

2

What is muscular dystrophy?

➔ Key points

- ◆ The muscular dystrophies are a group of inherited diseases in which various genes controlling muscle function are defective.
- ◆ In most forms of dystrophy the basic underlying protein defect is now known (a deficiency of the muscle protein dystrophin in Duchenne muscular dystrophy, for example).
- ◆ 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.

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 that 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 that, when cells are treated with an appropriate dye and then viewed down the microscope, appears as a darkly stained structure within the cell (Fig. 2.1). 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 banding pattern when stained with certain dyes. The arrangement of the chromosomes in a standard manner is referred to as a *karyotype* (Chapter 8).

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 about 30 000 genes in each nucleus. We still know very little about the many genes that determine and control such common traits as intelligence, stature, and our general ‘appearance’. Oddly, we know more about genes that result in diseases such as dystrophy (Chapter 8).

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. DNA is composed of four bases (abbreviated to C, T, A, G). Any combination of three bases specifies or codes for different amino acids. The amino acids so produced then join up to form a particular protein or part of a protein. 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 that 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 that causes dystrophy in a family

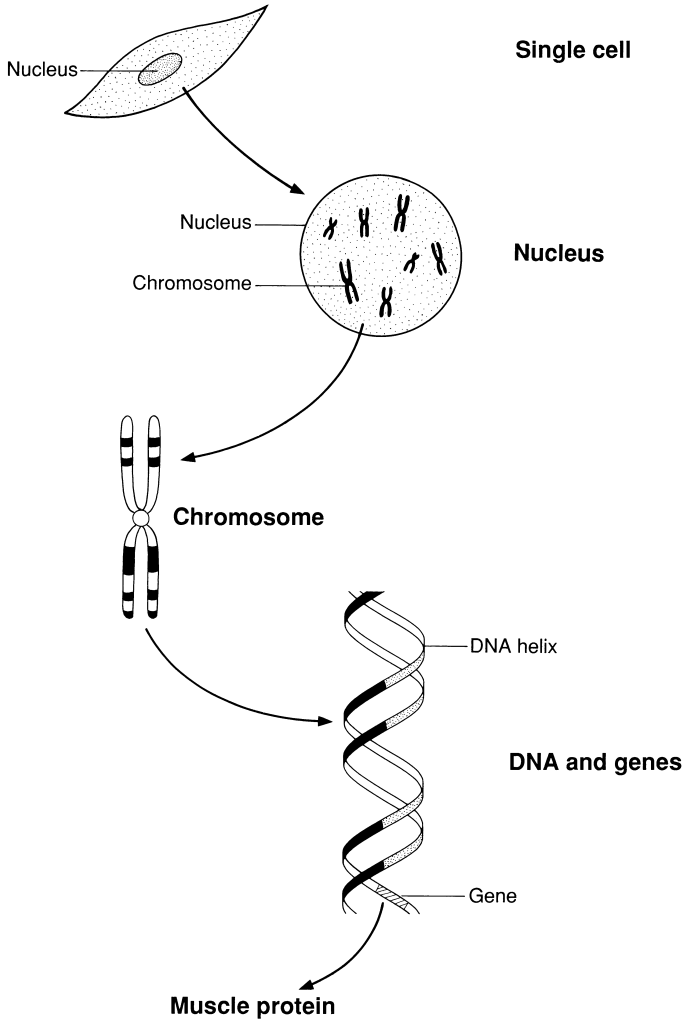


Figure 2.1 Diagram of the relationship between the cell nucleus, chromosomes, DNA, and genes.



Muscular dystrophy: the facts

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 that causes the disease can be traced back several generations. In others, the causative mutation occurs in the egg or sperm that 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 20 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 that have allowed 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 can 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 that 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.



Muscular dystrophy

This term includes many conditions presenting with muscle wasting and weakness. All are genetic, but different types are due to different genes and differ in severity.

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 that 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 that *primarily* affects muscle tissue, though in some dystrophies other tissues and organs may also be affected.

Muscle weakness

The muscle weakness that occurs in all types of dystrophy has certain features in common. It is usually *symmetrical*, i.e. 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



Muscular dystrophy · the facts

physiotherapy and other measures it is possible to prevent or delay certain complications, such as *contractures*. These are usually 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 that result from weakness of the affected muscles. Sometimes, especially in those types of dystrophy that 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’. However, 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. As these muscles mainly, but not exclusively, move bones that 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 you 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 restriction of calorie intake by dieting.

Apart from voluntary muscle, there are two other types of muscle (heart and smooth) that 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 that surrounds the wall of the intestines and is responsible for involuntary contractions that 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. However, 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 that are visible to the naked eye when a joint of meat is cut across (Fig. 2.2). 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 that 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.

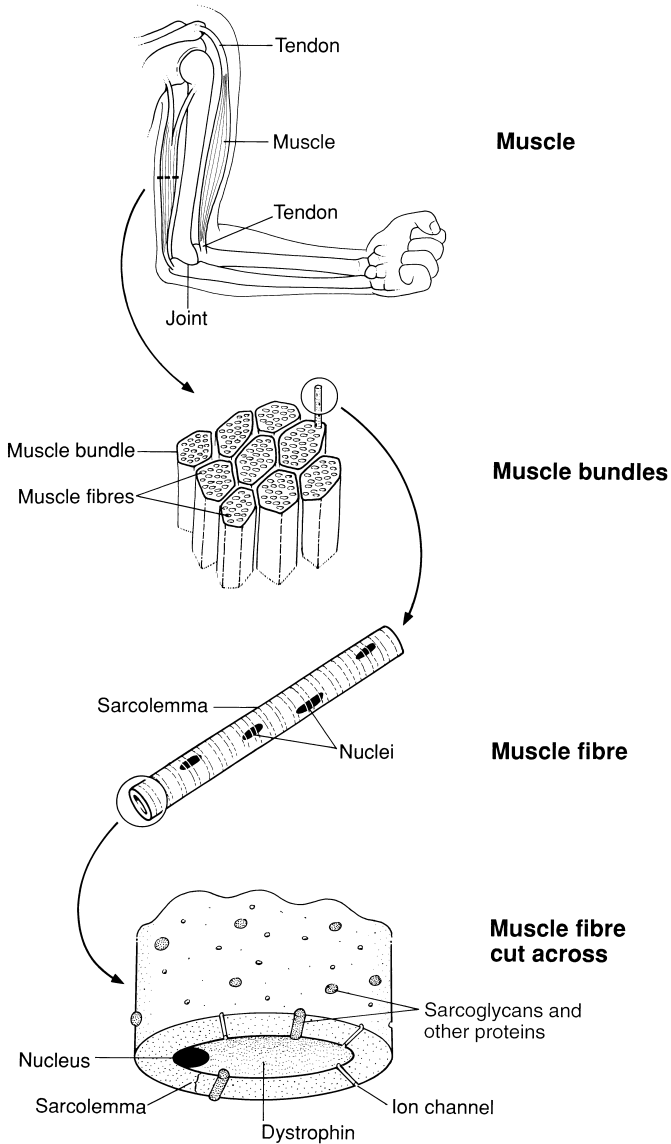


Figure 2.2 Diagram of the relationship between muscle, muscle bundles, muscle fibres, and the muscle fibre membrane (sarcolemma).

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 of two layers. Traversing between these two layers are minute pores or channels that open and close and that 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 that 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 as dystrophin was only present in normal muscle. However, it is now universally accepted for the name of the protein that is absent in Duchenne muscular dystrophy.

Cause of muscle weakness

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 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 that leak out is a muscle enzyme called *creatine kinase*. Enzymes are proteins within the cell that 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 the last few years the basic underlying protein defects in many other forms of dystrophy have been identified. Most of these proteins are located on the inside of the sarcolemma, such as dystrophin, within the sarcolemma itself, or even on the surface of the muscle fibre (Fig. 2.3). Those proteins defective in particular forms of dystrophy include, for example, laminin $\alpha 2$ (also known

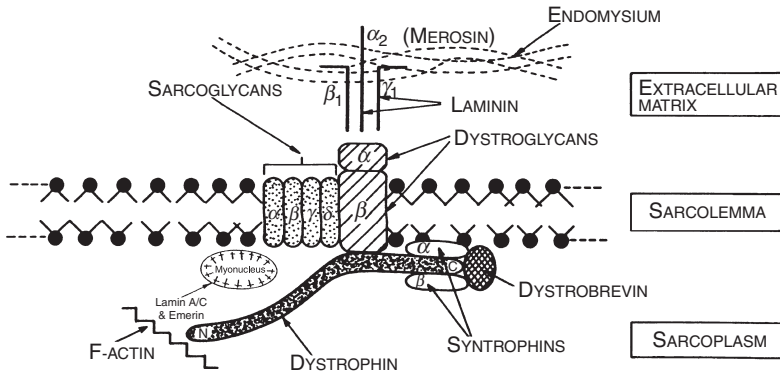


Figure 2.3 Diagram of the various proteins associated with the muscle sarcolemma or muscle nucleus (myonucleus).

as merosin), caveolin, various sarcoglycans, dysferlin, and dystrophin. The absence of any one of these proteins results in the disruption and breakdown of the muscle membrane and is probably the explanation for the weakness in these disorders. However, there are two exceptions referred to as laminin A/C and emerin proteins. These proteins are not associated with the sarcolemma but are located on the inner surface of the muscle nuclei (myonuclei)! How a deficiency of these proteins results in weakness is at present a complete mystery.

Many scientists believe that weakness 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 that 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 that 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 that 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, and chicken.

But none of these has proved to be strictly comparable with human muscular dystrophy. However, more recently two 'animal models' have been found with diseases that 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 Duchenne dystrophy, and could prove an excellent subject 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 that 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 but the mouse does not become progressively weaker or die from the disease. 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.

