tensilon) provides a useful diagnostic test for myasthenia gravis. Patients with the purely ocular form of myasthenia gravis (Benign ocular myasthenia) do not usually develop generalised myasthenia if symptoms remain confined to the extraocular muscles for more than a year.

Myasthenia may be a feature of certain intrathoracic tumours, particularly the oat cell carcinoma, and this disorder must be distinguished from myasthenia gravis. This syndrome is known as pseudomyasthenia, the myasthenic syndrome, or the Eaton-Lambert syndrome and is due to impaired release of acetylcholine from the nerve ending with distinct clinical and therapeutic features. Cholinesterase inhibitors are of little benefit in this disorder but the response to guanidine (250 mg three times a day) is often good.

Medical treatment

The principal agents used to treat myasthenia gravis are the reversible anticholinesterase compounds. They act by inhibiting

cholinesterase, the enzyme that breaks down acetylcholine, thereby increasing the effective concentration of acetylcholine at the motor end-plate. Neostigmine and pyridostigmine are the drugs of choice. Ambenonium is occasionally used. Edrophonium has no place in treatment as its period of action is so short. These drugs are watersoluble and hence do not cross lipid barriers readily. They are thus distributed in the extracellular space and do not enter the central nervous system. These drugs are active by mouth but may if necessary be given parenterally. When given at regular intervals during the day muscle strength can usually be restored to an adequate even if not a normal level. It is important to establish the dose of anticholinesterase drug which gives the maximum therapeutic response.

Most myasthenic patients can be improved only up to a certain level. Increasing the drug dosage above the maximum response level if in the forlorn hope of improving physical activity will produce the opposite effect, and progressive muscle weakness may finally end in a cholinergic crisis. The dose response curve for anticholinesterase compounds has a rapid fall-off once the peak is reached. This may be because to some extent these agents may occupy the acetylcholine receptors and if present in excess prevent the normal action of acetylcholine. Overdosage thus not only increases the quantity of acetylcholine at the neuromuscular junction but also reduces the number of free receptors available for its effect. Like other people, myasthenic patients are subject to the fatigue of mental and physical strain, and the temptation to increase the dosage to counter such physiological fatigue must be resisted. Intercurrent infection may also cause deterioration of myasthenia, but here the cautious and carefully supervised increase in drug dosage is justified. An increase may be required to cope with stress and occasionally premenstrually.

Neostigmine is given in a dose of 15 mg by mouth four-hourly or more often if necessary. It is effective within 30 minutes. The optimum frequency of administration must be decided and then the precise dose determined. When given parenterally a dose of 0.5 mg is equivalent to 15 mg by mouth. There are two varieties of peripheral cholinergic activity. Muscarine activity affects smooth muscle and glandular tissue while nicotinic activity affects autonomic ganglia and neuromuscular junctions. The cholinesterase inhibitors enhance both the muscarine and the nicotinic effects of acetylcholine. As muscarine activity affects

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smooth muscle and exocrine glands it is shown by abdominal colic, diarrhoea, nausea, salivation, sweating, and lachrymation. Atropine may reduce these side-effects. These symptoms, however, usually indicate overdosage, and it is therefore unwise to prescribe atropine routinely.

Pyridostigmine (Mestinon) has the advantage of more prolonged action and it is rarely necessary to give it more often than four-hourly. It does, however, take longer to act. A dose of 60 mg is equivalent to 15 mg neostigmine. A dose of pyridostigmine of 60 mg four times a day should be used initially and the size of the dose increased until the maximum benefit is obtained. Patients who tend to be weak on waking benefit from a dose of the quicker acting neostigmine with the first dose of pyridostigmine.

NON-CHOLINESTERASE INHIBITORS

Drugs other than cholinesterase inhibitors have a place in the treatment of myasthenia gravis. The beneficial effect of ephedrine has long been recognised though the response is rarely striking. A dose of 30 mg, however, thrice daily should be tried if the response to anticholinesterase agents is inadequate. Hypokalaemia aggravates muscle weakness so that potassium supplements may be useful. The response to corticosteroids is often dramatic. A good response can be expected in about half of the patients. In some series patients with a longer history of myasthenia have shown the best response, while in other series patients who have not been ill so long have fared better. Transient exacerbation of myasthenia commonly precedes the improvement. Deterioration tends to occur between the first and sixth day and is usually maximal by the 10th day. Patients should therefore not be treated with corticosteroids unless there are facilities for assisted respiration. Neither deterioration nor benefit has been associated with any change in serum electrolytes. The usual dose of steroids has been about 30-60 mg of prednisolone daily for 10 days. Continuous corticosteroid treatment is sometimes required and alternate day treatment has been advocated to avoid some of the complications of prolonged steroid treatment. Prednisolone may be effective when ACTH has failed. By starting treatment with a small dose of prednisolone, such as 25 mg on alternate days, and gradually increasing the dose, the initial, though transient, deterioration that is characteristic of steroid therapy in this disease may be prevented. The results reported by different observers vary and it is not possible to make any final assessment on the various regimens that have been recommended.

We do not know the reason for the beneficial effects of steroids. It is unlikely to be due to their thymolytic effect as patients benefit after thymectomy. Improvement may occur after a ten-day course has been completed or during treatment. Patients on alternate day therapy report reduced strength when prednisolone is not given and this suggests that steroids facilitate the release of acetylcholine at the neuromuscular junction in the myasthenic patient. The cause of the initial deterioration so commonly seen is difficult to explain but could be the result of enhanced effects of the cholinesterase inhibitors provoking a cholinergic crisis. It has been suggested that good results may occur in patients on steroids when the cholinesterase inhibitors are discontinued. It is not possible to withdraw anticholinesterase in most patients as this would result in a dangerous increase in the myasthenia. The effects of corticosteroids are often most beneficial and allow a reduction in dose of anticholinesterase drugs and this beneficial effect may continue for many weeks after steroids have been discontinued. Complete remissions have also been recorded. Nevertheless, prolonged corticosteroid therapy should be given only to patients who have been offered thymectomy as there is increasing evidence that this operation offers the best chance of remission.

It is important to remember that there are drugs which aggravate myasthenia. Myasthenic patients are obviously much more sensitive to the neuromuscular blocking drugs. Antiarrhythmic drugs reduce the excitability of muscle membrane and probably also inhibit neuromuscular transmission and so

quinine, quinidine, procainamide, lignocaine, and propranolol should be avoided. Antibiotics of the aminoglycoside group impair neuromuscular conduction by inhibiting the release of acetylcholine so that streptomycin, gentamicin, kanamycin, neomycin, and polymyxin should be avoided. Patients with myasthenia are sensitive to the central nervous system depressants so that drugs such as morphine and barbiturates must be used with caution.

Myasthenic and cholinergic crises

A myasthenic crisis may result from a natural deterioration of the disease or it may be precipitated by infection or surgery. Often there is no obvious reason for the deterioration and such exacerbations are usually characterised by a decreased responsiveness to anticholinesterase compounds which cannot be overcome by giving larger doses. When the relapse is precipitated by infection the symptoms may be due to a relative deficiency of acetylcholine and can often be corrected by increasing the anticholinesterase drug dosage. A cholinergic crisis, on the other hand, is the result of excessive doses of cholinesterase inhibitors and the treatment demands withholding these drugs. Both these crises present with severe weakness leading to paralysis. The differential diagnosis may be difficult but will usually be made by the cautious administration of 10 mg edrophonium intravenously. If the crisis is myasthenic temporary improvement will follow, but if the crisis is cholinergic no such improvement occurs, and indeed the situation may deteriorate. The duration of the drug's action is so short that any deterioration due to increased anticholinesterase activity is unlikely to have any serious consequence. Nevertheless, facilities for assisted respiration should always be available.

One of the difficulties that may arise after edrophonium is that one muscle group sometimes becomes stronger and another weaker. It is therefore important that emphasis should be placed on the response of the essential bulbar and respiratory muscles rather than the less essential ocular and limb muscles. If a cholinergic crisis is suspected the cautious intravenous injection of 1 to 2 g of pralidoxime, a cholinesterase reactivator, has been recommended. This will intensify a myasthenic crisis but usually improves a cholinergic crisis. It is more dangerous than the edrophonium test and is therefore better avoided. If there is any doubt about the nature of the crisis it is wiser to stop all medication and maintain respiration with assisted ventilation. This will steer a critically ill patient through a cholinergic crisis. Furthermore, in a myasthenic crisis responsiveness to anticholinesterase compounds can often be restored after a period of complete withdrawal of medication for about 72 hours. In practice valuable time may be lost in trying to differentiate myasthenic from cholinergic crises. The most effective treatment for both these crises is to stop anticholinergic drugs and institute assisted ventilation.

Thymectomy

The risks of thymectomy have been dramatically reduced over recent years as a result of the advances in the management of ventilatory failure with assisted respiration and the better differentiation of myasthenic and cholinergic crises. Increasing numbers of patients with myasthenia are now being offered thymectomy and the benefits of operation are becoming more apparent. The incidence of remission increases with the number of years after thymectomy. Complete remission or substantial improvement may be expected in 80% of patients without a tumour of the thymus, though it may take three to five years before the benefits of operation are apparent. In patients with a tumour early operation is also indicated but the prognosis of patients with a thymic tumour is worse. With the exception of those with the purely ocular form of the disease, most patients with myasthenia should be offered thymectomy provided that

the operation is undertaken in a centre with good facilities for intensive care and in a unit with experience of the operation. Prolonged corticosteroid therapy should be reserved for patients who have not responded to thymectomy and should not precede thymectomy.

The monthly *MIMS* index of proprietary preparations available in Britain includes the following trade names for the main drugs mentioned in this article (other than broad groups such as corticosteroids): ambenonium: Mytelase; edrophonium: Tensilon; neostigmine: Prostigmin; pyridostigmine: Mestinon.

Conference Report

A British view of Danish medicine

FROM A SPECIAL CORRESPONDENT

British Medical Journal, 1975, 4, 154-156

Looking for all the world like a top-secret military base, the exterior of the low concrete building of the Scanticon hotel at Aarhus, Denmark, belied the comfort and efficiency found inside by the BMA delegation of just over 150 doctors and their families who had crossed the North Sea to join the Danish Medical Association in a clinical meeting from 25-28 September. By the end of the stay their overall impression was one of good-tempered envy; for there was no doubt that Danish doctors have a good life, both professionally and socially. They seemed happy with their pay (at £12 000 a year for a hospital registrar and distinctly more for GPs and hospital staff they have reason to be) and there was no evidence of any serious discontent about the organisation of the medical services.

The visitors were naturally curious about the differences in culture and customs to be found in Scandinavia, and many of their questions were answered in a witty and stimulating lecture by Mr Ole Bernt Henriksen. In 80 minutes he outlined 7000 years of history (including a Danish view of Nelson's behaviour at the battle of Copenhagen) and went on to explain the current political system and the taxation laws—apparently the Danes can't yet compete with the highest British levels but they're trying their best.

Danish Health Service

The entire population of Denmark receives free hospital treatment (inpatient and outpatient), which is financed by

taxation, and there is only a tiny proportion of private hospital practice. Primary care is organised on the basis of health insurance. Most people—80% of the total population of 5½ million—are covered by the State insurance scheme. The remaining 20%, who have higher incomes, are included in a contributory insurance scheme. A full explanation of the system was given by Dr Eric Holst (assistant professor at the University of Copenhagen Institute of Social Medicine), who convinced his British colleagues of the general contentment that existed in the Danish health services at all levels. This he attributed to cordial and efficient relations between the profession and those responsible for health care in the Government. In contrast to Britain there is no Ministry of Health as such, but a civil servant who is also a doctor is in close contact with the Danish Medical Association—which has an almost 100% membership and so provides adequate representation of all sections of the profession. (The cost of membership of the DMA is nearly £120 a year for an average general practitioner, but membership is a condition of participation in the State health insurance scheme. Hospital doctors can choose whether or not to be members; almost all are.) The harmony between Government administration and the profession has resulted in development of health care services which on the one hand take account of the wishes and ideas of the Danish doctors and on the other recognise the restrictions which must be imposed by the State. Having invested heavily in hospital and specialist centres in the early part of this century, the Government is now anxious to develop primary health care.

Denmark's 2300 general practitioners caring for a population of 5½ million have on average 2400 patients each. The general practitioner is independent of the State and does not receive a salary, nor does he receive direct allowances in the running of his practice. Payment to the GP is on an item-of-service basis; in the case of 80% of the population covered by the State insurance scheme the patient simply signs the appropriate form at the end of the consultation and it is then sent off for payment. The other 20% of patients pay their doctors directly and receive only part of the fee from their insurance scheme. As a result, the demands on general practitioners out of hours tend to come more from the 80% in the State plan than from the others, who have to pay part of the higher night and weekend fees themselves.

Visitors were entertained with characteristic hospitality by a number of general practitioners in Aarhus and had the opportunity of seeing practice premises and studying the administrative details of the system. The surgeries had a bright and friendly atmosphere and were well equipped. An appointment system operated in most areas and the general practitioners did not work unduly long hours—the official working day ends at 4 pm. Calls at weekends and at night accounted for only 7% of the total work load. A rota system generally operated in the

Professor Eric Holst giving his inaugural address