Muscle weakness is a feature of many illnesses but the present discussion will be confined mainly to conditions in which it is a manifestation of defects in the anterior horn cells, the motor nerves, the neuromuscular junction, or the muscle itself.

The pathogenesis of these disorders is often ill-understood and more than one component of the neuromuscular system may be involved. Moreover, knowledge about the effect of muscle relaxant drugs upon patients with such conditions is often inadequate and in some conditions entirely absent. This situation is easily understood in view of the rarity of many of these diseases, the relative infrequency with which operations are performed on such patients, and the natural reluctance of anaesthetists to administer relaxant drugs to patients with known weakness. The purpose of this article is to review the information available on this subject with emphasis on the clinical implications in regard to anaesthesia.

Disorders of neuromuscular transmission will be considered first with particular reference to myasthenia gravis. The functional pathology of this condition has been extensively studied and it is the most important of all the muscle disorders as far as the anaesthetist is concerned, because of its unique effect on the response to muscle relaxants. The general principles of the anaesthetic management of patients with myasthenia gravis can, however, be applied to all other disorders involving muscle weakness.

**MYASTHENIA GRAVIS**

Although this term implies severe muscular weakness, it is really a condition of pathological fatigability in which muscle power is rapidly exhausted by activity and slowly recovers with rest. The estimated incidence of the disease in Great Britain is 1 in 40,000 (Garland and Clark, 1956). It is twice as common in women and the mean age of onset is about 26 years (Simpson, 1960). The initial symptoms are frequently ocular (diplopia or ptosis) with weakness of the limb girdles and neck as the next commonest complaint. Other features of this disease are its insidious onset and the spontaneous remissions which occur especially during the first three years (Simpson, 1960).

It has been appreciated for many years that myasthenia gravis is due fundamentally to a defect in neuromuscular transmission. For a fuller understanding of the effects of the muscle relaxants in this disease, it is necessary to consider the functional pathology of the neuromuscular junction, which may be considered under four main theories.

**Altered response by the motor endplates.**

A number of pharmacological studies support the theory that myasthenic motor endplates behave abnormally and that a neuromuscular block is produced either by the acetylcholine released from the motor nerve terminals or by the choline subsequently formed by hydrolysis (Grob, Johns and Harvey, 1956).

Churchill-Davidson and Richardson (1953) have shown that myasthenic patients are resistant to the muscle relaxant decamethonium iodide and that a phase II neuromuscular block develops when this drug is given to a myasthenic as opposed to the characteristic depolarization block seen in normal subjects. The initial depolarization block changes rapidly to one of antidepolarization.

**Deficient synthesis or release of acetylcholine.**

Two recent reports support the hypothesis that there is a prejunctional deficiency of acetylcholine in myasthenia gravis. Desmedt (1957, 1961) has investigated the electrical and mechanical responses in myasthenic muscle. Following a brief faradization he found a phase of increased neuromuscular block lasting for 20 minutes which he has termed post-tetanic exhaustion. A similar response is seen in cat's muscle treated with hemicholinium, a substance which inhibits acetylcholine synthesis.
Dahlbäck and his colleagues (1961) studied the release of acetylcholine from the neuromuscular junction by using intracellular electrodes to record endplate potentials. These investigations were carried out on biopsy specimens of intercostal muscles taken from both myasthenic patients and normal subjects. It was concluded in both these studies that in myasthenia gravis there was impairment in either the synthesis or the release of acetylcholine from the motor nerve endings.

Circulating neuromuscular blocking agent.

Several reports have suggested the presence of substances capable of depressing neuromuscular transmission in tissue extracts and sera from myasthenic patients, including extracts from the thymus gland (Wilson and Wilson, 1955). At the present time, however, there is no conclusive evidence to substantiate the theory that there is a circulating blocking agent in myasthenia gravis (Nastuk et al., 1959).

Autoimmune response.

A tenable explanation for the well-known association between the thymus gland and myasthenia gravis is provided by the recent suggestion of an auto-immune mechanism (Simpson, 1960; Burnet, 1962). It is postulated that in myasthenia the body has lost the ability to distinguish its own tissues and that a disordered thymus gland forms antibodies against endplate protein as if it were foreign material. It is suggested that the action of acetylcholine at the motor endplates is blocked as a result of the changes produced by the antigen-antibody reaction and the subsequent binding of serum complement. Supporting evidence for this concept is afforded by reports that wide variations of serum complement activity occur in myasthenia gravis (Nastuk et al., 1960, 1961). The altered response to acetylcholine and its impaired synthesis at the motor nerve terminals may follow as a sequel to this auto-immune mechanism at the myoneural junction.

Muscle relaxant drugs and myasthenia gravis.

Antidepolarizing agents. It is well known that the myasthenic endplate shows an increased sensitivity to d-tubocurarine and the intravenous injection of small doses of this relaxant has been advocated as a diagnostic test for myasthenia gravis (Bennett and Cash, 1943). The diminution in muscle power is assessed both clinically and also objectively by means of a dynamometer or ergograph.

Foldes and McNall (1962) inject 0.5 to 1 mg of d-tubocurarine intravenously every 3 minutes up to a total dose of 4 mg. If there is no marked fall in grip strength or in vital capacity then these workers think the patient is unlikely to have myasthenia gravis. Rowland and his colleagues (1961) reported that 84 per cent of patients with myasthenia gravis were sensitive to 0.016 mg/kg of d-tubocurarine given in eight divided doses. Negative results were noted amongst patients with purely ocular manifestations of the disease.

It had been previously pointed out by Churchill-Davidson (1955) that hypersensitivity to antidepolarizing agents is only present in those muscles which are clinically weak. Muscles which exhibit no weakness may well show a similar response to that of a normal subject. This is especially true of the respiratory muscles which are rarely affected in mild cases of the disease. The use of small test doses of d-tubocurarine prior to anaesthesia in such patients may be misleading unless careful attention is paid to the muscle groups likely to be clinically involved.

The maintenance of complete paralysis by means of d-tubocurarine together with the use of intermittent positive pressure ventilation via a tracheostome has been recommended as a method of treatment for patients who have become resistant to neostigmine (Churchill-Davidson and Richardson, 1957). The value of “resting” the endplates in this manner has not been fully established.

Depolarizing agents. The action of decamethonium in myasthenia gravis has been fully reported by Churchill-Davidson and Richardson (1953). In myasthenic patients with only ocular symptoms, there is an extraordinary tolerance to decamethonium and at times as much as 10 mg can be given without signs of paralysis. The fact that resistance is shown by motor endplates throughout the body is indicative of the generalized nature of the disease. At a later stage of the disease, paralysis occurs after intravenous decamethonium (2.5 mg) but the muscles show evidence of a phase II response (Churchill-Davidson, 1955). This response to decamethonium forms the basis of a diagnostic test for myasthenia gravis which is especially use-
ful in early cases or during remissions (Churchill-Davidson and Richardson, 1953).

The technique is to inject 2.5 to 3 mg of decamethonium intravenously over a period of 6 minutes and to assess the degree of paresis electromyographically.

In a normal subject the action potentials recorded from the hypothenar muscles fall to less than 20 per cent of their initial amplitude. The values in patients with myasthenia sometimes remain unchanged and never fall below 30 per cent while the majority of recordings keep above 50 per cent of their initial amplitude.

The response to neostigmine or to edrophonium affords a further distinguishing feature, because whereas the depolarizing block in a normal subject is enhanced, the phase II neuromuscular block in myasthenia is reversed and the action potentials increase in amplitude.

Suxamethonium produces a similar effect to decamethonium but with the large dosage commonly used clinically, it is difficult to demonstrate the stage of resistance. The phase II neuromuscular block which subsequently develops may result in a less rapid recovery from suxamethonium than in a normal subject.

Anaesthetic techniques in myasthenia gravis.

If general anaesthesia is considered necessary for myasthenic patients, a thiopeptone, nitrous oxide, oxygen sequence, supplemented if necessary by halothane, will prove satisfactory for most operations. Endotracheal intubation and controlled ventilation can be readily achieved with this technique.

Foldes and McNall (1962) have advocated the use of small doses of d-tubocurarine to facilitate intra-abdominal surgery when the abdominal muscles are not implicated in the disease. Epidural analgesia may well be preferred in these circumstances, thereby avoiding the potential hazards associated with the use of muscle relaxants. Mushin (1959) suggests withholding the dose of neostigmine due to be given before the operation. This provides ample relaxation in most cases.

There may be a place for the occasional use of suxamethonium when brief periods of profound relaxation are required in patients with minimal weakness. As a general rule, however, the muscle relaxants have no place in the anaesthetic management of myasthenic patients.

BRITISH JOURNAL OF ANAESTHESIA

MYASTHENIC SYNDROME ASSOCIATED WITH BRONCHIAL CARCINOMA

A number of reports have described the occurrence of myasthenic weakness in certain patients with bronchial carcinoma (Anderson et al., 1953; Henson et al., 1954; Eaton and Lambert, 1957; Croft, 1958; Lambert et al., 1961; Wise, 1962).

The term myasthenic syndrome has been introduced by Eaton and Lambert (1957) to differentiate this condition from the true myasthenia gravis. The weakness and fatigability, which mainly affect the proximal muscles, respond poorly to neostigmine in contrast to the situation in myasthenia gravis.

The myasthenic symptoms usually precede the discovery of the neoplasm which is almost invariably an anaplastic (small-cell) bronchogenic carcinoma. The electromyogram plays an important part in confirming the diagnosis of this syndrome. Abnormally small action potentials which decrease in size are recorded at slow rates of supramaximal nerve stimulation. In contrast, at fast rates of stimulation the action potentials progressively increase in amplitude even to as much as six times the initial height.

A short-lived increase in strength on exertion corresponding to this facilitation of transmission can sometimes be observed in these patients. This electromyographic pattern appears to be diagnostic for this syndrome and differs quantitatively from the response in myasthenia gravis.

Patients with the myasthenic syndrome show an abnormal sensitivity to muscle relaxants which may cause difficulties during anaesthesia or in the postoperative period (Wise, 1962). A previously undiagnosed case may first become apparent as a result of a prolonged apnoea lasting several hours following an average clinical dose of d-tubocurarine. These patients are especially susceptible to the antidepolarizing relaxants and the neuromuscular block is not readily reversed with neostigmine.

The increase in sensitivity with an average clinical dose of a depolarizing muscle relaxant is less pronounced and this stands in contrast to the tolerance shown to these agents by most patients with myasthenia gravis.

The problems of anaesthesia in patients with the myasthenic syndrome are similar to those discussed in the section on myasthenia gravis. Muscle
relaxants should be avoided, although in certain circumstances small doses of suxamethonium may be justifiable when profound relaxation must be provided without subjecting the patient to the hazards of deep inhalational anaesthesia.

THYROID GLAND AND MUSCLE DISORDERS
Contradictory reports have appeared about the relationship between disorders of the thyroid gland and muscle dysfunction.

(a) Thyrotoxic myopathy.
Weakness and wasting of muscles is a not uncommon feature of thyrotoxicosis. There is also a considerable impairment in the efficiency of muscular contraction which is probably due to disturbances in the basic chemical processes involved (Boshes and Mier, 1961). In thyrotoxic myopathy the pelvic and shoulder girdles are predominantly affected but this process is reversible and regresses when the thyrotoxicosis is treated (Millikan and Haines, 1953).

(b) Thyrotoxicosis and myasthenia gravis.
A see-saw relationship between these two conditions has been described by some authors (McEachern and Parnell, 1948; MacLean and Wilson, 1954). It has been suggested that improving the thyrotoxic myopathy by antithyroid treatment may aggravate the myasthenia gravis. Millikan and Haines (1953) reported an incidence of hyperthyroidism during or after myasthenia gravis in 5 per cent of patients but their experience does not correspond with the concept of a functional antagonism between the two conditions, since myasthenic weakness may increase when hyperthyroidism becomes superimposed.

The neuromuscular junction in thyrotoxicosis.
Even in the absence of true thyrotoxic myopathy, muscular weakness is a frequent and early finding in thyrotoxicosis. In addition to disturbances in the enzyme systems concerned with muscular contraction, there appear to be alterations in neuromuscular transmission.

Lehmann (1955) reported that some patients, who were being operated on for toxic goitre, were resistant to suxamethonium and that upon investigation their pseudocholinesterase levels were at the higher limit of normal. He considered that there is an overall increase in the level of pseudocholinesterase in hyperthyroidism. It has been postulated that the muscle weakness in thyrotoxicosis is due to overactivity of the cholinesterase system (Boshes and Mier, 1961). This would also explain the exacerbation of myasthenia gravis in the presence of thyrotoxicosis and the improvement that occurs with antithyroid treatment.

Burns and Paton (1951) showed that an excess of acetylcholine can cause muscular paralysis and it is possible that increased synthesis of acetylcholine may also contribute to the muscle weakness in thyrotoxicosis. This assumption is based upon the known dependence of acetylcholine production on the presence of co-enzyme A, the tissue levels of which are markedly influenced by thyroxine (Tabachnick and Bonnycastle, 1954). Thus it is reasoned that a rise in the level of thyroid hormone would increase acetylcholine synthesis. Tabachnick and his co-workers (1958) demonstrated that hyperthyroid animals were significantly more sensitive to decamethonium and neostigmine. Although antagonism to d-tubocurarine would be anticipated in the presence of increased acetylcholine production, none was found. The ineffectiveness of suxamethonium was attributed by the authors to a rise in the serum cholinesterase. An increased sensitivity to neostigmine may account for the reduced requirements of the drug by patients with myasthenia gravis who develop thyrotoxicosis.

McCorkle (1952) found no increased sensitivity to d-tubocurarine in patients with thyrotoxicosis. During electromyographic studies upon two patients with a thyrotoxic myopathy, the present author (unpublished observation) noted an enhanced response to decamethonium.

In conclusion, if there is increased acetylcholine synthesis in thyrotoxicosis, the elevated serum cholinesterase may be compensatory. These factors may account for a normal response to d-tubocurarine and resistance to suxamethonium. The possibility exists, however, that such patients may show an increased sensitivity to decamethonium, depending upon the balance between the production of acetylcholine and its inactivation at the motor endplates.

AMYOTROPHIC LATERAL SCLEROSIS
(MOTOR NEURONE DISEASE)
This is an adult disease of the motor system which begins insidiously and progresses to a fatal termination usually in three years (Mulder, 1957).
Progressive muscular atrophy and progressive bulbar palsy represent different aspects of the disease. The classical clinical picture is of a man aged 40-50 years presenting with progressive weakness, atrophy and fasciculations of his skeletal muscles often beginning in the hand but gradually becoming widespread.

Lateral sclerosis from involvement of the pyramidal tracts shows itself by increased tendon reflexes, by spasticity, and sometimes by abnormal plantar reflexes. The onset of bulbar palsy usually ushers in the terminal stages of the disease, death occurring from mechanical respiratory failure or aspiration pneumonia. Involvement of the dorsal nucleus of the vagus may cause sudden death.

The underlying pathological process in amyotrophic lateral sclerosis is a selective degeneration of the anterior horn cells in the spinal cord, the motor nuclei of the medulla and of the pyramidal tracts.

Rooke and his co-workers (1961) described a patient with amyotrophic lateral sclerosis who had muscular weakness in his upper extremities. The strength of his arms increased appreciably after the subcutaneous injection of 1 mg of neostigmine and the intravenous injection of 10 mg of edrophonium. After the injection of one-tenth of a curarizing dose of d-tubocurarine his forearm weakness increased and he was unable to flex his forearm against gravity. (These workers define a curarizing dose of d-tubocurarine as 3 mg per 40 lb. of body weight.)

In diseases affecting the anterior horn cells Wohlfart (1957) has demonstrated a peripheral sprouting in some of the motor nerve fibres supplying the affected muscles. It has been suggested that neuromuscular transmission is defective in these newly created fibres and motor endplates (Rooke et al., 1961).

In a number of cases a defect of neuromuscular conduction has been demonstrated (Lambert and Mulder, 1957; Rooke et al., 1961). During electromyographic studies, the action potentials evoked by supramaximal nerve stimulation, showed a progressive decline in amplitude, not unlike the response seen in patients with myasthenia gravis. Similar findings to these were observed in patients with syringomyelia, in the wasted muscles of patients recovering from poliomyelitis, and in some patients who had atrophy of proximal muscles. It is of interest that a similar defect of neuromuscular transmission to that present in myasthenia gravis can occur in amyotrophic lateral sclerosis and in other diseases in which the lower motor neurone is involved. The policy governing the use of muscle relaxants in such patients should be similar to that adopted in myasthenia gravis.

MUSCULAR DYSTROPHIES

In this group of disorders, which often have a familial or hereditary basis, the muscles undergo a progressive degeneration. Although there is no record of any specific sensitivity to the relaxants, these drugs should be avoided in patients with severe weakness, as any persistence of the neuromuscular block may precipitate respiratory failure (McClelland, 1960). The use of small intermittent doses of suxamethonium, however, is thought justifiable by Witslicki (1962).

DYSTROPHIA MYOTONICA

This is the most important of the three conditions comprising the myotonic syndrome. It is a hereditary disease characterized by muscular dystrophy, myotonia, cataracts and gonadal atrophy.

The myotonia leads to a persistence of contraction after a voluntary effort has ceased. It is most evident in the hand where a patient has difficulty in releasing his grasp. The defect is in the muscle and not at the neuromuscular junction. Geschwind and Simpson (1955) demonstrated that the myotonia was unchanged after producing a neuromuscular block with 10 mg of d-tubocurarine or 1.5 mg of decamethonium.

Kaufman (1960), in reviewing the hazards of anaesthesia in dystrophia myotonica, stressed the dangers arising from the use of respiratory depressant drugs but considered that antidepolarizing relaxants were not contraindicated. Depolarizing relaxants, on the other hand, must not be administered to those patients owing to the risk of precipitating an attack of myotonia. Paterson (1962) reported the effect of suxamethonium upon a patient with myotonia congenita of mild degree. Generalized myotonia was induced when this drug was given on three occasions at short intervals. During these episodes it was impossible to inflate the lungs.

Intravenous quinine (300-600 mg) has been recommended to control attacks of myotonia of the respiratory muscles. The slow intravenous in-
jection of procaine amide (500–1000 mg) should be equally effective for this purpose (Geschwind and Simpson, 1955). These drugs are thought to have a stabilizing action on the muscle membrane in myotonia.

COLLAGEN DISEASES

This group of disorders includes polymyositis, dermatomyositis, systemic lupus erythematosus and polyarteritis nodosa. These conditions may be associated with muscle weakness and fatigability which responds to neostigmine. This has been termed a myasthenic state (Rees and Harman, 1954; Bonduelle, Bouygues and Coulon, 1955).

Potts and Thornton (1961) have described a patient suffering from polyarteritis nodosa, who developed a prolonged apnoea after the administration of suxamethonium. This was ascribed to a low level of serum cholinesterase which is a recognized feature of disturbed liver function. Liver involvement, which may be unrecognized, is a not uncommon finding in these disorders.

The possibility that the clinical response to muscle relaxants may be altered in the presence of either the myasthenic state or disturbed liver function necessitates great caution in the use of these drugs.

PORPHYRIA

This is an uncommon familial defect of metabolism in which there may be widespread demyelination in the nervous system. Acute attacks, which may present as an acute abdominal emergency or with severe circulatory disturbances, may be precipitated by thiopentone. The selection of anaesthesia for these patients has been discussed by Norris and McNab (1960); although d-tubocurarine has been used to relieve the abdominal cramps associated with porphyria, suxamethonium is considered to be the drug of choice when muscular relaxation is required.

FAMILIAL PERIODIC PARALYSIS

This is a rare disorder in which episodes of muscular weakness are associated with a low level of serum potassium. Owing to the increased sensitivity of the myoneural junction to d-tubocurarine under these conditions, the antidepolarizing relaxants should be used with caution. The serum potassium level can be corrected pre-operatively with oral potassium chloride, 2 grams 6-hourly in fruit drinks providing 100 milli-equivalents per day.

CONCLUSION

In certain disorders in which muscle weakness is a prominent feature, there may be an abnormal response to the muscle relaxants. These drugs should be avoided or used with caution in such cases.

Ultimately the anaesthetic management of these patients must depend upon the experience of the anaesthetist coupled with a critical pre-operative assessment of the functional disability that is present.

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