The muscular dystrophies

Alan E H Emery

The muscular dystrophies are inherited myogenic disorders characterised by progressive muscle wasting and weakness of variable distribution and severity. They can be subdivided into several groups, including congenital forms, in accordance with the distribution of predominant muscle weakness: Duchenne and Becker; Emery-Dreifuss; distal; facioscapulohumeral; oculopharyngeal; and limb-girdle which is the most heterogeneous group. In several dystrophies the heart can be seriously affected, sometimes in the absence of clinically significant weakness. The genes and their protein products that cause most of these disorders have now been identified. This information is essential to establish an accurate diagnosis and for reliable genetic counselling and prenatal diagnosis. There is, as yet, no way of greatly affecting the long-term course of any of these diseases. However, advances in gene manipulation and stem-cell therapy suggest cautious optimism for finding an effective treatment in the not-too-distant future.

The commonest form of these inherited disorders—Duchenne muscular dystrophy—was originally described by Edward Meryon, an English doctor. At a meeting of the Royal Medical and Chirurgical Society in 1851,1 and later published in the transactions of the society,2 he described in detail the clinical presentation of this disorder, beginning in early childhood with progressive muscle wasting and weakness and leading to death in late adolescence. He showed that the disease was familial and only affected boys; most importantly, he demonstrated that the spinal cord at necropsy was normal. Therefore, this was a disease of muscle (myogenic) and was not secondary to anterior-horn cell degeneration. Furthermore, his detailed histological studies led him to conclude that the muscle membrane or sarcolemma was broken down and destroyed. This observation was singularly important, because we now know that the primary defect resides in the sarcolemma. However, Meryon’s observations were neglected for many years for various reasons,3 and the disorder became eponymously associated with Duchenne in Paris, who detailed the clinical and muscle histology some years later.4,5

Over the following years, investigators gradually realised that, although Duchenne muscular dystrophy was by far the commonest and one of the most serious forms of the disease, muscular dystrophy was in fact a group of inherited disorders, all characterised by variable degrees and distribution of muscle wasting and weakness.

Clinically defined types of muscular dystrophy

On the basis of distribution of predominant muscle weakness, six major forms can be delineated (figure 1), with the addition of congenital dystrophy, in which muscle weakness is more generalised (panel 1).

Congenital muscular dystrophy

Children with this heterogeneous group of autosomal recessively inherited disorders present with hypotonia and weakness at birth or within the first few months of life. Several different forms have been recognised, some with and some without significant mental retardation.6 Two forms without mental deficiency are caused by an absence of merosin (laminin α2, a muscle extracellular protein)7 or very occasionally integrin α7.8 Deficiency of merosin can be shown by western-blot analysis or muscle immunohistochemistry, and also with chorionic villus material for prenatal diagnosis.9 Although children with merosin-deficient congenital muscular dystrophy are not mentally retarded, magnetic resonance imaging of the brain invariably shows white-matter changes. Most affected children might eventually be able to stand with some support, but few learn to walk. Muscle weakness is usually non-progressive, but many joint contractures develop with immobility. Although cardiac function is normal, the long-term outlook is not good because many patients develop serious feeding and respiratory problems.

The incidence of Fukuyama congenital muscular dystrophy in Japan is second only to Duchenne muscular dystrophy, but is rare elsewhere. This disorder is named after Yukio Fukuyama from Tokyo, who first described the condition in 1960.10 Onset is in infancy with hypotonia and muscle weakness. Affected children are rarely able to walk. Most are mentally retarded and many have epilepsy. The protein product of the responsible gene has been named fukutin,11 but its function is not clear. Of the rarer variants of congenital muscular dystrophy, the responsible genes and their gene products have only been identified for rigid spine syndrome and muscle-eye-brain disease.

Duchenne and Becker muscular dystrophy

The clinical features of these X-linked disorders have been described in detail.12 In Duchenne muscular dystrophy, onset is in early childhood, with difficulties in running and, later, climbing stairs. Weakness of the knee and hip extensors results in Gower’s manoeuvre: a child climbs up his thighs, pushing down on them, to extend the hips and trunk. Some degree of mental impairment is usual, about 20% of affected boys have an IQ of less than 70. Most patients have enlarged calves, hence a previous term for the disorder was pseudohypertrophic muscular dystrophy; however, calf hypertrophy not only is seen in Duchenne muscular dystrophy but also is present in other dystrophies, such as Becker dystrophy. Weakness is mainly proximal and...
Loss of ambulation also varies from adolescence onwards, with death usually in the fourth or fifth decade. A proportion of cases, as in Duchenne muscular dystrophy, have some degree of mental impairment.

In both Duchenne and Becker muscular dystrophies, about 5–10% of female carriers show some degree of muscle weakness, and frequently have enlarged calves—so-called manifesting carriers. Such weakness is often asymmetric, and it can develop in childhood or not become evident until adult life, and could be slowly progressive or remain static. Because weakness is essentially proximal, differentiation from limb-girdle muscular dystrophy is essential for genetic counselling. Most importantly, female carriers might develop dilated cardiomyopathy, which can arise even without apparent weakness.

The Duchenne gene is located at Xp21,17,18 which affects the sarcosomal protein dystrophin,19 and is allelic with Becker muscular dystrophy. Dystrophin is usually absent in patients with Duchenne muscular dystrophy, but is reduced in amount or abnormal in size in people with Becker muscular dystrophy.20 However, in rare cases of Duchenne muscular dystrophy, dystrophin can be detected, or is occasionally undetectable in mild cases of this disorder.21

Emery-Dreifuss muscular dystrophy
This disorder is characterised by a triad of manifestations. First, there are early contractures—before there is any clinically significant weakness—of the Achilles tendons, elbows, and posterior cervical muscles, with initial limitation of neck flexion; later, forward flexion of the entire spine becomes restricted. Second, slowly progressive muscle wasting and weakness with a humero-peroneal distribution—ie, proximal in the upper limbs and distal in the lower limbs—happens early in the course of the disease. Later, the proximal limb-girdle musculature becomes affected. Third, cardiomyopathy arises, which usually presents as cardiac conduction defects, ranging from sinus bradycardia, prolongation of PR interval, to complete heart block. Atrial paralysis with absent P waves on electrocardiography should always prompt exclusion of this muscular dystrophy. Cardiac involvement generally becomes evident as muscle weakness progresses. Evidence of cardiac disease is usually present by age 30 years.

The X-linked form of Emery-Dreifuss muscular dystrophy is caused by mutations of the STAC gene at Xq28, which encodes the nuclear membrane protein emerin.24 In almost all cases of this dystrophy, there is complete absence of emerin in muscle. Immunohistochemistry of skin fibroblasts or exfoliative buccal cells shows a mosaic pattern of expression of this protein in

Figure 1: Distribution of predominant muscle weakness in different types of dystrophy
A, Duchenne-type and Becker-type; B, Emery-Dreifuss; C, limb-girdle; D, facioscapulohumeral; E, distal, F, oculopharyngeal. Shaded=affected areas. (Reproduced from BMJ 1998; 317: 991–95 by permission of the BMJ Publishing Group).
female carriers, and thus provides a valuable test for identification of such individuals. The autosomal dominant type of this disorder is clinically very similar to the X-linked forms, but is caused by mutations of the LMNA gene at 1q21. This gene encodes lamin A and C, which make up part of the nuclear lamina—a fibrous layer on the nucleoplasmic side of the inner nuclear membrane. These lamins interact with chromatin and other proteins of the inner nuclear membrane (lamina-associated proteins) and emerin (figure 2). Diagnosis of autosomal dominant Emery–Dreifuss muscular dystrophy can only be verified by mutation analysis, and not by muscle protein studies. There is a rarer more serious autosomal recessive form of this dystrophy, which is also caused by mutations of the LMNA gene.

Emery–Dreifuss muscular dystrophy with serious cardiac manifestations can arise in the absence of any muscle weakness. For this reason, the disorder could contribute to one of the causes of sudden death in apparently healthy young adults.

**Distal muscular dystrophy**

In this muscular dystrophy, weakness is mainly distal. The disorder can be divided into two main groups: late onset (over 40 years of age) with autosomal dominant inheritance, including Welander’s disease; and early onset (less than 30 years of age) with autosomal recessive inheritance. However, apart from one recessive form (Miyoshi type), which is associated with deficiency of the sarcolemmal-associated protein dysferlin, the underlying cause of these dystrophies is unknown. Since variations in fibre size and rimmed vacuoles—rather than dystrophic changes—are seen on muscle histology, these disorders might better be regarded as myopathies rather than dystrophies.

**Facioscapulohumeral muscular dystrophy**

This dystrophy derives its name from the muscle groups that are mainly affected first: facial and shoulder girdle. Later, foot extensors and pelvic-girdle muscles become involved. The heart is not implicated in most cases, though arrhythmias and conduction defects have been described. Mental impairment is not a feature, but retinal vascular disease and hearing loss can arise. This autosomal dominant disorder is associated with subtelomeric deletion of chromosome 4q, with loss of 3·3 kb tandem-repeat units. Loss of ten or fewer repeats causes the disorder, and in general, the lower the number of repeats the more clinically serious the disorder. However the function of the particular gene (or genes) that causes the disorder is not clear.

**Oculopharyngeal muscular dystrophy**

This disorder has mainly been studied in French Canada, where the disease can be traced back to immigrants from France in 1634. However, although most frequent in Canada, the disorder also occurs in other parts of North America and Europe. Onset is around the third decade of life, affecting the extraocular muscles (though frank diplopia is rare), and upper facial muscles with ptosis, and there is weakness of the neck and proximal upper (and even lower) limb musculature. Dysphagia is a serious feature. A frequent presentation is ptosis and dysphagia.

The gene locus (at 14q) codes for the poly-(A)-binding protein; in the first exon there is usually a (GGC) triplet expansion. In affected individuals, this expansion has a further two to seven repeats. The resultant expansion hampers normal transport of mRNA from the nucleus.

**Limb-girdle muscular dystrophy**

In this disorder, weakness affects mainly the proximal limb-girdle musculature. So far, 15 genetically different types have been identified, which show great clinical and genetic heterogeneity. Autosomal dominant forms are very rare and generally less severe than recessive types; they have been reviewed in detail elsewhere. Several of these disorders are associated with clinically significant cardiac involvement (types 1B, 1D, 2C, 2E, and 2F), and affected individuals should therefore be carefully monitored for signs of cardiac disease.

**Laboratory diagnosis**

**Serum creatine kinase**

Measurement of serum concentration of creatine kinase is a simple and inexpensive diagnostic test for severe forms of dystrophy known to be associated with high concentrations. In Duchenne muscular dystrophy, serum creatine kinase values are raised from birth, and testing in neonates for early diagnosis could reduce the possibility of further affected boys in a family. There is still a worrying delay in diagnosis of the disorder in early childhood.

**Electromyography**

This method is important for establishment of the myopathic nature of dystrophy and for exclusion of neurogenic causes of weakness, including peripheral nerve function.

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**Panel 1: Gene loci and protein defects in the commonest forms of muscular dystrophy**

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<thead>
<tr>
<th>Disorder</th>
<th>Gene locus</th>
<th>Protein defect</th>
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<tbody>
<tr>
<td>Congenital (AR)</td>
<td>6q</td>
<td>Lamin α2 (merosin)</td>
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<tr>
<td></td>
<td>12q</td>
<td>Lamin receptor (α7 integrin)</td>
</tr>
<tr>
<td></td>
<td>9q</td>
<td>Fukutin (Fukuyama dystrophy)</td>
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<tr>
<td></td>
<td>1p</td>
<td>Selenoprotein N1 (rigid spine syndrome)</td>
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<td></td>
<td>1p</td>
<td>Glycosyltransferase (muscle-eye-brain disease)</td>
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<tr>
<td>Duchenne and Becker (XR)</td>
<td>Xp21</td>
<td>Dystrophin</td>
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<tr>
<td>Emery-Dreifuss (XR)</td>
<td>Xq28</td>
<td>Emerin</td>
</tr>
<tr>
<td>Distal (AD)</td>
<td>1q</td>
<td>Lamin A/C</td>
</tr>
<tr>
<td>Distal (AR)</td>
<td>14q, 2q</td>
<td></td>
</tr>
<tr>
<td>Facioscapulohumeral (AD)</td>
<td>4q</td>
<td>Dysferlin</td>
</tr>
<tr>
<td>Oculopharyngeal (AD)</td>
<td>14q</td>
<td>Poly(A)-binding protein 2 (PAB 2)</td>
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<tr>
<td>Limb-girdle (AD)</td>
<td>1A</td>
<td>Myotilin</td>
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<tr>
<td></td>
<td>1B</td>
<td>Lamin A/C</td>
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<tr>
<td></td>
<td>1C</td>
<td>Caveolin 3</td>
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<tr>
<td></td>
<td>1D</td>
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<td>1E</td>
<td>7q</td>
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<tr>
<td></td>
<td>1F</td>
<td>2q</td>
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<tr>
<td>Limb-girdle (AR)</td>
<td>2A</td>
<td>Calpain-3</td>
</tr>
<tr>
<td></td>
<td>2B</td>
<td>Dysferlin</td>
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<td></td>
<td>2C</td>
<td>γ-sarcoglycan</td>
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<td></td>
<td>2D</td>
<td>α-sarcoglycan (adhalin)</td>
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<tr>
<td></td>
<td>2E</td>
<td>β-sarcoglycan</td>
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<td></td>
<td>2F</td>
<td>δ-sarcoglycan</td>
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<tr>
<td></td>
<td>2G</td>
<td>Teletomin</td>
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<tr>
<td></td>
<td>2H</td>
<td>9q</td>
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<tr>
<td></td>
<td>2I</td>
<td>19q</td>
</tr>
</tbody>
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Modes of inheritance: AR=autosomal recessive; AD=autosomal dominant; XR=X-linked recessive. ?=unknown.
disorders. Because electromyography is an invasive technique, it is becoming less favoured in the investigation of children, but it still has an important role in diagnosis of adult disease.

Muscle histology

The one unifying feature of the dystrophies is regarded as their muscle histological findings, with variations in fibre size, fibre necrosis, invasion by macrophages, and ultimately, replacement by fat and connective tissue. This picture is seen in the more severe forms of dystrophy, such as Duchenne type. However, in facioscapulohumeral and limb-girdle 2B muscular dystrophy, invasion of tissue by mononuclear cells (so-called inflammatory changes) is often the main feature. These changes—associated with very high serum concentrations of creatine kinase in limb-girdle 2B muscular dystrophy—might lead to confusion with polymyositis. In oculopharyngeal muscular dystrophy, rimmed vacuoles and nuclear inclusion bodies are typical. In distal muscular dystrophies, rimmed vacuoles are also a frequent finding, though, as in mild cases of other dystrophies (such as Emery-Dreifuss muscular dystrophy), the only finding might be increased variation in fibre size.

Immunohistochemistry and mutation analysis

In dystrophies associated with deficiency of a sarcolemmal-associated protein, immunohistochemistry (or western-blot analysis) with labelled antibodies to these proteins are the basis for diagnosis (figure 3). However, there are interactions between these proteins: dystrophin deficiency can be associated with secondary reduction (but not absence) of sarcoglycans; deficiency of a particular sarcoglycan is often associated with secondary reduction of other sarcoglycans; and in dysferlinopathy, secondary reduction of calpain-3 can take place. In cases such as these, and in autosomal dominant disorders (which are believed to be the possible result of a so-called dominant negative effect of the mutation), or in cases for which specific antibodies are not yet available or the protein is not sarcolemmal, then mutation analysis might be the only way to establish a diagnosis. Mutation analysis is also important for genetic counselling and prenatal diagnosis.

Epidemiology

Because X-linked Duchenne muscular dystrophy has been clearly defined for many years, its incidence has been fairly well established. On the basis of some 40 studies including several million male births, incidence at birth of Duchenne muscular dystrophy is around $300/10^6$, and its prevalence in the population (in terms of the total male population) is around $60/10^6$. Epidemiological figures for other dystrophies have, in the past, not been very reliable, but as these disorders become better clinically and genetically defined, reliability is improving. For example, in a careful and detailed study from Sweden, the prevalence in children under the age of 16 years was estimated to be $25\times10^6$ for congenital muscular dystrophy, $8\times10^6$ for limb-girdle muscular dystrophy, $8\times10^6$ for facioscapulohumeral muscular dystrophy, and (only in boys) $16\times10^6$ for Becker muscular dystrophy, but in all cases the confidence limits were wide. These data are useful for comparison of the relative prevalences of different disorders in one population, and agree in broad terms with some recent findings for individual disorders.

Some dystrophies are especially frequent in certain populations but are rare elsewhere: for example, autosomal dominant distal muscular dystrophy in Scandinavia, Fukuyama muscular dystrophy in Japan, oculopharyngeal muscular dystrophy in French Canada,
and several autosomal recessive limb-girdle muscular dystrophies in communities in Brazil, North America, and the Middle East.

Broadening the definition of muscular dystrophy
Recognition of the molecular basis of certain dystrophies has led to further research, which has shown a broadening of the associated phenotype. Most importantly, an association with cardiomyopathy has been recorded for many forms of dystrophy, which in some cases is associated with conduction defects. In several disorders—most notably some cases of Becker and Emery-Dreifuss muscular dystrophy—the associated cardiomyopathy might be the presenting and main feature, rather than muscle weakness. This finding has implications for management (panel 2).

Intrafamilial and interfamilial variation
The accepted idea of one gene—one protein—one disease is, in many monogenic disorders, now proving to be an oversimplification. In the β-thalassaemias for example, the associated phenotypes indicate not only the heterogeneity of mutations in the β-globin gene but also the effects of modifier genes and environmental factors.40 This problem is now clearly evident in the dystrophies. For example, different mutations of the LMNA gene can present not only as Emery-Dreifuss muscular dystrophy but also as dilated cardiomyopathy associated with conduction defects but no muscle involvement,41 limb-girdle 1B muscular dystrophy,42 and even Dunnigan partial lipodystrophy.43 These quite different disorders are therefore allelic. There is as yet no satisfactory explanation for this occurrence, though evidence is emerging that defective assembly of the nuclear lamina could be a shared feature of these disorders.44

However, the same specific mutation of the LMNA gene can result in different phenotypes in the same family: the full syndrome of Emery-Dreifuss muscular dystrophy might be present in one branch of a family, but in another branch affected individuals might only ever develop cardiac problems.45 Families have also been reported in which an identical mutation of the dysferlin gene can result in some family members developing limb-girdle 2B muscular dystrophy whereas others develop a quite distinct (Miyoshi-type) distal muscular dystrophy.46 Identical mutations of the CAV3 gene can cause not only limb-girdle 1C muscular dystrophy but also non-dystrophic disorders of hereditary rippling muscle disease and idiopathic high creatine kinase in blood with no muscle weakness.47 The answer to these, and associated, occurrences might be found in the search for modifier genes,48 possibly retrotransposons,49 by expression profiling,50 by proteomics and protein binding and folding,51 or even the effects of certain infectious agents.52

Pathophysiology
Although much research is focused on future availability of some form of gene therapy, discovery of an effective drug treatment is also possible. However, this finding would depend on a clear understanding of the pathophysiology of these disorders. When dystrophin was discovered to be the protein defect in Duchenne muscular dystrophy, researchers naturally assumed that, since this protein is

<table>
<thead>
<tr>
<th>Disorder</th>
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<tr>
<td>*Limb-girdle 1B muscular dystrophy</td>
<td>Lamin A/C</td>
</tr>
<tr>
<td>*AD Emery-Dreifuss muscular dystrophy</td>
<td>Lamin A/C</td>
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<tr>
<td>*Limb-girdle 1D muscular dystrophy</td>
<td>γ-sarcoglycan</td>
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<tr>
<td>Limb-girdle 2C muscular dystrophy</td>
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<td>a-sarcoglycan</td>
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<td>Limb-girdle 2F muscular dystrophy</td>
<td>Emerin</td>
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<tr>
<td>XR Emery-Dreifuss muscular dystrophy</td>
<td>Dystrophin</td>
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<tr>
<td>XR Duchenne muscular dystrophy</td>
<td>Dystrophin</td>
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<tr>
<td>XR Becker muscular dystrophy</td>
<td>Dystrophin</td>
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*Conduction defects. AD autosomal dominant; XR X-linked recessive; ? unknown.
Deficiency of dystrophin would result in breakdown of muscle membrane. This process would then lead to loss of muscle enzymes, including creatine kinase, and subsequent development of muscle weakness. However, for many reasons, this structural hypothesis is proving an oversimplification. Furthermore, although several forms of dystrophy are associated with deficiencies of various proteins associated with the muscle membrane (figure 4), others—eg, Emery-Dreifuss, oculopharyngeal, and limb-girdle 1A, 1B, 2A, and 2G muscular dystrophies—are not. For example, there is no satisfactory explanation about how defects in nuclear membrane proteins can result in muscle weakness and cardiac disease.

Binding relations of various sarcolemmal-associated proteins are proving far more complex than was previously believed. One possibility is that interactions between these various proteins might induce conformational changes in calcium channels resulting in their enhanced activity, particularly through abnormal acetylcholine-receptor-cytoskeletal interactions. This process would then lead to mitochondrial dysfunction, and ultimately, to cell death. Increased intracellular calcium has been known for some time to be an important early finding in Duchenne muscular dystrophy. Therefore, relations between sarcolemmal-associated proteins and calcium channels might be a relevant process in the pathophysiology of at least some dystrophies.

**Genetic counselling and prenatal diagnosis**

Prevention by counselling and prenatal diagnosis is now possible for almost all muscular dystrophies. However, for prevention to be reliable a precise diagnosis is essential. Diagnosis is based mainly on careful clinical examination to establish the main type of dystrophy, followed by relevant laboratory investigations, which in many cases—and certainly when prenatal diagnosis is to be considered—should include identification of the specific mutation. These laboratory investigations are often complex and need considerable expertise. For these reasons, referral to a centre specialising in such disorders is important. The European Neuromuscular Centre (now based in the Netherlands) has published a comprehensive listing of clinicians and scientists in Europe who are specialists in these disorders, with further information available on its websites (www.enmc.org and enmc.spc.ox.ac.uk).

**Management and treatment**

Management of individuals with dystrophy depends very much on the type of dystrophy and its severity. Because of the severity and high frequency of Duchenne muscular dystrophy, most concern has centred on management of this disorder.

**Surgery**

In general, early surgery (eg, division of heel cords) is not recommended: not only does it fail to improve muscle strength or walking ability but also there are anaesthetic risks (see later), and the period of bed-rest after such surgery might actually be detrimental. However, surgical correction of contractures might be helpful in later stages of disease when walking is becoming difficult, and is the aim then to prolong ambulation. Surgical correction of scoliosis is now becoming widely accepted. After the operation (usually the Luque technique) sitting becomes much easier and more comfortable. Surgery might help to preserve lung function and possibly lengthen life for a few extra years. However, this procedure is a major
operation with significant complications. The indications for surgery in Duchenne and other types of dystrophy have been reviewed.60

**Medical management**

There is no cure for any of the dystrophies: emphasis is on respiratory care and treatment of cardiological complications.61 With respect to respiratory care, symptoms that suggest nocturnal hypventilation and that are often under-recognised include disturbed sleep with nightmares, early morning headaches, and daytime drowsiness. If reduced respiratory function is suspected it should be confirmed by measurements of vital capacity. Respiratory insufficiency can be treated by non-invasive intermittent positive-pressure ventilation with some form of nasal mask, which has revolutionised care of such patients. Workers have concluded in a consensus report77 that ventilatory support should be available for all patients with symptoms. Furthermore, elective tracheostomy—ie, doing the procedure to ensure adequate lung function for the future and not in response to acute infection—is gaining acceptance.55 With a tracheostomy and assisted ventilation, boys with Duchenne muscular dystrophy for example, can now survive into their third decade.

All individuals with muscular dystrophy are at risk of chest infections and respiratory complications postoperatively. Furthermore, patients with Duchenne and Becker muscular dystrophy are at high risk of myoglobinuria, and succinylcholine should be avoided.12 The anaesthetist needs to be informed of the diagnosis of dystrophy before any operation needing general anaesthesia is done.

Early detection of a cardiomyopathy in dystrophy is important, and methods of detection include electrocardiography and echocardiography. Treatment of symptoms includes conventional use of diuretics, angiotensin-converting-enzyme inhibitors, and digitalis glycosides. Early detection of cardiac-conduction defects (eg, in Emery-Dreifuss muscular dystrophy) is essential, since fitting of a pacemaker can be lifesaving.

**Drug treatment**

Many pharmacological agents have been tried in Duchenne muscular dystrophy,13 but none has proved effective in arresting the course of the disease. However, there have been no less than 16 trials of glucocorticoids, beginning with the encouraging study of Drachman and colleagues in 1974,14 which suggested a possible slowing of the disease process, at least in the short term. Yet there is no agreement on long-term effectiveness of these agents on the course of the disease, because different steroids with different regimens have been used in various centres with no universal agreement.15 Therefore, there is a need for a Cochrane-style systematic review of published trials. On the basis of the findings of such a review, a large trial with agreed criteria could be set up.

**Future prospects for treatment**

An effective pharmacological agent might be found when more is understood about the pathophysiology of these disorders. However, other approaches are also possible. These include some form of gene or stem-cell treatment. With respect to gene therapy,16 one possibility is use of a viral vector. There are undoubtedly many problems with this approach.17 Nevertheless, some success has been achieved, with an adeno-associated virus carrying a human $\delta$-sarcoglycan gene in the hamster model of limb-girdle 2F muscular dystrophy.68 Similarly, adenovirus-mediated gene transfer prevents muscular dystrophy in $\alpha$-sarcoglycan-deficient mice.69 However, two drawbacks to this approach in treatment of man will be to ensure delivery of vector to all important muscle groups, including the heart, and to keep the host’s immunological response to the vector and the protein product of the transferred gene to a minimum.

Other molecular approaches being studied include use of oligonucleotides to circumvent or repair a particular mutation70 or use of an aminoglycoside antibiotic (eg, gentamicin), which causes read-through of stop codons;71 however, these mutations make up a small proportion of all cases in Duchenne muscular dystrophy, and gentamicin can have serious oto-neurotoxic side-effects. Another antibiotic with the same molecular effect but that is less toxic might prove therapeutic (eg, negeamicin).

Another approach could be to upregulate a protein that could compensate for a deficient protein, comparable with upregulation of fetal haemoglobin in certain haematological conditions.72 In the mdx mouse there is good evidence that upregulation of utrophin, a dystrophin-related protein, ameliorates the dystrophy.73,74 Furthermore, in mice with congenital muscular dystrophy with a deficiency of lamin $\alpha_2$ (merosin) protein, upregulation of agrin ameliorates the disorder.75 In man, the hope is that pharmacological agents with the ability to upregulate these proteins can be found, which might then be of therapeutic value.

Finally, the possibility of stem-cell therapy is being explored. Researchers have shown that a small proportion of bone marrow (haemopoietic) stem cells from normal mice can relocate in the muscle of mdx mice and produce dystrophin.67 This approach is especially exciting and opens up the possibility of perhaps being able to replace dystrophin-deficient muscle cells in the heart and elsewhere in the body with stem cells derived from various sources.76

**Conflict of interest statement**

None declared.

**References**


A word of advice

Henry Gans

In research, chance observations are not uncommon. In 1958, when studying the effect of endotoxin on haemostasis in the dog, I happened to notice that in the presence of fibrinolysis a decline in the fibrinogen didn’t always mean it was consumed or broken down. If I repeated the procedure on plasma samples that by the clotting technique contained little or no fibrinogen I would find, to my great surprise, that it was present if I used the salting-out technique instead. I was mystified. I pursued this strange finding for months. Since I was new to the field, I tried to learn all I could but couldn’t find anything on it. I talked to my advisor but he was involved in other matters and since I had just started to work in his lab, ascribed my findings to errors in technique. Subsequently he raised other objections that took a lot of time to refute. I had the feeling that he thought I was suffering from some kind of delusion. I became sidetracked and never got down to really study the problem in earnest. However, after some time I collected all the data and wrote them up. I called this phenomenon cryptofibrinogenaemia. My advisor barely looked at the paper. It just didn’t fit in with anything known at the time. The next spring, my advisor helped to organise a continuation course in haematology for general practitioners. He invited me to lunch at the Campus Club, where he introduced me to the two visiting haematology professors and urged me to tell them about my findings. After a brief outline, one of the visitors exclaimed laughing: “Crypto-fibrinogenaemia, my foot! You have discovered a phenomenon that has been described by two Polish investigators. What you have demonstrated is the anticoagulant or anti-thrombin effect of the fibrinogen breakdown products released during fibrinolysis. Their presence interferes with the clotting of fibrinogen!”

Sure enough, the phenomenon I had observed had recently been described and we had missed it because it had been initially published in French.¹ This taught me to think for myself. Had I done so from the start and pursued the problem singlemindedly, I might well have come up with the right answer.