Muscular Dystrophy: Some Recent Advances in Knowledge*

JOHN N. WALTON,† M.D., F.R.C.P.

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It is perhaps fitting that I should spend a few moments in reminding you of some details of the life of the man to whose memory this lecture is dedicated. Theodore Goulston was the son of a country rector; he was born in 1574, took his M.D. of Oxford in 1610, and in the same year passed the examinations of the College of Physicians, being elected to the Fellowship in 1611. He was rapidly successful in his career as a physician, and in 1614 was credited with saving the life of the Archbishop of Canterbury (Keevil, 1953). He first became a Censor of the College in 1615, and in 1619 his important translation of the works of Aristotle appeared. Among the bequests in his will it is interesting to note that he bequeathed £20 for the repair of St. Paul's Cathedral and a similar sum for the relief of the poor of the parish, but gave £200 to the Royal College of Physicians to endow this lecture. I have been relieved to learn that whereas originally the lecturer was asked to treat of two, three, or more diseases and to lecture in the forenoon and afternoon of three successive days, the Board of Censors in their wisdom subsequently decreed that two Goulstonian Lectures should be given, and in comparatively recent years that number was reduced to one.

Historical Details

Probably the first recognizable report of muscular dystrophy in the literature was that of Meryon (1852), who described a form of granular degeneration of the voluntary muscles occurring in four brothers. It was, however, Duchenne in 1868 who gave the first clear-cut description of pseudohypertrophic muscular paralysis in children, and although at first these cases were believed to be similar pathologically to progressive muscular atrophy in adult life, the subsequent descriptions of Leyden (1876) and Möbius (1879), each of whom described a form of progressive atrophy of proximal limb muscles, made it apparent that this group of disorders was pathologically distinctive. Further support for this view, based not only upon clinical descriptions but also upon careful pathological observations, came in 1884 from the work of Erb, who described a juvenile or scapulohumeral form of muscular dystrophy. In the same year the facioscapulohumeral variety was described by Landouzy and Dejerine (1884). Myopathic weakness of the external ocular muscles had been described in 1879 by Hutchinson, and a subsequent report by Fuchs (1890) confirmed the existence of such a syndrome, while in 1902 Gowers showed that there was a group of uncommon cases in which a similar myopathic process sometimes involved the distal muscles of the limbs and that these cases could be distinguished from the peroneal muscular atrophy of Charcot, Marie, and Tooth. Shortly afterwards (Batten and Gibb, 1909; Steinert, 1909) myotonia atrophica or, as it is now often called, dystrophia myotonica, was described, in which a progressive dystrophic process was seen to involve the facial and sternomastoid muscles and those in the periphery of the limbs, but was also accompanied by the phenomenon of myotonia and by other non-muscular manifestations, including cataract, frontal baldness, and testicular atrophy (in the male).

I propose to concentrate upon the non-myotonic varieties of muscular dystrophy. It is my intention to attempt to bring together information concerning recent advances in our knowledge of this group of diseases, knowledge which has been acquired by clinical and genetic study and by the application of biochemical, pathological, and electrophysiological methods of investigation. For too many years there has been a feeling in the medical profession that inherited disorders such as muscular dystrophy, which I have defined elsewhere (Walton, 1961, 1963, 1964) as "genetically-determined, primary, degenerative myopathy," are not fruitful subjects for research, being essentially incurable and unlikely to be influenced by any form of treatment. This attitude has not unnaturally created a sense of despair, not only among sufferers and their relatives but also in those who are called upon to care for them; it is my view, as it must surely be that of anyone who has observed recent advances in biochemical genetics, that such an opinion is wholly unjustified. It is only necessary to quote the example of phenylketonuria to indicate that because a disease is genetically determined there is no reason to suppose that it cannot be controlled by appropriate measures once the basic biochemical defect which produces it is elucidated.

Classification

The classification of cases of muscular dystrophy into discrete categories based upon clinical, genetic, and biochemical criteria is not simply of academic interest, as it is only on the basis of such accurate classification that one can offer an accurate prognosis in any individual case. Perhaps equally if not more important is the fact that the fullest possible knowledge concerning inheritance is needed before parents and relatives of dystrophic patients can be properly advised concerning the possibility that other members of a family in the same or subsequent generations will suffer from the disease. It has been recognized for many years that classification according to the "classical" criteria of Duchenne (1868), Leyden (1876), Möbius (1879), Erb (1884), Landouzy and Dejerine (1884), and others is unsatisfactory for the very good reason that if one attempts to place all cases with pseudohypertrophy in one group, all atrophic pelvifemoral cases in another, juvenile scapulohumeral cases in another, and facioscapulohumeral cases in yet another, one will find a marked overlap between the various categories and an almost complete inconsistency of genetic information. For example, if the presence of muscular

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† Neurologist, Regional Neurological Centre, Newcastle General Hospital; Physician in Neurology, Royal Victoria Infirmary, Newcastle upon Tyne

pseudohypertrophy is taken alone as a guide to classification, one will find in families containing patients showing this phenomenon patterns of inheritance including now a sex-linked recessive mechanism, now an autosomal recessive, and in yet others a dominant mode of inheritance.

I do not propose to describe in any detail the many attempts at reclassification which have been made in the last 20 years, but would mention that important contributions to this subject have been made by Tyler and Wintrobe (1950), Stevenson (1953), Walton and Nattrass (1954), Becker (1953, 1957), Morton and Chung (1959), Dubowitz (1960), and many others. I have myself considered this question on several occasions elsewhere (Walton, 1961, 1963, 1964) and can only conclude that yet further information from large family surveys will be needed before the question can finally be settled. Indeed, no absolutely firm basis for classification may ever be possible until some reliable method of identifying individual genes is found. For the present, however, there seems to be general acceptance of the classification of Walton and Nattrass (1954) as subsequently modified by Morton and Chung (1959), Walton (1961), and Morton, Chung, and Peters (1963). This divides cases of muscular dystrophy into the following clinical and genetic categories:

1. The Duchenne-type muscular dystrophy: (*a*) sex-linked recessive, (b) autosomal recessive.
2. Limb-girdle muscular dystrophy: (*a*) autosomal recessive, (*b*) sporadic.
3. Facioscapulohumeral muscular dystrophy.
4. Ocular myopathy.
5. Distal muscular dystrophy.
6. Congenital muscular dystrophy.

Before going on to describe some of the new information which has arisen from clinical, genetic, biochemical, and electrophysiological research, I propose to mention briefly the clinical characteristics of each of these forms of muscular dystrophy.

Clinical Varieties

Duchenne Type

In identifying this group of cases the eponymous title "Duchenne" is preferred to the classical term "pseudohypertrophic" for the very good reason that pseudohypertrophy can occur in any form of muscular dystrophy, and the term "childhood muscular dystrophy" suggested by Tyler and Wintrobe (1950) is also unsatisfactory, since in a small proportion of such cases the disease may begin in adolescence or adult life.

Sex-linked Recessive Form.—In the usual course of events this condition affects only boys and and begins at or about the third year of life with slowness and clumsiness in walking and running, frequent falling, difficulty in climbing stairs, and difficulty in rising from the floor. There is steady deterioration; the child walks with an accentuated lumbar lordosis, a protuberant abdomen, and a waddling gait, and gradually begins to "walk on his toes." Eventually, by the time he is about 10 years old, he is unable to walk and is confined to a wheelchair. Progressive contractures at the elbows, knees, and in the Achilles tendons supervene and are followed by gross skeletal distortion and atrophy. Eventually the child, pitiably deformed, is confined to bed and dies, as a rule, from an insistent respiratory infection or from cardiac failure (due in many cases to involvement of cardiac muscle) before the end of the second decade. In a few families, though the pattern of the disease is clinically indistinguishable from that described above, the condition is of substantially later onset and runs a slower course, so that a few patients in this category survive into middle life, being nevertheless very severely disabled. This benign subgroup of the sex-linked recessive cases probably accounts for 10% of the total in this category (Becker and Kiener, 1955; Gresham and Cruickshank, 1960).

Autosomal Recessive Form.—The clinical picture of this subvariety of the Duchenne type is very similar to that of the sex-linked recessive form, but this mode of inheritance explains the occasional occurrence of this form of the disease in girls. On the whole, although the age of onset is similar, the tempo of the disease is somewhat slower and many such patients are still able to walk in the middle of the second decade, though most of them are severely disabled by the time they are 20 years old. In all cases of the Duchenne-type dystrophy, but particularly in young affected males, there may be a period of apparent spurious improvement between the ages of 5 and 7 or 8 years, when increasing physical strength resulting from the processes of normal development is outstripping the deterioration due to the disease process.

Limb-girdle Muscular Dystrophy

This form of the disease, being usually inherited by an autosomal recessive mechanism, can affect either sex and may begin at any age, but usually does so in the second decade, though there are a few patients in whom the first symptoms and signs of muscular weakness do not appear until middle life. Differential diagnosis between these cases of late onset and polymyositis is sometimes a matter of considerable difficulty (Walton and Adams, 1958; Barwick and Walton, 1963). Muscular weakness may begin first in the shoulder girdle and is often asymmetrical. The disease process may seem to be confined to muscles in this region for 10 or even 20 years before a spread to the pelvic-girdle musculature is apparent.

In some individuals the disease process begins, by contrast, in the pelvic-girdle muscles, involving particularly quadriceps and hamstrings, and in these cases the tempo of the condition is generally more rapid and the shoulder girdle is usually involved within 10 years. Pseudohypertrophy of the calf muscles is not uncommon in such cases. A dystrophic process limited to the quadriceps muscles over many years (Walton, 1956a) is probably a forme fruste of this variety of dystrophy. Whereas those patients in whom muscular weakness begins first in the shoulder girdle show on the whole slower deterioration than those with onset in the pelvic girdle, most patients in this category become severely disabled in middle life and many are condemned to a wheelchair existence during the fifth decade, though there is a good deal of variability in the rate of clinical deterioration.

Facioscapulohumeral Muscular Dystrophy

This form of the disease, as first described by Landouzy and Dejerine (1884), involves first the facial muscles and those around the shoulder girdles. The face is typically unlined, with inability to close the eyes completely and a typical pouting appearance of the lips. Inheritance is usually as an autosomal dominant factor, though there is an impression of sex-limitation to females in some families. It is also notable that abortive or partially affected cases occur in this category, showing only very limited muscular weakness in the face or shoulder girdles, often confined to only one or two groups of muscles and showing no subsequent spread over many years of observation. In all but the abortive cases involvement of the pelvic girdle, with accentuation of the lumbar lordosis, a waddling gait, and progressive difficulty in walking, supervenes sooner or later, but the prognosis of this form of muscular dystrophy is immeasurably better, on the whole, than that of the limb-girdle type and many patients survive

to a normal age, though with increasing disability. There are, however, a small number of cases in which the disease progresses much more rapidly and disability becomes severe in early adult life or middle life. One curious unexplained feature is that within the same family one may find abortive, mild generalized, and severe generalized forms of this type.

Ocular Myopathy

This comparatively rare form of muscular dystrophy gives, as a rule, progressive bilateral ptosis and external ophthalmoplegia with impairment of ocular movement in all directions. Almost always there is weakness of the orbicularis oculi (Kiloh and Nevin, 1951) and sometimes of lower facial muscles, while after several years there is usually some diffuse atrophy of the muscles of the neck, trunk, and upper limbs. Dysphagia occurs in about 50% of cases, and no clear pattern of inheritance of this variety of the disease has emerged. Many such cases have been erroneously referred to in the past as examples of progressive nuclear ophthalmoplegia.

Distal Myopathy

The experience of recent years has amply confirmed Gowers's (1902) view that a distal form of muscular dystrophy may be seen, beginning as a rule in the small muscles of the hands and feet and slowly spreading proximally. The condition may initially be confused with peroneal muscular atrophy, but the sensory impairment (loss of vibration sense) which is almost invariably observed in the latter disease never occurs in the dystrophic condition, in which the muscular weakness also spreads much more proximally as the disease advances than it ever does in peroneal atrophy. The two disorders may readily be differentiated by means of electromyography. Although distal myopathy is a rare condition in Great Britain and in the United States, it is not uncommon in Sweden, where Welander (1951, 1957) has reported her experience of over 250 cases. In her families the condition usually began in adult life and was comparatively benign and slow to progress.

Congenital Muscular Dystrophy

The nosological status of this rare variety of muscular dystrophy remains the most confusing of all. Batten (1909) first suggested that some cases of amyotonia congenita (Oppenheim, 1900) were the result of a simple atrophic myopathy. Most patients subsequently diagnosed as suffering from amyotonia congenita were found to be cases of infantile spinal muscular atrophy (Werdnig–Hoffman disease), but others (Turner, 1940, 1949; Walton, 1956b, 1957; Turner and Lees, 1962) have confirmed that some infants who are born severely hypotonic show slow progress but have small and generally weak muscles throughout life. There is some evidence to suggest that they are suffering from a non-progressive myopathy whose nature is as yet poorly understood. It is, however, apparent that some few infants born with the syndrome of widespread muscular weakness and multiple contractures which has been referred to as arthrogryphosis multiplex congenita are found to be suffering from a progressive muscular dystrophy which appears to have begun in foetal life (Banker, Victor, and Adams, 1957).

What, if any, relationship exists between benign congenital myopathy or hypotonia, congenital muscular dystrophy, and the curious condition of so-called central-core disease (Shy and Magee, 1956; Engel, Foster, Hughes, Huxley, and Mahler, 1961) which also gives rise to hypotonia in infancy but is shown to be due to the presence of inactive central core areas in large numbers of muscle fibres, can be decided only by subsequent research. Much work remains to be done to clarify the nature and interrelationship of many of these obscure myopathies of early infancy. Yet another addition to the list, also giving rise to profound hypotonia, is the so-called nemaline myopathy with rod-body structures (Shy, Engel, Somers, and Wanks, 1963).

Clinical Research and Clinical Pathology

Diagnosis

A good deal of clinical research carried out in recent years has been concerned particularly with developing improved methods of diagnosis of muscular dystrophy. It has been well recognized that the *electromyogram* is of considerable value in this connexion; the pattern of voluntary effort recorded by means of concentric needle electrodes inserted into an affected muscle reveals a disintegration of motor unit potentials, many of which become polyphasic and of short duration (Kugelberg and Petersén, 1949; Gilliatt, 1962), and a technique of automatic frequency analysis may be useful in picking out the earliest changes of this type (Walton, 1952), although statistical measurement of mean action potential duration (Buchthal, 1962) is probably even more valuable. It is, however, well recognized that electromyography may give equivocal changes in very early cases of muscular dystrophy, and this is never a technique which is easy to carry out in young children. Furthermore, in the myopathies of late onset it may not be possible by means of electromyography to distinguish between various forms of myopathy, although the spontaneous activity of polymyositis is often reasonably distinctive (Walton and Adams, 1958).

The traditional method of diagnosis has been by means of *muscle biopsy*. In reviewing the literature, Adams, Denny-Brown, and Pearson (1953) concluded that the most striking histological features of progressive muscular dystrophy were, first, marked variation in fibre size with or without evidence of fibre-splitting; secondly, the central migration of sarcolemmal nuclei into the substance of the muscle cell and the formation of nuclear chains; thirdly, infiltration with fat and fibrous tissue was almost always present along with evidence of muscle fibre disintegration. They suggested that actual necrosis and phagocytosis of segments of muscle fibres was rarely if ever seen in muscular dystrophy and they did not describe regenerative activity in muscle obtained from these cases. Indeed, Denny-Brown (1951) went so far as to suggest on the basis of experimental work that the essential defect responsible for the muscular wasting in cases of muscular dystrophy was a total inability of the muscle cell to regenerate. However, Walton and Adams (1956) claimed that evidence of abortive regeneration was seen in biopsy specimens taken from areas of muscle which had previously been subjected to trauma in dystrophic patients. Recently, too, Pearce and Walton (1962), in reviewing the biopsy findings in a large series of cases of muscular dystrophy, confirmed that actual muscle-fibre necrosis with phagocytosis of necrotic remnants of fibres is a common histological feature of all varieties of dystrophy, though it is most commonly seen in the Duchenne type; furthermore, histological evidence of abortive regeneration is often seen in such biopsy samples.

Unquestionably the major advance of the past fifteen years is the development of methods of diagnosis using *serum enzyme estimation*. The first enzyme shown to be of value in this connexion was the serum aldolase (Sibley and Lehninger, 1949). It has subsequently been shown by many workers—for example, Evans and Baker (1957), Dreyfus, Schapira, and Schapira (1958), Thomson, Leyburn, and Walton (1960), and many others—that a rise in the activity of this enzyme in the serum is seen particularly in early cases of the Duchenne type

muscular dystrophy and that the activity declines progressively as the disease progresses. Whereas the normal upper limit is about 8–10 units, many patients with the Duchenne-type dystrophy have values exceeding 100 units in the early stages. Subsequently Pearson (1957) showed that aldolase activity could be raised in the serum long before overt clinical signs of the disease appeared; he discovered this by testing serum samples from younger male sibs of patients with the Duchenne-type dystrophy and therefore concluded that it was possible to detect the disease in its preclinical form. Subsequently (Pearson, 1962) he demonstrated that muscle biopsy samples taken from such preclinical cases showed dystrophic changes.

An important recent addition to the list of serum enzymes of value in diagnosis is the creatine kinase (Ebashi, Toyokura, Momoi, and Sugita, 1959). In agreement with the findings of others, we (Pearce, Pennington, and Walton, 1954a,b) have found that whereas the normal upper limit of activity of this enzyme in the serum is about 3.5 units and that this activity is unaffected by such factors as age and physical activity, values even as high as 1,000 units can be obtained in early cases of muscular dystrophy of the Duchenne type. As with the serum aldolase, much less striking rises in activity are observed in the serum of patients suffering from muscular dystrophy of other types. We have amply confirmed Pearson's (1957) observations and now have no doubt that by carrying out an estimation of the serum creatine kinase in a young infant shortly after birth it is possible to detect preclinical cases of muscular dystrophy; we have also confirmed Pearson's (1962) views that there are recognizable histological changes in the muscle fibres in this preclinical phase. From our observations to date in eight preclinical cases, we feel that the peak level of serum-enzyme activity occurs at about the age of 1 year, but many more results need to be obtained before this suggestion can be confirmed. There can, however, be no doubt that in the serum creatine kinase we have an extremely sensitive tool for the diagnosis of muscular dystrophy.

Electroencephalography

Wayne and Browne-Mayers (1959) first suggested that the electroencephalogram (E.E.G.) was abnormal in many patients with muscular dystrophy, and Perlstein, Gibbs, Gibbs, and Stein (1960) suggested that from their observations in over a hundred cases the percentage of abnormalities which they found suggested "a basic maturational neurophysiological involvement" which was an integral part of the disease process. Barwick, Osselton, and Walton (1962) carried out detailed studies in a total of 40 cases of muscular dystrophy, 10 of the Duchenne type, 10 limb-girdle, 10 facioscapulohumeral, and 10 dystrophia myotonica. The findings in these records were compared with those in a series of control individuals of comparable age and sex, and it was found that the incidence and type of abnormality was no higher in the patients suffering from Duchenne, limb-girdle, and facioscapulohumeral dystrophy than in the controls; subsequently additional cases of dystrophia myotonica were examined and it was found that 61% of these had abnormal recordings. The significance of this finding is now being investigated, but it is my view that no significant abnormalities are to be found in the E.E.G. of patients with uncomplicated muscular dystrophy.

Treatment

I do not propose to dwell upon the principles of physical and psychological management of cases of muscular dystrophy, but would mention first that it is vital to keep these patients active for as long as possible. Prolonged periods of rest in bed often produce deterioration and are therefore contraindicated, as are surgical methods of tendon-lengthening. All one can do in an attempt to avoid contractures is to advise passive stretching of those tendons, such as the Achilles tendons, which tend to shorten, but in children with the Duchenne-type dystrophy these contractures inevitably develop in the end. Judicious dieting and care of the posture, particularly in the child who is living in a wheelchair, are of considerable importance in the avoidance, for as long as possible, of severe skeletal distortion and atrophy.

Many forms of treatment have been advised for muscular dystrophy in the past and many of these have been hailed as being of considerable value, only to be discarded when eventually subjected to a strictly controlled double-blind trial. Two recent additions to the list have been anabolic steroids and digitoxin (Dowben, 1963) and a mixture of nucleotides and nucleosides known as "laevadosin" (Thomson and Guest, 1963). I do not wish to express any final or definitive opinion upon these methods of treatment at the present stage, but would mention that with Drs. Barwick and Newell (Barwick, Newell, and Walton, 1963) I reported early in 1963 the results of a double-blind controlled trial using anabolic steroids not dissimilar from those given by Dowben; in our trial the results were completely negative. Many carefully controlled trials of laevadosin therapy are in progress in various centres throughout Great Britain at the moment, including our own, and we hope that before many months have passed we shall be able to draw firm conclusions on whether this drug has any value. Personally I can only say that neither Dowben's report nor that of Thomson and Guest seems to me to be convincing, and they suffer from the serious defect that in neither instance was any real attempt made at carrying out a controlled trial.

[*The conclusion of this lecture, together with a list of references, will appear next week.*]