Gout
Haemochromatosis
Lipoidosis
Multicentric Reticulohistocytosis (Lipoid Dermatoarthritis)
Myositis ossificans
Ochronosis
Osteomalacia
Osteoporosis
Renal transplant syndrome
Xanthomatosis (primary hypercholesterolaemia)

Vascular:
Avascular necrosis (fat, caisson, etc.)
Giant-cell arteritis
Polyarteritis nodosa
Takayasu's (pulseless) disease
Wegener's granulomatosis

Neoplastic; Arthropathies associated with benign and malignant tumours:
Chondrosarcoma
Haemangioma
Left atrial myxoma
Metastatic malignant disease
Multiple myelomatosis
Osteoid osteoma
Paget sarcoma
Pseudohypertrophic pulmonary osteoarthropathy
Synovioma

Neuropathic:
Carpal tunnel median nerve compression
Charcot's joints, tabetic or syringomyelic
Diabetic arthropathy (neuropathic and infective)
Osborne's syndrome (ulnar nerve compression and other compression neuropathies)
Paraplegia syndrome
Shoulder-hand syndrome

Therapeutic:
Alcoholism
Corticosteroid arthropathy
Hydrallazine syndrome (procaine amide, oral contraceptives, etc.)
Anticoagulant therapy
Isoniazid shoulder-hand syndrome
Serum sickness

Miscellaneous:
Acro-osteolysis syndrome
Degos' syndrome
Dupuytren's contracture
Knuckle pads (Hale White's syndrome)
Paget's disease of bone
Periostitis deformans (Soriano)
Septic focus syndrome
Xyphoid syndrome

Today's Drugs

With the help of expert contributors we print in this section notes on drugs in current use

Treatment of Myasthenia—II

Severe weakness leading to paralysis may result from either a deficiency (myasthenic crisis) or an excess (cholinergic crisis) of acetylcholine at the neuromuscular junction. The differential diagnosis between these two conditions is often difficult, and the results of giving 10 mg edrophonium intravenously may provide crucial information. This drug produces improvement in a myasthenic crisis but not in a cholinergic crisis—which may, indeed, become slightly worse. Nevertheless, the drug has such a short duration of action that for a patient in cholinergic crisis any deterioration due to increased anticholinesterase activity is unlikely to have serious consequences.

Edrophonium Test

For these reasons the edrophonium test is invaluable in diagnosing paralytic problems in myasthenic patients. It may have to be resorted to repeatedly in titrating a patient's requirements of parenteral neostigmine. Even so, in employing this test it is important that the response of essential (respiratory and bulbar) muscles should be examined rather than that of non-essential (limb or ocular) muscles. This precaution is mandatory, because the same patient may have weakness in some muscle groups because of inadequate acetylcholine and simultaneous paralysis of muscle groups because of an excess of acetylcholine.[1] In other words, a cholingergic and myasthenic crisis may coexist in the same patient at the same time.

Myasthenic Crisis

The myasthenic crisis is a medical emergency requiring immediate availability of artificially assisted respiration. Tracheostomy may prove necessary. A crisis may develop as a spontaneous deterioration in the natural history of myasthenia gravis, or it may be precipitated by infection, by exertion (as in childbirth), or by surgery. Drugs which exacerbate myasthenia gravis may also provoke a crisis. These include agents which impair neuromuscular condition (such as streptomycin or neomycin), substances which reduce the excitability of muscle membrane (such as quinine or quinidine), and drugs which depress respiration (such as morphine or barbiturates). It has also been claimed that menstruation, emotional stress, and thyrotoxicosis can precipitate rapid paralysis.

A myasthenic crisis can usually be corrected by administration of an anticholinesterase. A dose of 0·5 mg neostigmine may be given by subcutaneous or intramuscular injection, repeating this every 20 minutes with frequent edrophonium tests. As previously mentioned, atropine (0·3-0·6 mg) should be administered to control the muscarinic effects of parenteral neostigmine.

Cholinergic Crisis

Like the myasthenic crisis, the cholinergic crisis is a medical emergency. Facilities must be available for tracheal intubation and positive pressure respiration. Anticholinesterases must, of course, be withheld and excessive muscarinic activity should be blocked by giving large doses of atropine. In these circumstances it is reasonable to give 2 mg atropine parenterally every hour until this treatment itself produces toxic effects. Cholinesterase reactivators have been produced as antidotes for poisoning by certain organophosphorus insecticides and "nerve" gases, and such agents—for example, pralidoxime—may be useful in cholinergic crises. A dose of 1-2 g of pralidoxime may be given by slow intravenous injection over two to four minutes. This may be repeated after 20 minutes if the response is transient or inadequate. Anticholinesterase drugs should not be started again until two successive edrophonium tests have given a "myasthenic" type of response.

Treatment Failures

As already mentioned, failure to respond to anticholinesterases may be due to overdosage (cholinergic crisis). In some cases the cause of the development of "neostigmine insensitivity" is more obscure. For example, patients may respond to edrophonium with increased muscle power but function in the corresponding muscles does not improve when longer-acting anticholinesterase agents are administered. Furthermore, the edrophonium test may be difficult to interpret, particularly if carried out within a short time of giving neostigmine. Problems of this kind are especially likely to be encountered in patients with fulminating myasthenia gravis with severe bulbar involvement, who readily develop respiratory distress. Neostigmine resistance may occur at the beginning of treatment, or it may develop at any stage after starting therapy. Patients with this type of difficulty, or with

neostigmine requirements which undergo rapid fluctuation (sometimes referred to as "brittle" myasthenics), represent a difficult therapeutic problem. Factors precipitating myasthenic crisis should naturally be avoided or treated, but patients may still deteriorate inexorably into respiratory insufficiency.

When the doctor is faced with the dilemma of failing respiration and neostigmine resistance which cannot be attributed to overdosage the patient should be curarized, positive-pressure artificial respiration should be started, and anticholinesterase drugs should be witheld. This treatment, which must be regarded as a last resort, generally results in a spontaneous resumption of responsiveness to neostigmine in three to ten days,[2] after which the patient can be weaned off the respirator. It has been suggested that "resting the end-plates" is the factor responsible for the improvement from this procedure.

Finally, long-standing cases of myasthenia gravis may ultimately progress to a myopathic disorder, in which there is wasting, permanent weakness, and failure to respond to anticholinesterase drugs. This condition presents as a chronic rather than an acute problem and is refactory to treatment.

Infantile Myasthenia

One out of every seven babies born to mothers with myasthenia gravis has a syndrome of rapid shallow respiration with defective sucking and swallowing. The severity of the disorder of neuromuscular conductions is not related to that of the mother and the condition clears spontaneously over days or weeks. Nevertheless, the disease may prove fatal if left untreated. An edrophonium test (1 mg intravenously) should confirm the diagnosis of infantile myasthenia and anticholinesterase treatment should then be started with neostigmine, 1-4 mg, or with pyridostigmine, 4-20 mg orally.

Very rarely myasthenia gravis may develop in a baby born to a healthy mother. This is treated in the way just described, but the disease usually persists, unlike that occurring in the infant of a myasthenic mother.

Eaton-Lambert Syndrome

This is also known as the myasthenic syndrome, atypical myasthenia gravis, pseudomyasthenia, or the myasthenic-myopathic syndrome.

Most cases of the Eaton-Lambert syndrome are due to bronchial carcinoma. Because long-term survival is rare nobody knows whether treatment of the primary lesion alters the course of the neurological disorder. At present the general view is that temporary improvement in muscle power may result.[3]

TREATMENT OF NEUROMUSCULAR DISTURBANCE

Since the Eaton-Lambert syndrome is due to defective release of acetylcholine at the neuromuscular junction, theoretically the myasthenia might be expected to improve with an anticholinesterase, and in fact neostigmine has some therapeutic action. Nevertheless, the response is not as satisfactory as in myasthenia gravis, and in the Eaton-Lambert syndrome better results may be obtained with guanidine—a drug which has been shown to aid the release of acetylcholine at the motor nerve ending.

Guanidine should be given in divided oral doses of 20-30 mg/kg/day. A reasonable initial regimen is 250 mg three or four times a day, increasing according to individual tolerance. Maximum benefit is not attained until treatment has been continued for several days and on stopping therapy improvement is correspondingly slow to disappear. At present no suitable pharmaceutical form of guanidine is commercially available. Preparations can be made fairly easily by a pharmacy provided precautions are taken to deal with the deliquescence of guanidine.*

The main adverse effects of treatment with guanidine are circumoral paraesthesiae, anorexia, diarrhoea, and an altered mental state—restlessness, agitation, and anxiety. More severe intoxication may cause vomiting, excessive salivation, tremor, hypoglycaemia, and circulatory disturbances. As in the case of anticholinesterase overdosage, many unwanted actions of guanidine can be corrected by administration of atropine.

Conclusion

Myasthenia gravis and the Eaton-Lambert syndrome are neurological disorders in which the application of basic pharmacological principles has resulted in very satisfactory therapy for most patients. Treatment is essentially rational: defective production or storage of acetylcholine in myasthenia gravis is overcome by the administration of neostigmine or pyridostigmine; impaired release of acetylcholine in the Eaton-Lambert syndrome is alleviated by guanidine. Overdosage with any of these drugs is treated by giving atropine.

References

1 Simpson, J. A., in *Disorders of Voluntary Muscle*, ed. J. N. Walton, p. 541. London, Churchill, 1969.
2 Glaser, G. H., *Annals of the New York Academy of Sciences*, 1966, **135**, Art 1, 335.
3 Lambert, E. H., and Rooke, E. D., in *The Remote Effects of Cancer on the Nervous System*, ed. Lord Brain and F. H. Norris, Jr., pp. 67-80, New York, Grune and Stratton, 1965.

* Advice may be obtained from Martindale Samoore Ltd., Salem Road, Queensway, London W.2.