

Duchenne muscular dystrophy: hopes for the sesquicentenary

We understand the molecular basis, and a cure may soon be possible

THE FRENCH NEUROLOGIST Duchenne de Boulogne (1806–1875) originally described *paralysie hypertrophique de l'enfance* in 1861, outlining the key clinical features, including lordosis and calf hypertrophy.^{1,2} Although the English physician Edward Meryon had recognised similar cases 10 years earlier, Duchenne's name became associated with this condition through a series of illustrated articles in which he described key features, including male predominance, progressive course, waddling gait, pseudohypertrophy of calf muscles, loss of ambulation by adolescence, and early death. Duchenne devised a muscle biopsy needle and established that hyperplasia of fibrous connective tissue and destruction of the muscle cytoarchitecture (arrangement of cells) are key abnormalities. By the 1880s, the English neurologist Sir William Gowers was able to identify 81 case reports confirming the clinical features established by Duchenne. Clinicians established the clinical heterogeneity of the muscular dystrophies, and various disorders were identified, including facio-scapulothoracic muscular dystrophy, limb-girdle muscular dystrophy and myotonic dystrophy. Importantly, Becker muscular dystrophy (BMD) was identified as a much less severe condition with some similarity to Duchenne muscular dystrophy (DMD).

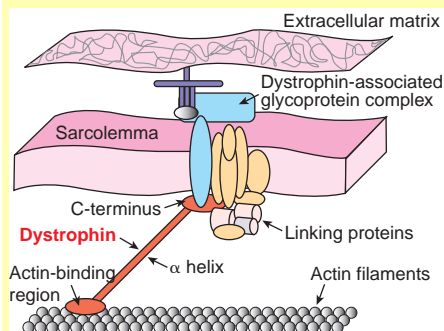
Success in delineating the basis of the dystrophies awaited the molecular era. Kunkel and coworkers identified a patient with a cytologically recognisable deletion on the X chromosome (Xp21) and realised that, if they allowed this to hybridise (pair) with normal DNA, they could find the gene.³ By ingenious use of their novel techniques, they created probes containing part of the Duchenne gene and found that one detected submicroscopic deletions in some affected boys.³ This led to the identification of the gene and eventual delineation of its sequence. Boys with DMD were found to have mutations that produced non-functional dystrophin protein.⁴ BMD patients were identified as having mutations that produced dystrophin protein with some function.⁴ The structure of the functional protein was predicted from the genetic sequence,⁵ and immunocytochemical investigation revealed a close relationship to the sarcolemma.⁶ Dystrophin's function as a key cytoskeletal protein was subsequently defined in elegant studies in many laboratories, but especially by Kevin Campbell and colleagues.⁷ Dystrophin links the actin filament of the contractile apparatus to a complex series of linking proteins in the cell membrane, and hence to the extracellular matrix (Box).

It was found that the C-terminus of dystrophin, which binds it to the sarcolemma, is crucial, as is the actin-binding zone, but the helical zone can be shortened with some preservation of function, explaining the differences between BMD and DMD. Subsequently, defects in the dystrophin-associated glycoprotein complex were found to underlie many other types of muscular dystrophy, including the limb-girdle syndromes and the congenital muscular dystrophies. Indeed, it was through pursuit of the cause of DMD that an understanding of much of what we now know about the muscle cytoskeleton has been achieved.^{7,8}

Much new knowledge, but what has been achieved of practical importance for the patients and their families? Diagnosis has improved a great deal. Established DMD is not difficult to diagnose, but molecular causation can now be defined in most cases, allowing accurate confirmation of female carrier status and, with in-vitro fertilisation techniques, selection of a healthy embryo for implantation.⁹ Advances in clinical management include the use of steroid therapy to improve muscle strength,¹⁰ orthopaedic techniques, especially Luque rods, to prevent kyphoscoliosis,¹¹ and regular respiratory monitoring, including sleep studies, to maximise use of non-invasive ventilatory techniques to improve quality of life. Later, depending on patients' wishes, tracheostomy-dependent ventilation can be used to prolong duration of life.

What of new potential treatments? The aim is to develop curative treatments, and it is somewhat disappointing that, more than 20 years after Kunkel's pioneering discoveries, this is yet to be achieved. Studies with cell therapy (myoblast transfer therapy) have not fulfilled initial promise, although they are still proceeding in several laboratories.¹² Major effort in gene therapy has led to an understanding of the key parts of the dystrophin gene that must be incorporated to achieve reasonable function.⁸ New techniques of gene repair are under evaluation in several laboratories, including our own.⁸ Skeletal muscle has an enormous capacity for regeneration, and there is every chance that effective strategies to achieve functional muscle remodelling will be achieved, especially if applied before irreversible fibrosis has occurred. Indeed, skeletal muscle, by virtue of its relatively simple structure, enormous capacity for regeneration, and easy and safe accessibility, is an ideal tissue for many of the new therapies in the cell and gene area. Correction of causative mutations through gene repair in autologous mesenchymal

Dystrophin: the key protein in Duchenne muscular dystrophy



Dystrophin links actin filaments to a complex of transmembrane proteins and hence to the extracellular matrix. Mutations that affect the C-terminus or actin-binding region cause Duchenne muscular dystrophy. Mutations that shorten the α helix cause Becker muscular dystrophy. Other muscular dystrophies are caused by defects in the dystrophin-associated glycoprotein complex.

stem cells derived from bone marrow, manipulation to a committed myogenic lineage, and systemic delivery, once a concept in the realm of science fiction, may be practical in the years ahead. However, even with the promise so close, there need to be further advances in several areas to achieve this. For example, we need better understanding of the factors that drive pluripotent stem cells into myogenic lineages, and of other factors, mainly immunological, that have limited stem cell survival *in vivo*. Gene vectors capable of encompassing the whole dystrophin gene are likely to be tested in human studies, and promising new techniques of gene repair are likely to reach clinical trials. It is important that various potential treatments be pursued in parallel, as it is not currently possible to determine which of the approaches available will enjoy most success.

Equally important to the search for a cure is the maintenance of quality of life for people who currently have muscular dystrophy. This necessitates adequate funding for clinical care in key paramedical areas, including access to state of the art wheelchair and ventilatory equipment. The role of the Muscular Dystrophy Association in providing support for carers and families is especially important.

The next decade is full of promise for robust advances in the management of the dystrophies, and there is real hope that by 2011, the 150th anniversary of Duchenne's landmark description, a cure for DMD will have been found.

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