INHERITED MUSCLE DISEASE

F. R. ELLIS

The inherited diseases of muscle form a reasonably well-circumscribed group of conditions which carry an increased risk with anaesthesia as a result of both the primary muscle involvement and secondary effects, such as skeletal deformities and heart muscle disease. These diseases can be considered under four separate headings: the muscular dystrophies, the myotonias, glycogen storage diseases and the myopathies.

THE MUSCULAR DYSTROPHIES

A logical classification of the muscular dystrophies suggested by Emery and Walton (1967) is based on the mode of inheritance:

- **X-linked**
  - (a) severe (Duchenne),
  - (b) mild (Becker).

- **Autosomal recessive**
  - (a) severe,
  - (b) mild limb girdle (i) with facial involvement, (ii) without facial involvement.

- **Autosomal dominant**
  - (a) facio-scapulo-humeral,
  - (b) distal,
  - (c) ocular,
  - (d) oculopharyngeal.

**Severe muscular dystrophy**

Although Duchenne in his original report included two girls, the X-linked recessive type of severe muscular dystrophy is named after him. Apart from the sex difference, the autosomal and the X-linked varieties of severe muscular dystrophy are similar in presentation and outcome. The disease presents in the early years of childhood in the muscles of the pelvic girdle and thighs, and the consequent weakness results in an inability to extend the trunk or the pelvis. Affected children characteristically use their arms to “climb” up their own legs when rising from the floor; this is known as Gower's sign. The disease progresses unremittingly to involve the shoulder girdle, causing winging of the scapulae, and the calves which are often found to be prominent as a result of fatty replacement of muscle tissue—the so-called pseudohypertrophy of the infant Hercules.

In the final stages the patient becomes inactive as a result of generalized muscle weakness and becomes a wheelchair invalid before death from restrictive respiratory failure, aspiration pneumonitis or from heart involvement. The age of death varies from 10 to 20 yr.

Quite early in the disease most patients develop an obstructive cardiomyopathy which can be detected on the e.c.g. and by right heart enlargement on chest x-ray. The characteristics of the e.c.g. include a large R wave in lead V1 and deep Q waves in V4–6. Inversion of the T waves in the V leads is common and there may be widening of the QRS complex with shortening of the PR interval. The standard leads often show R axis deviation. The right ventricular outflow obstruction predisposes to heart failure, a feature which can easily be overlooked because of the patient’s inanition. A demonstration of the covert heart failure is a sustained increase of central venous pressure after an acute i.v. fluid load.

The diagnosis of severe muscular dystrophy can be confirmed by a greatly increased resting c.p.k. which correlates well with the progressive breakdown of muscle. C.p.k. and its isoenzymes have been used to detect the carrier state in females in families with the X-linked type.

Anaesthetic considerations

Rapid and permanent deterioration can occur with bed rest and with febrile illness, making early ambulation imperative. In the later stages of the disease respiratory weakness, which may not be recognized initially because of inactivity before operation, may result in a restrictive respiratory failure. The consequences of the weakness of the respiratory muscles and the associated weak cough predispose to sputum retention which requires active intervention to avoid the inevitable downward trend.
A sudden tachycardia may develop during surgery, which heralds failure of the heart muscle.

Difficulty in swallowing may lead to aspiration pneumonitis in the period after operation.

In a proportion of children hyperpyrexia after operation is found, but this does not develop into malignant hyperpyrexia and is amenable to simple measures, such as surface cooling.

Hyperkalaemia may result from the rapid breakdown of muscle, hence suxamethonium and other depolarizing neuromuscular blocking drugs are inadvisable.

Other muscular dystrophies

There are several forms of muscular dystrophy which run a chronic course and do not significantly endanger or shorten life. The clinical manifestations are variable and it is often difficult to give a precise diagnosis because of overlap between them. For anaesthetists the naming of many of these conditions is largely academic as most do not involve the muscles of respiration or swallowing, and heart disease is rarely a feature.

**Mild limb girdle dystrophy** is an autosomal recessive condition, which affects the proximal muscles of the shoulder girdle and presents in early adult life. In the past there has been some confusion between this condition, chronic spinal muscular atrophy and polymyositis. Some patients have facial involvement and this is thought to be genetically determined.

**Becker's muscular dystrophy** is similar to Duchenne dystrophy, but milder. It may be confused with limb girdle dystrophy although hypertrophy of calf muscles can be obvious. Patients usually survive into middle life and there is frequently cardiac involvement similar to Duchenne dystrophy.

**Dominant fascio-scapulo-humeral dystrophy** has an onset in adolescence and the first symptoms are facial and shoulder muscle weakness. Later, muscles of the hips and legs are involved.

**Distal muscular dystrophy** is a late onset disease with presenting features associated with atrophy of the small muscles of the hands and feet. The muscles of the lower arms and legs become involved eventually.

**Ocular muscular dystrophy** presents with bilateral ptosis and weakness of the orbicularis muscle in middle-aged subjects. The inheritance is dominant. Sporadic cases may be confused with myasthenia gravis which also often presents with similar eye symptoms. In one form of the disease the pharyngeal muscles are involved, causing dysphagia.

**Anaesthetic considerations** for these conditions depend on the severity of the muscle weakness and on pharyngeal and cardiac involvement.

**THE MYOTONIAS**

**Dystrophia myotonica**

This is the most serious of the myotonic dystrophies and is inherited as an autosomal dominant characteristic. The onset is in early adult life and the disease is slowly progressive, terminating in death in middle age. It is characterized by mild myotonia, especially in cold weather and with a progressive muscular atrophy affecting initially the muscles of the face, neck, pharynx and distal limbs. The myotonia is not as severe as that seen in myotonia congenita and is not greatly incapacitating, whereas the atrophy is slowly progressive and causes severe muscle weakness in the terminal stages of the disease. The atrophy of facial muscles gives the patient a typical “myopathic” facies with ptosis, and the atrophy of the sternocleidomastoid muscle is responsible for the so-called “swan-neck” appearance.

Dystrophia myotonica involves several systems and the typical appearance of the patient is caused by the facial muscle atrophy, frontal baldness and cataracts. Testicular atrophy results in infertility. These signs are so characteristic that the diagnosis is usually not in doubt.

One of the major problems for patients with this condition is the associated heart disease. In the later stages conduction defects are commonly found and patients often die of heart failure. The electrocardiogram shows a prolonged PR interval and this may be associated with heart block. Sometimes the P wave is reduced in amplitude and there is ST elevation. Cardiac arrhythmias are common and include flutter, bradycardia and extrasystoles which are usually of ventricular origin.

The respiratory reserve is reduced, and in the more severely affected there may be a restrictive respiratory failure as a result of involvement of the respiratory muscles including the diaphragm. Respiration may be further compromised by aspiration of gastric contents, which itself may be a consequence of an abnormal swallowing mechanism resulting from involvement of the pharyngeal muscles in the disease process.

It has been suggested that patients with dystrophia myotonica have a central nervous system component and an abnormal degree of somnolence has been found.
Dystrophia myotonica can be recognized in young children and neonates, particularly if one parent is known to have the disease. In infants it may be detected as a floppy baby with delay in milestones or localized weakness with secondary skeletal abnormalities such as scoliosis. The typical myopathic facies may also be an early sign. Mental subnormality is not infrequent. Diagnosis of dystrophia myotonica can be greatly facilitated by demonstrating the spontaneous high amplitude potentials on the e.m.g. The gradual reduction in these bursts of activity produces the so-called “dive bomber” sounds when the e.m.g. is played through an audio system.

The generalized nature of the disease is evident by the lowering of plasma IgG immunoproteins which occurs as a consequence of increased catabolism.

Anaesthetic considerations

An acute and generalized myotonia has been observed with depolarizing neuromuscular blocking drugs (Paterson, 1962). All depolarizing agents and anticholinesterases should be avoided as all these drugs have been shown invariably to increase muscle tone (Orndahl and Stenberg, 1962).

Respiratory failure is caused by respiratory muscle weakness with decreases in vital capacity and maximum ventilatory volume. Oropharyngeal involvement is commonly seen and the embarrassed swallowing mechanism leads to aspiration and pneumonia.

Heart disease leads to major problems during anaesthesia. Heart block with Stokes–Adams attacks and ventricular extrasystoles with coupling can be observed frequently. Heart failure is common.

Most anaesthetic and relaxant drugs have been stated to be dangerous in patients with dystrophia myotonica. Opiates and other central respiratory depressants seem to have an exaggerated effect and this may be related to the somnolence exhibited by some patients. Body temperature should be maintained to avoid shivering after operation, which can induce generalized myotonia which itself is accentuated in cold muscles.

Myotonia congenita

Myotonia congenita was first described in 1876 by Dr Thomsen, who recognized this disease in himself and other members of his family. The distribution of the disease within his family enabled him to suggest a dominant inheritance. It has been estimated that the frequency of the dominant form of myotonia congenita is $5 \times 10^{-6}$ being one-tenth of the frequency of dystrophia myotonica.

In 1948 Thomasen in Denmark recognized an autosomal recessive form of the disease which affected two siblings of unaffected parents. Becker, in extensive surveys in Germany in 1961 and 1966, found the recessive form to be commoner than the dominant and to be more severe in its clinical manifestations. He found consanguinity was present in 10% of parents of 30 of his patients in which more than one sibling was affected, and was present in eight of 69 families he investigated, that is 12%.

The clinical manifestations, which are often present at birth, are related to a tendency to develop widespread myotonia in response to rest and cold. The myotonia causes a painless stiffness of muscles which is usually relieved by exercise. Sudden movements can induce an “intention myotonia”. One characteristic feature is the marked muscular development. Infants may exhibit a “strangled” cry and have difficulty in feeding.

On microscopic examination there is increased variation in fibre diameter, internal migration of nuclei and hypertrophy in some muscle fibres. Unfortunately, the diagnosis of myotonia congenita is difficult to make because of the features it shares with paramyotonia congenita, hyperkalaemic familial periodic paralysis and, to a much lesser extent, with dystrophia myotonica.

The e.m.g. is characterized by high frequency discharges even without symptoms and this abnormality may show an abrupt onset and termination. As this is also seen in polymyositis, muscular dystrophy, myxoedema and hyperkalaemic periodic paralysis it is not pathognomonic for myotonia congenita.

Anaesthetic considerations

Depolarizing neuromuscular blocking drugs are specifically contraindicated as they will induce myotonia. Similarly, anticholinesterases are ill-advised for the antagonism of non-depolarizing relaxants because of the risk of cholinergic overactivity.

Body temperature should be monitored and hypothermia prevented by appropriate measures. It is worth noting that the hypothermic process in patients often starts before operation in response to premedication, inadequate clothing and starvation. There has been one case report (Saidman, Harvard and Eger, 1964) of malignant hyperpyrexia in a patient with myotonia congenita. Myotonia developing...
in response to direct surgical activation of muscle is difficult to prevent and to treat. It is uninfluenced by non-depolarizing relaxants and cannot be prevented by spinal blockade with local anaesthetics. Quinine and procainamide have been used to control myotonia in ambulant patients and it seems to lessen the abnormalities seen on the e.m.g. It may be that dantrolene could prove to be a useful drug in uncontrolled myotonia caused by direct muscle stimulation.

**Familial periodic paralysis**

Hypokalaemic periodic paralysis was first described in 1882. Sporadic attacks of muscle weakness affect mainly the proximal muscles. The attacks, which usually start in the second decade of life, occur frequently at night, or during a rest period after strenuous exercise, and can be brought on by eating a heavy meal especially if it contains a high proportion of carbohydrate. Other predisposing conditions are mental stress, trauma, infections and cold. An attack may last for 1–2 days, but it may be as short as a few hours. If severe, the muscle weakness results in a flaccid quadriplegia and may even affect breathing, talking and swallowing. There may be e.g. changes characteristic of hypokalaemia and bradycardia, and apical systolic murmurs have been described. Occasionally the attack is so severe as to cause death from respiratory failure, aspiration pneumonia or heart failure.

This disease is inherited as an autosomal dominant characteristic which is fully penetrant in males and incompletely penetrant in females. The disease is less severe in females and eventually the attacks cease. The frequency is approximately $8 \times 10^{-6}$.

It is now known that during an attack there is a positive balance for potassium, with influx of potassium into muscle cells. Patients susceptible to this condition develop a muscle weakness when the serum potassium concentration decreases to 3 mmol, but there is a marked weakness with serum potassium concentrations between 2 and 2.5 mmol. It seems that these patients are unduly sensitive to decreases of potassium, as concentrations which would not cause muscle weakness in normal individuals cause severe weakness. During an attack there is an increased thirst and a reduction in urine output and this is followed, after the attack, by a diuresis.

Various drugs have been shown to predispose to an attack of muscle weakness including insulin and glucose, adrenaline, thyroid and parathyroid hormones, ACTH, glucocorticoids and mineralocorticoids (except aldosterone). The attacks are prevented by spironolactone, diuretics, potassium therapy and a low sodium diet.

During an attack the e.m.g. shows prolongation of action potentials which, if the attack is severe enough, leads to electrical silence.

Several recent papers have described anaesthetic experiences in patients with hypokalaemic periodic paralysis. Horton (1977) reported two patients from one family who were receiving acetazolamide at the time of anaesthesia. The first patient was given droperidol and fentanyl uneventfully on one occasion and during a second anaesthetic was given droperidol, fentanyl, thiopentone, pethidine and nitrous oxide without untoward effects. The second patient had an increased arterial pressure at induction and was anaesthetized with enflurane and nitrous oxide, which produced hypotension. The patient was then given morphine and nitrous oxide. She did not recover consciousness and died of a ruptured cerebral aneurysm. In a review of their families the author reported 21 anaesthetics in eight patients and noted that on three occasions patients who had received muscle relaxants awoke with muscular weakness.

Bashford (1977) described a patient who received thiopentone, nitrous oxide and halothane for a dilatation and curettage with no untoward effects. Three years later she was admitted to hospital during pregnancy when suffering from a prolonged attack of muscle weakness, with a serum potassium concentration of 2.2 mmol. She had a Caesarean section uneventfully with thiopentone and suxamethonium, nitrous oxide, tubocurarine and papaveretum, and antagonism of the relaxant with atropine and neostigmine. It was noted that the body temperature remained constant at 36.8 °C throughout.

Siler and Discavage (1975) described a general anaesthetic in a 44-yr-old man with hypokalaemic periodic paralysis receiving long term acetazolamide and potassium chloride who required an emergency appendicectomy. Anaesthesia was induced with sodium thiopentyl and maintained with halothane, nitrous oxide and a slow infusion of suxamethonium. After operation the serum potassium concentration was 2 mmol and the patient had bilateral numbness and a weakness of his toes which progressed to complete muscle paralysis. Mechanical ventilation was required for 36 h. A second anaesthetic was performed on this patient with a paravertebral block and was uneventful. A third anaesthetic for gastric surgery was performed under spinal anaesthesia...
using amethocaine and a general anaesthetic involving thio- pentone, suxamethonium, enflurane and nitrous oxide. After operation he was satisfactory, yet the next day the patient experienced numbness and weakness of his feet and legs. Serum potassium concentration was found to be 2.6 mmol and potassium chloride was administered, with a rapid recovery.

Mental or physical trauma may lead to an attack of paralysis. Induced hypothermia during anaesthesia can lead to postoperative muscle weakness which can also occur after muscle relaxants. Serum potassium concentration should be carefully monitored and potassium supplements given as required.

Hyperkalaemic periodic paralysis. In 1957 it was recognized that familial periodic paralysis could be caused by hyperkalaemia. The characteristics of the attacks of the muscle weakness are that they are of a shorter duration (less than 1 h) than the hypokalaemic type and that they usually occur in the day and frequently whilst the patient is resting after strenuous exercise. The onset of this condition is frequently in the first decade. The weakness usually starts in the lower back and, if severe, involves the thighs, calves, and eventually the hands and arms. In very severe attacks coughing and swallowing may also be affected and occasionally blurring of vision has been encountered. Patients find that an attack can be aborted by mild exercise, although this can lead to painful lumps developing in the calf muscles. Attacks may be brought on by cold, hunger, infection and anaesthesia.

In some families myotonia is a feature of the disease and this may be a genetically distinct variety. In these patients percussion myotonia can be elicited. The inheritance of hyperkalaemic periodic paralysis is as an autosomal dominant characteristic and there is a high degree of penetrance in both sexes. The frequency of this condition is $2 \times 10^{-6}$.

Occasionally a proximal myopathy can develop with diminished or absent tendon reflexes. During an attack the serum potassium concentration increases to more than 5 mmol, at which concentration the patient experiences weakness. If the serum potassium increases to more than 7 mmol, severe paralysis ensues. During an attack the renal excretion of potassium increases.

The e.m.g. shows high frequency and fibrillation potentials. During an attack the e.c.g. shows evidence of hyperkalaemia and peaking of the T waves often precedes paralysis.

One way of aborting the attack is to reduce the serum potassium concentration by driving it back into the cells with insulin and glucose. Other drugs have been tried, including glucagon, noradrenaline and calcium, but with limited success. The frequency of attacks can be reduced by giving the patient a high-sodium, low-potassium and high-carbohydrate diet.

In 1969 Egan and Klein described their anaesthetic experiences in three patients with this condition. Two patients developed postoperative paralysis for several hours. A prolonged period of starvation before anaesthesia may exacerbate the condition and induce an attack of paralysis. The deleterious effects of starvation can be avoided by giving the patient carbohydrate in the form of a dextrose drip. Other infusates should be potassium-free but contain sodium as the major cation.

Normokalaemic periodic paralysis may produce attacks of weakness and paralysis which last from 1 day to several weeks. The attacks are induced by stress, exertion and cold, and as with hypokalaemic periodic paralysis they occur early in the morning. The importance of this condition is that there may be cardiac involvement and arrhythmias are common. Miller and Katz (1973) suggest the use of large doses of sodium to correct both the paralysis and the cardiac arrhythmias and wonder whether procainamide or i.v. lignocaine would be helpful in countering the arrhythmias, as they are known to be suppressed by the use of quinidine.

Paramyotonia congenita
This condition bears some resemblance to both hyperkalaemic periodic paralysis and myotonia congenita, there being some overlap between these three conditions. The inheritance of paramyotonia is by a single autosomal dominant gene. The characteristics of this condition are myotonia and weakness which develop in response to cold. The condition frequently develops in childhood and affects mostly those muscles exposed to cold environmental temperatures such as muscles of the face and neck. Transient dysarthria or dysphagia can occur on eating ice cream. Weakness can be generalized or it may be localized to cold muscles and may persist for several days.

One characteristic feature of this condition which differs from hyperkalaemic periodic paralysis is that the muscle weakness is not improved by exercise. It is often possible to demonstrate percussion myotonia in the tongue and in the muscles of the thenar eminence.
Anaesthetic considerations

Hypothermia or even localized cooling must be avoided otherwise myotonia and muscle weakness may develop. Muscle relaxants, especially of the depolarizing variety, should be avoided in view of the danger of producing a generalized myotonic spasm.

GLYCOGEN STORAGE DISEASES

Glycogen is a high molecular weight branched polysaccharide which is formed from glucose (fig. 1). The main stores are contained in liver and both skeletal and cardiac muscle. Glycogen storage disease results from either a deficiency of one of the enzymes responsible for the breakdown of glycogen, such as phosphorylase, phosphoglucomutase or glucose-6-phosphatase, or a deficiency of one of the enzymes responsible for the branching of glycogen, such as amylo-1,6-glucosidase (debranching enzyme) or amylo-1,4- or -1,6-transglucosidase (branching enzyme).

The symptoms and signs presenting in this group of diseases depend on the target organ. Thus, if the liver is the main site of the enzyme deficiency, hepatomegaly and liver failure will result, whereas if the heart is primarily affected cardiac enlargement and heart failure will occur.

In several of these diseases skeletal muscle is involved, producing muscle weakness, pain on exertion and sometimes myoglobinuria as a result of the breakdown of the most severely affected muscle fibres.

The Cori classification of the glycogen storage diseases is shown in table I; the two most commonly encountered glycogen diseases which affect skeletal muscle are dealt with at greater length. In Cori type III disease the skeletal muscle is affected, producing hypotonia and muscle weakness. In Cori type VII disease the myopathy is mild, but marked contracture of the calves have been described. In Cori type VIII (phosphofructokinase deficiency) the clinical picture is very similar to that of McArdle's disease.

There seems to be a dearth of papers describing any anaesthetic experiences in the glycogen storage diseases.

<table>
<thead>
<tr>
<th>Type</th>
<th>Enzyme deficiency</th>
<th>Organs affected</th>
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<tbody>
<tr>
<td>Cori I (von Gierke's)</td>
<td>Glucose-6-phosphatase</td>
<td>Liver and kidneys</td>
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<tr>
<td>Cori II (Pompe's)</td>
<td>α-1, 4-glucosidase</td>
<td>Skeletal and cardiac muscle</td>
</tr>
<tr>
<td>Cori III (Cori's, Forbe's)</td>
<td>Amylo-1,6-glucosidase (debranching enzyme)</td>
<td>Liver, skeletal and cardiac muscle and blood cells</td>
</tr>
<tr>
<td>Cori IV (Andersens's)</td>
<td>Amylo-1,4→1,6-transglucosidase (branching enzyme)</td>
<td>Liver, skeletal and cardiac muscle and blood cells</td>
</tr>
<tr>
<td>Cori V (McArdle's)</td>
<td>Muscle phosphorylase</td>
<td>Muscle</td>
</tr>
<tr>
<td>Cori VI (Hers')</td>
<td>Liver phosphorylase</td>
<td>Liver and white blood cells</td>
</tr>
<tr>
<td>Cori VII (Thompson)</td>
<td>Phosphoglucomutase</td>
<td>Muscle</td>
</tr>
<tr>
<td>Cori VIII (Tarin)</td>
<td>Muscle phosphofructokinase</td>
<td>Muscle and red blood cells</td>
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diseases. The one paper devoted to this topic, by Cox (1968), describes anaesthetic experiences in type I glycogen storage (Von Gierke's) disease on many occasions.

On histology the fine aggregates of glycogen accumulate in the centre of the fibre, displacing the myofibrils to the periphery. This results in a complete disorganization of the muscle fibre and the most severely affected degenerate. The glycogen content may increase to 12% of the total weight of the muscle tissue.

In a child with Pompe's disease (Cori type II), anaesthetized for a motor-point muscle biopsy investigation, the author induced anaesthesia with nitrous oxide and a small percentage of halothane. After a couple of minutes a cardiac arrest occurred which was unresponsive to treatment. It was only after postmortem examination that it was realized that the child had Pompe's disease.

**McArdle's disease**

In 1951 McArdle described this condition which is characterized by muscle pain, weakness and stiffness during exercise. The onset is usually in childhood and there is diminished activity associated with muscle cramping with exercise followed by weakness. With further exercise the affected muscles may develop contractures which can only be relieved by rest. In milder degrees of exercise the muscle symptoms may regress and this has been referred to as "second wind".

McArdle's disease is a rare metabolic myopathy. The condition is inherited as an autosomal recessive and is progressive, with the development of muscle atrophy which usually occurs in the 5th decade.

Myoglobinuria can occur and it is thought that the myoglobin is released from damaged or destroyed muscle cells because of the accumulation of some metabolite as a consequence of the muscle activity exceeding the nutritional supply. The development of muscle contracture in response to severe exercise reduces blood supply to the affected muscles which become hypoxic, thus aggravating the basic metabolic defect. It has been suggested that the muscle contracture may be a result of the inability of the sarcoplasmic reticulum to reaccumulate calcium ions so that relaxation cannot be initiated.

The absence of muscle phosphorylase seems to be restricted to skeletal muscle, although one case has been described with abnormal electrocardiographic findings (Ratinov, Baker and Swaiman, 1965). In 1959 Schmit and Mahler described the chronic progressive myopathy of McArdle's disease and demonstrated that there was a glycolgenolytic defect in the muscle. In the same year Schmit, Robins and Traut investigated a patient with McArdle's disease in whom they found a greatly reduced phosphorylase activity down to 0.5% of normal and also a deficiency in the enzyme which synthesizes glycogen from glucose-1,6-phosphate via the uridine diphosphate glucose pathway.

The histology of muscle usually demonstrates an increased muscle glycogen to 2–5% of the tissue weight, although in some cases it is found to be normal or even less than normal. The most specific feature is the demonstration of a greatly reduced muscle phosphorylase on neurohistochemical staining. Later in the disease muscle atrophy is found with degeneration of some fibres.

The diagnosis of McArdle's disease can be made by measuring the venous lactate and pyruvate concentrations with ischaemic exercise. In normal individuals the lactate and pyruvate concentrations increase, whereas in McArdle's disease there is a decrease as the muscle uses the lactate and pyruvate for metabolism because of its inability to break down glycogen. Patients with McArdle's disease have an ischaemic exercise tolerance of 10–20% of normal. Another characteristic feature of this condition is the rapid decrement of evoked muscle response using electromyography with a supramaximal stimulation of a peripheral nerve. The reduction in electrical activity of these active muscles can lead to electrical silence, even in the presence of an observable muscle contracture (Dyken, Smith and Peake, 1967).

**Phosphofructokinase deficiency (Cori type VIII)** is a rare glycogen storage disease affecting the muscle and also red blood cells and produces a clinical picture very similar to that of McArdle's disease in which there is pain, stiffness and muscle weakness on exercise. Myoglobinuria has also been described following exercise. The inheritance of this condition is autosomal recessive and it has been shown that both parents of an affected child also have low phosphofructokinase activity in their muscle.

**Anaesthetic considerations**

Suxamethonium, by virtue of its muscle-activating properties, can result in myoglobin release causing myoglobinuria.

The use of tourniquets is contraindicated as the ischaemia may lead to muscle atrophy.
If myoglobinuria is present renal failure can be avoided by producing a forced diuresis by giving mannitol after a fluid load.

Excessive heat loss should be avoided as this would lead to shivering, especially in the period after operation, with consequent muscle damage. Also, pyrexia should be avoided as these patients do not respond well to a hypermetabolic state.

It is recommended that dextrose, fructose or lactate should be infused throughout surgery as these substances can all be used as energy sources.

INHERITED MYOPATHIES

Most of the conditions mentioned in this section are more usually known as “congenital” myopathies, although there is a clear genetic component in all of them with an autosomal pattern of inheritance.

Congenital myopathy. This condition may be either rapidly progressive or slowly progressive, both being recessively inherited. In the rapidly progressive type children are born with weakness, hypotonia and even contractures. In the slowly progressive type the child is hypotonic or floppy and may have secondary changes such as dislocation of the hips. It is sometimes difficult to distinguish a baby hypotonic as a result of muscle disease from one with subnormality.

Central core disease is a slowly progressive myopathy in which a histological defect is found. The defect is characterized by areas of rarefaction in the muscle cytoplasm and it is presumed these areas, which probably extend throughout the length of the muscle, are non-functional. One interesting feature of this condition is that it is sometimes found in association with malignant hyperpyrexia. Denborough (1973) believes the two conditions to be directly related, whereas in our experience central cores are infrequently found in malignant hyperpyrexia myopathy.

Nemaline myopathy is another histologically diagnosed condition, in which rod-shaped bundles are seen. The clinical picture may resemble Marfans syndrome with high arched palate and prognathous jaw as well as muscle weakness or hypotonia. Other skeletal abnormalities, including kyphoscoliosis, pigeon chest and pes cavus, are sometimes found. The skeletal abnormalities may reduce vital capacity, and heart failure in childhood has been described.

Myotubular myopathy is a very rare dominant condition in which muscle weakness and delay in motor milestones is associated with retention of the myotubules characteristic of fetal muscle with centrally placed nuclei. The disease progresses to produce kyphoscoliosis, ptosis and ophthalmoplegia.

Paroxysmal myoglobinuria occurs in some subjects in response to unaccustomed exercise which causes muscle breakdown with liberation of myoglobin. Repeated attacks can lead to muscle atrophy and weakness.

Anaesthetic considerations

Little is known of the way patients with the inherited myopathies respond to anaesthesia. Respiration may be embarrassed by skeletal deformity or weakness. It would seem sensible to avoid suxamethonium and similar drugs and to avoid changes of body temperature.

Malignant hyperpyrexia myopathy

Malignant hyperpyrexia myopathy (Harriman, Sumner and Ellis, 1973) is a term used to describe the abnormal pathological features found in the muscles of many patients susceptible to malignant hyperpyrexia (MHS). Unfortunately, the pathological features of MH myopathy are inconstant and great variation is found between siblings and between parents and children. The degree of morphological muscle abnormality does not in itself correlate with the severity of the MH reaction encountered and we have investigated one family in which a death occurred from MH without any abnormal muscle pathology being found in other susceptible members.

In our Investigation Unit we use two terms to describe susceptible patients. Malignant hyperpyrexia myopathy denotes susceptibility and a definite pathological abnormality, and in malignant hyperpyrexia susceptibility no pathological abnormality is found.

Pathological features

The pathological abnormalities which are commonly found in muscle include internal migration of nuclei, variation in fibre size, hypertrophy of some fibres and moth-eaten appearance of fibres stained for NADH and muscle phosphorylase. Other defects include fibre splitting, angular fibres, atrophy of one or other fibre type, degeneration and regeneration, mitochondrial swelling, central cores and targetoid fibres.

As mentioned previously, central cores which are found infrequently in our patients have been described as a consistent feature of MH myopathy.
Some of the commonly found abnormalities are seen in myotonia congenita, such as hypertrophy and internal migration of nuclei, and it is possible that there may be some overlap between these three conditions.

**Clinical features and diagnostic criteria**

Hyperpyrexia is a constant finding in most cases of human MH. The increase in body core temperature is progressive and often fulminating in the continued presence of the trigger drugs. Although the greatest temperature reached has an important bearing on the prognosis, it is the rate of increase which should alert to the presence of the condition. From published case reports, an increase of body temperature of 6 °C per hour is common, although the skin temperature may decrease, especially in the early stages of the disease.

*Muscle contracture* (rigidity, spasm) is found in most patients. It may occur after the administration of suxamethonium, although a normal response to this drug is often seen with muscle contracture developing in response to halothane or one of the other inhalation anaesthetic vapours. In a minority of patients muscle contracture either does not develop or develops at a late stage of the disease or even during recovery.

*Myoglobinuria* should be looked for in all suspected cases in the period immediately after operation. It may be so intense as to cause renal failure as a result of tubular obstruction. It is often possible to avoid renal failure by maintaining an increased urine output.

*Hyperkalaemia* is an almost invariable finding and presumably related to the muscle defect. Its presence can be detected by observing the characteristic changes on the e.c.g.

*Acidosis* is also an invariable finding and is caused by a rapid increase in carbon dioxide production and a marked lacticacidemia.

*Cyanosis* and *tachycardia* are both frequent presenting signs, and occasionally increased oozing from wounds is seen as a result of a consumptive coagulopathy.

As anaesthetists become more aware of MH, there are increasing numbers of patients in whom a provisional diagnosis has been made before the syndrome fully develops. There are many causes of operative pyrexia, and muscle contracture with suxamethonium may indicate the presence of a myotonic muscle disease. When a provisional diagnosis of MH is made it is essential to confirm the diagnosis otherwise all members of the patient's family will have to be warned of the possible risks of anaesthesia.

**Screening procedures**

Patients with a history suggestive of MH and members of known MH families should be investigated to detect the presence of the MHS phenotype. The importance of the family studies lies in the fact that less than 5% of members of MH families will have inherited the abnormality and it can be argued that it is largely for the benefit of the 95% normal members that the tests should be performed.

Blood tests such as c.p.k. estimations have been proved to be too fallible for any reliance to be placed on them (Ellis et al., 1975). The only satisfactory methods are those involving muscle biopsy.

*The caffeine contracture test* was the first method used to identify susceptibility to MH and was developed in Toronto by Kalow and Britt (Kalow et al., 1970). All human muscle develops contracture in the presence of a sufficient concentration of caffeine, but MHS muscle is especially sensitive. At 37 °C, MHS muscle develops a significant contracture with caffeine 4 mmol, whereas normal muscle is usually unaffected. Problems may be encountered in the interpretation of results because of population overlap, and false negatives may result from poor muscle viability in vitro.

*The halothane contracture test* was first used in Leeds by Ellis and others (1971). At 37 °C MHS muscle develops a marked contracture in the presence of halothane, diethyl ether, chloroform, methoxyflurane, enflurane and trichloroethylene, whereas normal muscle is unaffected. It has been claimed by Denborough (1973) that, occasionally, normal human muscle can develop a small halothane-induced contracture and that this could lead to a false positive diagnosis. Details of the halothane contracture test are described by Ellis and others (1978). One of the major advantages claimed for this test is the lack of population overlap as a result of the idiosyncratic nature of the halothane-induced contracture in MHS muscle.

*The halothane/caffeine contracture test* results correlate very well with the halothane contracture test and may offer little advantage over it as a screening procedure.

Other muscle contracture tests are used, including the potassium chloride and suxamethonium contracture test (Moulds and Denborough, 1974) and the suxamethonium/caffeine contracture test (Halsall and
Ellis, 1979). The depletion of ATP in halothane-treated muscle occurs more rapidly in MHS muscle than in normal muscle and this can be used as a screening procedure (Harrison et al., 1969).

Most investigators perform a battery of tests rather than place complete reliance on one, although in our laboratory the halothane contracture test gives the most consistent results.

Treatment of MH crisis

The treatment can be considered under two headings: specific treatment and symptomatic treatment.

Specific treatment. The first drug thought to have specific properties in the treatment of MH was procaine. To be effective, a large dose was recommended and this proved to be so cardiodepressant that positive inotropic agents were required.

High-dose glucocorticoids have been successfully used on many occasions, and a direct effect of these drugs has been shown to occur by the suppression of the halothane-induced contracture by methylprednisolone in vitro (Ellis et al., 1974).

The recent introduction of dantrolene sodium may revolutionize the treatment of MH if the early claims for this drug can be substantiated in humans (Harrison, 1975). It can easily be demonstrated that dantrolene will reverse the halothane-induced contracture of MH muscle in vitro. In vivo, it has been shown that the increased carbon dioxide production is rapidly controlled by dantrolene (Liebenschutz, Mai and Pickerd, 1979).

Symptomatic treatment. For a successful outcome it is usually necessary to treat the metabolic derangements aggressively and to cool the patient. Hyperkalaemia, hypoxia and acidosis all require effective and rapid reversal. After the initial treatment it may be necessary to correct hypokalaemia and to treat renal failure. Patients may remain comatose for hours or even days and, even in the latter event, full recovery is often seen.

Because of the rarity of MH, most anaesthetists should have access to a programme for its treatment. Several of these have been published and the following regime is offered only as a guide which can be adapted to particular circumstances:

1. Terminate surgery if possible, but in any event
2. Discontinue all potent inhalation agents and depolarizing relaxants.
3. Give 100% oxygen, preferably from an anaesthetic machine without a vaporizer.
4. Monitor body core temperature (and limb skin if possible).
5. Insert i.v. cannula and take venous blood sample for potassium but retain serum in laboratory for further investigations. Start infusion of glucose in water.
6. Take arterial blood sample for pH, PCO₂ base excess and PO₂.
7. Establish e.c.g.
8. Correct electrolyte and pH imbalance on the basis of the results; repeat estimations may be needed. (Hyperkalaemia may be controlled with dextrose 50 g with insulin 20 units.)
9. Steroid therapy: dexamethasone 1.5–2 mg kg⁻¹ or methylprednisolone 7.5–10 mg kg⁻¹ or hydrocortisone 30–40 mg kg⁻¹.
10. Repeat in 15 min if no effect on rate of increase of body core temperature.
11. Dantrolene 100 mg i.v.
12. Give cool 5% dextrose 10–20 ml kg⁻¹ h⁻¹ i.v. (preferably from refrigerator or using a blood warmer” filled with iced water). Remove all covering from patient, apply ice to groins and axillae or use fans in conjunction with tepid- or cold-water sponging using a wetting agent such as cetrimide if possible, cold water blankets, etc.
13. Consider the following:
   (a) Procedures:
      (i) Catheterization (save first sample of urine for detection of myoglobin).
      (ii) Control of cerebral oedema and renal failure with mannitol 1 g kg⁻¹.
   (b) Drugs:
      (i) Diazepam 1 mg kg⁻¹.
      (ii) Droperidol 0.1 mg kg⁻¹ as alpha-adrenergic blocker.
      (iii) Practolol 0.1 mg kg⁻¹ to control arrhythmias.
      (iv) Isoprenaline 2 mg in 500 ml to increase cardiac output.

Anaesthesia for known MHS patients

General anaesthesia. As the minimum dose of halothane and other vapours which induce MH is not known, it is recommended that all vaporizers should be removed from the anaesthetic machine and that new rubber or plastic hoses, bags and connections be used.

Atropine should be avoided in premedication, but diazepam and neuroleptic drugs have proved to be reliable and safe. Thiopentone or Althesin are safe...
as induction agents and may be preceded by fentanyl. We use 50% nitrous oxide and if relaxation is required, pancuronium is the drug of choice, but reversal of the relaxant with anticholinesterases is not recommended, to avoid cholinergic overactivity.

Local anaesthesia. It is probably wise to avoid adrenaline in local anaesthetic solutions. Lignocaine should be avoided as it is known to activate muscle. Procaine and the other ester-linkage local anaesthetics have been recommended, although in our experience bupivacaine has proved also to be safe.

For dental extraction prilocaine has been used regularly in MHS patients and has been uneventful. There may be a place for pretreatment of MHS patients with dantrolene although it is now possible to anaesthetize all susceptibles for any type of surgery using drugs known to be safe.

Future developments
Malignant hyperpyrexia is an eminently treatable condition. Early diagnosis is essential for a successful outcome, but this depends on monitoring body temperature during all anaesthetics in which trigger agents are being used if the time of exposure is greater than 15 min. At present, as a result of anaesthetists’ greater awareness of MH, there are an increasing number of provisional diagnoses of MH made and those patients require further investigation by muscle biopsy to prove the diagnosis, followed by family studies if appropriate. As MH is a rare disorder it is hoped that, with an aggressive screening programme, the vast majority of potential cases will be screened out of the anaesthetized population.

REFERENCES


