

## **Muscular dystrophy, the facts / Alan E.H. Emery.**

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# MUSCULAR DYSTROPHY

## THE FACTS



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ALAN E. H. EMERY





## MUSCULAR DYSTROPHY: THE FACTS

ALAN E. H. EMERY

*Muscular dystrophy: the facts* is about living with muscular dystrophy and coping with its physical and psychological effects. Written specifically for people with muscular dystrophy and their families, it will answer many of the questions that are often asked about how and why it occurs, and how it will affect the life of a recently diagnosed child.

The muscular dystrophies are a group of genetic diseases that severely affect children and adults. The different types of muscular dystrophy are described with the minimum of technical jargon. Questions relating to exercise, physiotherapy, surgery, and the emotional effects of the disease are answered, and advice is given on the problems of schooling and choice of career. At the end of the book Professor Emery also provides a useful list of international muscular dystrophy groups and associations.

All royalties earned from the sale of this book will be donated to support research into neuromuscular diseases.

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# Muscular Dystrophy

THE FACTS

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## Acknowledgements Preface

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This little book has been written specifically for those with muscular dystrophy and their families in the hope that it will provide answers to some of the many questions which often arise with this group of diseases. In recent years research has revealed much about the cause of muscular dystrophy and opened up new approaches to possible treatment. In fact at no time in the history of the subject have the prospects for an effective treatment seemed better. I have tried to present some of these findings in terms which anyone interested will be able to appreciate. Questions relating to exercise, physiotherapy, surgery, and the psychological effects of the disease are discussed as well as problems of schooling and choice of employment. Since all the dystrophies are genetic, the ways in which the various forms are inherited and their possible prevention are also discussed. Finally, the importance of professional organizations and voluntary support groups is emphasized since these can play an important role in helping to overcome feelings of isolation which are all too frequent.

The hope is that you may find answers to some of the many problems which often have to be faced, though I am well aware that not everything can be learnt from a book! Nothing can really replace the advice and help of an experienced and sympathetic doctor, physiotherapist, nurse, or counsellor.

All royalties earned from the sale of this book will be donated to Green College, Oxford, to support medical research and education.

*Edinburgh and Baarn*

May 1994

A. E. H. E.





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Various drugs are mentioned in the text. None of these should ever be taken unless prescribed by a doctor and taken under medical supervision.

Dose schedules are being continually revised and new side effects recognized. Oxford University Press makes no representation, express or implied, that the drug dosages in this book are correct. For these reasons the reader is strongly urged to consult the drug company's printed instructions before administering any of the drugs recommended in this book.



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# 1. Introduction

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If you have muscular dystrophy, or you have an affected son or daughter or other affected relative, the first thing to remember is that you are not alone and that there are many others who are similarly affected and share the same worries and concerns. Muscular dystrophy or, more accurately, the muscular dystrophies, since there are many different types, are not uncommon. There are nearly 70 000 individuals affected with a *severe form* of dystrophy in the various countries of western Europe and *at least* 40 000 in the United States of America. It has no predilection for any particular group of individuals but affects all races, all strata of society, and occurs throughout the world. Why then is it not more obvious? The simplest answer is that those with a physical disability often avoid society and, moreover, are often avoided by society. Furthermore, in most forms of dystrophy the resulting disability may not be obvious to the casual observer, and affected individuals often become quite adept at disguising their problems. But for whatever reason muscular dystrophy has, for a long time, been a neglected subject. It began to reach public awareness as a result of television programmes specifically organized for this purpose, such as the Jerry Lewis TV appeal in the United States, and Téléthon in France. Both of these raise a great deal of money each year for research and for the treatment of dystrophy.

Now at last society is beginning to recognize and appreciate more and more the problems of physical disability which are often caused by dystrophy. This has been partly due to media coverage but also to major advances in scientific medicine in the last few years. For a very long time, and certainly since I first became interested in the subject some 30 years ago, there was a general feeling of powerlessness on the part of the medical profession to deal with a problem which seemed intractable. The dystrophies were recognized as being genetic but there was no way of knowing who carried the gene until perhaps they became affected. And approaches to treatment were often 'stabs in the dark' because their cause was quite unknown.

This is now all changing. For the very first time we are beginning to understand the fundamental causes of these disorders and to unravel their complex biochemistry. Furthermore, and most importantly, these findings are beginning to focus the attention of physicians on *rational approaches to treatment* which are based on the cause of the disease and therefore are much more likely to be effective.

Thus the important things to remember are that you are not alone, and that there are now good reasons for entertaining cautious optimism that effective treatments for these distressing conditions will be found in the not-too-distant future.



## 2. What is muscular dystrophy?

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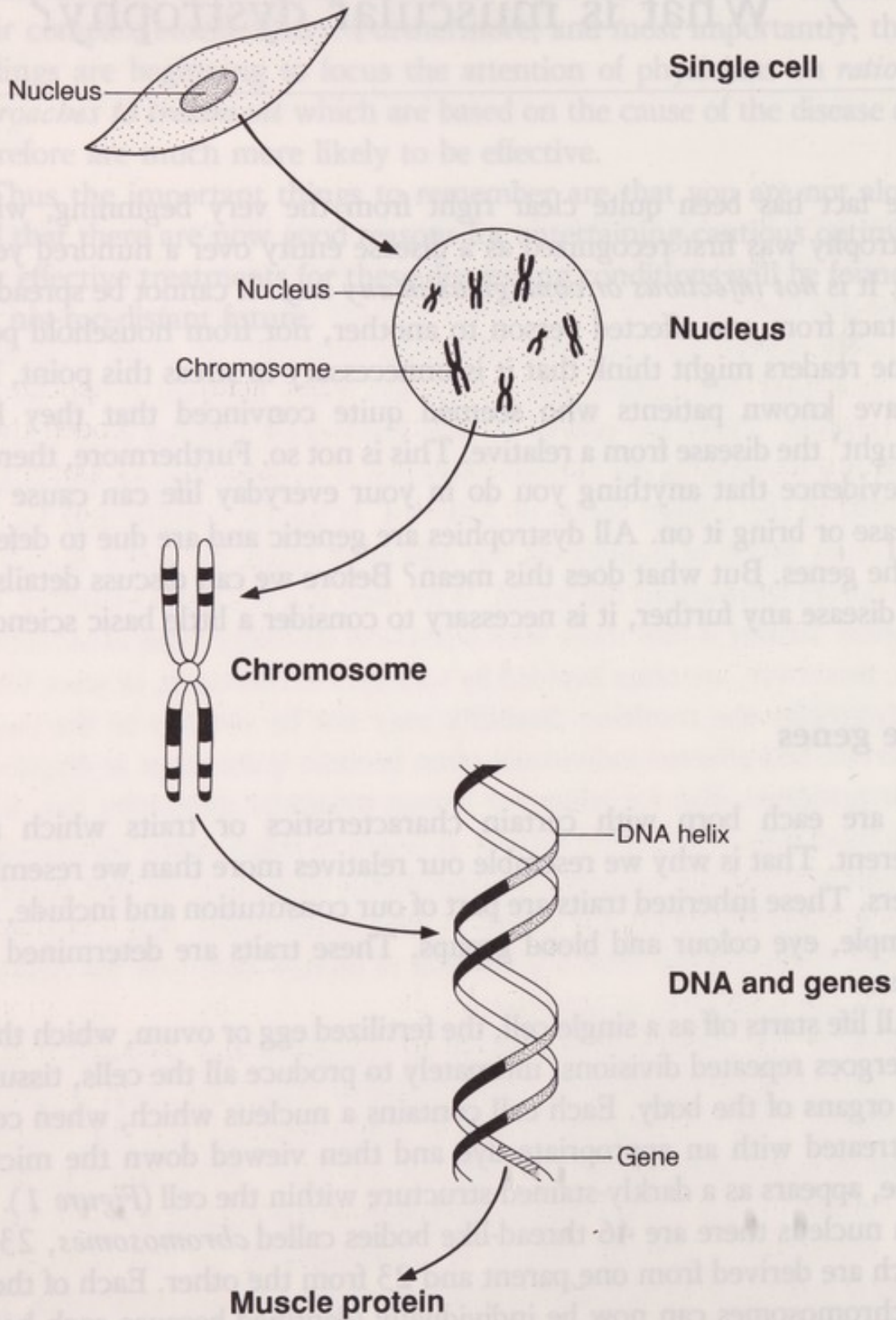
One fact has been quite clear right from the very beginning, when dystrophy was first recognized as a disease entity over a hundred years ago. It is *not infectious or contagious in any way*. It cannot be spread by contact from one affected person to another, nor from household pets. Some readers might think that it is unnecessary to stress this point, but I have known patients who seemed quite convinced that they had 'caught' the disease from a relative. This is not so. Furthermore, there is no evidence that anything you do in your everyday life can cause the disease or bring it on. All dystrophies are genetic and are due to defects in the genes. But what does this mean? Before we can discuss details of the disease any further, it is necessary to consider a little basic science.

### The genes

We are each born with certain characteristics or traits which are inherent. That is why we resemble our relatives more than we resemble others. These inherited traits are part of our constitution and include, for example, eye colour and blood groups. These traits are determined by *genes*.

All life starts off as a single cell, the fertilized egg or ovum, which then undergoes repeated divisions, ultimately to produce all the cells, tissues, and organs of the body. Each cell contains a nucleus which, when cells are treated with an appropriate dye and then viewed down the microscope, appears as a darkly-stained structure within the cell (*Figure 1*). In each nucleus there are 46 thread-like bodies called *chromosomes*, 23 of which are derived from one parent and 23 from the other. Each of these 23 chromosomes can now be individually identified because each has a particular branding pattern when stained with certain dyes. The arrangement of the chromosomes in a standard manner is referred to as a *karyotype* (p. 83).

# What is muscular dystrophy?



**Figure 1** Diagram of the relationship between the cell nucleus, chromosomes, DNA, and genes.



The chromosomes carry the genes, and the same genes are present in every cell of the body—although only certain genes are active in particular tissues or organs. For example, a gene making muscle protein is active only in muscle tissue and a gene making haemoglobin, the oxygen-carrying chemical in red blood cells, is only active in blood-forming cells.

Estimates vary, but there are probably around 100 000 genes in each nucleus. We still know very little about the many genes which determine and control such common traits as intelligence, stature, and our general 'appearance'. Oddly we know more about genes which result in diseases such as dystrophy.

Genes are composed of *DNA* (deoxyribonucleic acid), a complicated double-stranded molecule (called a double helix) in which is coded the information for making amino acids and proteins, essential components of our bodies. The simplest way to visualize the cause of dystrophy is to imagine that normally a particular gene makes (synthesizes) a protein essential for normal muscle activity. However, if this gene changes, a change which we refer to as a *mutation*, then the gene either does not synthesize the protein or synthesizes an abnormal protein so that the muscle no longer functions properly. Though X-rays and certain chemicals are known to cause mutations in animals, the cause of the vast majority of mutations in humans is at present quite unknown. They seem to occur randomly and the mutation which causes dystrophy in a family appears to be a purely chance event. Certainly we have no explanation for why dystrophy should originate in one family rather than another. In some families the mutant gene which causes the disease can be traced back several generations. In others, the causative mutation occurs in the egg or sperm which led to that particular affected individual. These and related matters will be discussed later in Chapter 8.

How we can tell which gene is abnormal out of several thousand is the province of *molecular genetics*. The most important development in the subject, whereby abnormal genes can be identified and traced in families and even shown to be present in the fetus while still in the womb, began some 15 years ago. In fact, Duchenne muscular dystrophy was the very first condition in which a disease-producing gene was identified using these techniques.

We now have laboratory tools which allow us to identify genes for various dystrophies, to isolate such genes, and then to determine what



they do. Knowing what they do normally, and therefore what goes wrong in disease, provides important clues for possible treatments. The interested reader may find details of this new and important science in several modern texts listed at the end of the book.

### The meaning of 'muscular dystrophy'

The word *dystrophy* originally comes from two Greek words: *dys*, meaning abnormal or faulty; and *trophe*, meaning food or nourishment. Thus the term muscular dystrophy implied that in some way the nourishment of the muscle was defective, in the same way that a person who does not eat the correct food will not grow properly. Early in the history of the subject the defect in the disease was thought in some way to be actually due to faulty muscle 'nutrition'. But this is not so, and the term is therefore something of a misnomer. Nowadays it is used to indicate abnormal muscle wasting and weakness which are the hallmarks of the disease.

The particular group of muscles which is predominantly affected, or the *distribution* of muscle weakness, is different in different types of dystrophy, and is used to distinguish between these types. In some, muscle weakness remains localized, for example, to the muscles of the eye and face. In others the major muscle groups responsible for moving the limbs become mainly involved, and later other muscles may also become affected. But whatever the particular type of dystrophy, the essential feature is muscle wasting and weakness.

There are many different causes of muscle wasting and weakness apart from dystrophy which the physician must first exclude when making the diagnosis. These other causes are not all genetic. For example, muscle weakness may result from a disease which affects the nerve supply to the muscle. A common cause for this in the past was poliomyelitis, but there are also some inherited diseases where this may occur. Muscular dystrophy however does *not* result from a disease of the muscle's nerve supply. It is a disease which *primarily* affects muscle tissue, though in some dystrophies other tissues and organs may also be affected.



## Muscle weakness

The muscle weakness which occurs in all types of dystrophy has certain features in common. It is usually *symmetrical*. That is, the weakness on the two sides of the body is often very similar, though one side may sometimes *seem* more affected than the other. Thus, a right-handed person may be more aware of weakness in that arm, though careful testing by the physician may well reveal a similar degree of weakness in both arms. The weakness is usually *progressive*, though this again differs very much from one type of dystrophy to another. Some types begin in infancy or early childhood and may be severe and progress rapidly, but others coming on in later life may be very mild. There is often quite a lot of variation between different affected people with the same type of dystrophy, even within the same family, and some may be concerned because they are more severely affected than a relative of the same age. We are just beginning to understand how this can occur in myotonic dystrophy, for example, but it has to be admitted that in other dystrophies we still have no satisfactory explanation to offer for such variation in families. On the other hand, in some types of dystrophy, such as Duchenne muscular dystrophy, the course of the disease is fairly uniform and does not usually vary a great deal.

Though weakness is progressive, it nevertheless often shows periods of *apparent* arrest. This slowing is often most obvious either in the very early stages or, more often, when a person first starts needing a wheelchair. At present we know of no way of completely arresting the course of the disease, but with physiotherapy and other measures it is possible to prevent or slow down certain complications from arising, such as *contractures*. These are the result of prolonged immobilization, when joints can become fixed and can no longer be moved freely.

The course and severity of a disease, its *prognosis*, depend very much on the particular type of dystrophy from which a person suffers. A precise diagnosis is therefore essential. This is possible from a careful examination by a doctor experienced in the disease and by relevant laboratory tests. Features of the various types of dystrophy will be discussed in more detail in Chapter 4.

Weakness is *not* usually associated with pain and the muscles are not tender to touch. There are usually few complaints apart from those which result from weakness of the affected muscles. Sometimes, especially



in those types of dystrophy which mainly affect the major limb muscles, cramps and stiffness are quite common. However, *severe* cramps and stiffness are very unusual and, especially if the muscles are also tender, may indicate some other cause for the muscle weakness.

Sometimes in certain types of dystrophy, some muscles actually seem to be enlarged rather than wasted. In athletes muscle enlargement is of course common. In dystrophy, however, the enlarged muscles are weak, and their enlargement has therefore been referred to as *pseudohypertrophy* (which means false hypertrophy). The calf muscles are most often affected in this way but other muscles may also become similarly enlarged. The cause of pseudohypertrophy is not entirely clear but is probably largely due to the muscle tissue becoming replaced by fat. Duchenne muscular dystrophy, in which this is a prominent feature, was often referred to in the past as 'pseudohypertrophic muscular dystrophy'. But pseudohypertrophy can occur in several other different types of dystrophy as well.

### Types of muscle

So far we have been considering muscle as merely the tissue responsible for moving limbs. The thigh muscles straighten and extend the knee, for example, and the shoulder muscles raise the arms. These are referred to as *voluntary* muscles because they are under voluntary control. You can will your arm to be raised and the message from your brain descends through the spinal cord to exit at the appropriate point via the nerves supplying the relevant muscles. Since these muscles mainly, but not exclusively, move bones which are hinged at joints, they are often also referred to as *skeletal* muscles. The muscles of respiration are somewhat of an exception because you can partly control their function, by holding your breath, but usually we are unaware of their activity.

There are no less than 434 different voluntary muscles in the human body, and one of the banes of the medical student's life is knowing the positions and functions of all these muscles! In an adult they constitute over 40 per cent of the total body weight. This explains why weight loss is not uncommon in patients with any degree of muscle wasting, though to some extent this can be compensated for by energy conservation resulting from lack of physical activity. In fact, in some individuals when



physical activity becomes severely restricted, weight gain becomes a serious problem, and the only remedy is then restriction of calorie intake by dieting.

Apart from voluntary muscle, there are two other types of muscle (heart and smooth) which are referred to as being *involuntary* because neither of them is under voluntary control. Though some people believe they can, for a period, slow their heart rate, most of us are unable to control this important function. Similarly, the smooth muscle which surrounds the wall of the intestines and which is responsible for the involuntary contractions which propel the contents along, called peristalsis, cannot be controlled voluntarily. In some dystrophies heart muscle and smooth muscle may become involved. For example, when the heart is affected this can result in breathlessness at rest. But only in certain types of dystrophy is this a predominant feature. Involvement of the smooth muscle of the gut may account, at least in part, for constipation, though this is more likely to be due to reduced physical activity and lack of dietary fibre.

## Muscle structure

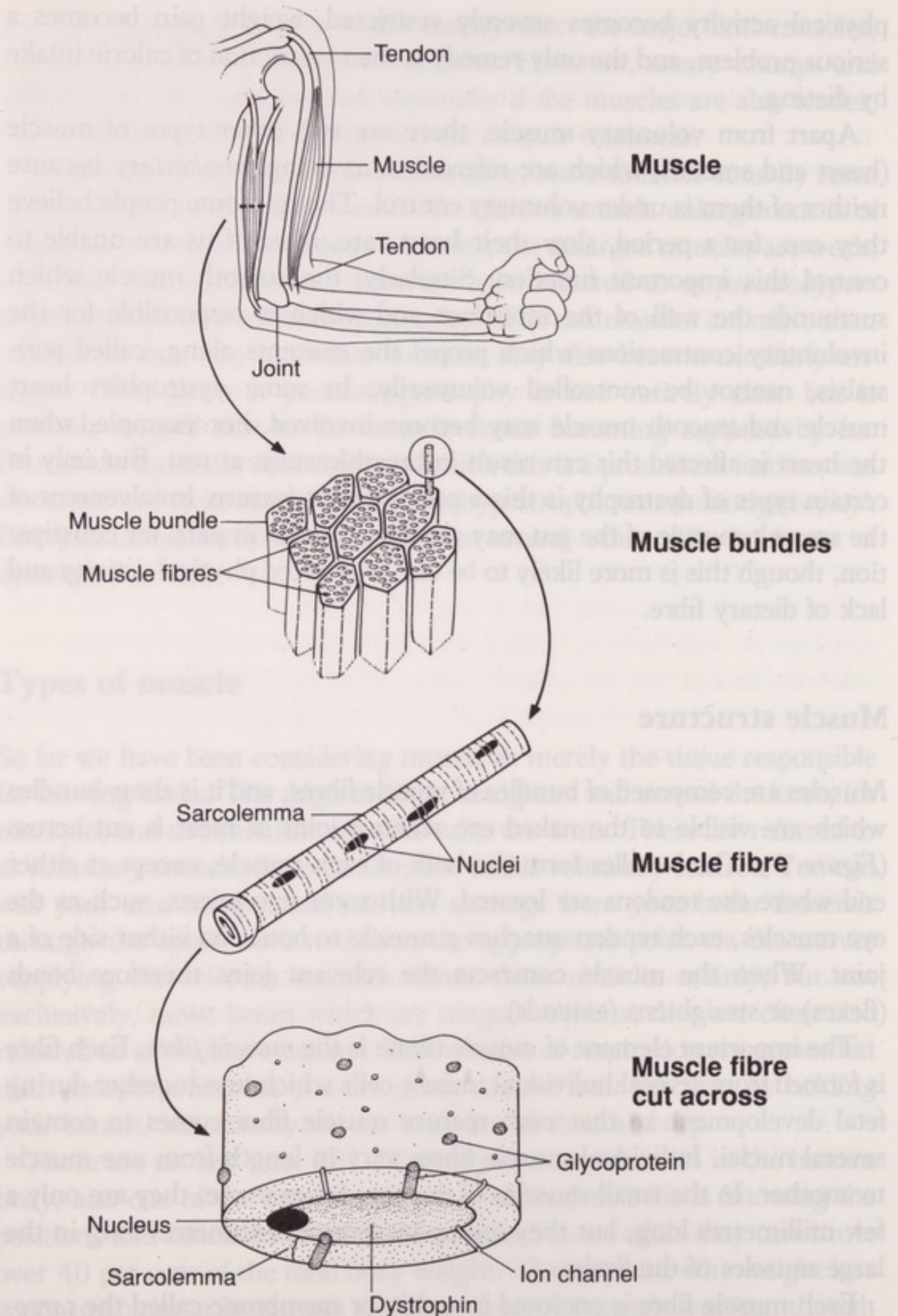
Muscles are composed of bundles of muscle fibres, and it is these bundles which are visible to the naked eye when a joint of meat is cut across (*Figure 2*). The bundles form the bulk of each muscle, except at either end where the tendons are located. With some exceptions, such as the eye muscles, each tendon attaches a muscle to bones on either side of a joint. When the muscle contracts the relevant joint therefore bends (flexes) or straightens (extends).

The important element of muscle tissue is the *muscle fibre*. Each fibre is formed from several individual muscle cells which fuse together during fetal development so that each mature muscle fibre comes to contain several nuclei. Individual muscle fibres vary in length from one muscle to another. In the small muscles of the eye, for example, they are only a few millimetres long, but they are up to several centimetres long in the large muscles of the limbs.

Each muscle fibre is enclosed in a skin or membrane called the *sarcolemma*. This covering of each muscle fibre is a complicated structure. Studies with powerful electron microscopes have shown that it consists



## What is muscular dystrophy?



**Figure 2** Diagram of the relationship between muscle, muscle bundles, muscle fibres, and the muscle fibre membrane (sarcolemma).



of two layers. Traversing between these two layers are minute pores or channels which open and close and which allow certain *ions* (electrically charged atoms such as sodium and calcium) to pass backwards and forwards across the membrane. The free movement of these ions is an important process in muscle contraction. On the inner side of the two layers is a lattice-like arrangement of protein molecules which holds the membrane together and stops it from tearing when the muscle contracts. An important protein in the lattice structure is *dystrophin*. It was discovered in 1987 that this protein is absent in Duchenne muscular dystrophy, and this led to our present understanding of the disease. The word dystrophin was, of course, derived from dystrophy, so emphasizing its importance in the disease—though at the time it was discovered some argued that the word was really not appropriate since dystrophin was only present in normal muscle. However it is now universally accepted for the name of the protein which is absent in Duchenne muscular dystrophy.

### Cause of muscle weakness

It is currently believed that the fundamental and basic defect in many dystrophies resides in the muscle fibre membrane. So far, however, convincing evidence for this idea comes mainly from studies in Duchenne and Becker muscular dystrophies.

In Duchenne muscular dystrophy, dystrophin is absent because the responsible gene fails to make this protein. In the clinically similar, but much milder disorder of Becker muscular dystrophy, the responsible gene synthesizes dystrophin but the protein is abnormal. Dystrophin, along with other related proteins (called *glycoproteins*) to which it is attached and anchored to the membrane, is responsible for retaining the structure of the muscle fibre membrane. If dystrophin is defective then the membrane breaks down and becomes 'leaky'. That is, substances and molecules within the fibre leak out into the circulation. Among the substances which leak out is a muscle enzyme called *creatine kinase*. Enzymes are proteins within the cell which are necessary for certain chemical reactions and creatine kinase is necessary for producing energy for muscle contraction. In several types of dystrophy, most notably Duchenne and Becker dystrophies, the level of this enzyme in the blood



is far higher than in normal people. The measurement of the level of this enzyme in a blood sample therefore provides a very useful test for these diseases.

In some other dystrophies the defect is an abnormality of one of the glycoproteins associated with dystrophin. The result, however, is essentially the same as a deficiency of dystrophin.

The membrane of the muscle fibre is essential for the muscle to work properly and if this becomes defective, either by an abnormality in dystrophin or an abnormality in a glycoprotein associated with dystrophin, this results in muscle weakness. The details as to how this results in weakness have still to be worked out. Many scientists believe that it is partly due to a leak of substances *from* the muscle fibre which are essential for muscle contraction. But it may also be due to substances leaking *into* the fibre which then damage processes necessary for muscle contraction and perhaps at the same time cause irreparable damage to the fibre. Calcium may be important in this way because it is well known that an increase in the level of calcium in cells results in damage to biochemical processes which are essential for cell survival. Knowledge of the trail of events which ultimately results in muscle cell damage and muscle weakness can lead to rational approaches to possible treatment.

### Animal studies of dystrophy

For obvious reasons it is very rarely possible to study different tissues from any one affected person. And of course for ethical reasons it is difficult to test experimental treatments which might prove to have untoward and serious side-effects. For these reasons, some scientists have turned their attention to animal studies. In the past various strains of animals with muscle weakness have been studied in this way, including mink, sheep, duck, cow, hamster, and chicken. But none of these has proved to be strictly comparable to human muscular dystrophy. However, more recently, two 'animal models' have been found with diseases which are genetically and biochemically very similar to the human condition. These are the so-called *mdx* dystrophic mouse and a particular strain of golden retriever dog. Of these the latter is proving the best model of the human disease, and could prove excellent subjects for studying the effects and value of any new treatments.



## Some unanswered questions

Though the picture has become very much clearer in the last few years, there are still many questions about muscular dystrophy which remain unanswered. For example, though we now know that a deficiency of dystrophin is the basic cause of Duchenne muscular dystrophy, we still have no idea why the disease only becomes obvious around school age when we know that the defect is present even before birth. This is also true of Becker muscular dystrophy yet here the disease may not become obvious until the twenties or even thirties. In the *mdx* mouse model there is the same absence of dystrophin yet the mouse does not become progressively weaker or die from the disease. And why in the human disease are some muscles (for example, those of the limbs) more affected than others? The facial muscles for example are rarely severely affected, except in one particular type of dystrophy (facioscapulohumeral muscular dystrophy), and chewing and swallowing are never affected (apart from in oculopharyngeal muscular dystrophy), nor are bladder and bowel control affected. Furthermore, as we have discussed already, why do some people with dystrophy become more severely affected than relatives of the same age with the same disorder? Answers to these and related problems will no doubt be found with further research in the next few years. Until then, we have to accept that there are many questions to which we still do not have answers.

## Summary

The muscular dystrophies are a group of inherited diseases in which various genes controlling muscle function are defective. In the case of certain types of muscular dystrophy the basic defect is already known (a deficiency of the muscle protein dystrophin in Duchenne muscular dystrophy, for example), and there is every reason to believe that the defects in other types of dystrophy will soon be identified. Scientists are beginning to understand how muscle weakness develops, though many questions still remain to be answered, not least being why some people become more severely affected than others in the same family. Nevertheless, the nature of these diseases is now better understood than at any other time in the history of the subject.



### 3. Confirming the diagnosis

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It has been said that an experienced and astute physician can often make the diagnosis of muscular dystrophy without resort to any laboratory tests. In a family in which others have already been diagnosed as having the disease, this is probably true. For example, if a boy has been diagnosed as having Duchenne muscular dystrophy and now his younger brother is found to have enlarged calves and difficulty in running and climbing stairs, then it seems more than likely that he too is becoming afflicted with the same disease. But the situation is not always so straightforward. A patient's impressions about his or her relatives who have not been examined can be misleading. This is a notorious problem, for example, in facioscapulohumeral muscular dystrophy. Here relatives are sometimes described as being unaffected when they are in fact in the early stages of the disease: facial appearance may be misinterpreted as familiar likeness rather than as an expression of facial weakness, and early weakness of the shoulder muscles may go unrecognized by both the patient and his or her relatives.

Not only may details given by relatives be misleading, but even a careful clinical examination may not always provide all the answers. For example, an early sign of weakness of the hip muscles is a so-called *waddling gait*; that is, the individual sways from side to side when walking. This is very common in various types of muscular dystrophy when the hip muscles are affected. But as a famous paediatrician has emphasized 'not everyone who waddles has muscular dystrophy'. Any disease which causes hip weakness will result in a waddling gait.

An important reason for confirming a suspected diagnosis of dystrophy with further tests, particularly in children, is to exclude the possibility of polymyositis which can closely mimic the disease. If diagnosed early and then given appropriate treatment, patients with polymyositis recover completely. But if the diagnosis is not made early and treatment is delayed, the results can be very serious.

Finally, and most importantly, the diagnosis of muscular dystrophy, and particularly the *type* of dystrophy, is essential for two reasons: first,



in order to be able to assess the possible course of the disease, which is important for future planning, and secondly to determine the mode of inheritance, which is essential for genetic counselling.

Therefore, though the doctor may be fairly convinced of the diagnosis after taking a detailed medical history and a careful physical examination, further tests are invariably necessary in order to confirm the diagnosis of what is after all a serious disease.

There are essentially three diagnostic tests which are often used in this way: a blood test, electromyography, and a muscle biopsy.

## Blood tests

There are two blood tests used in the diagnosis of dystrophy: one is to measure the level of the enzyme *creatine kinase* in a test tube, and the other is for *DNA studies*. It is possible to do both tests on the same sample of blood and at the same time, though often DNA studies may be delayed until a later date.

### *The CPK test*

As we have seen (p. 11), creatine kinase (*CK*), often called creatine phosphokinase (*CPK*), is an important muscle enzyme which in several types of dystrophy leaks into the circulation from the muscle, an observation first made over 30 years ago by Professor Ebashi in Japan and Professor Dreyfuss in Paris. In normal, healthy people the level ranges from around 100 to 200 units, being slightly higher in males than in females. Levels are somewhat raised (200–300 units) in normal newborn babies and in normal children and adults after vigorous exercise. In comparison, the levels in Duchenne muscular dystrophy, even in newborn baby boys, are grossly elevated (50–100 times normal). This also occurs in the early stages of Becker muscular dystrophy. Such grossly elevated levels occur in very few other conditions in children and these can be excluded on the medical history and physical examination. Thus a young boy who is having increasing difficulty running, rising from a chair, or climbing stairs, who has enlarged calves, and is found to have a *grossly* elevated creatine kinase level, is almost certain to have Duchenne muscular dystrophy. In an adult suspected of having Becker muscular



dystrophy the situation is a little more complicated because in adulthood there are several conditions which can result in similarly raised creatine kinase levels, but these can usually be excluded on the basis of the medical history and results of the physical examination.

Moderately elevated levels (up to ten times normal) can occur in some other forms of muscular dystrophy (notably limb girdle, Emery-Dreifuss, and facioscapulohumeral muscular dystrophies) and here the test is less helpful in establishing a diagnosis because there can be many causes for such levels of creatine kinase. Finally, slight elevations (up to around five times normal) can occur in healthy females who carry the gene for Duchenne and Becker muscular dystrophies. This can therefore, with certain reservations which will be discussed later (p. 90), be a useful test in helping to identify such carriers.

The creatine kinase test is simple to perform, requiring at most a *venepuncture* where a small sample of blood is removed from a vein, usually at the elbow, or in small children by a heel prick. Its further attraction is that it costs only pennies to carry out! This is an extremely useful test in diagnosis but its limitations have to be recognized. It is *not* a specific test for dystrophy.

### *DNA studies*

For genetic studies a blood sample is usually also required. In this case it is not the level of a chemical in the blood serum which is studied, but DNA and gene markers in the white cells (leucocytes). As far as the patient is concerned, this involves no more than for a CPK test—that is, a small sample of blood is removed from a vein at the elbow by venepuncture—but the laboratory studies themselves are much more complicated and require considerable expertise.

DNA studies involve first separating off the leucocytes from the blood sample and then extracting DNA from these cells. The DNA is then examined by various molecular genetic techniques. The most widely used is called *Southern blot* after Ed Southern who invented and developed the technique. It will tell us if a specific mutant gene is present or absent. If the mutant gene which causes a particular type of dystrophy is known, as in the case of Duchenne and Becker muscular dystrophies, these DNA tests can tell us whether or not the mutant gene is present in



a particular patient. If the mutant gene is present, then the diagnosis of a specific type of dystrophy can be made with confidence.

Unfortunately, in other types of dystrophy though the responsible gene may have been located on a particular chromosome, the gene itself has not yet been identified. In this case DNA tests are carried out not only on the person but also on relatives in order to determine if the disease is inherited along with an identifiable DNA marker which is known to be very close to the mutant gene on a particular chromosome. If a person proves to have the marker, then he or she may therefore possess the disease gene as well. These latter studies are complex and time-consuming. Fortunately, they will become less necessary as we are able to identify the specific mutant gene in each type of dystrophy. Details of these DNA studies can be found in several modern texts listed at the end of the book.

## Electromyography

When muscles contract, they generate small amounts of electricity. This electrical activity can be detected by inserting a small needle (called an *electrode*) into the muscle and amplifying the small amount of electrical activity produced. This activity can then be displayed on an oscilloscope, a sort of TV screen. This technique of recording electrical activity from contracting muscle fibres is referred to as electromyography or EMG. The electrical activity appears as a blip or wave on the screen which is known as an *action potential*. The study of the shape and size of these action potentials provides very useful information about the muscle and is a very valuable diagnostic aid in neuromuscular disorders. For example, in the muscular dystrophies the action potentials are very small, whereas in other diseases they may be very large (so-called 'giant potentials'). Furthermore, in healthy individuals, as well as in those with dystrophy, after an electrode has been inserted into the muscle there are no potentials when the muscle is at rest. On the other hand, in certain other disorders (such as spinal muscular atrophy and Lou Gehrig's disease or ALS) there are spontaneous bursts of small potentials. Thus an EMG examination can be used to confirm the diagnosis of dystrophy and distinguish this from other types of neuromuscular disease, but it cannot tell us what type of dystrophy a patient may have.



Unfortunately an EMG does involve having a needle-electrode inserted into a muscle (sometimes into several muscles) and not everyone is able to tolerate this, though actually it causes no more discomfort than a pin prick. It is, however, a difficult test to perform in small children since the patient's cooperation, in voluntarily contracting various muscle groups, is important. For these reasons the test is becoming less widely used in diagnosing muscular dystrophy. It is perhaps more important in diagnosing non-dystrophic muscle diseases, especially in adults.

### Muscle biopsy

After the CPK test, the most important method for diagnosing dystrophy is a muscle biopsy.

The technique involves removing a small amount of tissue from a muscle which is clearly affected, but not severely so. If a severely affected muscle is biopsied then the material obtained may contain mainly fat with little actual muscle tissue on which the diagnosis can be made.

There are two ways in which a muscle biopsy may be performed: an *open* biopsy or a *needle* biopsy. An open biopsy, as the name implies, involves making a small cut in the skin (about 2-3 cm) and then removing a piece of the underlying muscle under sterile operative conditions. This can be done with local anaesthesia though most prefer a general anaesthetic so that they can be unaware of the surgeon's activities.

However, all surgical operations which involve general anaesthesia, no matter how minor (and a muscle biopsy is considered a minor surgical operation), involve some risk. In patients with dystrophy the risk can be greater than normal. Patients do not always tolerate anaesthetic agents well and, in any event, their lung and heart functions may already be somewhat compromised by the disease (p. 48). For these reasons needle biopsy is gaining favour. This involves inserting a sterile, special cutting and hollow biopsy needle under local anaesthetic through the skin and into the muscle. A small fragment of muscle is then sucked up the needle and withdrawn. Although Duchenne himself, the French neurologist after whom the disease Duchenne muscular dystrophy is so named, advocated the use of the biopsy needle over 100 years ago, for a long time this did not meet with much support. This was largely because it was seen as a 'blind' procedure and there might therefore be the danger



of inadvertently damaging nerves or blood vessels. In fact, such hazards, using modern equipment, are very rare and for this reason many doctors now prefer to use this technique since it does not require general anaesthesia. Some medical scientists in their research have even been known to carry out the procedure repeatedly on themselves with no untoward effects.

### *Muscle histology*

Once a small piece of muscle has been removed, it is taken to the laboratory and after careful preparation thin sections are cut. These sections are placed on a glass slide and stained, and then carefully examined under the microscope. The microscopic study of tissues in this way is referred to as *histology*. In a clear-cut case the difference in appearance from normal muscle is quite striking. Normally, muscle fibres are of fairly uniform size and packed closely together with little fatty or fibrous tissue between them. But in dystrophy the muscle fibres vary greatly in diameter—some are very large and others very small. Furthermore, many of the fibres often appear to be breaking down (*necrosis*) and being invaded by certain other cells called *macrophages* which consume them (phagocytosis). Ultimately, almost all the muscle fibres may be destroyed in this way and replaced by fatty-fibrous tissue.

In less severe types of dystrophy, and in minimally affected muscles from severe cases, not all these changes may be very evident. The pathologist's skill then comes into play in interpreting minimal changes which indicate dystrophy.

### *Muscle histochemistry*

The various changes described above can occur in almost all types of dystrophy and are not specific to any particular type. An important recent development in this regard, however, has been the use of stains which identify specific proteins known to be abnormal in some way in particular types of dystrophy. The microscopic study of tissues using chemical stains in this way is referred to as *histochemistry*. For example, chemical stains are now available for identifying dystrophin. In normal tissue the outer membrane (sarcolemma) of all the muscle fibres stains uniformly for dystrophin. In Duchenne muscular dystrophy, where



dystrophin is absent, the muscle fibres fail to stain at all. In Becker muscular dystrophy where dystrophin is present but abnormal, most fibres do stain but the staining is not uniform and varies a great deal from one fibre to another. This variability with dystrophin stains gives a clue to the diagnosis.

Stains are also available for various glycoproteins and these stains can now be used to diagnose certain other types of dystrophy (see p. 30).

No doubt in the not-too-distant future stains will become available for a variety of other specific muscle proteins, each of which is known to be abnormal in particular types of dystrophy. In this way it will be possible to diagnose many more types of dystrophy by histochemical methods.

### Other investigations

Apart from a blood test, EMG, and muscle biopsy, other tests may also be requested by the physician, depending on a particular person's problems. For example, an electrocardiogram (ECG or EKG) is essential to check the heart. This is a simple, straightforward, painless investigation to allow the activity of the heart to be recorded and studied. Ultrasound and computerized tomography (*CT scan*) are sometimes also used nowadays to show up and to localize muscle weakness. These tests are non-invasive and painless procedures.

### Summary

Most essential in the diagnosis of muscular dystrophy is a careful clinical examination by an experienced doctor. In order to confirm a case of dystrophy a blood test (for serum creatine kinase levels and DNA studies), electromyography (EMG), and muscle biopsy are important.

By certain tests (DNA and special muscle protein stains) it is now becoming possible to make the diagnosis of a specific type of dystrophy, which is important in order to assess the possible course of the disease in a person and for reliable genetic counselling.



## 4. Different types of muscular dystrophy

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The muscular dystrophies have been defined as a *group of genetic disorders with progressive muscle wasting and weakness where the disease primarily involves muscle in which there are characteristic microscopic changes* (p. 18). But as we have mentioned, muscular dystrophy is not one disease. There are various types. Some medical scientists have suggested that there may be as many as twenty different types. Some of these, however, are very rare or occur only in certain parts of the world. The existence of others is a matter of debate, but as we learn more of the causes of these various conditions much of this confusion will no doubt be resolved. Here we shall limit our discussion to those types of dystrophy which are well defined and relatively frequent.

These various types are diagnosed on the basis of the distribution of the groups of muscles which are *predominantly* affected (*Figure 3*).

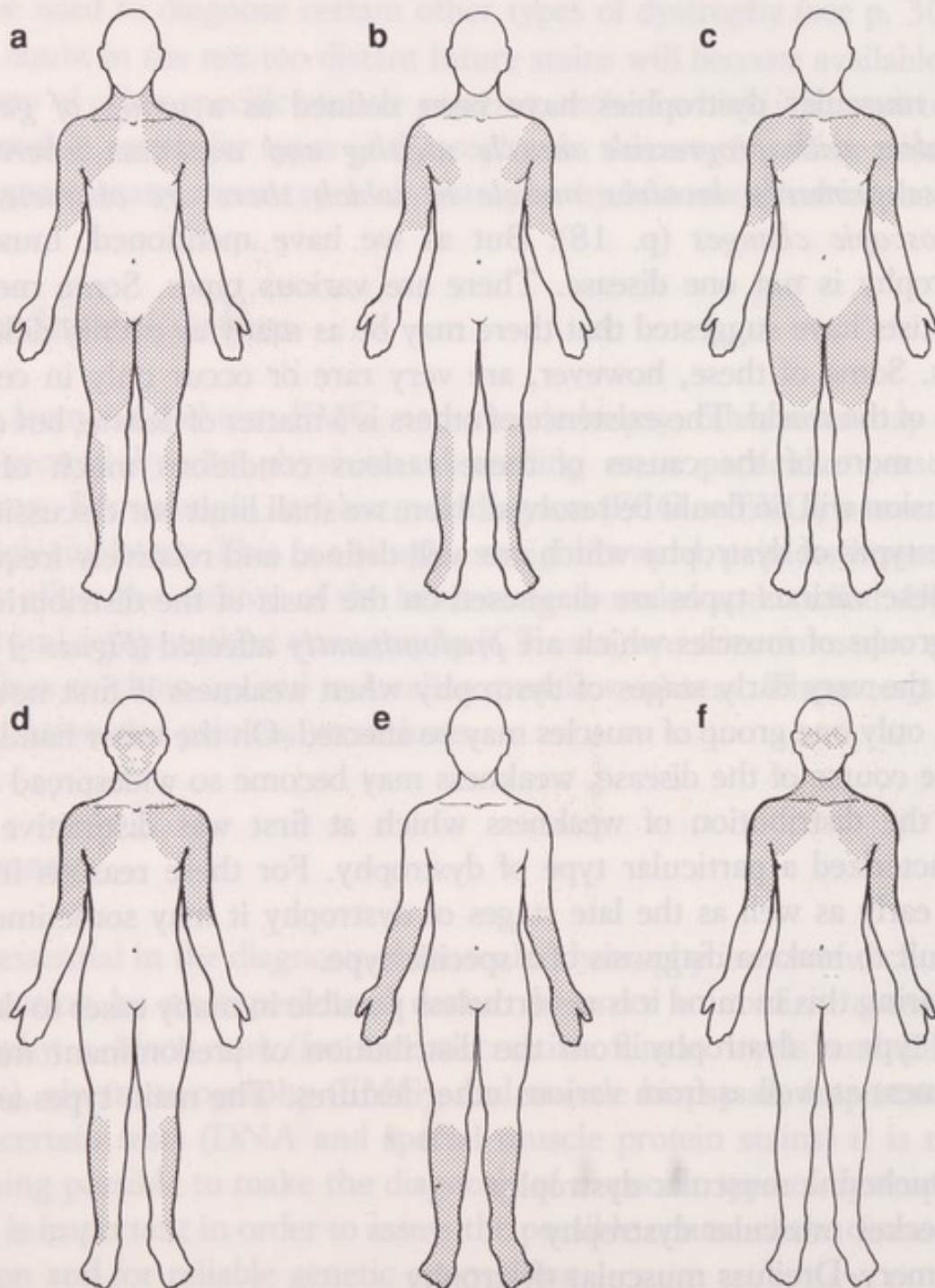
In the very early stages of dystrophy when weakness is first noticed, often only one group of muscles may be affected. On the other hand, late in the course of the disease, weakness may become so widespread as to blur the distribution of weakness which at first was distinctive and characterized a particular type of dystrophy. For these reasons in the very early as well as the late stages of dystrophy it may sometimes be difficult to make a diagnosis of a specific type.

Bearing this in mind it is nevertheless possible in many cases to decide on a type of dystrophy from the distribution of predominant muscle weakness as well as from various other features. The main types are:

- Duchenne muscular dystrophy
- Becker muscular dystrophy
- Emery-Dreifuss muscular dystrophy
- limb girdle muscular dystrophy
- facioscapulohumeral muscular dystrophy
- distal muscular dystrophy

- oculopharyngeal muscular dystrophy
- congenital muscular dystrophy

For the sake of completeness *myotonic dystrophy* will also be discussed, though this is unique in so many different ways that some no longer consider it a muscular dystrophy.



**Figure 3** Distribution of predominantly affected muscle groups in various dystrophies. a Duchenne and Becker; b Emery-Dreifuss; c limb girdle; d facio-scapulo-humeral; e distal; f oculopharyngeal.



## Duchenne muscular dystrophy

This, the commonest form of dystrophy, is so named after the French neurologist Guillaume Benjamin Amand Duchenne (*Figure 4*), or Duchenne de Boulogne (1806–1875), who described the disease in his book *De l'électrisation localisée* of 1861 and in greater detail in several publications in 1868. However, as so often happens in the history of medicine there is some disagreement as to who actually described the disease first. In fact recent historical research has now revealed that the



**Figure 4** Duchenne de Boulogne (1806–1875). (Reproduced from *The founders of neurology*, edited by Webb Haymaker, 1953. Courtesy of Charles C. Thomas, Publishers, Springfield, Illinois.)



**Figure 5** Edward Meryon (1809–1880). (By John Linnell, private collection.)

English physician Edward Meryon (1809–1880) (*Figure 5*) described the disease in considerable detail several years before Duchenne and quite independently. However, the appellation Duchenne muscular dystrophy is so well established that it would be a brave person who now tried to change it.



Duchenne muscular dystrophy is due to a mutation on the X chromosome and is therefore inherited as a so-called X-linked trait. This will be discussed further in Chapter 8. It means, however, that only boys are usually affected.

The onset is often ill-defined. Looking back over the child's history there may have been some delay in learning to walk. In one survey of affected boys about half had not been walking by the age of 18 months, whereas almost all normal children are walking by this age. Sometimes the first thing parents notice is that the calf muscles are enlarged but usually medical attention is not sought until the parents begin to realize that something seems to be seriously wrong. They may become aware that their son falls over more than other children, or he is never able to run well, or cannot get up from the floor or climb stairs properly. It has been said that any little boy who shows signs of a problem with muscle development should have a CPK test to exclude the possibility of Duchenne muscular dystrophy.

Sometimes the diagnosis of Duchenne muscular dystrophy is not made perhaps until school age. By then difficulty in walking is usually obvious. He often walks on his toes with his abdomen pushed forwards and with a waddling gait. These are early hallmarks of the disease and result from weakness of muscles of the pelvis which normally extend the hips in order to retain the upright position when standing. When these muscles are weak there is a tendency for the pelvis to tilt forward and in order to compensate for this the affected boy pushes his abdomen forward and his shoulders backward. This results in what is called *lordosis* as it resembles the gait of a peer of the realm.

Rising from the floor unaided also becomes increasingly difficult which, like the waddling gait, is due to weakness of the muscles around the hips. This results in what is referred to as *Gower's sign* after the English physician who first described it. Whenever there is weakness of the hip muscles (which is not limited to Duchenne muscular dystrophy but can also occur in other dystrophies and diseases) when attempting to rise the person presses on his thighs and then climbs up them in order to extend the hips and straighten up (*Figure 6*).

At the same time as weakness of the hip muscles becomes evident there is also weakness of the shoulder muscles so that the affected boy has increasing difficulty raising his arms. The hip and shoulder muscles are referred to as *proximal* muscles, as opposed to *distal* muscles of the



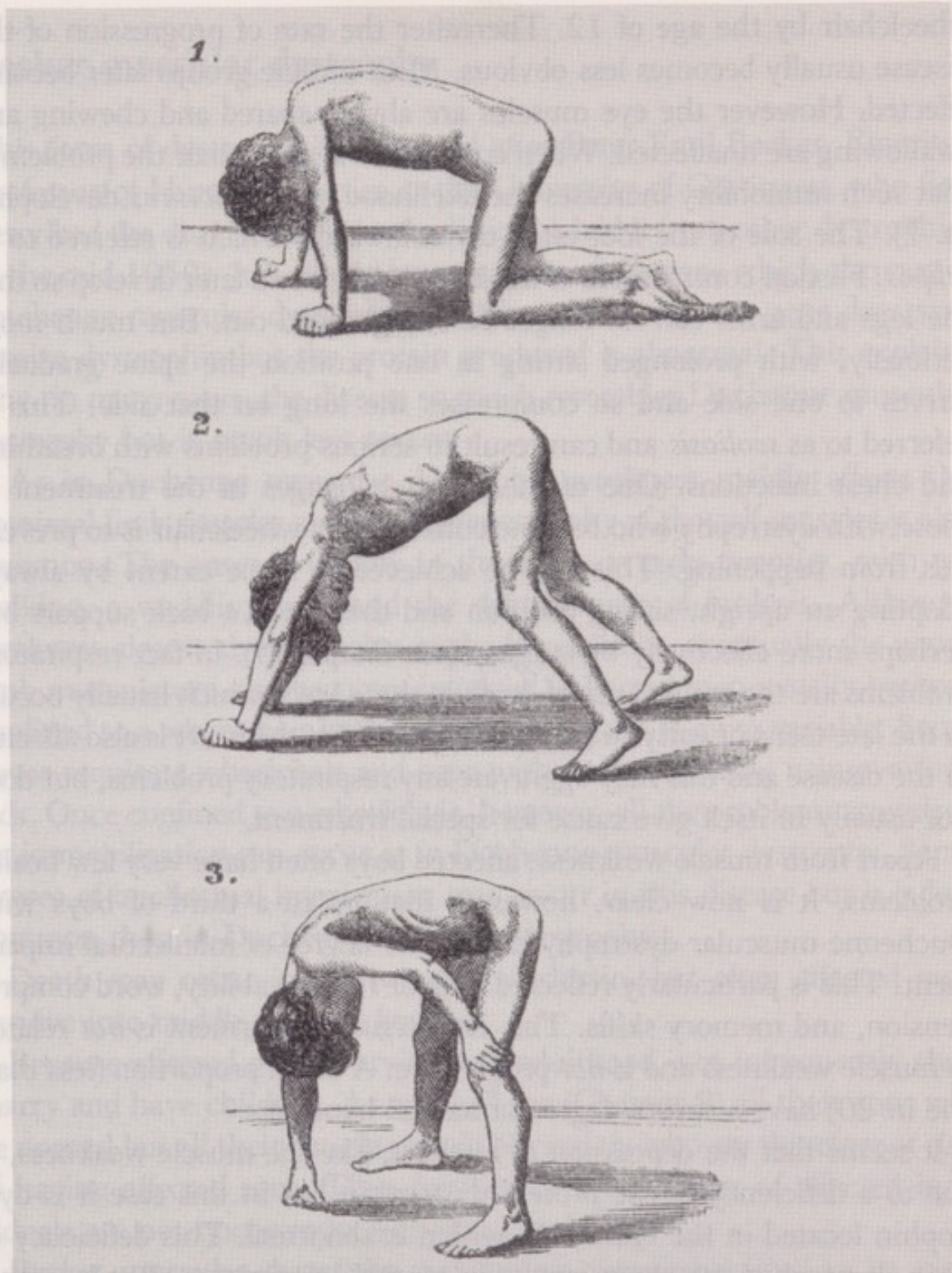


Figure 6 Gower's sign or manoeuvre from his book *Pseudohypertrophic muscular paralysis* published in 1879.

lower legs and forearms. The weakness, at least at the beginning, is therefore mainly proximal in this disease.

As weakness of the hips and thighs progresses, so walking becomes increasingly difficult and affected boys usually become confined to a



wheelchair by the age of 12. Thereafter the rate of progression of the disease usually becomes less obvious. Most muscle groups later become affected. However the eye muscles are always spared and chewing and swallowing are unaffected. When confined to a wheelchair the problem is that such immobility increases the likelihood of *contractures* developing (p. 7). The sole of the foot often turns inwards, which is referred to as *talipes*. Flexion contractures of the knees and elbows later develop so that the legs and arms can no longer be straightened out. But much more seriously, with prolonged sitting in one position the spine gradually curves to one side and so compresses the lung on that side. This is referred to as *scoliosis* and can result in serious problems with breathing and chest infections. One of the main challenges in the treatment of those with dystrophy who become confined to a wheelchair is to prevent this from happening. This can be achieved to some extent by always adopting an upright sitting position and the use of a back support but perhaps more effectively by surgery (see Chapter 5). In fact respiratory problems are the main cause of death in these boys, which usually occurs in the late teens or early twenties. We know that the heart is also affected in the disease and this may aggravate any respiratory problems, but does not usually in itself give cause for special treatment.

Apart from muscle weakness, affected boys often have very few health problems. It is now clear, however, that up to a third of boys with Duchenne muscular dystrophy have some degree of intellectual impairment. This is particularly reflected in poor reading ability, word comprehension, and memory skills. This intellectual impairment is *not* related to muscle weakness and is *not* progressive. A small proportion (less than one in 20) have a severe degree of mental handicap.

It seems that the depression of intellect, like the muscle weakness, is due to a deficiency of the protein dystrophin but in this case it is dystrophin located in the brain cells which is abnormal. This deficiency of brain dystrophin somehow results in mental impairment. But how this occurs and why only some boys are affected and not others is ill understood at the present time. Many affected boys have no impairment of intellect and I personally know of several who have reached college and university standards in their education.

Epilepsy is not particularly frequent in this disease and visual and hearing acuity are normal.



## Becker muscular dystrophy

This form of dystrophy is so named after Peter Emil Becker, Emeritus Professor of Human Genetics at the University of Göttingen, who first described the disorder and clearly distinguished it from other dystrophies in the mid-1950s. It is caused by mutations of the gene which also causes Duchenne muscular dystrophy. In this case the mutant gene does synthesize dystrophin but the protein produced is abnormal. This explains why, in many ways, the disease so much resembles Duchenne muscular dystrophy but is much less severe.

As in Duchenne muscular dystrophy, weakness mainly affects the proximal limb muscles and pseudohypertrophy of the calf muscles is also common. The onset is usually in the teens or early twenties, with toe walking, a waddling gait, and the development of lordosis. Although weakness almost always begins in the lower limbs, eventually the upper limb musculature also becomes involved. Affected men usually become confined to a wheelchair in their thirties, but this is quite variable. Some never require a wheelchair and cope with everyday living using various aids. Once confined to a wheelchair, however, all the problems attendant on immobilization can occur as in Duchenne muscular dystrophy. Some degree of intellectual impairment may occur in this disease but it is less common than in Duchenne muscular dystrophy.

Death may occur in the twenties or thirties but often affected men survive into middle age and beyond.

Because affected males survive into adulthood, not infrequently they marry and have children. As we shall see (Chapter 8) all their sons will be normal but all their daughters will be carriers who are therefore at risk of having affected sons. Thus families with a number of affected individuals are not uncommon with this condition.

Becker muscular dystrophy was at one time considered to be rare. However, recent DNA studies in affected males with no family history of the disease, who were thought previously to have other disorders, have now shown many of them to have Becker muscular dystrophy. The result is that we now believe that though rarer than Duchenne muscular dystrophy, it is probably commoner than many other dystrophies.

Different mutations of the Duchenne gene are now known to result in a spectrum of diseases. At one extreme there is the severe Duchenne



type of muscular dystrophy, followed by boys with relatively early onset but who survive longer than in classical Duchenne dystrophy, males with Becker muscular dystrophy and finally, at the other extreme, men who develop relatively mild weakness only in later life. Such a spectrum reflects different mutations of this gene and their different effects on the synthesis of dystrophin. Detailed knowledge of the mutation and its effect on dystrophin synthesis provide the best ways for determining the precise diagnosis and ultimate course of the disease in a particular person.

### Emery-Dreifuss muscular dystrophy

This is an uncommon type of dystrophy but because it is so distinctive and because early recognition and appropriate treatment can be life saving, it deserves special mention. Cases of this disease have no doubt been noted by physicians in the past, but it was described in detail for the first time in the mid-1960s by Dr F. E. Dreifuss of Charlottesville and myself. The recognition of this type of dystrophy grew out of studies of a large family with the disease in Virginia which did not fit into any of the types of dystrophy which had been described up to that time. We therefore considered it a separate disease. This has since been confirmed by others, and individuals and families with this disease have now been reported from various parts of the world.

It is a relatively benign muscular dystrophy which, like Becker muscular dystrophy, is inherited as an X-linked recessive trait. But the onset is in early childhood and the distribution of muscle weakness is different. In the early stages the weakness predominantly affects the shoulder and upper arm muscles as well as the anterior tibial and peroneal muscles of the lower legs. The latter raise the foot and so the main complaint at the beginning is not so much difficulty in climbing stairs, for example, but a tendency to trip over carpets and steps. Later on, the pelvic girdle musculature also becomes affected and some people require a wheelchair in later life.

Apart from this distinctive distribution of muscle weakness, another distinguishing feature is the *early* development of muscle contractures *before* there is any significant degree of muscle weakness. These contractures predominantly affect three regions of the body: the heel cords



(Achilles tendons) (so from an early age affected boys walk on their toes), elbows (so that the elbows cannot be extended fully even from childhood), and the muscles at the back of the neck (so that bending the neck forward is difficult). There is never any calf enlargement or pseudo-hypertrophy.

The progression is relatively slow and most affected boys survive into middle age with varying degrees of incapacity. There does not appear to be any intellectual impairment, but there is one other feature which is singularly important.

The heart often becomes affected in a very distinctive way which is referred to as *heart block* and which results in abnormal slowing of the heart rate. This does not occur in every patient and may not develop until later in life. On the other hand, exceptionally it may occur in youth before significant weakness is apparent. It has to be recognized because effective treatment (which often involves inserting a pacemaker) is life saving (individuals with a pacemaker can then live more or less normal lives). One man I know with this condition who has a pacemaker is a keen naturalist and has crossed the Sahara in quest of specimens, though such feats are not recommended for most patients.

Features which indicate that heart block may be developing include slowing of the pulse rate, drowsiness, dizzy spells, and fainting attacks. If these symptoms should develop in a man with this condition, medical advice should be sought immediately.

## Limb girdle muscular dystrophy

In this type of dystrophy weakness predominantly affects the *limb girdle* muscles, that is, the muscles around the hips and shoulders. But there are many causes for such limb girdle weakness. They include, for example, certain rare congenital myopathies, spinal muscular atrophies, polymyositis, and so-called acquired myopathies associated with various glandular disturbances. Even certain infections and some drugs, most notably steroids, may produce limb girdle weakness. These possibilities have to be excluded by a careful medical examination and by appropriate tests.

Limb girdle weakness in a female may be due to her being a so-called *manifesting carrier* of Duchenne muscular dystrophy. This is not



common but has to be considered because such a woman is at risk of having sons affected with the disease (p. 89). Also limb girdle weakness in a male may be due to *Becker muscular dystrophy* and this can also be a diagnostic problem when no-one else in the family is affected. Thankfully both these latter possibilities can now be excluded by appropriate DNA and muscle dystrophin studies (p. 19). If these two possibilities are excluded, we are left with a group of disorders which we refer to as the limb girdle muscular dystrophies, since there are now recognized to be several types of this disease. They differ in their age at onset, severity, and mode of inheritance.

In all cases there is involvement of the shoulder girdle and hip girdle musculature. The weakness may be progressive and can eventually extend to other muscles. A wheelchair may become necessary after several years and contractures and scoliosis may then develop. Thereafter respiratory function often declines and life expectancy is reduced, though the heart itself is not affected. However, the disease is quite variable. In some it is very slowly progressive and affected people can remain mobile throughout their lives. Intellect is unimpaired.

At this stage of our knowledge this disease can be roughly divided into two main groups, depending on the age at onset: limb girdle Duchenne-like muscular dystrophy of childhood, and limb girdle muscular dystrophy of adulthood. However, neither of these disorders is likely to be a single disease entity and problems of diagnosis will only be satisfactorily resolved once the responsible genes and their products have been identified.

#### *Limb girdle Duchenne-like muscular dystrophy of childhood*

This is sometimes also referred to as *severe childhood autosomal recessive muscular dystrophy* or *autosomal recessive Duchenne-like muscular dystrophy*. Clinically it very much resembles Duchenne muscular dystrophy but is inherited as an autosomal recessive trait (p. 87) and therefore affects both boys and girls. When however there is only one affected boy in the family the distinction from Duchenne muscular dystrophy can only be made on DNA and muscle protein studies. In Duchenne muscular dystrophy muscle dystrophin is absent, as are *all* the dystrophin-associated glycoproteins, whereas in this condition, the gene for which is on chromosome 13, muscle dystrophin is normal and only a particular glycoprotein is deficient.



The distinction between this and Duchenne muscular dystrophy is very important because, though the outcome is very similar, the mode of inheritance is quite different. In Duchenne muscular dystrophy a healthy sister may prove to be a carrier and therefore at high risk of having affected sons. In this disorder, because it is inherited as an autosomal recessive trait, an unaffected sister is most unlikely to have affected children. This is a rare disorder in North America and western Europe where it is roughly 20 times less common than the clinically similar Duchenne type of dystrophy. It seems to be more common in Brazil, and almost as prevalent as Duchenne muscular dystrophy in certain Arabic communities, most notably in northern Africa.

Another type of dystrophy first becomes apparent somewhat later in life and is less severe. The serum level of creatine kinase is only moderately raised and because the basic defect is unknown the diagnosis is often made by first excluding other possible causes of limb girdle muscle weakness. A number of tests may therefore be necessary before the diagnosis can be established. One form of this type of dystrophy is inherited as an autosomal recessive trait and is especially common among the Amish of North America, the responsible gene being located on chromosome 15.

#### *Limb girdle muscular dystrophy of adulthood*

Another rarer form with adult onset and slower progression is inherited as an autosomal dominant trait and the responsible gene is on chromosome 5.

The basic biochemical defects in these forms have not yet been identified, but because the locations of the defective genes are known, it is possible to trace the disease in affected families. In this way we can identify those who, in later life, may develop the disease. In certain rare families males are predominantly affected and in others females, but the reason for this is unknown. In most families with limb girdle dystrophy both males and females are affected equally.

#### **Facioscapulohumeral muscular dystrophy**

As the name implies there is facial weakness which results in an inability to close the eyes properly and to whistle. The smile is often described as



being 'transverse' and the lips appear to pout. Speech may become indistinct if the facial weakness is marked. The other characteristic feature is wasting and weakness of the shoulder muscles, particularly around the shoulder blades or scapulae. The shoulders droop and there is increasing difficulty in raising the arms. A notable feature is that the shoulder blades become very prominent, for which the term 'winging' is often used. This disorder is an exception to the general rule that in dystrophy weakness is usually symmetrical: in facioscapulohumeral muscular dystrophy, muscle weakness often affects one side more than the other at the beginning.

The other muscles affected early on are the anterior tibial and peroneal muscles which raise the foot, so that tripping over carpets and steps is a frequent problem; there is a 'stepping gait' and running becomes impossible.

As the disease progresses the pelvic girdle musculature may also become affected with a resultant waddling gait and lordosis, and people affected in this way may eventually require a wheelchair. Hearing loss, which may be unilateral, is not infrequent. This is now recognized as being part of the disease but in most cases does not produce serious problems.

Onset of the disease varies a great deal from childhood to adulthood although almost all individuals will show some signs of the disease by the age of 20 and certainly by 30.

More than any other type of dystrophy, the expression of this disease varies considerably from one person to another, sometimes within the same family. Some may have only mild facial weakness and no more than minimal shoulder weakness all their lives which may even go unrecognized. About half never have any pelvic girdle weakness which causes them serious problems. However some, fortunately few, eventually become confined to a wheelchair. Life expectancy in general is not significantly reduced and many remain active throughout their lives. The heart is not affected and there is no intellectual impairment.

This type of dystrophy affects both sexes equally and is inherited as an autosomal dominant trait. The gene has now been located on chromosome 4 and so with appropriate DNA markers it is possible to determine within a family who is likely to carry the gene, even though they may be clinically unaffected at the time of examination.



## Distal muscular dystrophy

In this type of dystrophy muscle weakness predominantly affects the *distal* limb muscles—those of the forearms and lower legs. But, as in limb girdle muscular dystrophy, there are several other disorders which can also produce this particular distribution of muscle weakness. These include diseases of the spine and spinal cord as well as of the nerves supplying this group of muscles. These possibilities must therefore be excluded before the diagnosis of distal muscular dystrophy can be made.

Weakness in the forearms and hands is present from the beginning and is first noticeable as clumsiness in fine movements, such as fastening buttons, sewing, or typing. Involvement of the lower leg muscles leads to tripping over carpets and steps and makes standing on the heels, or less often on the toes, difficult if not impossible. The proximal limb muscles only occasionally become affected, the disease is slowly progressive, and life span is normal.

This disease, beginning in the twenties or thirties decade or even later, appears to be prevalent in Sweden, though cases have now been reported from various other countries throughout the world. It affects both males and females and is inherited as an autosomal dominant trait.

A somewhat similar disease but with earlier onset and more severe muscle involvement, inherited as either an autosomal recessive or dominant trait, has been described in various countries including Japan. However, it has to be admitted that there is no complete agreement concerning the division of distal muscular dystrophy into various types. Until the defective gene or genes have been identified and the basic biochemical cause is known, any attempt to resolve this problem will never be entirely satisfactory.

## Oculopharyngeal muscular dystrophy

Much of our knowledge of this autosomal dominant disorder has come from studies of French Canadian families with the disease which can be traced back to immigrants from France in 1634. However the disease is now known to occur also in the United States of America as well as in Europe.



Onset is usually in the thirties or later. As the name implies, the eye muscles are affected early on. At first movements of the two eyes may be incoordinate and double vision (*diplopia*) can result. Later all eye movements are restricted, so to change the field of vision the head has to be turned. At the same time weakness of the upper facial muscles develops with drooping of the eyelids, called *ptosis*. Mild weakness of the neck muscles and the proximal upper limb muscles commonly occurs. A serious symptom which may develop is difficulty in swallowing, known as *dysphagia*, for which surgery (cricopharyngeal myotomy) may be helpful.

A somewhat similar disease but with earlier onset has been reported in Israel among Ashkenazim where it is inherited as an autosomal recessive trait.

Recent research has shown that more and more cases with this syndrome are proving to have muscular dystrophy due *not* to mutations of nuclear genes, but to mutations of *mitochondrial* genes. That is, there are mutations of the DNA in the parts of the cell which are important for producing the body's energy. Such subtle differences might seem unimportant—but establishing a precise diagnosis is essential for counselling and the advice of a specialist is particularly important in this form of dystrophy.

## Congenital muscular dystrophies

The word congenital simply means 'present at birth'. The congenital muscular dystrophies are therefore a group of dystrophies in which weakness and other problems are evident in the newborn period, or certainly within the first month or so of life.

This is quite a different group of diseases from the so-called *congenital myopathies*. The features of muscle histology seen in congenital myopathies are quite different from those features, characteristic of dystrophy, seen in the congenital muscular dystrophies (p. 19). Thus, in any infant who at birth or shortly thereafter appears to be weak, usually expressed at this time as 'floppiness' and feebleness of voluntary movement, a muscle biopsy is important in order to arrive at the correct diagnosis.



Though it is difficult to generalize because there are probably several different types of congenital muscular dystrophy, in most cases the disease is relatively slowly progressive with many affected children ultimately learning to walk though some may require various aids in order to make this possible. The serum creatine kinase level is often only slightly raised—in contrast to Duchenne muscular dystrophy, for example. Most cases seem to be inherited as autosomal recessive traits with a one in four chance of recurrence in subsequent children (p. 87). Apart from the Fukuyama type of congenital muscular dystrophy, which merits separate consideration, our knowledge of this group of diseases at present is very limited. They are currently the subject of a great deal of research directed at determining their causes.

#### *Fukuyama congenital muscular dystrophy*

After Duchenne muscular dystrophy this type of congenital muscular dystrophy is the second most common type of dystrophy in Japan, but seems to be rare outside this country. It is named after Dr Yukio Fukuyama in Tokyo who first described the disease in 1960. The onset is in infancy with generalized muscle weakness and though able to crawl, few affected children are ever able to walk. Calf pseudohypertrophy is common, and all patients are severely mentally retarded; many also have epilepsy. As in Duchenne muscular dystrophy the serum level of creatine kinase is grossly elevated at first and then gradually declines over the years. Often affected children die in childhood but some survive into their twenties. This type of congenital muscular dystrophy is inherited as an autosomal recessive trait with a one in four chance of recurrence in subsequent children.

### **Myotonic dystrophy**

This is quite a unique condition in many ways. Firstly, unlike any other type of dystrophy, *myotonia* is a significant feature—this is the *delayed relaxation* of muscle which occurs after voluntary contraction. Affected people usually refer to this as 'stiffness'. This particularly affects the small muscles of the hands so that after making a fist or gripping an object the muscles relax only slowly. Especially in the cold it may be



some time before the hand is completely relaxed again. This is often considered more as a nuisance than as a handicap. This prolonged relaxation can be demonstrated by the doctor by tapping the muscle, whereby the tapped or percussed muscles are seen to contract and then relax only slowly. It can be demonstrated conclusively by electromyography, which is therefore a very important diagnostic test for this disorder.

Secondly, unlike other dystrophies, other organs and tissues are frequently affected. Individuals may develop cataracts, as well as various glandular (endocrine) problems—including perhaps a reduction in fertility, increased likelihood of fetal loss (through spontaneous abortions, stillbirths, and deaths in the newborn), and in males early frontal baldness is common. Lethargy and general apathy are also quite common. Children can be severely affected from birth (so-called congenital form) with marked facial weakness, feeding and breathing problems early on, and mental retardation.

Thirdly, the features of muscle histology so characteristic of dystrophy are absent in this condition. Instead, the most prominent characteristic is increased nuclei in the *centre* of muscle fibres, whereas normally they are situated at the periphery of the fibres. Fibre necrosis, phagocytosis, and replacement by fatty connective tissue do not occur.

Despite these differences there are certain similarities with muscular dystrophy, most notably muscle wasting and weakness. This affects the face and neck muscles, lower leg and forearm muscles, and the small muscles of the hands. The heart can also be affected with the development of some degree of heart block (p. 29). However, unlike the 'true' dystrophies where muscle weakness is the main complaint, myotonic dystrophy is a more generalized disorder.

Only occasionally do all these features of the disease occur in any one person. Sometimes there may be symptomless minute cataracts which are only detected (using a slit lamp) by chance when examining relatives in an affected family. At the other extreme is the congenitally affected infant of an affected mother who often may herself be minimally affected. Children of affected fathers do not have this serious form of the disease, but the reason for this difference is not known.

This disease frequently increases in severity from one generation to the next, a phenomenon referred to as *anticipation*. Thus a grandfather with cataracts and mild myotonia may have a daughter with myotonia and muscle weakness who, in her turn, has a child with the serious con-



genital form of the disease. This is not uncommon and has now been explained by DNA studies. Such studies can also provide an idea of the possible course of the disease in the individual case.

Though many affected persons have little disability they frequently fail in employment. While the outlook is poor in congenital myotonic dystrophy, adults who are mildly affected with little or no muscle involvement may be expected to survive into middle age and even beyond. The prognosis is worse when there is significant cardiac involvement.

Finally, as in all suspected cases of dystrophy, a careful clinical examination by an experienced physician is essential in establishing the diagnosis. In less severe and minimally affected persons the following tests may be carried out in order to confirm the diagnosis: electromyography to confirm the presence of myotonia, a slit-lamp examination of the eye for the characteristic symptomless multicoloured lens opacities (cataracts) which are often seen early in the disorder, and most importantly DNA studies for the molecular abnormality specific for this disorder.

### Other forms of dystrophy

Though the discussion here has centred on the principal, clearly defined types of muscular dystrophy, there is little doubt that other types also exist. Some have been given special names, such as the so-called Mabry and Bergia types, others defined by their apparent distinctive muscle involvement (scapuloperoneal, scapulohumeral) or by their muscle histology (X-linked myopathy and autophagy). But these are rare and in some cases their inclusion as dystrophies is a matter of some dispute among medical scientists. For these reasons they are not discussed here, but details will be found in major reference texts listed at the end of the book.

### Summary

It is possible on the basis of the distribution of predominant muscle wasting and weakness, along with certain other features, such as age at onset, to define at least eight major types of muscular dystrophy.



Myotonic dystrophy is unique in so many ways that it should perhaps not really be considered a muscular dystrophy; I have included it here for the sake of completeness.

A precise diagnosis of a specific type of dystrophy is essential in order to determine the probable course and outcome of the disease in an affected person and for reliable genetic counselling.



## 5. Treatment

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A *cure* for muscular dystrophy would mean replacing the defective causative gene mutation by a normal gene. Since in dystrophy the defective gene is active in every muscle cell of the body as well as in the brain, and in the case of myotonic dystrophy in various other tissues and organs as well, it seemed a forlorn hope that a cure in this sense would ever be possible. The problem seemed insuperable—even to scientists working in the field. Yet very recently there have been technological developments which raise hopes that this might in fact become a distinct possibility, perhaps before not too long. The topic of *gene therapy* as this is referred to, will be discussed briefly at the end of this chapter.

So, though there is as yet no cure, a great deal can be done to relieve many of the problems associated with dystrophy and to improve the quality of life. Because of the unrelenting course of muscular dystrophy there was a tendency on the part of health-care professionals in the past to adopt a somewhat indifferent attitude to treatment. This view is no longer justified. A great deal can be achieved by adopting a positive approach. This positive approach involves three Ps:

- *p*romotion and maintenance of good health in general
- *p*revention of deformities through exercises, physiotherapy, orthoses, and surgery
- *p*reservation of respiratory function

### Promotion and maintenance of good health

Whatever the type of dystrophy and whatever stage the disease has reached, there are certain general principles always to be considered. Foremost, there is the need to maintain good health in general. A good, well-balanced diet with adequate fibre is essential to overcome the common problem of constipation, especially when individuals become immobilized. Of particular importance is to prevent weight gain, which



often requires professional advice; most muscular dystrophy groups and associations, as well as doctors involved in the disease, can provide helpful information sheets or dietary advice. Plenty of fresh fruit and vegetables are key elements of a good diet. There is no evidence that 'megavitamin' therapy or dietary supplements are of any real value.

Prolonged periods of bed rest after, say, an infection should be discouraged because this may lead to an acceleration of muscle weakness. As a general principle in the early stages of any of the dystrophies and before walking becomes difficult, individuals should be encouraged to try to lead as normal a life as possible.

### Active exercise

A question frequently asked is 'Will exercise improve my muscle strength or slow down the progress of the disease?' The answer is that vigorous or violent exercise or strenuous callisthenics are certainly *not* recommended. They may do actual damage to the muscle and rather than preserving muscle strength, may well have the opposite effect. Severe exercise may also aggravate any heart problems that may be present.

There is no doubt, however, that moderate active forms of exercise do no harm and often have a beneficial psychological effect. Activities of a recreational nature are often preferred and are more likely to be maintained. In this regard swimming is particularly valuable as the buoyancy of the water makes exercises easier to perform, but again it should not be pursued to the point where it becomes exhausting. It is always advisable to have an able-bodied person present at the time just in case any untoward difficulties arise. The best advice is to encourage normal everyday activities wherever possible, supplemented with moderate exercise when this is appropriate and enjoyable.

### Passive exercise and physiotherapy

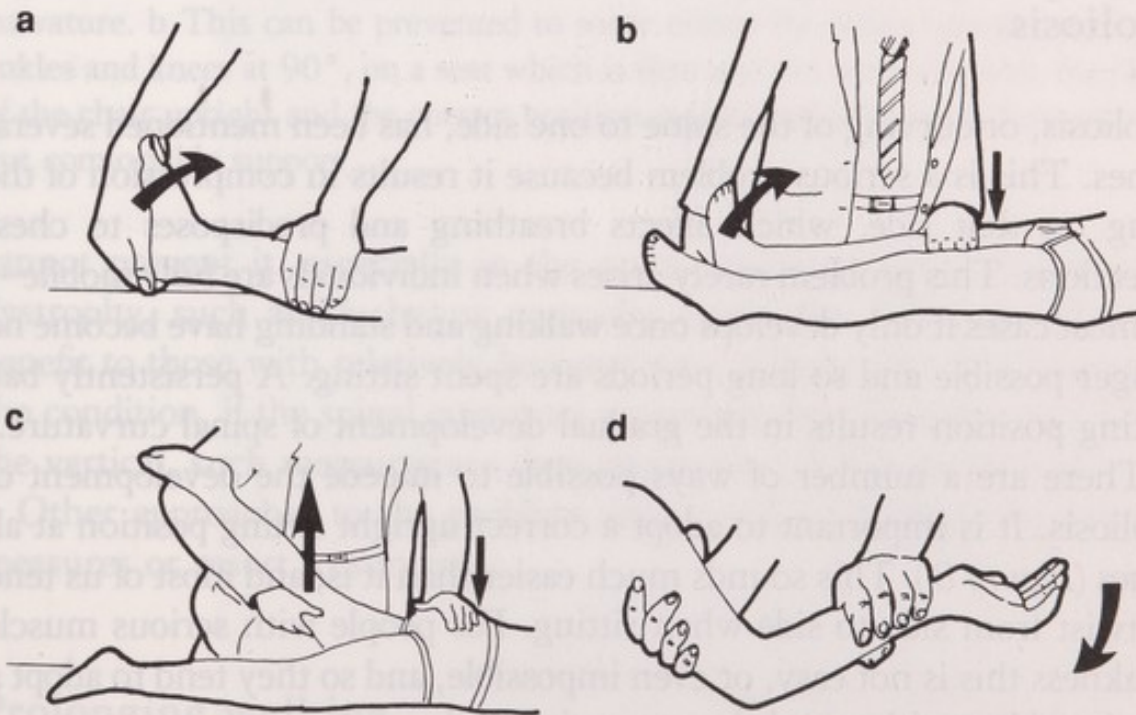
Passive exercise refers to the movement of limbs by another person rather than by the affected individual. The aim is to keep the joints freely mobile and, by *gentle* stretching exercises, to prevent the development of



muscle contractures. Parents, partners, and friends can soon learn many of these techniques though it is advisable to have a professional physiotherapist explain and demonstrate the various procedures at the beginning. The emphasis is on firmness yet gentleness. *Force must never be used.*

Different techniques are indicated for different problems. Thus in those dystrophies where the heel cords (Achilles tendons) become tight and associated with toe-walking, passive stretching by pushing the foot upwards may be helpful (Figure 7). Passive stretching of the knee and hip joints becomes important after mobility has been lost and where prolonged sitting is leading to contractures of these joints. All such exercises are best carried out on a regular basis at specific times of the day so that they become a routine. After a warm evening bath is a good time for small children. Sylvia Hyde's excellent booklet on the subject entitled *Duchenne muscular dystrophy: a parent's guide to physiotherapy in the home*, is available in the United Kingdom from the Muscular Dystrophy Group of Great Britain (see end of book for address).

However, although such exercises may delay the development of contractures, once these occur passive stretching is often ineffective and



**Figure 7** Some passive stretching exercises designed to prevent contractures of the a heel cords (Achilles tendons); b knee; c hip; d elbow joints. (After Hyde (1993) with permission.)



the use of force can cause serious damage to the muscles and joints. In these circumstances the only solution may be surgery, as will be discussed later.

Some propose the use of night splints in order to help prevent the development of contractures of the ankle and knee joints, but it is very doubtful if such measures have any real value while the individual is still ambulant. They should be measured and fitted by a specialist and must be comfortable to wear, otherwise they are likely to be discarded after a time.

### **Chronic low-frequency electrical stimulation**

There was a great deal of interest a year or two ago in the possible benefits of stimulating weak muscles to contract using low-frequency electrical pulses. Evidence however has shown that this time-consuming and expensive technique is of very doubtful value and cannot be recommended.

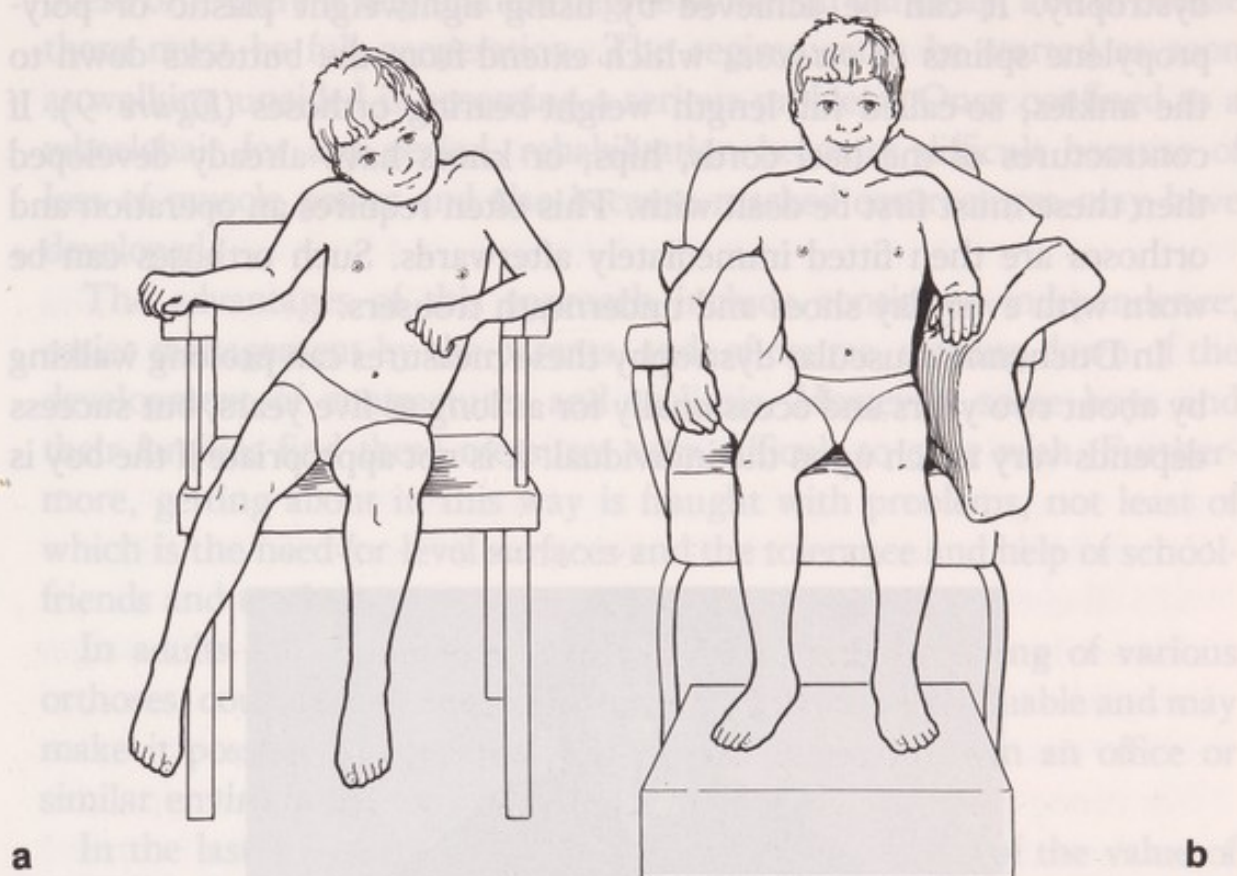
### **Scoliosis**

Scoliosis, or curving of the spine to one side, has been mentioned several times. This is a serious problem because it results in compression of the lung on that side, which affects breathing and predisposes to chest infections. This problem rarely arises when individuals are fully mobile—in most cases it only develops once walking and standing have become no longer possible and so long periods are spent sitting. A persistently bad sitting position results in the gradual development of spinal curvature.

There are a number of ways possible to impede the development of scoliosis. It is important to adopt a correct upright sitting position at all times (*Figure 8*). This sounds much easier than it is, and most of us tend to twist from side to side when sitting. For people with serious muscle weakness this is not easy, or even impossible, and so they tend to adopt a comfortable position and then stay sitting that way.

Individually-designed firm back supports, body jackets, and braces made of lightweight materials are now available commercially. But although such measures may slow the development of scoliosis, they





**Figure 8** a A bad sitting position results in the gradual development of spinal curvature. b This can be prevented to some extent by sitting upright with the ankles and knees at  $90^\circ$ , on a seat which is firm and not too wide, with the back of the chair upright and the correct position maintained with some form of firm but comfortable support.

cannot prevent it, especially in the more rapidly progressive forms of dystrophy, such as Duchenne muscular dystrophy. They are of more benefit to those with relatively benign forms of dystrophy, but whatever the condition, if the spinal curvature progresses beyond about  $40^\circ$  from the vertical, such measures are then impractical and of limited value.

Other approaches to the problem are to prolong walking by various measures or resort to surgery.

## Prolonging walking

Prolonging walking beyond the point where this is normally no longer possible is a difficult problem, particularly in the more serious forms of



dystrophy. It can be achieved by using lightweight plastic or polypropylene splints or *orthoses* which extend from the buttocks down to the ankles, so-called full-length weight-bearing orthoses (*Figure 9*). If contractures of the heel cords, hips, or knees have already developed then these must first be dealt with. This often requires an operation and orthoses are then fitted immediately afterwards. Such orthoses can be worn with everyday shoes and underneath trousers.

In Duchenne muscular dystrophy these measures can prolong walking by about two years and occasionally for as long as five years, but success depends very much upon the individual. It is not appropriate if the boy is

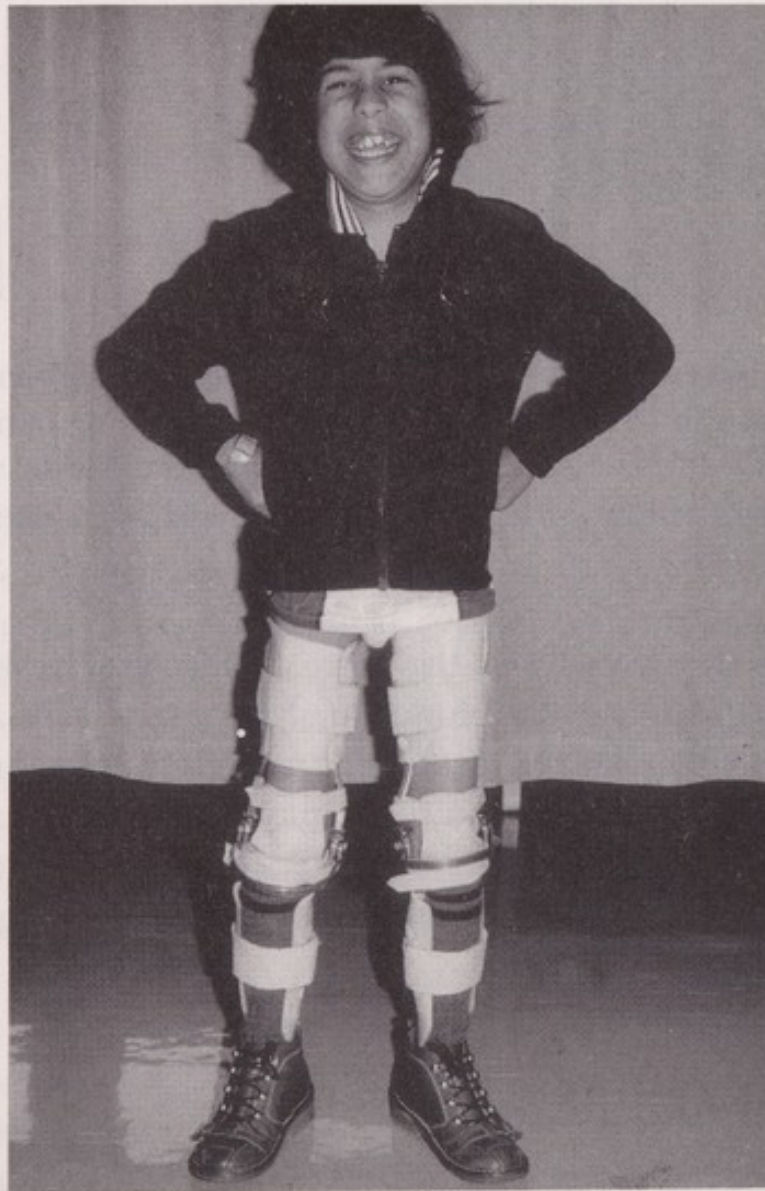


Figure 9 Orthoses have to be comfortable.



obese or if there is any marked degree of mental handicap, and of course there must be full cooperation. The regime must be started as soon as walking unaided is becoming a serious problem. Once confined to a wheelchair for any period, rehabilitation becomes difficult because of loss of muscle power and also because marked contractures may have developed.

The advantages of this approach include continued independence, easier management by the parents, and, of course, slowing down of the development of contractures and scoliosis. However, some boys and their families find these measures very difficult to cope with. Furthermore, getting about in this way is fraught with problems, not least of which is the need for level surfaces and the tolerance and help of school-friends and teachers.

In adults the situation is very different. Here the fitting of various orthoses, coupled with surgery, often proves extremely valuable and may make it possible to continue with gainful employment in an office or similar environment for several years afterwards.

In the last few years there has been much discussion of the value of *standing frames*. The device is strapped to the body, so enabling the individual to maintain an upright standing position which otherwise would be impossible. This is only possible, however, if the knee and hips are kept straight by some form of splintage. Wheelchairs can be modified for the same purpose. Such measures are more likely to find use in adults with more slowly progressive forms of dystrophy where they can be of psychological benefit. Maintaining an upright position may also have a beneficial effect on lung function. Some find they can work in this way, for example with a computer or drawing board, for quite long periods of the day.

## Aids for the disabled

There are now commercially available many different types of aids for the disabled. Some have been designed for other conditions, such as severe arthritis, but can often be easily modified for people with dystrophy. For example, kitchen aids designed for those with rheumatoid arthritis often prove helpful to those with weakness of their hands due to dystrophy.



Aids range from major modifications to the home (including lifts, ramps, and bathroom fitments) to those which help with mobility (wheelchairs), seating, methods of communication (adapted computers and word processors), and even leisure pursuits (such as gardening). Relevant literature and information is available from the various muscular dystrophy associations and groups listed at the end of the book. In Britain there are two particularly valuable sources: Phillipa Harpin's *With a little help*, available from the Muscular Dystrophy Group of Great Britain, and George Cochrane's *Walking aids*, available from the Mary Marlborough Lodge in Oxford. In the United States of America information on equipment suppliers can be obtained from:

National Association of Medical Equipment Suppliers (NAMES)  
625 Slaters Lane, Suite 200  
Alexandria  
Virginia 22314-1171  
USA

For those who become severely disabled there are now available wheelchair-mounted robotic manipulators and computers. Control panels can be modified to suit individual needs and may permit many everyday activities which otherwise would be impossible. Just what can be accomplished under such circumstances is well illustrated in the case of the world renowned Professor of Mathematics Stephen Hawking, famous as the author of *A brief history of time*. Such equipment is of course expensive but no doubt with the modification of commercially available equipment this will become less of a problem in future. *Anything which makes an individual's life more independent and enables the continued pursuit of employment, or even interesting pastimes and hobbies, has to be encouraged.* Perhaps the worst situation of all for those with dystrophy is to feel helpless, worthless, and isolated.

## Surgery

At one time there was a vogue for dividing the heel cords in young boys with Duchenne muscular dystrophy, but this and other *early* surgical procedures are now no longer recommended. Not only does it fail to improve muscle strength or walking ability, but the period of bed rest following such surgery may actually be detrimental. Often following prolonged bed rest affected boys are no longer able to walk again.



But as we have seen, surgical correction of contractures can be valuable in the *later* stages of the disease when walking unaided is becoming increasingly difficult and when it is then designed to prolong ambulation.

Surgery in order to correct scoliosis is also becoming widely accepted. The technique used is referred to as the Luque operation, after Dr Eduardo Luque of Mexico who pioneered the operation. During the operation the spine is straightened as far as possible and the individual vertebrae wired to two stainless steel rods which are thereby fixed to the spine. This produces a rigid and stabilized spine and further curvature is prevented. Postoperative recovery is usually uneventful and requires no more than a week or two in hospital.

Some have advocated this operation as a preventive measure *before* the development of scoliosis but most agree it is best considered when ambulation has been lost and it is becoming obvious that scoliosis is beginning to develop. The surgeon has to decide, however, if the individual is fit enough for surgery and in particular that lung function is relatively good. The idea is to plan well ahead. If referral is delayed the patient may in fact be found to be unsuitable for surgery.

In Duchenne muscular dystrophy (in which this operation has so far been most used) there is evidence that it helps to preserve lung function and *may* actually prolong life for a few extra years. Certainly, sitting becomes much easier and more comfortable, and in adults with dystrophy there is no doubt that many years of useful and productive life may be made possible in this way.

The decision to undergo surgery requires careful thought and discussion with a surgeon experienced in the disease. No doubt there are advantages but this is a major operation and, like all such operations, carries certain risks which have to be considered. Increased muscle breakdown results in increased amounts of muscle protein (myoglobin) in the urine, which can sometimes lead to kidney damage. More importantly, the functioning of the heart may be adversely affected. In any dystrophy there is also the risk of chest infection due to retention of bronchial secretions, resulting from weakness of the respiratory muscles and associated weak cough. Postoperative respiratory care and appropriate physiotherapy are therefore essential.

However, despite these risks—which nowadays are all well recognized by anaesthetists and surgeons—the majority of patients tolerate surgery very well indeed and postoperative recovery is usually unevent-



ful. In several recent large surveys of patients with Duchenne muscular dystrophy who have had major surgery to correct spinal deformities there were very few serious problems. Furthermore, if surgery becomes *necessary* for any reason (for example, cholecystectomy for gall bladder disease), dystrophy in itself should not generally be a reason against having the operation.

In all cases it is essential that the anaesthetist is fully informed of the diagnosis *before* any procedures are undertaken. As we say, 'forewarned is to be forearmed', and in this way any problems which might arise during surgery will either be prevented from happening or recognized as soon as they occur and then treated immediately before complications develop.

Since not all hospital nursing staff will have come across a patient with muscular dystrophy before, in order to help them know what a particular patient can do, it is useful to have a 'hospital card' which records the diagnosis and what the patient can do physically in regard to feeding and toilet arrangements. The Muscular Dystrophy Group of Great Britain, for example, makes such cards available for patients who may be planning to go into hospital.

## Fractures

Some people with dystrophy, due to their muscle weakness, frequently sustain bone fractures as a result of minor accidents such as falling. This is partly due to the fact that the long bones of the limbs are often less strong than normal due to disuse. Because of the adverse effects of prolonged immobilization on muscle function, fractures are often treated with minimal splintage so that mobility can be resumed as soon as possible. Otherwise fractures in patients with dystrophy present no additional problems: they heal normally and call for no special orthopaedic measures.

## Respiratory problems

Not only does chest deformity restrict airflow on the compressed side, but respiratory problems are also aggravated by weakness of the respira-



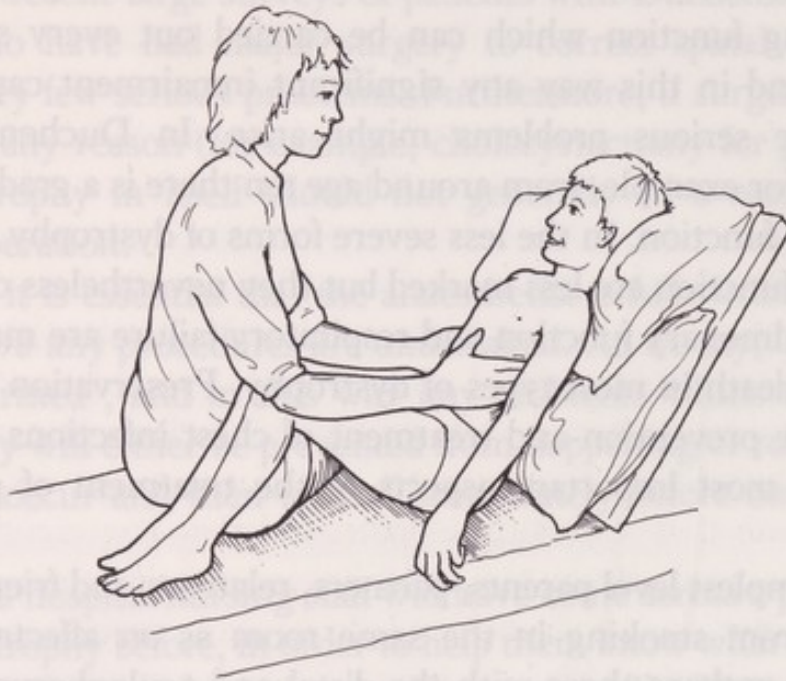
tory muscles themselves. There are now available simple, non-invasive tests of lung function which can be carried out every six months if necessary and in this way any significant impairment can be detected early before serious problems might arise. In Duchenne muscular dystrophy, for example, from around age ten there is a gradual deterioration in lung function. In the less severe forms of dystrophy the effects on respiratory function are less marked but they nevertheless occur. In fact, impaired pulmonary function and respiratory failure are major causes of illness and death in most types of dystrophy. Preservation of lung function and the prevention and treatment of chest infections are therefore among the most important aspects of the treatment of patients with dystrophy.

At the simplest level parents, partners, relatives, and friends should be dissuaded from smoking in the same room as an affected individual. Apart from perhaps those with the distal and oculopharyngeal types of dystrophy where lung function is not affected, people with dystrophy *should never smoke*, particularly cigarettes. I am all too aware that such advice is sometimes hard to accept. Nevertheless, it cannot be emphasized too strongly that not smoking is one of the most important things that people with dystrophy can do for themselves to help preserve their lung function.

Many advocate vaccination against influenza at the beginning of the winter months and *all* infections of the respiratory tract must be treated *thoroughly*, and with a course of antibiotics where necessary. Even seemingly mild chest infections should never be ignored. In those who are at all severely affected and where there is already some breathing difficulty, hospitalization should be considered for any respiratory infection.

Any attempt to impede the development of scoliosis will have a beneficial effect on respiratory function. Deep breathing exercises can help (*Figure 10*). Parents, partners, and friends can also be instructed in how to carry out the procedure of so-called *postural drainage* which helps to remove the accumulation of mucous secretions in the lungs which, because of a weak cough, can be a problem in those who are more severely affected (this is not usually necessary in those who are fully ambulant). In postural drainage the head has to be lower than the chest to encourage drainage and this can be achieved by lying face down with a pillow under the hips or by lying flat, face down, and raising the foot of the bed (*Figure 11*). With a slightly cupped hand, the lower part of the chest is clapped and the patient encouraged to cough at the same time,





**Figure 10** Deep breathing: the helper's hands apply gentle pressure over the lower part of the rib cage while the person breathes in as much as possible, trying to move the ribs outwards against the hands, and the breath is then held for a few seconds before breathing out. This should be repeated, say, ten times at each session.

if this is possible. The mucous secretions which drain into the throat can then be removed, with suction apparatus if necessary. To be effective this technique is best if first learned from a doctor or physiotherapist who can demonstrate exactly how the clapping should be carried out and which positions are best adopted by a particular patient in order to encourage the drainage of secretions which may have accumulated.



**Figure 11** Postural drainage: the person is placed face down with the head lower than the chest.



## Assisted ventilation

Despite rigorous treatment of all chest infections and of scoliosis by surgery if necessary, in more severe cases lung function will inevitably decline as the muscles of respiration become increasingly affected. Lung function tests will of course detect these changes. But there are certain symptoms which are a warning of an impending serious decline in lung function. Normally when we sleep our breathing becomes slower and shallower. In dystrophy respirations may be quite adequate during the day but become so inadequate at night that there is very poor oxygenation of the blood and so-called *nocturnal hypoxia* develops. Symptoms which indicate that this is developing and that respiratory function is therefore becoming seriously affected include restless sleep, nightmares, morning confusion, headache, and drowsiness during the day. Later, more obvious signs of poor lung function become evident with increasing breathlessness and difficulty speaking. If symptoms suggestive of nocturnal hypoxia develop, medical attention should be sought and, if confirmed, *assisted ventilation* may be necessary. A number of methods are available.

Patients often find a *rocking bed* less intrusive than many other forms of assisted ventilation. This type of bed rocks in such a way as to use the abdominal contents to compress and then decompress the chest cavity. Such equipment can be maintained at home, though it is expensive and requires some adaptation of the home. Neither this nor an iron lung is appropriate for daytime use for those who wish to sit up.

Another approach is to use the *cuirass* or body shell, such as the Tunnicliffe jacket for example. These jackets consist of a rigid shell which encloses but does not touch the chest wall and abdomen. The shell is covered by an airtight jacket to which negative pressure is applied. Other jackets employ alternating positive pressure, but all have the disadvantages of being difficult to put on and cold to wear at night.

The method perhaps most favoured is to use an *intermittent positive pressure ventilator* connected to a nasal tube, mouth adaptor, or facial mask, depending on individual preference. This is the most efficient way of artificial ventilation as it provides a fixed volume of inspired air and then allows passive expiration. At first this may only be necessary during or immediately after an acute respiratory infection or later on at night when it can transform an individual's life. On questioning, most of those



on this form of intermittent ventilation say that it has definitely improved the quality of their lives. But unfortunately lung function often continues to deteriorate, necessitating ever longer periods of ventilation.

Eventually, which may be several years later in some cases, a *tracheostomy* may have to be considered. This involves inserting a tube into the windpipe (trachea) just below the 'Adam's apple'. This is usually done under local anaesthesia. The tube is then connected to a ventilator.

Tracheostomy sometimes has to be performed as an emergency procedure during an acute and severe respiratory infection in order to ensure adequate respiration and so that secretions can be removed by suction directly from the upper airway. However, having once started this means of ventilation it may later prove difficult to wean the patient off the machine.

In recent times there has been increasing interest in *elective* tracheostomy, that is, carrying out the procedure as a means of ensuring adequate lung function for the future and not as a response to an acute infection, but this raises serious problems of maintenance and nursing care which need to be carefully considered. Nevertheless, an increasing number of patients are now being managed in this way.

### Heart problems

In those disorders in which heart block is a particular problem, such as Emery-Dreifuss dystrophy and myotonic dystrophy, regular ECG (EKG) examination is important in order to detect the problem early on. Specific treatment may then be indicated and a permanent pacemaker may have to be considered. The decision whether or not to insert a pacemaker rests very much on the cardiologist in discussion with the patient.

Long-term preventive treatment, with digitalis compounds for example, has no value. However, in the later stages of dystrophy when heart involvement may become evident, then conventional treatment with appropriate drugs is indicated as would be the case in anyone with heart disease.

### Drug treatment

In myotonic dystrophy there are certain drugs which can be used to treat myotonia on the rare occasions when this is troublesome. These include



*quinine* and *procainamide* but because the former often produces a disturbing ringing in the ears (tinnitus) and both may adversely affect the heart in myotonic dystrophy, the drug *diphenylhydantoin* is now preferred. Caution should be exercised in taking the drug during pregnancy however, because of the risk of inducing cleft lip and palate in the fetus. Though this is relatively small, even a small risk is important when the symptom being treated is relatively benign and may not have really warranted treatment in the first place.

Table 1 Drugs which have been used in various therapeutic trials, mainly in Duchenne muscular dystrophy

Drug	Basis for use	First reported trial
Allopurinol	Increases nucleotide formation, believed to be depleted in dystrophic muscle	1976
Amino acids	Deficiency of muscle proteins	1953
Anabolic steroids	Anabolic effect	1955
Aspirin, propranolol, etc.	Counteract proposed defect in biogenic amine metabolism	1977
Calcium blockers	Reduce muscle intracellular calcium	1982
Catecholamines	Counteract proposed defect in muscle sympathetic innervation	1930
Coenzyme Q	Possible benefit in murine dystrophy	1974
Dantrolene	Inhibits release of calcium from sarcoplasmic reticulum	1983
Digitalis and other cardiac glycosides	Prevent progressive cardiomyopathy	1963
Glycine	Believed to stimulate muscle creatine synthesis	1932
Growth hormone	Anabolic effects	1973
Growth hormone inhibitor	Growth hormone deficiency ameliorates disease	1984
Ketoacids	Reduce muscle protein degradation	1982
Leucine	Increases protein synthesis	1984
Nucleotides (e.g. laevadosin)	Replacement of nucleotides believed to be depleted in dystrophic muscle	1960



Table 1 (cont.)

Drug	Basis for use	First reported trial
Oestrogens	Anabolic effect	1972
Pancreatic extract	Possible benefit in murine dystrophy	1976
Penicillamine	Possible benefit in avian dystrophy	1977
Prednisone	Anabolic effect	1974
Protease inhibitors	Possible benefit in murine dystrophy	1984
Superoxide dismutase	Removal of superoxide radicals associated with membrane damage	1980
Testosterone	Anabolic effect	1955
Thyroxine	Thyroxine depresses SCK	1964
Vasodilators	Counteract proposed defect in muscle microcirculation	1963
Vitamin B6	Vitamin B6-deficient rats develop a myopathy	1940
Vitamin E	Vitamin E-deficient animals develop a myopathy	1940
Zinc	Membrane 'stabilizer'	1986

For other types of dystrophy, no drug has yet been found which significantly improves muscle strength in the long term. In the past many have been tried and claimed to be beneficial (*Table 1*), but with subsequent carefully controlled trials this optimism has invariably proved to be ill-founded. There are a number of reasons for this. The diagnosis may not have been precise and the inclusion, for example, of cases of Becker muscular dystrophy in a study of the effects of a drug on Duchenne muscular dystrophy could have given the mistaken impression of slowing the course of the disease. Since various dystrophies often show periods of *apparent* arrest or slowing of the disease process, this too could be misinterpreted as being due to the drug being used. Over-enthusiasm by the investigator, coupled with understandable optimism on the part of those treated, may also influence the interpretation of the



results of a drug trial. For these and for various other reasons a trial of any therapy must be very carefully designed and executed.

First, a *precise diagnosis* must be established in all those included in the trial. Secondly, *objective* means of determining any improvement must be used. For example, muscle strength may be assessed using a special measuring instrument called a *myometer*. Thirdly, an *adequate number* of people must be included in the trial in order that any results may be statistically valid. Fourthly, and most importantly, in order to avoid any bias in the interpretation of results, all studies should be *carefully controlled*. That is, the patients should be divided into two groups which are matched exactly for age, sex, and severity of the disease. One group is then given the active drug (the treated group) and the other group (the control group) is given a *placebo* (an inactive compound which closely resembles the active drug, both in appearance and texture). This approach is not restricted to drugs to be taken by mouth, however, but could equally apply to other trials. For example, with injected drugs the control group might be injected with normal saline solution. Fifthly, such trials should be *double-blind*. This means that neither the patient and family, nor the investigator, knows who is taking the active drug and who is taking the placebo: the code is maintained by an uninvolved third party, usually the pharmacist. After a suitable period, at least six months and often longer, the code is broken and the two groups carefully compared for any differences.

This has only been a somewhat superficial review of the design of treatment trials and further details can be found in many modern texts. In 1984 a colloquium was held in Bangor, Pennsylvania, sponsored by the Muscular Dystrophy Association of America, which addressed many of the problems involved in drug trials, particularly in Duchenne muscular dystrophy. The Proceedings have been published and provide much useful information and guidance (*Muscle and Nerve* 1985, volume 8, pages 451-92).

If you are wondering why this topic has been discussed in such detail, the reason is that all too often in the past ill-designed studies have led to spurious claims being made for the effectiveness of particular treatments. This still occurs today, though the majority of responsible investigators are now well aware of the need for carefully designed studies in order to prevent this happening. Raising false hopes in those with a disease such as muscular dystrophy is inexcusable.



Currently three different approaches to treatment are under active investigation: the use of the drug prednisone and related compounds, myoblast transfer, and gene therapy.

### *Prednisone*

In the last few years therapeutic trials have concentrated on two major groups of drugs: 'calcium blockers' and prednisone and its related compounds. The reason behind testing the former was that the inflow of calcium into muscle fibres has been shown to be an important factor in muscle damage in dystrophy (p. 12). Unfortunately, not only have carefully controlled trials so far failed to show any beneficial effects of these drugs, we now know that they can have severe side-effects in dystrophy. The story regarding prednisone is more promising.

The possible value of prednisone in the treatment of dystrophy was first considered over 20 years ago. Recent, more carefully controlled trials suggest that it *may* lead to some improvement in muscle strength, at least in the short term. The long-term effects are more problematical, and this drug can also have serious side-effects (including weight gain and suppression of the immune system). It is early days but hopefully a compound related to prednisone, but with fewer side-effects, might be found which slows the progress of the disease.

Meanwhile, as we understand more of the detail of the biochemical processes which lead to muscle weakness in dystrophy, it may be possible to select or even design a drug which influences or interrupts these processes. In this way progressive weakness may be slowed, arrested, or even reversed. But it is also possible that an effective treatment might still be found by chance. The history of medicine is full of such examples, and there will always be a place for clever and original ideas in finding a drug treatment for dystrophy.

### **Myoblast transfer**

Early in 1989 Dr Terry Partridge and his colleagues in London published a paper in which they showed that injecting muscle cells (myoblasts) from normal mice into the muscles of dystrophic mice made many of the



muscle fibres near the site of the injection become dystrophin-positive (remember that muscle dystrophin is absent in dystrophic mice, as it is in people with Duchenne muscular dystrophy—p. 11). The injected normal (dystrophin-positive) myoblasts had presumably fused with the mouse's dystrophin-negative muscle fibres. The implication was that if this could be repeated in humans, it might provide a unique way of replacing the missing protein in Duchenne muscular dystrophy and so become an effective new treatment—and also that it might work in other dystrophies as well.

A number of problems were foreseen, however. There was the possibility, as with any other transplantation procedure, that the injected material might be rejected by the patient. Furthermore, to be effective it would seem that multiple injections into several different muscles might be necessary and there are formidable technical problems in trying to grow enough myoblasts in culture in order to treat any one patient. And, of course, such an approach would not influence heart muscle or the brain.

Aware of these possible difficulties, several investigators in the United States of America and Canada set up therapeutic trials using cultured myoblasts, usually obtained from muscles of the patients' fathers. As a control in the best designed studies, normal sterile saline solution without myoblasts was injected into the opposite limb to the one injected with myoblasts and, as in any double-blind trial, neither the patient nor the medical personnel were aware of which was the treated side. Some of these trials have now been running for more than a year and it does seem that the technique is feasible, is tolerated well, and is a safe procedure. But there is now doubt as to whether it significantly increases the proportion of dystrophin-positive fibres in humans and carefully controlled trials have so far failed to demonstrate any significant effect on muscle strength. It may be that more myoblasts need to be injected at any one time and injections may have to be repeated several times. Ongoing studies of the dystrophic dog (in which dystrophin is lacking and the animal develops progressive weakness as in Duchenne muscular dystrophy) may well provide important answers to these crucial questions. Only if the results of these studies show a definite and unequivocal effect on muscle strength would it then be justified to offer this as a possible treatment for people with muscular dystrophy.



## Gene therapy

At the beginning of this chapter we mentioned that until very recently the idea of compensating for a defective mutant gene by adding a normal gene seemed quite unrealistic, and seemed more in the realms of science fiction. But this is no longer so. Though the particulars of the complex technology need not concern us too much, a few details may convey some of its exciting potential.

First, DNA is extracted from, say, white blood cells of a normal healthy individual; the particular gene of interest is then isolated from this DNA. In the case of the very large dystrophin gene, only the most important part (so-called mini-dystrophin gene) is used. Secondly, for a gene to be active and to synthesize a specific protein in a particular tissue (for example dystrophin in muscle) it is necessary also to include along with the gene a *promoter*, a sequence of DNA which ensures that the gene is 'turned on' in the appropriate tissue. The promoter and associated gene are then *cloned*, a process whereby a micro-organism is induced to synthesize millions of copies. The cloned gene with its promoter is then transferred to the patient in the hope that it will take over from the defective mutant gene and so synthesize the particular protein which is absent or abnormal in the patient. There are several ways in which genes can be transferred.

In the case of muscular dystrophy the simplest way would be to inject the cloned mini-dystrophin gene *directly* into the patient's muscle. This has been shown to work in dystrophic mice but the results indicate that the technique as used so far is not very efficient. Only a very small proportion of the muscle fibres in injected animals appear to synthesize dystrophin. A method has to be found to increase the efficiency of the system if sufficient fibres are to be induced to synthesize enough dystrophin to be clinically effective. But there is considerable potential in this approach because animal experiments have now shown that DNA can also be injected directly into the heart of the affected animals. Dystrophin synthesis then occurs in this tissue as well, though admittedly at a low level and only for a limited period.

Yet another way to transfer a gene is to use a virus as a carrier or vector. Here some of the genes of the virus are replaced by a normal human gene and a promoter and then the virus is used as a vehicle to



convey them to the patient. Of course the virus has to be 'disarmed' or 'crippled' in some way so that it is no longer infectious, but there are relatively straightforward ways of doing this. In fact the replacement of a large part of the virus's own genes by human DNA ensures that the engineered virus is unable to divide and be infectious. This approach is currently being used to treat, for example, certain genetic diseases which affect the immune system. With regard to muscular dystrophy, experiments have shown that when a virus carrying a mini-dystrophin gene and promoter are injected into affected mice, in some experiments up to 90 per cent of the muscle fibres subsequently synthesize dystrophin.

So far all the research in this field has involved animal studies. Gene therapy has not been attempted in any patient with dystrophy because there is still much basic research to be done. The hope is that the technology will prove to be safe as well as effective in treatment. This technology also opens up the possibility of perhaps one day even treating the affected fetus in the womb before birth—but we are still a very long way from this.

Of course the most straightforward way of correcting any inherited disease would be to 'reverse' in some way the gene mutation which caused the disease in a patient. At present, we have absolutely no idea how this might be achieved, but I have no doubt that one day a clever and original scientist will think up some way.

Meanwhile gene therapy, by whatever means, should be seen as a very exciting and novel approach to treatment for dystrophy. But it is still in the experimental stage. The reality for patients may yet be some time off.

## Patients and therapeutic trials

With perhaps the exception of some surgical procedures, as we have seen, all therapeutic trials should include controls. In a double-blind study this means that some patients will be allocated to the control group with a placebo or some form of sham treatment. If there is no evidence before the trial to suggest that the proposed therapy has any beneficial effect, then the possibility of being placed in the control group will be acceptable. But if there is any suggestion at all that the treatment could be effective then there is sometimes an understandable resentment that a participant in the trial might be included in a control group. After all,



this would mean being denied treatment as long as the study lasts. The reassurance that one can give is that the investigator would be the first to offer the treatment to all his or her patients if, on breaking the code, the results showed that it was at all effective. A solution to this problem is to compare the course of the disease in patients being treated with the *expected* course, known from past studies of untreated patients—*natural history controls*.

Another sort of problem which can occur in a therapeutic trial was brought home to me personally a few years ago. We were engaged in a double-blind controlled study of a calcium-blocker drug in Duchenne muscular dystrophy. After a year we noticed that several boys were developing some unexpected heart problems. This forced us to break the code, only to discover that these boys were all taking the active drug and not the placebo. Furthermore, on analysing the results the drug was shown not to be significantly affecting the course of the disease. For both these reasons we decided to abandon the trial. But we met with very stiff opposition from some of the parents who were by then firmly convinced that the drug was having a beneficial effect (although they did not know if their son was on the drug) and wanted to continue with the trial. This was a very upsetting time for all of those involved until we were able to convince the parents of the scientific validity of our findings.

For all these reasons, the decision to participate in a therapeutic trial needs to be thought about very carefully beforehand. All the pros and cons should be discussed with the clinical staff involved as well as, if possible, an independent medical adviser who is also experienced in muscular dystrophy. In this way the patient, or the parents in the case of a child, will be better able to make a reasoned decision as to whether or not to participate. If there is any doubt, these doubts should be expressed. Medical staff will respect such feelings and there is nothing to stop an individual changing his or her mind later on and taking part in a trial at some future date.

## Summary

Above all, patients and their families should have a positive attitude to the disease. This involves three P's: *p*romotion and maintenance of good health in general; *p*revention of deformities; and the *p*reservation of



respiratory function. This means having a good, well-balanced diet, avoiding obesity, taking physiotherapy, using special orthoses, and even surgery. There are methods of assisted ventilation that are also now available which can transform an individual's life in the later stages of the disease.

Trials of various drugs in the treatment of dystrophy are nowadays being more carefully designed in order to avoid false claims being made. Prednisone may possibly slow down the disease process, at least in the short term, and this is currently being investigated.

Novel approaches to therapy are now being considered where the hope is to replace the defective gene by a normal gene. Myoblast transfer seemed to offer such an opportunity but studies so far, though indicating that the procedure is feasible and safe, have failed to show any significant improvement in muscle strength. In the long term, however, some form of gene therapy may actually prove to be the best approach to replacing a diseased gene by its normal equivalent.

All these developments augur well for patients with muscular dystrophy.



## 6. Living with muscular dystrophy

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A detailed examination of all the possible social and psychological effects of living with dystrophy is beyond the scope of this little book whose emphasis is more on medical problems and their management. But since the subject is so very important, some indications of the sort of problems which may occur, along with their possible solutions, will be discussed. Much more detailed treatment will be found in some of the specialized texts listed at the end of the book.

### **When and how much to tell**

An intelligent affected child will no doubt sooner or later become aware of his or her problem. With children it is probably not a good idea to discuss the full implications of the diagnosis at the beginning. In many ways it is best to encourage questions and to answer them sensibly and honestly, in a way appropriate to the age and level of understanding. The best way is to provide a little information at a time and as often as questions and opportunities arise.

The natural inclination for most parents is to shield their affected son or daughter from what they themselves perceive as a cruel blow, and they respond by being overprotective. This should be avoided as much as possible otherwise feelings of independence which normally surface around adolescence may be stifled and the resulting frustration lead to more stress within the family. It is important that affected persons at any age never feel overprotected. They should be encouraged, within the limits of their disabilities of course, to feel free to enlarge their social contacts and circle of friends.

In the case of adults, more and detailed information can be provided from the beginning. However, there is always a need to be guided by the person's questions and their response. To go into too much detail about the ultimate outcome could prove very distressing. On the other hand, some people may be quite willing to accept such information in order to



plan for the future with regard to housing and employment, for example. As in all other emotionally charged situations, tactful questioning can often indicate how far to proceed and open and frank discussions are invariably helpful.

### Individual responses

Since the psychological effects of dystrophy (or for that matter any disabling condition) are often suppressed or concealed, it is easy to believe that they don't exist. Most affected people give every impression of being well adapted and having come to terms with their disability. In some cases this may well be true, but in others it would be entirely wrong to assume that they are emotionally and psychologically unscathed by the disease. Several studies have shown that feelings are often harboured of isolation, inadequacy, and worthlessness. Furthermore, needs for privacy, affection, and sexual satisfaction may never be expressed.

As with any of life's major events not everyone reacts in the same way. This is certainly true in dystrophy. Even affected brothers may each respond differently to their increasing physical disability. In a family with Becker muscular dystrophy which I know, one affected brother in his thirties seems to have come to terms with his problems, is happily married, and gainfully employed in an office environment. His brother, a year or two older, seems never to have accepted his disability and remains isolated and depressed. He has never married and has not worked for several years. The former has effectively adapted to his problems, whereas the latter has withdrawn because to him the situation appears hopeless.

Commonly, those affected often feel physically unattractive and if, at the same time, there is any intellectual impairment they may well feel inferior and as a result become depressed. However, major depressive illness is uncommon. In some the response to the disease is reflected in serious behavioural problems.

Although some deny that their inability to find sexual satisfaction is a cause of distress, to others this can be a problem, particularly in the more slowly progressive forms of dystrophy which begin in adolescence or later. It is also quite a common problem in boys with Duchenne muscular dystrophy as they approach adolescence.



Quite apart from these sorts of emotional responses to physical handicap, which will vary from one individual to another, there are others of a more *social* nature which in their turn may also produce psychological reactions. Physical disability may be viewed as a social stigma and become a source of embarrassment to the entire family. In fact the psychological and social consequences of dystrophy almost always involve other family members to varying degrees. The impact of the disease is very rarely if ever limited to the affected people themselves.

In order to do anything about these problems it is first necessary to recognize and accept that they do exist. Let us begin at the beginning when the diagnosis is first made.

### The coping process

Because dystrophy often begins in a vague and ill-defined way there may be some delay before the diagnosis is made, which in the past has often been the case in Duchenne muscular dystrophy. However, this is gradually becoming less of a problem as family doctors increasingly become aware of the possibility of dystrophy in young boys with a walking problem. But this delay often means that the parents may have been suspicious that something was seriously wrong for some time. When the diagnosis is made and the nature of the disease explained, then inevitably the parents of an affected child or the patients themselves in late-onset dystrophies, will experience shock and often disbelief: 'Why has this happened to us?'; 'It can't be true, he is so well and no one else in the family is affected'; 'I have never had a day's illness in my life until now. How can it be muscular dystrophy?'; and so on.

The psychological sequence of events which occurs following any stressful event, such as when the diagnosis of a serious disease such as dystrophy is first made, is referred to as the *coping process*. It also occurs, for example, after divorce or during bereavement.

This sequence of events has been much described by psychologists and five sequential stages are recognized:

- shock and denial
- anxiety
- anger and guilt



- depression
- psychological homeostasis

The duration of each stage varies from one person to another. Some may eventually reach the stage of depression only to return for a time to the first stage. Very rarely a parent, or even an affected person, may never progress beyond the first stage. They never accept their child is affected or that they themselves are affected.

### *Shock and denial*

At this stage there is often denial that anything untoward is wrong. That is why it is so important that no discussion of diagnostic possibilities should take place until all the necessary investigations have been completed (Chapter 3). The paediatrician or physician can *then* with confidence explain what the diagnosis is and what the outcome is likely to be. Any discussion of the various possibilities before a definitive diagnosis has been established could be confusing and ultimately prove misleading. For these reasons it is therefore unwise to pressurize the paediatrician or physician into giving a diagnosis before all the investigations are complete.

### *Anxiety*

At this stage the situation has been accepted but now anxiety about the future begins to emerge. Judgement and reason are often impaired and therefore firm decisions about the future should be delayed. A major decision taken at this time about future children or about housing, for example, is likely to be too influenced by the trauma of events to be rational. The situation needs to be carefully assessed before any major decisions are made and this will require long discussions with a counsellor who can provide emotional support. This stage usually precedes, but on occasion may follow, the next stage.

### *Anger and guilt*

This is perhaps the most difficult stage of all. Parents or the patient may feel anger towards the physician or counsellor. Parents may be resentful



if, for example, they were never offered prenatal diagnosis so that it could have been prevented. An adult may be angry that the diagnosis was not made sooner. Very often parents and patients blame themselves and harbour serious feelings of guilt. In X-linked recessive disorders, such as Duchenne muscular dystrophy, which are transmitted by females who carry the disease but are themselves unaffected (Chapter 8), mothers may feel especially guilty. Fathers may also harbour such feelings, perhaps blaming themselves for some peccadillo in the past. To the outsider this may all seem quite irrational, but to parents under stress these can be very real problems. Careful understanding and sympathetic counselling are essential.

### *Depression*

At this stage the situation has been completely accepted: the diagnosis is clear, the course and prognosis are understood. The result is then often a feeling of depression. Rarely is this profound and sufficient to require treatment. Usually it is more a general feeling of low spirits. It is probably only when this stage has been reached that meaningful discussions about the future are possible. Discussions about family planning or prenatal diagnosis, for example, can now be made.

### *Homeostasis*

This term implies normality and at this stage the emotional response to the disease is now believed to have returned to normal. But it is doubtful if this stage is ever really reached. There will inevitably always be a sense of loss and deprivation throughout life.

### **When there is a family history**

In late-onset dystrophies some unaffected family members may harbour deep-seated anxieties throughout childhood and adulthood that they may also become affected. In the case of Becker muscular dystrophy, for example, a CPK test will be helpful in resolving the problem but in other disorders more investigative tests may be necessary. These may include DNA studies and also, in myotonic dystrophy, electromyography and



slit-lamp examination (p. 36). The possibility that such fears may exist should never be dismissed lightly. They are often not expressed openly, and direct and careful questioning by a parent or partner may be necessary to elicit the admission that such fears exist. In many such cases complete reassurance is possible.

There is, however, one positive aspect of having a family history of dystrophy. Parents and partners may benefit from the advice and support of relatives who have already had experience of the disease. In some communities where families are closely knit and family ties are strong, this can work to considerable advantage. But unfortunately nowadays families are often dispersed and such close support is not possible. And occasionally relatives may not wish to share their experiences and anxieties with others in the family because of embarrassment or for other reasons.

### The affected person

Above all the affected person, whether a child or adult, should be allowed to talk about his or her frustrations, disappointments, and anxieties for the future. As Ian Pullen, a psychiatrist experienced in the field, has written about Duchenne muscular dystrophy:

Many people, including parents do not allow the child to talk about these areas for fear of putting ideas into his head. The ideas certainly are there already but most children are denied the opportunity of communicating them to others. This may make them feel more isolated and abnormal because it prevents others from empathising accurately with their position.

Furthermore, about one-third of parents of boys with Duchenne muscular dystrophy who Pullen interviewed had great difficulty even talking to each other about the disease.

In the case of people with late-onset types of dystrophy, partners also often complain that there is a lack of communication.

All experts in the field now agree that frank and open discussions with parents or with partners are to be encouraged. If this is not possible, for whatever reason, then such discussions should take place with a professional counsellor or similar person who has had wide experience of the disease.



So far we have been discussing these problems in generalities, but some problems are particularly important in certain types of dystrophy. For example, we have seen (Chapter 5) that there are advantages to be gained from prolonging walking beyond the point when this might normally be lost and that this can be achieved by surgery and by fitting various orthoses. However, boys with Duchenne muscular dystrophy may not wish to have surgery and their wishes must be respected. Or later they may find that walking with full-length orthoses is too difficult, and they feel insecure and frightened of falling. In these circumstances it would be unkind and perhaps even harmful to persist. Another significant period in the course of Duchenne muscular dystrophy is when surgery may be contemplated in order to prevent scoliosis and impede any deterioration in lung function (p. 47). There is only a relatively brief period when this can be done—when walking unaided has become impossible and before significant spinal curvature and deterioration in lung function has occurred. This 'window of opportunity' only lasts perhaps one or two years and forces the parents and child to confront the disease in a way they have not had to do in the past. Difficult decisions have to be made during this short time and the strain on all concerned can be considerable. Open discussions some time beforehand are often helpful. These discussions could involve another family which has already gone through this difficult decision-making period in the past.

### **Psychosexual problems**

The existence of psychosexual problems in the disabled was often ignored or dismissed by many professionals in the past—but attitudes are changing. After adolescence many boys with Duchenne muscular dystrophy appear not to be distressed by sexual problems, while others become frustrated in their inability to find sexual satisfaction. Physical disability may actually preclude any relief they might obtain from masturbation. In adults with dystrophy these problems often become magnified. Not only may they feel physically unattractive and have a poor body image, but there may be very limited opportunities for mixing with people of the opposite sex. This however is now also becoming less of a problem with social clubs designed for the physically disabled.



After marriage there may be problems of impotence and infertility, as in myotonic dystrophy. In other types of dystrophy the main problem may be the actual physical act of intercourse because of muscle weakness. Sympathetic discussions with a mature counsellor experienced in such matters often help a great deal. In Britain there is an organization called The Association to Aid the Sexual and Personal Relationships of People with a Disability (SPOD) which can provide help and advice. Their address is listed at the end of the book.

### Effects on the parents

When a child is diagnosed as having muscular dystrophy, usually Duchenne muscular dystrophy, the effects on the parents are of course devastating. As we have seen they cope by gradually adapting to the fact that the child has a serious and progressive disease for which at present there is no cure. But they also have to realize that this is likely to affect their own relationships to each other.

Understandably one parent, usually the mother, will have to devote a great deal of time to caring for her affected son, especially when walking becomes significantly affected. The other parent, usually the father, may be excluded from this caring because he is absent at work during the day. As a result the mother may feel overburdened by the problem which she may feel should be shared more. In addition, she may also feel isolated from her friends and neighbours by having an affected son. The extra attention given to the son may make his father feel rejected and isolated. This often goes unrecognized because many men are reluctant to reveal their feelings.

For whatever reason, parents may find they have little opportunity to be together or to have a holiday. Furthermore the very real fear of perhaps have another affected son may seriously affect their sexual relationship. In one survey half the couples had serious marital problems and a quarter had become divorced. What can be done about this?

Parents should realize from the very beginning that these sorts of problems can occur and are quite common. And again, open and frank discussions between themselves, perhaps with other similarly affected families or with a counsellor, can often be helpful. Couples have to accept that caring has to be shared and that neither should feel rejected by the



other partner. On a purely practical level, couples should find a mature and reliable babysitter and be encouraged to go out together at least once a week. A mother or partner might consider part-time employment as a change of environment and should not feel guilty in doing so. After all, they are then more likely to feel refreshed and cope better with their responsibilities.

A definitive approach to contraception (such as tubal ligation or vasectomy) often removes fears of pregnancy and makes the sexual relationship once more a relaxed and enjoyable experience. To others sexual abstinence may be the only acceptable solution.

Having said all this it has to be remembered that many couples cope extremely well. An affected child may actually have the effect of bringing parents and the family closer together. I am repeatedly touched by the sensitive and loving relationship I come across between an affected person and his or her caring partner. There is no doubt that to some the experience of having an affected child or partner brings out their best qualities.

### Effects on unaffected siblings

In Duchenne muscular dystrophy an unaffected brother may well worry that he too will become affected. This possibility should never be ignored and the solution is to have a CPK test (p. 15) with complete reassurance when this is found to be normal. Apart from the often unexpressed fear that they might also become affected like their brother or sister, siblings often feel isolated and ignored. Though parents may try to be even-handed to all their children, inevitably the affected child will warrant more attention. In this way unaffected brothers and sisters may feel neglected or even jealous or resentful. When these feelings are admitted the unaffected sibling may increasingly feel shame and guilt.

Irwin Siegel has written a very helpful booklet on this subject in regard to Duchenne muscular dystrophy entitled *Hey, I'm here too*, which in Britain is available from the Muscular Dystrophy Group. In it he suggests that unaffected siblings should be encouraged to think about their attitudes to their affected brother. He lists a number of questions which they should discuss with their father or mother, teacher, doctor,



social worker, or psychologist. Apart from questions about the disease itself, some others are:

1. Are you afraid of ever asking questions about muscular dystrophy? Why?
2. How would life be different for you if you didn't have a disabled brother?
3. Does he worry you? In what ways?
4. Do you ever feel that your brother always gets what he wants because he is ill and you aren't?
5. How is life different in your house than in homes where there is not a child who is disabled?
6. Is more expected of you at home because your brother is disabled?
7. How do you feel your parents should act towards your disabled brother or towards you?
8. Are you ever angry about the fact that your brother has muscular dystrophy? Why?
9. How are you different from your friends who don't have a brother with muscular dystrophy?
10. What concerns you most about your brother's muscular dystrophy?

At least such questions help to concentrate the mind on the possible concerns and anxieties which an unaffected brother or sister may be harbouring. As in all problems of an emotional or psychological nature associated with dystrophy, open discussion can often prove beneficial. Allaying fears and anxieties among their unaffected children, as well as reassuring them of their love and affection, are essential responsibilities of parents with an affected child.

### Effects on the children of an affected parent

In many respects the emotional and psychological effects of having a parent seriously affected with dystrophy are not unlike those faced by the unaffected brothers or sisters of a boy with Duchenne muscular dystrophy. There may be fears that they too may become affected, and they



**Table 2** Living with muscular dystrophy: some suggestions for consideration in discussions with professionals

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*Information about the disease*

Nature and outcome  
 Regular follow-up  
 Dietary advice  
 Physiotherapy, orthoses, surgery  
 Respiratory care  
 Treatment  
 Genetics and mode of inheritance  
 Contraception, prenatal diagnosis

*Psychosocial matters*

Feelings of guilt, anger, isolation  
 What and when to tell  
 Effects on unaffected siblings, children, partner  
 Sexual problems  
 Expression and sharing of emotions  
 Bereavement counselling

*Information about more general matters*

Address of the national muscular dystrophy group, local support group, family care officer, social worker, health visitor, genetic counsellor, etc.  
 Welfare services and benefits  
 Education, learning difficulties, residential schooling  
 Holiday and baby sitting schemes  
 Aids and home adaptations  
 Transport  
 Employment opportunities

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may even come to resent the attention being bestowed on their disabled parent to their exclusion. They may also be fearful and anxious about their future should the parent die. In addition the normal parental role model may suffer. For example, a father confined to a wheelchair will be unable to take an active part in playing games with his children. In my experience this is usually more a problem for the affected father than for his children. Nevertheless there is little doubt that children growing up



in a home where a parent is physically disabled are often emotionally affected in some way, usually in childhood rather than later. Again, open and frank discussions within the family should be encouraged as far as this is possible.

## Bereavement

The response to the loss of an affected child or affected spouse or affected parent varies greatly. Though this may have been foreseen for some time, the event when it occurs is always traumatic. Some seem better able to deal with their emotions than others. But no amount of careful planning beforehand is ever entirely effective. Ideally counselling should not end with the death of the patient but should be available to all close relatives until grieving has passed. Parents and spouses may experience some sense of relief after all the years of anxiety and concern. This is all too natural and should not be a reason for feeling guilty.

The problems of bereavement in muscular dystrophy are discussed in detail in Leon Charash's book *Psychosocial aspects of muscular dystrophy and allied diseases* and in a booklet available from the Cystic Fibrosis Research Trust, both of which are listed at the end of the book.

Finally, for parents of affected children and for affected persons themselves, listed in *Table 2* are some suggestions for consideration in discussions with professionals. The list is clearly not exhaustive but will help focus attention on some of the more important and immediate problems where help and advice may be required.

## Summary

The emotional and psychological effects of dystrophy on the affected person as well as on the family are often suppressed and ignored. Individuals vary in their response. Some adapt very well but others may withdraw and become isolated and depressed. The relationship between the parents of an affected child may suffer. They have to learn to share responsibilities and often need time for each other so that their own relationship does not deteriorate. When there is already a family history



of the disorder, relatives may well be able to provide additional support and comfort.

Affected people themselves often harbour feelings of poor self esteem and fears about the progressive nature of the disease and its prognosis. Sexual problems may also arise.

It should not be assumed that the unaffected brothers and sisters of an affected child, or the children of an affected parent, are emotionally unscathed. They often have their own emotional problems in response to the disease.

There is no simple answer to all these matters, but open and frank discussions with relatives, friends, and professionals involved in dystrophy are often helpful. Voicing fears and concerns often helps to resolve them.



## 7. Education and employment

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In all forms of muscular dystrophy careful consideration has to be given to future education and possible employment. It has been emphasized that those affected with dystrophy should be encouraged, within the limits of their disability of course, to lead as normal a life as possible and to enlarge their social contacts and circle of friends. In this way they are less likely to feel isolated and rejected. The school environment as well as employment can help a great deal in this regard. But the possibilities are very much dictated by the type of dystrophy: whether or not there is any mental impairment, the severity of the disease, and the likely degree of disability in the future. For these reasons it is helpful to consider the opportunities and problems in a severe type of dystrophy such as Duchenne muscular dystrophy, and in the late-onset, more benign types of dystrophy.

### Schooling in Duchenne muscular dystrophy

There are two problems which have to be borne in mind when considering the future education of a boy with Duchenne muscular dystrophy. There is the problem of gradually increasing muscle weakness with the prospect of a wheelchair around the time he may be entering senior school, and the possibility of some degree of intellectual impairment, particularly in regard to reading skills and word comprehension (p. 26). But not all boys are affected in this way and some have high IQs.

Assessment by a paediatrician or psychologist at school age will indicate whether or not there is any reduction in intelligence. For those with *severe* mental impairment (with an IQ less than 50) education in a normal school is not possible. Depending on the particular home circumstances it may become necessary to consider special schooling. This can be on a daily basis or be residential with the boy returning home at weekends.



Most boys with Duchenne muscular dystrophy who are not severely handicapped can derive considerable benefit from attending a normal school. Most teachers nowadays are sensitive to the particular needs of children with physical handicap and there is much to be said for visiting the school beforehand in order to discuss the situation with the head teacher and his colleagues. A school with many stairs is not going to be appropriate in future years, but increasingly educational establishments are being adapted to the needs of the disabled. Parents should convince themselves that a particular school is going to provide a happy, supportive, and sympathetic environment for their son.

### Choice of subjects

In the early school years, choice of subjects is not so important. But later, boys with Duchenne muscular dystrophy should be encouraged in subjects which they enjoy and which may well centre on hobbies.

It would be wrong to expect too much. Many problems affect a boy's educational ability quite apart from any inherent reduction in intellect. For instance, progressive motor disabilities make the acquisition of new skills more difficult, and even writing may become a problem. There will inevitably be more frequent absences from school in order to attend hospital for check-ups or for treatment. And boys with Duchenne muscular dystrophy often tire easily and may lack initiative and motivation. Continual encouragement is therefore important.

Attention should focus on a boy's positive abilities. Many excel in model making and some are artistically inclined. Over the years I have made a collection of paintings and drawings by patients. Their skill and ability is a frequent source of admiration by visitors to our home.

### Later years

The inevitable advance of the disease makes the boy with Duchenne muscular dystrophy more vulnerable. He finds it increasingly difficult to keep up with able-bodied friends, and active participation in any sport is impossible. His school life may become much easier in fact once he has a wheelchair. But this then means that the school must be able to deal with



this situation. There may come a point when continuation at a normal school is no longer practical and a special school for the physically disabled may then have to be considered. Some of these schools are residential with the boy returning home at weekends. A special day or residential school may be the only solution if both parents are out all day working. And there is no doubt that the mixing together and the friendships which develop between similarly affected boys is often beneficial in reducing any feelings of isolation. The alternative, of sitting for long periods at home alone in front of a television set, should never be encouraged and should be avoided if at all possible. Plans to avoid this eventuality should be made some time beforehand. Friends should be encouraged to visit. A bedroom or study, preferably on the ground floor, should be set aside for his exclusive use with TV, hi-fi and other devices he may choose (*Figure 12*). In this way he will have a place which he can consider his private sanctum to entertain his friends and be on his own when *he* chooses. Such arrangements become particularly important when he reaches normal school leaving age. Hobbies then become increasingly important and every effort should be made to encourage visitors in order to maintain his social circle.



Figure 12 Computers offer many attractions.



## More benign types of dystrophy

In more benign types of dystrophy, where onset may not occur until after school-leaving age and where wheelchair dependence may not be anticipated until the twenties or thirties or even later, the problems of education and future employment are very different.

Firstly, in most of these types of dystrophy intellect is *not* significantly impaired. In this situation every encouragement should therefore be given to a good education commensurate with the individual's abilities and interests. Secondly, since limitation of mobility can be expected later in life, this can be planned for, both in terms of education as well as possible employment opportunities.

Discussions with teachers and planning for the future are therefore essential. Few limits should be placed on what subjects might be pursued since the career opportunities for those with physical disabilities are increasing yearly.

## Career opportunities

With a few obvious exceptions, such as sporting activities and those requiring physical stamina, almost any career is now open to those with physical disability. I know of one young man with limb girdle dystrophy who nevertheless completed a course in medicine and is now a successful and internationally famous pathologist, though he is obliged to conduct his work from a wheelchair. However, it would be quite wrong to plan for a career which will ultimately prove to be physically too demanding. It all depends on the likely progression of the disease and in this regard professional advice is important.

Sedentary office-based occupations provide the best solution to the problem. Computer activities, such as graphic design or desk-top publishing, have much to commend them since they can be carried out from home. As we have seen, by fitting various orthoses as well as with appropriate surgery, many with dystrophy can hopefully look forward to employment, often for many years to come.

Motor vehicles can also be suitably modified for the disabled driver and the resulting mobility which this then permits can transform a person's



life. But motor vehicle licensing authorities and insurance companies will require a doctor's medical report in order to assess the individual's ability to drive.

## Summary

In planning the future education and possible employment of those with dystrophy, careful consideration has to be given to the possible effects of the disease on intellectual ability and the severity of the disease. In all cases it is important to plan ahead.

In the case of Duchenne muscular dystrophy those boys who prove to be severely mentally handicapped may well require special care. Otherwise the boys' interests are usually best served by attending a normal school as long as possible. Accepting the limitations which may impair their academic performance at school and ultimately their physical capabilities, boys with Duchenne muscular dystrophy should be encouraged as much as possible to pursue subjects which they themselves find interesting and rewarding. A room at home specifically set aside for his use and interests and where he can entertain his friends is important. In the later stages, when physical disability becomes severely limiting, special schooling may be considered.

In the late-onset type of dystrophy, where independent mobility can be retained for several years, adequate schooling and the careful choice of subsequent career are very important. With fitted orthoses and appropriate surgery, sedentary-type employment can be made possible for many years to come.



## 8. Inheritance and genetic counselling

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Before considering the details of how various types of muscular dystrophy are inherited, it is first useful to consider how frequent each type is in the population.

### Frequency of muscular dystrophy

Knowing the number of affected persons in a population can be very useful information, for example to medical administrators in planning health care. But since different populations are of different sizes, the number of affected persons in itself is not meaningful. Comparisons are only possible if the *total* number of individuals in a given population is also taken into account. By dividing the number of cases by the total number of individuals in a population we obtain the frequency of the disorder. There is, however, a further complication. In the case of Duchenne muscular dystrophy, for example, the frequency should ideally only relate to the number of *boys* of *similar age* living at the same time. To include both sexes and of all ages would result in a spuriously low figure. However, in other disorders which do affect both sexes and where affected persons survive into adulthood and beyond, it is then appropriate to use the total population as the denominator in these calculations.

The frequency (or *prevalence* as this is often referred to) of various types of dystrophy has been much studied over the years, but figures in the past often varied a great deal from one study to another. This was because different types of dystrophy were sometimes erroneously lumped together and not all investigators applied the same painstaking diligence in finding cases. More recent and reliable estimates for some of the commoner types of dystrophy are given in *Table 3*. The figure given for Becker muscular dystrophy is probably too low and that for limb girdle



**Table 3** Prevalence figures for some of the commoner types of muscular dystrophy

Duchenne	1 in 4000 boys
Becker	1 in 20 000 males of all ages
Limb girdle	1 in 25 000 of the total population
Facioscapulohumeral	1 in 50 000 of the total population
Myotonic dystrophy	1 in 20 000 of the total population

muscular dystrophy too high because, in the past, the former was often mistakenly diagnosed as limb girdle dystrophy. In facioscapulohumeral muscular dystrophy and myotonic dystrophy the figures are only for more severely affected individuals because mildly affected cases often go undiagnosed. There are as yet no *reliable* figures for other types of muscular dystrophy. Furthermore, some types of dystrophy may be very common in some populations (such as Fukuyama type dystrophy in Japan), but rare elsewhere. An overall figure must therefore be very approximate. But if *all* types of dystrophy are added together the overall prevalence of *severely* affected individuals in the population is probably at least 1 in 5000.

### Modes of inheritance

The fact that muscular dystrophy can be familial and affect different members of the same family has been recognized for over a hundred years from when both Meryon and Duchenne noted that the disease they were studying often affected several members in a family. But the precise details as to how this Duchenne type of dystrophy was inherited was not firmly established until very much later.

As we have seen in Chapter 2, all the muscular dystrophies are *genetic*, that is, they are caused by mutations in different genes which, in varying ways, are essential for normal muscle growth and function. But the fact that they are genetic does not necessarily mean that they are always familial and affect other members of a family. In fact they often do



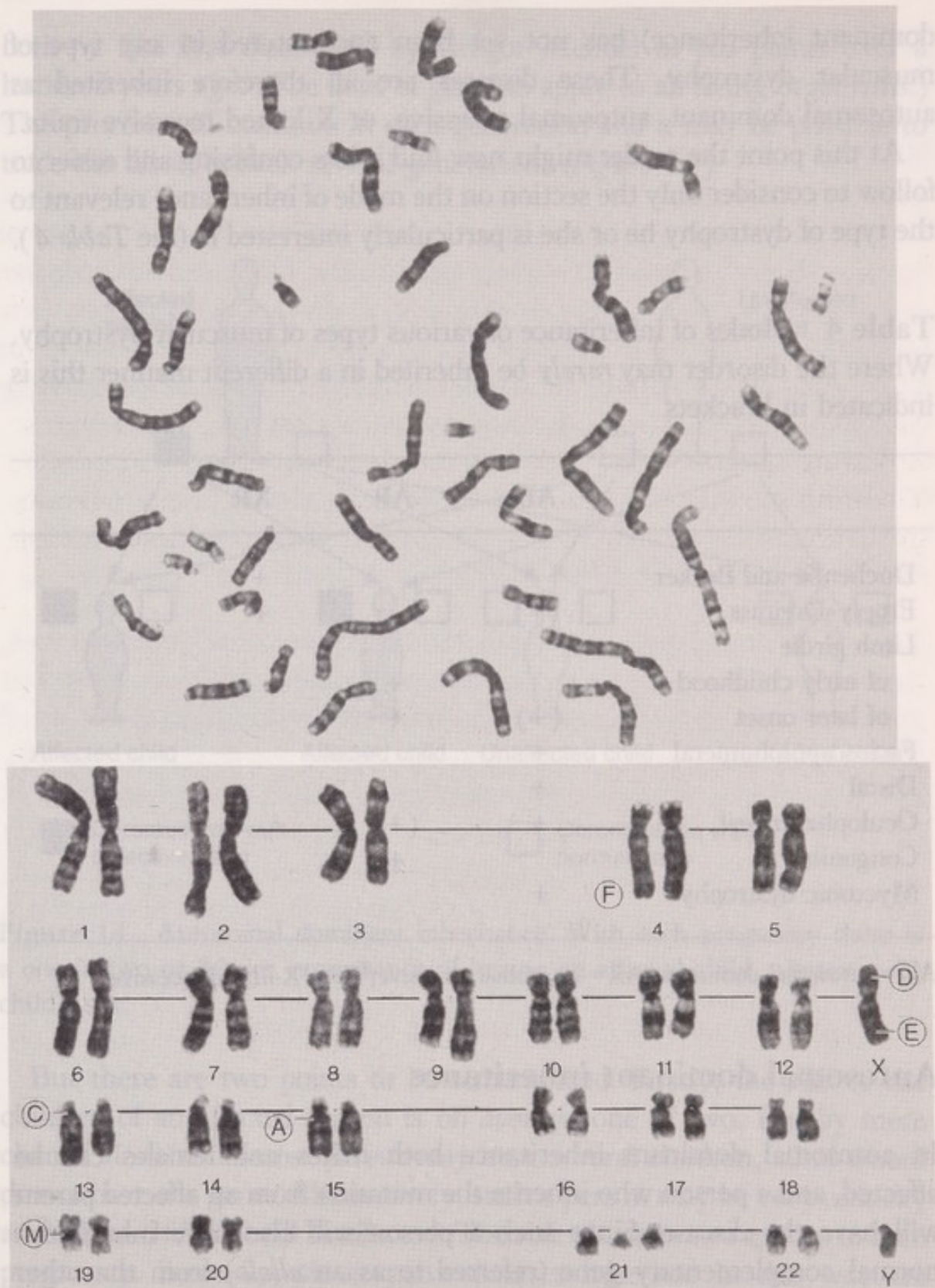
*not* affect other members of the family. The reason will become clear as we consider the various ways in which dystrophy can be inherited.

As we have seen in Chapter 2, each of us has 46 chromosomes, 23 derived from one parent and 23 from the other. Twenty-two of these pairs are referred to as *autosomes* and are unrelated to the sex of the individual. The remaining pair are referred to as the sex chromosomes because they determine a person's genetic sex (*Figure 13*). These are designated as the X and Y chromosomes. Each female has two X chromosomes and each male has an X plus a small Y chromosome. It is the latter which determines that he will be male. Each egg or ovum contains a single X chromosome so that when it becomes fertilized by an X-bearing sperm it will result in a female fetus, but if fertilized by a Y-bearing sperm it will result in a male fetus. Since X- and Y-bearing sperm are produced in more or less equal numbers the number of male and female babies born is roughly equal.

Now it is helpful to imagine that each genetic trait we possess is determined by a pair of genes—one derived from our mother and the other from our father, the number of chromosomes and therefore the genes they carry being halved during the process of egg and sperm formation. If the two genes of a pair which a person inherits from his or her parents are the same then the individual is said to be *homozygous* for that gene. If the two genes are different—one being the normal gene and the other a disease-producing mutant gene—then the person is said to be a *carrier* or to be *heterozygous*. If the abnormal gene of the pair carried by the heterozygous person is 'suppressed' by the complementary normal gene then the mutant character or *trait* is said to be *recessive*. If, however, the disease-producing mutant gene is expressed and shows itself in the heterozygote, the mutant trait is said to be *dominant*. In other words, if *both* genes of a pair have to be abnormal in order to produce the disease, then the disease is said to be recessive. On the other hand, if *only one* gene of a pair needs to be abnormal to produce the disease, then the disease is said to be dominant.

No diseases are yet recognized to be due to genes on the Y chromosome. Disease genes are either located on the X chromosome (*X-linked*) or on one of the 22 pairs of autosomes. And since such disease genes may be either dominant or recessive, so genetic diseases can be inherited in four possible ways: autosomal dominant, autosomal recessive, X-linked recessive, or X-linked dominant. The last possibility (X-linked





**Figure 13** Chromosomes stained to show banding patterns by which each can be identified. *Top*: a chromosome 'spread'. *Below*: the karyotype derived from the chromosome spread. Indicated are the positions of the genes for various dystrophies. Duchenne and Becker (D); Emery-Dreifuss (E); limb girdle of childhood (C) and (A); facioscapulohumeral (F); and myotonic dystrophy (M).



dominant inheritance) has not yet been encountered in any type of muscular dystrophy. These diseases are all therefore inherited as autosomal dominant, autosomal recessive, or X-linked recessive traits.

At this point the reader might now find it less confusing and easier to follow to consider only the section on the mode of inheritance relevant to the type of dystrophy he or she is particularly interested in (see *Table 4*).

**Table 4** Modes of inheritance of various types of muscular dystrophy. Where the disorder may *rarely* be inherited in a different manner this is indicated in brackets

	AD	AR	XR
Duchenne and Becker			+
Emery-Dreifuss	(+)		+
Limb girdle			
of early childhood		+	
of later onset	(+)	+	
Facioscapulohumeral	+		
Distal	+		
Oculopharyngeal	+	(+)	
Congenital		+	
Myotonic dystrophy	+		

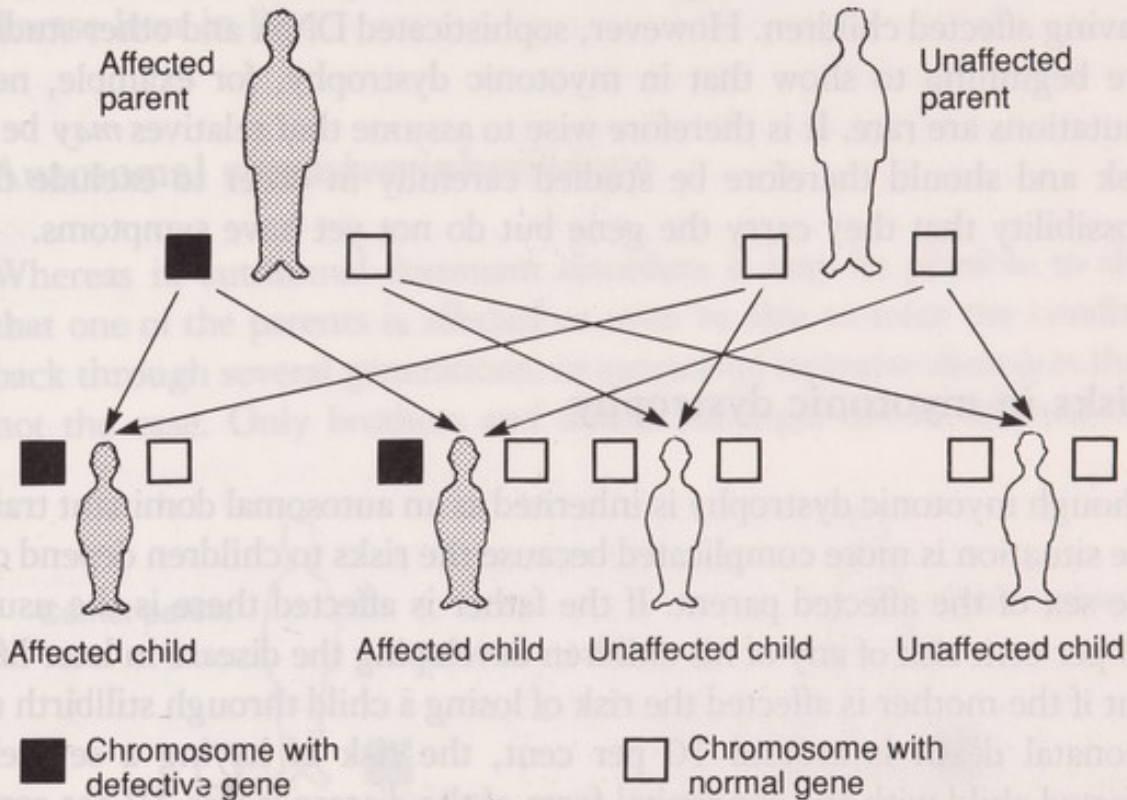
AD = autosomal dominant; AR = autosomal recessive; XR = X-linked recessive

### Autosomal dominant inheritance

In autosomal dominant inheritance both males and females can be affected, and a person who inherits the mutation from an affected parent will have the disease. Since such a person will also have inherited a normal complementary gene (referred to as an *allele*) from the other parent, he or she will be heterozygous. In due course if this person then marries a homozygous normal individual (which is usual since these are relatively rare disorders) there is a one in two (50 per cent) chance that any child will inherit the mutant gene. This is because a person passes on *either* of a pair of genes (alleles) to any particular offspring but never



both—a fact first discovered by Gregor Mendel in pea plants over a hundred years ago. (The laws of genetics apply to all living organisms.) The process will continue in each generation and it may be possible to trace the disorder back several generations (*Figure 14*).



**Figure 14** Autosomal dominant inheritance. With each pregnancy there is a one in two or 50 per cent chance of having an affected child, whatever the child's sex.

But there are two points to be remembered. Firstly, the risk to the children of an affected person is on *average* one in two. But by mere chance alone an affected parent may have several children, all of whom do not have the gene. Alternatively, such a person may be very unlucky and all the children will be affected. The risk of one in two applies to each pregnancy. Secondly, since many diseases inherited in this way are serious, an affected person may not survive to marry, or survive and not marry, or marry but have no children. In these circumstances it may not always be possible to trace the disease back over several generations.

In those types of muscular dystrophy inherited as autosomal dominant traits (*Table 4*) it is usually possible to show that the disorder has been



inherited from an affected parent. But where a careful clinical examination and appropriate studies (for example DNA studies) fail to indicate any abnormality in either parent, then the affected person is likely to be the result of a *new mutation* in the egg or sperm transmitted to that particular individual. In this situation others in the family at the time would not be at risk although later the affected person will be at risk of having affected children. However, sophisticated DNA and other studies are beginning to show that in myotonic dystrophy, for example, new mutations are rare. It is therefore wise to assume that relatives *may* be at risk and should therefore be studied carefully in order to exclude the possibility that they carry the gene but do not yet have symptoms.

### Risks in myotonic dystrophy

Though myotonic dystrophy is inherited as an autosomal dominant trait, the situation is more complicated because the risks to children depend on the sex of the affected parent. If the father is affected there is the usual 50 per cent risk of any of his children developing the disease in later life. But if the mother is affected the risk of losing a child through stillbirth or neonatal death is around 10 per cent, the risk of having a severely affected child with the congenital form of the disease is also 10 per cent, and the risk of having a child who will develop the disease in later life is 30 per cent. The risk of having an unaffected child is 50 per cent. Why women with myotonic dystrophy are at such a high risk of losing a baby or of having a severely affected infant is not known.

### Detection of preclinical cases

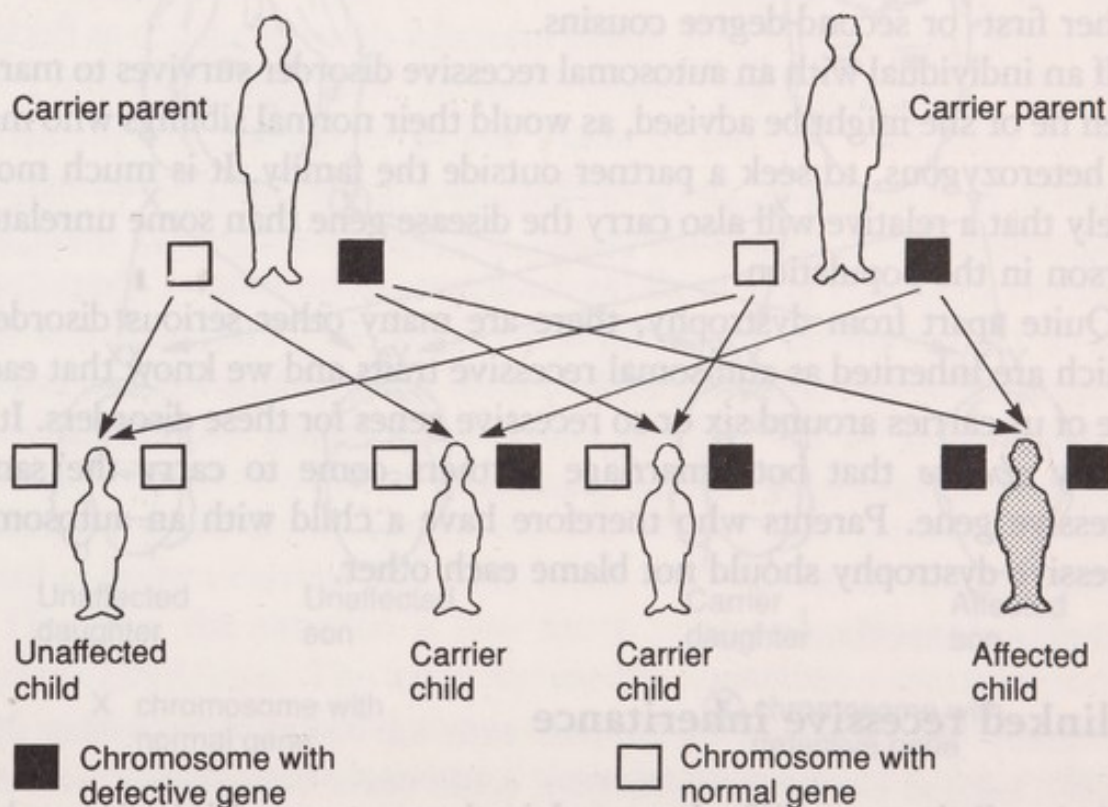
Among the dystrophies inherited as autosomal dominant traits, DNA tests are now becoming available for detecting *preclinical* cases. These are individuals who are heterozygous for the mutant gene, that is, they carry the mutant gene, but have not yet developed symptoms. Such tests are often requested by healthy people in affected families who are concerned that they may carry the dystrophic gene and so be at risk of having affected children.



There is a general consensus among medical scientists that testing children for a late-onset disorder such as myotonic dystrophy can lead to a great many problems. It is usually advocated that such testing be delayed until they are old enough to give consent and appreciate the implications. But clearly when an effective treatment is found, then testing could be justified at any age if this could prevent the onset of the disease later in life.

### Autosomal recessive inheritance

Whereas in autosomal dominant disorders it may be possible to show that one of the parents is affected or even be able to trace the condition back through several generations, in autosomal recessive disorders this is not the case. Only brothers and sisters (siblings) can be affected. The



**Figure 15** Autosomal recessive inheritance. With each pregnancy, there is a one in four or 25 per cent chance of having an unaffected child (of either sex) who does not carry the mutant gene, a one in two or 50 per cent chance of having an unaffected child who carries the mutant gene, and a one in four or 25 per cent chance of having an affected child.



reason is as follows. In autosomal recessive disorders, parents who carry the mutant gene appear perfectly normal. They will not know they carry the gene until they marry someone who by chance also carries the same mutant gene and they subsequently then have an affected child. Both parents may transmit either the normal gene or the mutant gene (allele) each carries to any particular child. There is then a one in four (25 per cent) chance that any child will inherit a normal gene from each parent. In this case the child will be unaffected and not carry the mutant gene. With each pregnancy of this couple there is also a one in two (50 per cent) chance of having an unaffected child who carries the mutant gene, and one in four (25 per cent) chance of an affected child who has inherited a mutant gene from both parents (*Figure 15*).

Since both parents must be heterozygous and carry the same rare mutant gene (allele) this is more likely if they are blood relatives, for example cousins, who have inherited the gene from a common ancestor. In some autosomal recessive disorders the parents not infrequently are either first- or second-degree cousins.

If an individual with an autosomal recessive disorder survives to marry then he or she might be advised, as would their normal siblings who may be heterozygous, to seek a partner outside the family. It is much more likely that a relative will also carry the disease gene than some unrelated person in the population.

Quite apart from dystrophy, there are many other serious disorders which are inherited as autosomal recessive traits and we know that each one of us carries around six or so recessive genes for these disorders. It is purely *chance* that both marriage partners come to carry the same recessive gene. Parents who therefore have a child with an autosomal recessive dystrophy should not blame each other.

### X-linked recessive inheritance

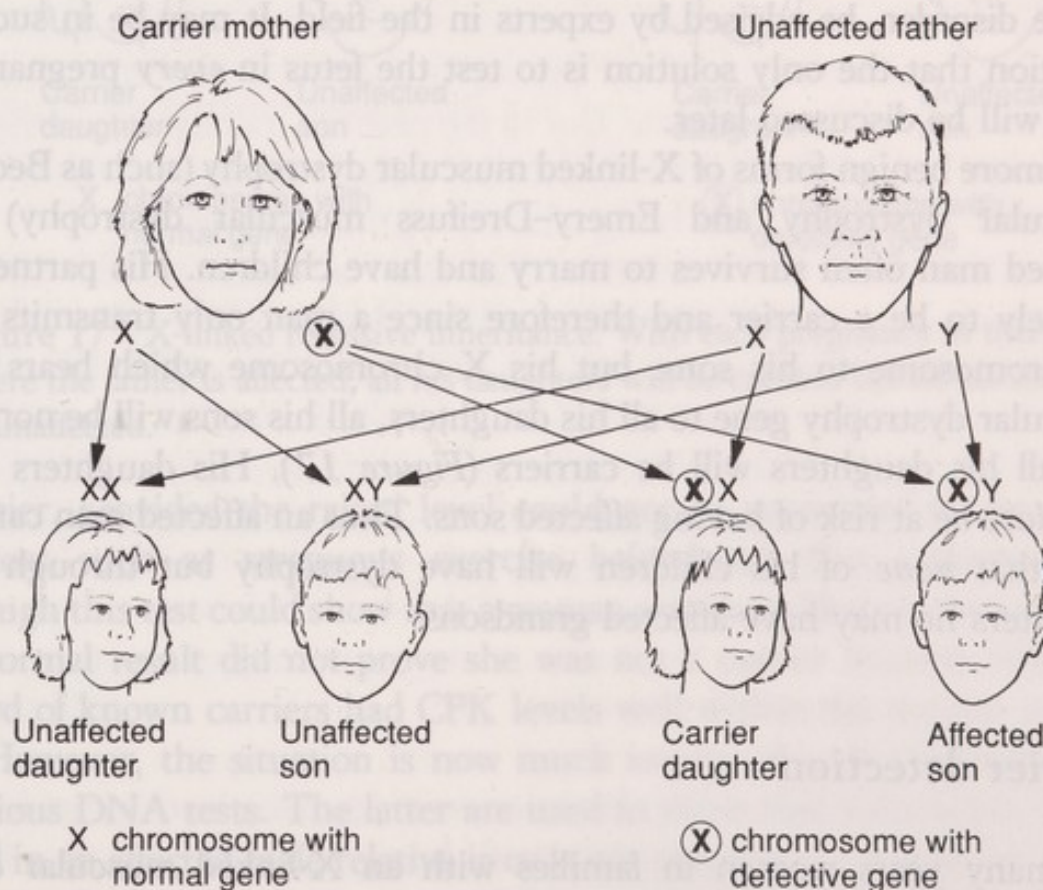
This is a little more difficult to explain than autosomal inheritance but is especially important because the most common form of dystrophy (Duchenne) is inherited in this way.

Since a woman has two X chromosomes, a mutation on one of her Xs will be dominated by the normal gene on the other X chromosome. She will be a heterozygous carrier who, in most cases, will be perfectly



normal. When she has children she may transmit either of her Xs to her sons and daughters. Any son who inherits the X chromosome with the mutant gene will be affected since he has only one X and therefore no normal gene to counter the effects of the mutant gene. Any son who inherits her X chromosome bearing the normal gene will be normal. Thus there is a one in two (50 per cent) chance that any son she has will be affected. Similarly there is a one in two (50 per cent) chance that any daughter she has will be a carrier like herself (*Figure 16*).

Since boys with Duchenne muscular dystrophy do not survive to have children, the disorder in this case is transmitted by women who carry the gene. It may be transmitted in this way through unaffected females for several generations. But in about a third of families the mutation arises in



**Figure 16** X-linked recessive inheritance. With each pregnancy in this family, where the mother is a carrier and the father is unaffected, there is a one in four or 25 per cent chance of having an unaffected daughter, a one in four or 25 per cent chance of having an unaffected son, a one in four or 25 per cent chance of having a carrier daughter, and a one in four or 25 per cent chance of having an affected son.



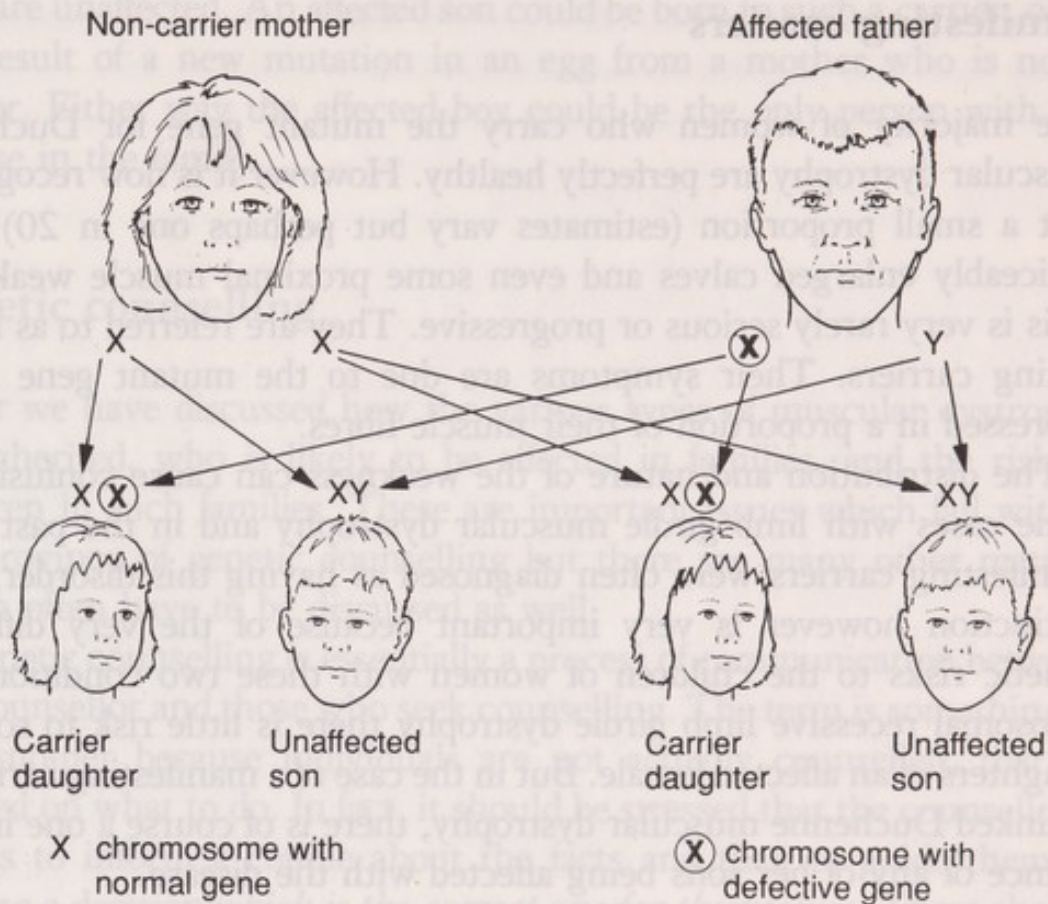
the egg of a woman who does *not* carry the mutant gene. In this case it would be expected that no-one else in the family would carry the gene and no-one else would be affected. Such a woman might be reassured that her affected son is the result of a new mutation which should therefore not occur again in any subsequent children she may have. However, DNA studies have now shown that the situation is more complicated than this. A woman may harbour the mutation in a whole segment of one of her ovaries and though she herself is negative for all carrier tests (see below) she is nevertheless at risk of having more than one affected son. Such women are referred to as *germline mosaics*, a mosaic referring to the fact that her ovaries are a mixture of cells, some of which have the mutant X and others which do not. It is essential therefore that any mother who has had an affected son but with no other family history of the disorder, be advised by experts in the field. It may be in such a situation that the only solution is to test the fetus in *every* pregnancy. This will be discussed later.

In more benign forms of X-linked muscular dystrophy (such as Becker muscular dystrophy and Emery-Dreifuss muscular dystrophy) an affected man often survives to marry and have children. His partner is unlikely to be a carrier and therefore since a man only transmits his Y chromosome to his sons, but his X chromosome which bears the muscular dystrophy gene to all his daughters, all his sons will be normal but all his daughters will be carriers (*Figure 17*). His daughters will therefore be at risk of having affected sons. Thus an affected man can be sure that *none* of his children will have dystrophy but through his daughters he may have affected grandsons.

### Carrier detection

For many years women in families with an X-linked muscular dystrophy, such as Duchenne dystrophy, could never be sure they were not carriers and only sure they were when they in their turn had an affected son. Then some 30 years ago it was found that around two-thirds of known carriers (women, for example, with an affected brother as well as an affected son) had significantly raised CPK levels (p. 16). If a woman in a family with Duchenne muscular dystrophy was tested and found to have a raised CPK level (over say 150 units) she was very likely to be a





**Figure 17** X-linked recessive inheritance. With each pregnancy in this family where the father is affected, all his daughters will be carriers but all his sons will be unaffected.

carrier, provided the raised level could not be accounted for by other factors such as strenuous exercise beforehand. But unfortunately, though this test could show that a woman was most likely to be a carrier, a normal result did not prove she was not a carrier because around a third of known carriers had CPK levels well within the normal range.

However, the situation is now much improved with the addition of various DNA tests. The latter are used to show that a mutation identified in an affected male relative is or is not present in a suspected carrier female. Problems arise however if there are no longer any living affected males in a family in order to identify the particular mutation in that family. These are very complicated issues which cannot be discussed in detail here. It is an area for specialists and an expert opinion should be sought in these circumstances. Suffice it to say that in *most* families it is possible to determine whether a woman is or is not a carrier by a combination of CPK and DNA tests.



### Manifesting carriers

The majority of women who carry the mutant gene for Duchenne muscular dystrophy are perfectly healthy. However it is now recognized that a small proportion (estimates vary but perhaps one in 20) have noticeably enlarged calves and even some proximal muscle weakness. This is very rarely serious or progressive. They are referred to as manifesting carriers. Their symptoms are due to the mutant gene being expressed in a proportion of their muscle fibres.

The distribution and nature of the weakness can cause confusion in some cases with limb girdle muscular dystrophy and in the past such manifesting carriers were often diagnosed as having this disorder. The distinction however is very important because of the very different genetic risks to the children of women with these two conditions. In autosomal recessive limb girdle dystrophy there is little risk to sons or daughters of an affected female. But in the case of a manifesting carrier of X-linked Duchenne muscular dystrophy, there is of course a one in two chance of any of her sons being affected with the disease.

Fortunately the two conditions can now be distinguished. In the manifesting carrier of Duchenne muscular dystrophy the CPK level is usually very high, the amount and distribution of dystrophin in muscle tissue are abnormal, and DNA studies may reveal a characteristic mutation associated with Duchenne dystrophy. A woman with any degree of proximal muscle weakness should seek expert advice on the possible cause and the genetic implications to her children.

### Why cases may *not* be familial

We can now see why cases of muscular dystrophy which are genetic may not necessarily affect other members of a family. In autosomal dominant inheritance, a person may be affected due to a *new* mutation in either the egg or sperm which he or she inherited, and so no-one else in the family will have been affected previously. Or with autosomal recessive inheritance since only siblings are affected, parents may have one child with the disease and this will be the only affected person in the family. And as we have seen in X-linked recessive inheritance, except where affected males survive to have children, the disorder is inherited through carrier females



who are unaffected. An affected son could be born to such a carrier, or be the result of a new mutation in an egg from a mother who is not a carrier. Either way the affected boy could be the only person with the disease in the family.

## Genetic counselling

So far we have discussed how the various types of muscular dystrophy are inherited, who is likely to be affected in families, and the risk to children in such families. These are important issues which fall within the province of genetic counselling but there are many other matters which often have to be discussed as well.

Genetic counselling is essentially a process of communication between the counsellor and those who seek counselling. The term is something of a misnomer because individuals are not actually counselled, that is, advised on what to do. In fact, it should be stressed that the counsellor's role is to inform a couple about the facts and then to guide them in making a decision *which is the correct one for themselves*. There should never be any coercion on the part of the counsellor.

At one time counselling was concerned purely with medical and scientific matters: to establish a precise diagnosis, and then to communicate factual information about the disease (its nature, whether or not there is any treatment, and its course and likely outcome) and its mode of inheritance. However, more emphasis is now being given to an appreciation of the *psychological* aspects of counselling—a move away from what one might term *content-orientated* to more *person-orientated* counselling.

There are a number of reasons for this change in emphasis. First, a disabling and progressive disorder such as Duchenne muscular dystrophy has, as we have seen, profound psychological effects on the immediate family which may extend to other relatives as well. Secondly, several studies have now shown that couples sometimes opt for a course of action which may be at variance with what the counsellor may have thought 'reasonable'. Your perceptions of the disease and its risk may not be the same as the counsellor's. For example, the counsellor may feel that it would be unwise to embark on a pregnancy with a risk of producing an affected child, but this is a decision which only you can make. It is



your prerogative *always provided that it is made in the full knowledge of all the facts and possible consequences.*

### Timing of genetic counselling

The timing of genetic counselling is very important. It should be timed as well as tailored according to the stage in the coping process which a couple has reached (p. 64). It would be inappropriate and largely ignored in the early stages, and it is usually only in the later stages that counselling is likely to be accepted and effective. Any doubts about the diagnosis, and any feelings of guilt and recrimination have to be dispelled first of all.

The discussions with the counsellor should take place in private in a relaxed and quiet atmosphere. Plenty of time should be allowed for questioning. It is often helpful to go armed with a list of questions which you want answered. It is always best if both partners can be present together; there is then less likelihood of misinterpretation. Counselling can rarely be completed in a single appointment and usually requires several sessions.

### Who should have genetic counselling?

The simple answer to this question is any family member who is concerned about the problem. This of course will include the parents of an affected child as well as adults with dystrophy and their partners. Furthermore, relatives who think they could be at risk may also seek counselling and often only require reassurance. If you are at all concerned about such matters then professional advice should be sought.

### Options available

Genetic counselling involves not only a discussion about a particular type of dystrophy and its risks of recurrence, but also about the various options open to a couple who consider their risk of transmitting the disorder to be unacceptable. Some may decide on abstinence from sexual intercourse—a difficult decision to make but one which can provide an acceptable solution for some couples.



An alternative is to consider some form of contraception. A dread of having an affected child may well generate serious psychosexual problems for some, and effective contraception can remove a great deal of worry and lead to a more relaxed relationship between husband and wife. But in this context expert advice is important because failure might be disastrous. For this reason *sterilization* by vasectomy for men or tubal ligation for women might have to be considered. It should be remembered, however, that though sterilization when performed on a healthy woman whose family is complete is likely to be entirely beneficial, in a young woman with a family history of Duchenne muscular dystrophy but who has no children of her own, this is a very serious decision to make and should not be taken lightly. It can have long-term psychological effects.

*Artificial insemination by donor* is a possibility where the father has a dominant form of dystrophy or if he and his wife both carry a gene for a *rare* autosomal recessive type of dystrophy. However, this technique has lost much of its attraction recently because of the need for very careful screening of donors in order to exclude, for example, HIV infection.

*Ova transfer* is in some ways analogous to artificial insemination. It is indicated when the mother has a dominant form of dystrophy but is able to bear children, if she is a carrier of an X-linked recessive type of dystrophy, or if she and her husband both carry a gene for a rare autosomal recessive type of dystrophy. The donor of the ova must be healthy and, if a sister for example, she must have appropriate tests to show that she is not also a carrier. Otherwise an unrelated female is best used as a donor. Ova are removed from the donor usually by a technique referred to as *laparoscopy*—a small incision is made in the abdomen, and a fine telescope is inserted through which ova can be retrieved from the ovaries. The ova are then fertilized *in vitro* with the recipient's husband's sperm. A fertilized ovum is then implanted into the recipient's uterus where it develops normally.

Alternatively, it is now possible to remove ova from the at-risk mother and, having fertilized them with her husband's sperm, allow them to develop in culture in the laboratory until around the eight-cell stage. A single cell is then removed without damaging the rest of the conceptus. By appropriate DNA studies this can be tested to see if the abnormal mutant gene is present. If the conceptus is found to be normal it is then implanted in the uterus to complete its development. This technique is



referred to as *pre-implantation diagnosis* because the diagnosis is made before the fertilized conceptus is implanted in the uterus.

Clearly these are very complicated procedures and are still at the experimental stage. If they can be shown to be feasible in the clinic and not to damage the fetus in any way then they may prove an alternative to prenatal diagnosis. After all, not all women are able to face the prospect of prenatal diagnosis with the implication of the possibility of abortion.

### Prenatal diagnosis

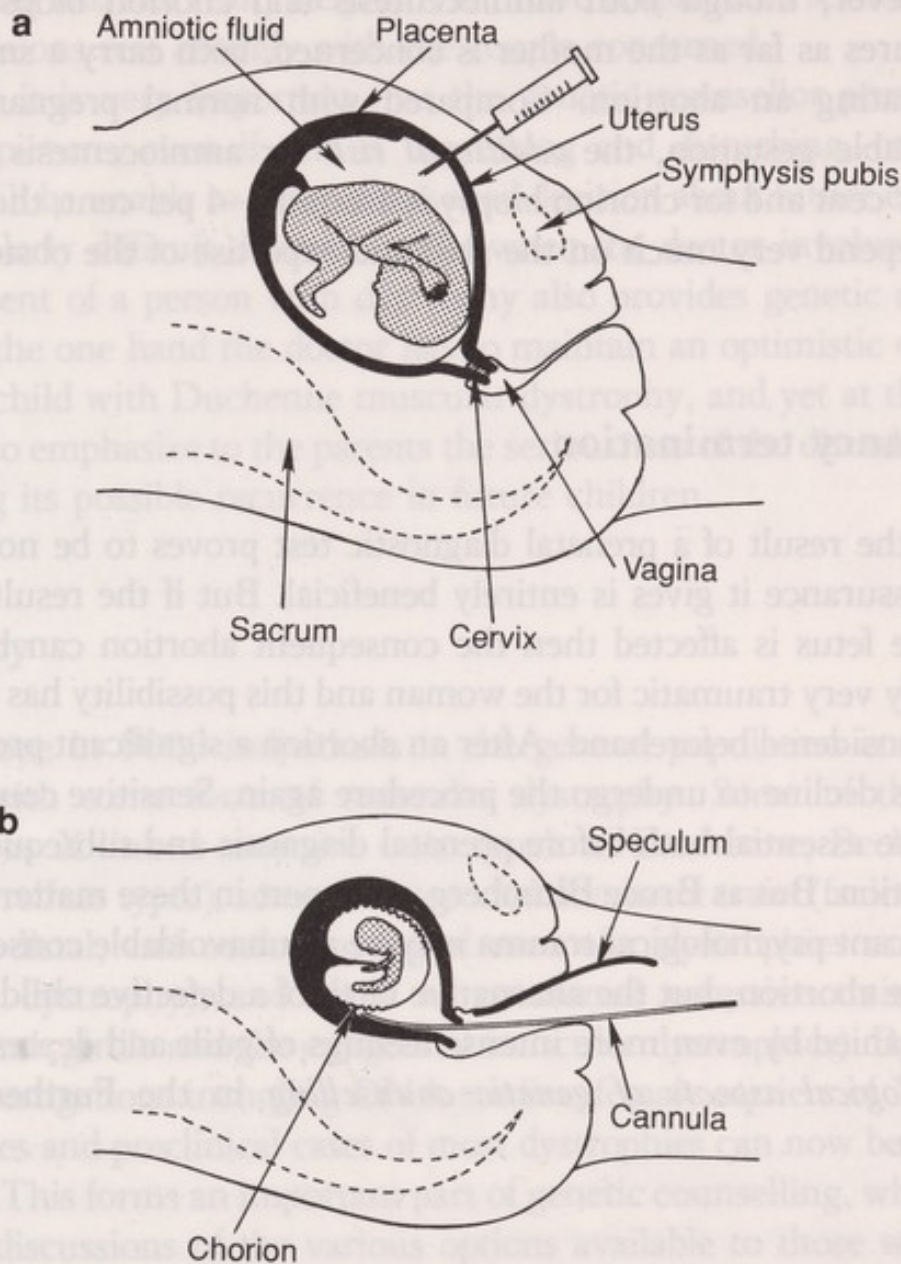
As the name implies, in this technique a diagnosis is made on the fetus before birth. If the fetus is shown to be affected then the pregnancy can be terminated.

In an X-linked recessive disorder where only males are affected, if a mother is a carrier the fetus can be sexed and, if it is a male, the pregnancy can be terminated. Though the technology for doing this is simple, the result is far from satisfactory because half the male fetuses aborted would have been normal. This is now being replaced by DNA studies, not only in X-linked dystrophies but also in other dystrophies where DNA markers are available. In this way an *affected* fetus is diagnosed prenatally.

Two methods are available for prenatal diagnosis: *transabdominal amniocentesis* and *chorion biopsy* (Figure 18). In transabdominal amniocentesis a needle is inserted through the abdominal wall into the uterus. A small amount of fluid surrounding the fetus (*amniotic fluid*) is removed. In this fluid are cells derived from the fetus. These are separated off and then grown in a culture medium in the laboratory. After about two weeks there are usually sufficient cells for DNA studies on which a specific diagnosis can be made. This technique, however, is usually not possible until around 16–18 weeks of gestation and if DNA studies indicate that the fetus is affected, then pregnancy termination has to take place relatively late in pregnancy. For this reason the newer method of *chorion biopsy* is often preferred.

In chorion biopsy (or *chorionic villus sampling—CVS*) a flexible catheter is inserted through the cervix, or through the abdomen, into the uterine cavity at around ten weeks' gestation. At this stage of pregnancy, on the outside of the small amniotic sac surrounding the fetus there are





**Figure 18** Techniques of **a** transabdominal amniocentesis and **b** chorion biopsy.

small, finger-like projections of cells called *chorionic villi* which are of fetal origin. A few of these are removed by the catheter and, since these villi are already living and dividing, they can often be studied directly or after only a few days in culture. The cells are then subjected to appropriate DNA studies.

Since prenatal diagnosis with chorion biopsy is possible much earlier than with amniocentesis, if pregnancy termination has to be carried out it is therefore likely to be much less upsetting for the mother.



However, though both amniocentesis and chorion biopsy are safe procedures as far as the mother is concerned, both carry a small risk of precipitating an abortion. Compared with normal pregnancies of a comparable gestation, the *additional risk* for amniocentesis is around 1-2 per cent and for chorion biopsy is around 3-4 per cent, though these risks depend very much on the skill and expertise of the obstetrician.

### Pregnancy termination

When the result of a prenatal diagnostic test proves to be normal then the reassurance it gives is entirely beneficial. But if the results indicate that the fetus is affected then the consequent abortion can be psychologically very traumatic for the woman and this possibility has to be carefully considered beforehand. After an abortion a significant proportion of mothers decline to undergo the procedure again. Sensitive counselling is therefore essential both before prenatal diagnosis and subsequently after an abortion. But as Bruce Blumberg, an expert in these matters, has said 'Significant psychological trauma may be an unavoidable consequence of selective abortion, but the alternative birth of a defective child is usually accompanied by even more intense feelings of guilt and depression' (see *Psychological aspects of genetic counselling* in the Further Reading section).

### Counselling for individuals

From what has been inferred so far it is clear that genetic counselling often involves a great deal more than discussing the nature of a disorder and risks of recurrence. It also involves the various options available if these risks are considered unacceptable. In discussing these options it is important to give careful consideration to their various advantages and disadvantages. It is important that if a couple has any reason (ethical, religious, or social) for reservations about, say, sterilization or prenatal diagnosis and abortion, they should make this clear to the counsellor from the beginning. Detailed discussion of such matters might otherwise



be upsetting and not really helpful. As I have emphasized several times, these decisions rest entirely with the couple concerned.

Finally, it is very important that the genetic counsellor presents an accurate picture, even if this is depressing and disturbing, otherwise parents will be unable to make a reasoned decision about future children. A particularly difficult dilemma arises when the doctor involved in the management of a person with dystrophy also provides genetic counselling. On the one hand the doctor has to maintain an optimistic outlook, say for a child with Duchenne muscular dystrophy, and yet at the same time has to emphasize to the parents the seriousness of the disorder when discussing its possible recurrence in future children.

## Summary

Roughly one in 5000 individuals in the general population is severely affected with some form of muscular dystrophy. Some of these are inherited as X-linked recessive traits (such as Duchenne, Becker, and Emery-Dreifuss types), some as autosomal dominant traits (facioscapulo-humeral, distal, and oculopharyngeal muscular dystrophies as well as myotonic dystrophy), and some as autosomal recessive traits (most notably limb girdle and the congenital muscular dystrophies). By appropriate investigations including DNA studies, female carriers of X-linked dystrophies and preclinical cases of most dystrophies can now be reliably detected. This forms an important part of genetic counselling, which also includes discussions of the various options available to those who consider the risks of having an affected child unacceptably high. These options include contraception, sterilization, artificial insemination by donor, ova transfer, or prenatal diagnosis. The latter can be achieved by either transabdominal amniocentesis at around 16-18 weeks or chorion biopsy at around ten weeks, the latter often now being preferred. But couples should never be pressurized into any course of action. They must feel free to choose the option which they see as the best and most acceptable to themselves. These decisions should never be taken lightly because the consequences can be profound and long-lasting. They should always be given the most careful consideration beforehand.



## 9. Professional and voluntary support

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A prevailing problem in dystrophy is a feeling of isolation. 'If only there was someone to talk to' is often heard. There is no easy solution to this problem, but there are two ways in which support can be found: through professional help and through various national organizations.

### Professional help

Seven stages can be recognized in the evolution of a genetic disorder such as muscular dystrophy:

1. positive family history;
2. abnormality first noted;
3. abnormality confirmed by the family doctor;
4. diagnosis established;
5. adaptation to the situation;
6. progressive handicap;
7. death and grieving.

Each of these stages presents different problems and concerns.

At stage 1 when there is a known family history of the disorder, those who feel at risk of either developing the disease themselves or of having affected children are often understandably anxious. The situation needs to be resolved and professional help and advice is essential. As we have seen, there is often a delay between the time when some abnormality is first noted and when this is confirmed by the family doctor (and not dismissed as being normal or even 'neurotic'). This period of uncertainty is very upsetting and in retrospect many parents of boys with Duchenne



muscular dystrophy, as well as older people with other forms of dystrophy, look back and wonder why it took so long for their complaints to be taken more seriously. Fortunately the situation is changing as family doctors become more aware of the possibility of muscular dystrophy and the need for specific diagnostic tests. At stage 4 the coping process begins (p. 64) and here it is essential that parents of affected children as well as adults with dystrophy are given every opportunity to express their anxieties and to seek professional help and advice.

During stages 5 and 6 the need for professional help continues but is usually not so compelling except in two situations. First, at the time of having to make a decision as to whether or not to undergo surgery (p. 46). Secondly, during the transition of boys with Duchenne muscular dystrophy from childhood to adolescence, increased medical, social, and educational services may well be required.

Finally the last stage 7 is again a very traumatic time. As mentioned earlier, professional support through counselling often proves very helpful. It should not end with the death of the patient, but be available to close relatives until grieving has passed.

## Specialist centres and units

There is an increasing move towards setting up regional specialist centres or units which provide *comprehensive management* for patients with muscular dystrophy. Here a team specializing in the disease is able to provide, or have local access to, all the medical and surgical expertise as well as genetic and welfare services needed.

The emphasis is on a team approach by experts in the field. Patients and their families can be seen on a regular basis and will know that they are receiving well-founded advice and treatment. Such centres, by concentrating expertise, reduce the need to travel to different hospitals for medical and other services. Often these centres are also involved in research and are therefore aware of the most recent advances. Some may also be involved in treatment trials. Those affected with dystrophy as well as their families can only benefit from these arrangements. It also means that they will meet others who have similar problems and will begin to feel less isolated.



### Hospital-based groups

Groups of parents or older patients may form around a centre or unit specializing in muscular dystrophy. They may be initiated and organized by a participant and run by a nurse or social worker. These informal groups are often a useful bridge between a purely medically orientated setting and the more social setting of outside voluntary organizations.

In such groups individuals can express their anxieties and also their needs. For example, they can provide an opportunity for discussions on the various merits of different wheelchairs or used to solicit the opinion of others on the value of surgery—how it has helped them and what were the problems. They can even discuss recent developments and research findings reported in the media. Here the paediatrician or physician in charge of the clinic can be enlisted to provide answers, but in my experience parents and patients often find it easier to discuss some matters with each other and with nurses and social workers, perhaps because they feel less intimidated and therefore less inhibited.

Meetings within a hospital setting do have their value, particularly when more medical matters are an issue, but often the problems causing concern are social or even economic and then informal meetings outside are perhaps more appropriate.

### Community-based groups

These informal groups initiated by parents or affected adults have much to commend them. Meeting at regular intervals in an informal way, perhaps as a coffee morning or during the evening in, for example, a school or participant's home, provide an excellent opportunity to dispel feelings of isolation. Such groups can arrange babysitting circles. These can be very valuable because the usual babysitter often feels inadequate and unable to cope with a child who is disabled. Furthermore, parents bring a competence and knowledge which would be difficult to find outside the group.

Affected adults may use such groups as the basis for a social gathering, perhaps even arranging outings and visits to places of interest.



These local groups or chapters can also become involved in fund raising for a charity organization, and in this way feel they are helping indirectly to contribute to research. They may also invite experts to address the occasional meeting and so keep up with developments in the field.

There is no doubt that through parent and patient groups many obtain a great deal of support, but not everyone finds such organizations attractive. Some would prefer to deal with matters themselves and would find participation in any association unhelpful to them personally. I have known several families like this but who, after the death of their affected son, later joined a group in order to help others.

### **National organizations**

Almost every developed country in the world, as well as some developing countries, now has a national organization concerned with muscular dystrophy. In addition, there are also two organizations which cater for European countries as a whole: the European Alliance of Muscular Dystrophy Associations, which is largely concerned with medical and social matters, and the European Neuromuscular Centre, concerned with research into muscular dystrophy and related disorders. These various organizations and their addresses are listed at the end of the book. They act as 'clearing houses' for information about muscular dystrophy. The Muscular Dystrophy Group of Great Britain, for example, produces a series of leaflets on the disease. Each deals with a specific disease, covering its clinical features and mode of inheritance. There are also leaflets on particular topics such as physiotherapy, weight control, care of respiratory function, equipment and aids, and the surgical correction of spinal deformity. Many organizations also produce and circulate newsletters at regular intervals. They also maintain lists of hospital units specializing in dystrophy to which a patient can be referred for treatment.

Importantly, these organizations often provide the first point of contact for sufferers from muscular dystrophy and their families.

Through their fund-raising activities, they raise significant sums of money for research which is channelled through various hospitals, universities, and research organizations. Without such support, and the



encouragement of these organizations, it is very doubtful if any significant advances in research into muscular dystrophy would have taken place.

### Summary

One of the most important problems in muscular dystrophy is a feeling of isolation. Help can, however, be obtained through local groups or through various national organizations. Professional help is obviously important and is nowadays often based in specialist centres and units. Here the emphasis is on the comprehensive management of the disease, ideally with all the various medical, genetic, and surgical expertise being available in the one centre. Out of such centres can develop 'hospital groups' of patients and relatives.

Outside the hospital environment 'patient groups' have much to commend them, not least being the opportunity they provide for social gatherings and for the sharing of worries and experiences.

Finally, almost every developed country in the world now has a national organization concerned with muscular dystrophy. They act as clearing houses for information about dystrophy and maintain lists of hospital units specializing in the disease. They often provide the first point of contact for sufferers and their families.



## 10. The future

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Until a few years ago, there seemed little chance of ever really understanding what caused muscular dystrophy, let alone finding a cure. Because the muscle histology (p. 19) in each of these disorders was so similar, there was a general feeling that they all might therefore share the same cause.

At first it was thought they might be due to some defect in the blood supply to the muscle. This was not a new idea because Duchenne had entertained a similar notion over 100 years ago, but the proponents never managed to produce any really convincing evidence. Then in 1970, based largely on electromyographic work, the idea that dystrophy might be due to a defect in the muscle's nerve supply came into vogue. It was suggested that perhaps some hypothetical substance which normally passed down a nerve to 'feed' the muscle (the so-called *trophic factor*) was missing or defective in muscular dystrophy. A great deal of research effort was expended on this idea, but when the original nerve studies on which it was based were seriously questioned the whole concept was thrown into doubt.

However, in the mid-1970s Allen Roses and his colleagues at Duke University, North Carolina, presented biochemical evidence of a possible defect in the *membrane* of various tissues in dystrophy and not just in muscle. These findings had instant appeal for many investigators working in the field because since the dystrophies are genetic one might therefore expect the defect to be also expressed in tissues other than muscle. Many of the subsequent abnormalities reported by different groups, for example in red-cell membranes, often proved controversial, but there was little doubt that a defect in the muscle fibre membrane did exist and would explain a great deal, including the leak of creatine kinase into the circulation (p. 15).

Then an entirely new approach to understanding the basic defects in genetic disorders began to be pursued by molecular geneticists. This approach involves first locating a defective mutant gene to a particular chromosome, and then to a particular place (its *locus*) on the chromo-



some. By a number of ingenious techniques the gene is then isolated and cloned and its protein product identified. With this new technology it thus became possible to identify the specific defects in various genetic disorders.

This approach resulted in the successful location of the gene for Duchenne muscular dystrophy to the short arm of the X chromosome (at a position referred to as Xp21). Subsequently Becker muscular dystrophy was shown to be due to a different mutation but at the same gene locus. Finally in 1987 the responsible gene was cloned and its protein product identified and named dystrophin. This protein is now known to be important in the structure of the muscle cell membrane (*Table 5*). This was the result of truly international efforts involving among others Dr Kay Davies of Oxford, Dr Ron Worton of Toronto, Dr Lou Kunkel of Boston, and Dr Eric Hoffman of Pittsburgh, and their associates. One important paper on the subject published in the scientific journal *Nature* listed no less than 75 co-authors from all over the world!

In other forms of dystrophy (Emery–Dreifuss dystrophy, limb girdle dystrophy of adulthood, facioscapulohumeral dystrophy, and myotonic dystrophy) the disease-causing genes have been located but their protein products not yet identified. We therefore still do not know the basic cause of these disorders. But now with ever improving technology,

**Table 5** Some landmarks in the history of Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD)

19th century	DMD recognized as a specific disorder
1955	BMD recognized as a specific disorder
1959–60	Serum CPK first shown to be raised in patients and carriers
1978–83	DMD gene located on the X chromosome (at position Xp21)
1983–4	BMD also located at Xp21
1985	DNA markers available for carrier detection and prenatal diagnosis
1987–88	Gene cloned and protein product identified (dystrophin)
1990–	Myoblast transfer trials begin; gene therapy in dystrophic animals



answers will no doubt soon be found, perhaps even as this book is being written.

Though an effective treatment has not yet been found for Duchenne muscular dystrophy, we are much closer to this now than at any other time in the past. This may well prove possible using a drug, perhaps designed for the purpose by pharmacologists, which specifically influences or interrupts the sequence of events between the deficiency of dystrophin and the development of weakness. Alternatively, replacement of the defective gene by a normal gene, gene therapy, may prove a more effective approach. If so, when this day comes and gene therapy is shown to work in Duchenne muscular dystrophy, the same approach will no doubt also be applicable to other dystrophies. The future now looks more hopeful and encouraging than at any other time in the history of muscular dystrophy.



## Living with muscular dystrophy



Even putting on splints can be fun.





The companionship of a pet is often very important.



An adapted car means greater independence.





Quite simple devices can often make everyday living much easier.





Painting can be a very rewarding pastime for the disabled.



## Further reading

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The following are texts which deal in greater detail with some of the topics discussed in this little book.

### Reference texts which deal with most aspects of muscular dystrophy

*Myology* (2 volumes)

H. G. Engel and B. Q. Banker (ed.)

McGraw Hill, New York (2nd edn) (1994)

*Muskelerkrankungen: Klinik-Therapie-Pathologie*

F. Jerusalem and S. Zierz

Thieme, Stuttgart (1991)

*Disorders of voluntary muscle*

J. N. Walton *et al.* (ed.)

Churchill Livingstone, Edinburgh (6th edn) (1994)

### Monographs on specific disorders

*Duchenne muscular dystrophy*

A. E. H. Emery

Oxford University Press, Oxford (2nd edn) (1993)

*Myotonic dystrophy*

P. S. Harper

W. B. Saunders, London (2nd edn) (1989)



## Texts which deal with particular topics relevant to muscular dystrophy

### *Bereavement*

There is a booklet available from The Cystic Fibrosis Research Trust, 5 Blyth Road, Bromley, Kent.

### *Living with grief*

T. Lake

Sheldon Press, London (1984, 1992)

### *Genetic counselling*

#### *Psychological aspects of genetic counselling*

A. E. H. Emery and I. Pullen (ed.)

Academic Press, London (1984)

### *Gene therapy*

#### *Treatment of genetic disease*

R. J. Desnick (ed.)

Churchill Livingstone, Edinburgh (1991)

#### *Therapy for genetic disease*

T. Friedmann (ed.)

Oxford University Press, Oxford (1991)

### *Thérapie génétique*

A. Kahn

John Libbey Eurotext, Montrouge (1993)

### *Physiotherapy*

#### *Duchenne muscular dystrophy: a parent's guide to physiotherapy in the home*

Sylvia Hyde

Muscular Dystrophy Group of Great Britain, London (1993)



*Prenatal diagnosis**Genetic disorders and the fetus*

A. Milunsky (ed.)

Johns Hopkins University Press, Baltimore (3rd edn) (1992)

*Preimplantation diagnosis of genetic disease*

Y. Verlinsky and A. M. Kuliev (ed.)

John Wiley, Chichester (1992)

*Psychosocial**Psychosocial aspects of muscular dystrophy and allied diseases*L. I. Charash *et al.* (ed.)

Charles C. Thomas, Springfield, Illinois (1983)

*Muscular dystrophy and other neuromuscular diseases: psychosocial issues*L. I. Charash *et al.* (ed.)

Haworth Press, New York (1991)

*Sexual matters*

Several booklets and leaflets are available from The Association to Aid the Sexual and Personal Relationships of People with a Disability (SPOD), 286 Camden Road, London N7 0BJ

### **Books about the disease written by patients or their relatives**

*Will to live*

H. Franks

Routledge &amp; Kegan Paul, London (1979)

*I have muscular dystrophy*

B. Pettenuzzo and T. Gwatkin

Franklin Watts, London (1989)



## Journals

Research developments are often reported in medical, paediatric, neurological, or scientific journals. Three journals in English *specifically* concerned with neuromuscular disorders are:

### *Muscle and nerve*

(Published six times a year by John Wiley, New York and Chichester)

### *Neuromuscular disorders*

(Published six times a year by Pergamon Press, Oxford)

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## Glossary

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This glossary gives definitions of scientific terms: in some cases the definitions given refer *only to their use in this book*. Words in italic are defined in the glossary.

**action potential:** electrical activity produced by contracting muscle fibres

**alleles:** alternate forms of the same gene—the normal and its mutant(s)

**amino acids:** small organic compounds which are the building blocks of *proteins*

**amniocentesis:** procedure for removing a small amount of *amniotic fluid* for *prenatal* diagnosis

**amniotic fluid:** fluid which surrounds the fetus in the womb (uterus)

**anterior tibial:** at the outer side of the front of the shin bone or *tibia*

**artificial insemination by donor:** insemination of a woman with sperm from a donor other than her partner

**autosome:** any chromosome other than the sex chromosomes

**biopsy:** removal of a small amount of tissue (usually muscle) for examination

**cardiac muscle:** heart muscle

**carrier:** an individual who has inherited a normal gene from one parent and a particular abnormal gene (*allele*) from the other; also referred to as a *heterozygote*

**cataracts:** opacities in the lens of the eye, sometimes also referred to as lenticular opacities

**catheter:** a long, slender, flexible tube

**chorion:** outer layer of cells which cover the developing embryo



**chorion biopsy:** removal of fetal *chorionic villi* for prenatal diagnosis, sometimes also referred to as chorionic villus sampling—CVS

**chorionic villi:** finger-like projections of the *chorion*

**chromosomes:** thread-like bodies within the *nucleus* which stain with particular dyes; they contain the *genes*

**clone:** all the cells derived from a single cell by repeated division and therefore all having the same genetic constitution

**conceptus:** the fertilized ovum and the embryo into which it develops

**congenital:** present at birth (or soon afterwards)

**consanguinity:** the genetic relatedness between individuals of the same family, such as cousins

**contractures:** shortening of muscles due to prolonged immobility which results in the associated joints becoming fixed and no longer able to move freely

**coping process:** the psychological sequence of events which follow any stressful situation

**CPK:** abbreviation for creatine phosphokinase, sometimes shortened to CK (creatine kinase), a muscle enzyme important in muscle contraction

**creatine kinase:** see *CPK*

**CT:** abbreviation for computerized tomography, a radiographic diagnostic technique for producing images of internal body organs, including muscle

**CVS:** see *chorion biopsy*

**cytoplasm:** the substance of the cell in which the *nucleus* and *mitochondria* are located

**diploid:** the number of *chromosomes* in the cells of the body (46); each cell contains two sets of chromosomes, one set derived from each parent

**diplopia:** double vision

**disorder:** another term for disease

**distal:** part of the limb most distant from the trunk (e.g. forearms and hands, lower legs and feet)



**DNA:** deoxyribonucleic acid—the chemical basis of genes in which is coded information for synthesizing *proteins*

**dominant:** an abnormal gene which is expressed in the *heterozygote*

**dysphagia:** difficulty in swallowing

**dystrophin:** a protein associated with the *membrane* surrounding each *muscle fibre*, which is absent in Duchenne muscular dystrophy and abnormal in Becker muscular dystrophy

**ECG (or EKG):** abbreviation for electrocardiogram, a non-invasive method for studying the function of the heart

**EMG:** abbreviation for electromyogram, an electrical test used in diagnosing dystrophy

**endocrine glands:** glands which secrete substances into the blood which then affect other organs (e.g. thyroid gland)

**enzymes:** particular proteins in the cell responsible for chemical reactions

**familial:** a term for a *trait* or disease which can affect several members of the same family

**gametes:** sperm and ova

**gene:** part of the DNA molecule which is responsible for synthesizing proteins

**gene marker:** a small segment (sequence) of *DNA* which is used to identify a mutant gene in an individual or trace its inheritance within a family

**gene probe:** a small segment (sequence) of *DNA* which is identical with part or all of a gene

**gene therapy:** treatment of inherited disease by the addition or substitution of a normal gene

**genetic:** any characteristic or *trait* which is inherited

**genome:** all the genes in a cell

**germ cell:** a sex cell

**germline mosaic:** the presence in the ovary of two different populations of cells



**glycoproteins:** a group of proteins which, with other proteins including *dystrophin*, are associated with and maintain the integrity of the muscle fibre *membrane*

**Gower's sign:** pressing on the thighs in order to straighten up

**graft rejection:** the rejection of a transplanted tissue or organ due to the host's *immune response* to the 'foreign' material

**haploid:** the number of *chromosomes* in each of the *gametes* (23)

**heart block:** a defect in the conducting system of the heart which results in abnormal slowing of the heart rate

**heterozygote:** an individual who has inherited a normal gene from one parent and a particular abnormal gene (*allele*) from the other; also referred to as a *carrier*

**histochemistry:** the microscopic chemical study of tissues such as muscle

**histology:** the microscopic study of tissues such as muscle

**homozygote:** an individual who has inherited a particular allele from *both* parents (two identical abnormal genes in a homozygous affected individual)

**humerus:** the upper arm bone

**hypoxia:** low oxygen level in the blood

**immune response:** the response by the body to 'foreign' material (transplant or infection) which is thereby destroyed

***in utero*:** literally, in the uterus

***in vitro*:** literally, in glass, meaning in the laboratory; thus, *in vitro* fertilization is the fertilization of an egg by a sperm in the test-tube in the laboratory

**ion:** an electrically charged atom

**isotonic:** a solution of salts of the same composition as the body fluids

**karyotype:** a photomicrograph of an individual's chromosomes arranged in pairs in a standard manner, from the largest (number 1) down to the smallest (number 22) autosomes and the two sex chromosomes



**laparoscopy:** insertion of a fine telescopic tube into the abdomen in order to visualize organs such as the ovaries

**lenticular (lens) opacities:** see *cataracts*

**leucocyte:** a white blood cell

**limb girdle:** hips and shoulders

**locus:** the location of a gene on a chromosome

**lordosis:** exaggerated forward curvature of the lower back

**macrophage:** a cell in diseased muscle which consumes necrotic fibres

**manifesting carrier:** a female *carrier* of an *X-linked* muscular dystrophy who has some weakness

**meiosis:** the process of cell division in the sex cells which results in *haploid gametes*

**membrane:** surrounding outer layer

**mitochondria:** minute structures or organelles within the cell concerned with the production of energy

**mitosis:** the process of division in the body cells

**molecular genetics:** the study of genes at the submicroscopic level

**mosaic:** two different populations of cells in the same tissue (e.g. ovary) of an individual

**muscle fibre:** the basic unit of muscle tissue; formed by the fusion of groups of muscle cells each having one *nucleus* to produce muscle fibres with many nuclei

**mutation:** changed and abnormal gene; sometimes used to describe an individual with a genetic abnormality not present in the genes of either parent

**myoglobin:** oxygen-carrying *protein* of muscle

**myometer:** instrument used to measure muscle strength

**myopathic:** originating in the muscle

**myopathy:** any disease of muscle

**myotonia:** delayed relaxation after muscle contraction



- necrosis:** literally, death; a descriptive term for the microscopic changes seen in muscle fibres in muscular dystrophy
- neurogenic:** originating in the nervous system
- nucleus:** the structure within the cell which contains the *chromosomes*
- ocular:** relating to the eye
- orthoses:** devices or aids to prevent or correct deformities
- pathogenesis:** the development of the disease process
- pectoral:** in the shoulder region
- pelvic:** in the hip region
- peroneal:** more or less synonymous with *anterior tibial*
- pharyngeal:** relating to the *pharynx*
- pharynx:** the upper part of the airway, at the back of the throat
- placebo:** an inactive compound which closely resembles an active drug
- preclinical diagnosis:** diagnosis of a genetic disorder *before* there are any symptoms of the disorder
- pre-implantation diagnosis:** diagnosis of a disorder in the fertilized *conceptus* before it becomes implanted into the uterus
- prenatal:** literally, before birth
- prevalence:** frequency of a disorder in a population
- prognosis:** probable course and outcome of a disease
- promoter:** a segment (sequence) of *DNA* which 'turns on' an associated *gene*
- proteins:** large molecules, composed of *amino acids*, which are essential components of the body; they include *enzymes*
- proximal:** part of the limb closest to the trunk (e.g. upper arms and shoulders, thighs and hips)
- pseudohypertrophy:** enlargement of muscles (usually the calves) which can occur in dystrophy
- ptosis:** drooping of the eyelids
- recessive:** an abnormal gene which is only expressed in the *homozygote*



- sarcolemma:** two-layered outer *membrane* of *muscle fibres*
- scapula:** the shoulder blade
- scapular:** around the shoulder
- scoliosis:** curvature of the spine to one side
- sex chromosomes:** the pair of non-*autosomal* genes which determine an individual's sex (XX in the female, XY in the male)
- sex-linked:** a gene on the X chromosome
- sibling (or sib):** brother or sister
- skeletal muscles:** those muscles which move joints
- slit lamp:** an instrument used by ophthalmologists to examine the lens of the eye
- smooth muscle:** involuntary muscles of the gut and blood vessels
- somatic cells:** cells of the body other than the sex cells (*gametes, germ cells*)
- Southern blot:** a method of transferring *DNA* fragments to a nitrocellulose filter where they can be tested using a *gene marker* or *gene probe*
- steroids:** a group of drugs which have a wide range of uses in medicine, including the suppression of the *immune response* (e.g. after a tissue transplant)
- syndrome:** the complex of signs and symptoms which occur together in any particular disorder
- talipes:** turning in of the sole of the foot
- tibia:** shin bone
- tibial:** relating to the *tibia*
- tracheostomy:** insertion of a tube (airway) into the upper trachea (windpipe)
- trait:** an inherited characteristic
- ultrasound:** sound waves above hearing frequencies, used to study internal body organs (e.g. muscle structure, the position of the placenta, and the fetus *in utero*)







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