Preface

The term "muscular dystrophy" (MD) describes a group of primary genetic disorders of muscle that often have a distinctive and recognizable clinical phenotype, accompanied by characteristic, but frequently not pathognomonic, pathological features. Research into the molecular basis of the MDs by a combination of positional cloning and candidate gene analysis has provided the basis for a reclassification of these disorders, with genetic and protein data augmenting traditional clinically based nomenclature. These findings have brought insights into the molecular pathogenesis of MD, with an increasing number of potential pathways involved in arriving at a dystrophic phenotype. Some common themes can be recognized, however, including the involvement of five members of the dystrophin-associated complex (dystrophin and four sarcoglycans) in different types of MD, and the involvement of two nuclear envelope proteins in producing an Emery-Dreifuss MD phenotype. Other disease-associated genes appear to cause MD in a completely unrelated way, such as the involvement of calpain 3 in a form of limb-girdle muscular dystrophy.

Section 1 of *Muscular Dystrophy: Methods and Protocols* reviews traditional strategies used to identify MDs. Meantime, techniques developed as a result of the research strategies described previously have become an integral part of the management of many patients with MD and their families, and these techniques are addressed in Sections 2 (DNA-based tests) and 3 (protein-based analyses). The continued effort to translate this enhanced understanding into a molecular cure or treatment for MD is reviewed in Section 4. *Muscular Dystrophy: Methods and Protocols* concentrates on those methods most likely to be relevant to clinical practice and most commonly applied to try to answer the questions that MD raises.

Katharine M. D. Bushby
Louise V. B. Anderson

2

Clinical Examination as a Tool for Diagnosis

Historical Perspective

David Gardner-Medwin

The purpose of diagnosis, since the days of classical Greece, when the concept was introduced, has been to provide a basis for prognosis and for the prescription of a regimen of management. Prognosis, i.e., explaining to the patient and family what the future holds, remains the central purpose of medicine, encapsulated in the private consultation. All other matters, including such important things as investigation as an aid to diagnosis and treatment as a component of management, are peripheral to this.

It is only in the past 50 yr that serious attention has been given to genetic prognosis, and for only half that period have most clinicians devoted the scientific care and compassion to this aspect of prognosis that justify the use of the term "genetic counseling." Indeed, as far as the muscular dystrophies (MDs) are concerned, it is the need for accurate genetic counseling that has been the spur to defining the diagnostic categories with precision.

Only occasional case reports of what is now called MD can be identified in the literature before the 1850s. Then Meryon in England, Aran and Duchenne in France, and Wachsmuth and Griesinger in Germany began to recognize the progressive degenerative diseases of muscle, distinguished neuropathic from myopathic muscle disease and developed systems of clinical, pathological, and electrical examination of muscles, which enabled them to begin to classify and name disorders. The term "progressive muscular dystrophy" was introduced by Erb in 1891 ***(1)*** for progressive myopathic degenerations. Although these early authors clearly recognized the hereditary nature of many of their cases, the concept of genetically determined disease did not become central to

From: *Methods in Molecular Medicine, vol. 43: Muscular Dystrophy: Methods and Protocols*
Edited by: K. M. D. Bushby and L. V. B. Anderson

the understanding of these disorders until the rediscovery of Mendel's work and the defining of the Mendelian modes of inheritance, in the first decade of this century; the idea that sporadic cases were somehow different in nature lingered on in the minds of some doctors until the 1960s. By about 1910, most of the commoner types of MD had been approximately identified, and then, for more than 30 yr, no further significant progress was made. Bell (1943) ***(2)*** attempted a genetic classification, revealing an unsatisfactory correlation between modes of inheritance and the then-recognized clinical types. Walton and Nattrass (1954) ***(3)*** began the modern process of attempting to combine clinical and genetic criteria in their classification. The introduction of the estimation of blood aldolase and creatine kinase (CK) activity, in the 1960s, and, shortly afterwards, the introduction of histochemical examination of muscle biopsies (which brought to light several previously unidentifiable congenital myopathies), provided two valuable new tools for differential diagnosis. Furthermore, the use of CK estimation in carriers of the Duchenne gene introduced a useful (though fallible) technique for the scientific study of the carrier state and its genetic implications.

By the early 1980s, before the molecular genetics revolution, matters stood thus: The MDs formed a discrete group of muscle disorders, readily distinguishable on clinical, histological, enzyme assay, and electromyographic grounds from the neuropathic disorders, the histochemically identifiable congenital myopathies, the endocrine myopathies, polymyositis, and various rarer myopathies. Within the group of true MDs, the clinical diagnosis was based on three criteria: the precise distribution of affected muscles, weak and wasted or, in some cases, hypertrophic; the related criteria of the age at the onset of symptoms and the rate of progression of the symptoms; and the mode of inheritance, when this was evident from the family history. Sporadic cases were naturally relatively difficult to identify. Muscle histology and serum CK activity were valuable adjuncts, electromyography was less so.

All these criteria, by then refined by much study and scientific discourse, resulted in a classification that included the X-linked Duchenne (DMD), Becker and Emery-Dreifuss muscular dystrophy (EDMD) types, the autosomal dominant facioscapulohumeral (FSHD), scapulohumeral, distal and oculopharyngeal types, as well as the multisystem disorder, myotonic dystrophy. It was among the autosomal recessive (AR) types, so often presenting as sporadic cases, that the most difficulty was encountered; the provisional categories of these were the limb-girdle muscular dystrophy (LGMD) types, presenting in childhood or adult life, and the congenital muscular dystrophy (CMD) types, together with some rarer forms, distal and Fukuyama CMDs.

The names of many of these types clearly indicate the primary diagnostic importance of detailed recording of the distribution of affected muscles; the

distinction between DMD and BMD, and between the CMD and LGMD types, depended on the timing and progression of symptoms. The problem with the AR types was that there seemed to be no consistent or clearly definable patterns of selective muscle involvement by which these might be positively identified or subdivided, nor was laboratory investigation sufficiently helpful to solve the problem. Indeed, it was recognized that at least one autosomal dominant form of LGMD existed, although its identification in the sporadic case was never secure. Distinction of LGMD from BMD or from the Duchenne carrier state, in which proximal muscular weakness sometimes occurs, was a particular problem, and serious errors in the consequent genetic advice were not uncommon.

In recent years, many new categories of AR MD have been identified by their genetic linkage to particular loci, and, more recently still, by their specific molecular pathology. In many cases, this has made it possible to recognize for the first time characteristic patterns of selective muscle involvement, not previously discernible among the muddled group of LGMDs. Whether every LGMD type will ultimately prove to be clinically recognizable, it is too early to say, but, at present, this looks unlikely. Because most of the MDs have characteristic patterns of selective muscle involvement, it should not be assumed to be axiomatic that all of them must.

This is not the place to describe in detail the precise patterns of muscle involvement that characterize the various classical types of MD. These may be found in clinical texts such as those by Walton, Karpati, and Hilton-Jones (1994) ***(4)***. A resumé would be valueless and potentially dangerous, because the essence of clinical diagnosis of these disorders lies in the details. For inspiration in the techniques involved the works of Duchenne (1870) ***(5)*** and Gowers (1881) ***(6)*** can be recommended.

The advent of molecular genetics has transformed the diagnosis and classification of the MDs as later chapters in this book show. The chief consequences can be listed as follows:

1. Molecular diagnosis has confirmed the validity of many previously identified entities, for example, DMD, BMD, EDMD, FSHD and myotonic dystrophies.
2. It has provided a firm basis for identifying carriers of the X-linked types, and for achieving preclinical and prenatal diagnosis.
3. It has resulted in the recognition of many new types of MD previously consigned to wrong categories or to the unsatisfactory limb-girdle group.
4. It has revealed the molecular basis or cause of many of these disorders for the first time, providing a means not only of identifying but of defining the different types of MD. Incidentally, this also provides a logical direction for the search for a cure.

Advances of the past 13 yr, since the discovery of dystrophin by means of reverse genetics, have been so fundamental that it is now a truism to regard the classification and genetic diagnosis of the MDs as firmly based on molecular biology. No other approach rivals it in precision.

But, crucial as it is, genetic advice is not the only information that patients seek. They (or their families) need to know also the prognosis for progression of the disability and for survival, and here it is plain that clinical information is vital. For example, merosin deficiency has been identified as the molecular basis for the commonest type of CMD in Europe and North America, but a partial deficiency of merosin is the basis of a wide variety of clinical predicaments, ranging from severe CMD, which causes profound weakness from birth and an ever-present risk of early death, to a much less severe LGMD type of proximal weakness, which causes mild to moderate disability in childhood and adult life, and which, only by careful enquiry, is traceable in its onset to early infancy. Other examples of variable clinical problems caused by identical molecular lesions are found in later chapters. Now, and for the foreseeable future, it will be prudent to offer a prognosis based, not upon a molecular genetics laboratory report alone (though that is essential), but also upon the evidence of serum enzyme activity and an experienced clinical opinion. A period of observation at follow-up, during at least the initial progressive stage of the disease, gives added confirmation of the prognosis, as well as providing an opportunity to support and guide patients and families.

They will need support. Having reviewed the general principles of diagnosis, one should here return to prognosis, telling the patient about the future, or, in the case of the early-onset forms, telling the parents (whenever possible, both parents together). The disease will have such an all-pervading influence on patient and family for the rest of their lives that the moment at which the news is broken will be remembered forever, and the content and atmosphere of the consultation will, to a great extent, determine their subsequent attitude to the disease and to medical care. The news must be broken with sensitivity and without haste, by a physician who knows the patient personally and has a full understanding of the disease and its many implications. Enough information must be given to allow the family to plan effectively for the future, and to have confidence that no further unexpected bad news remains to be discovered. The news should be accompanied by an offer of support and a constructive plan for management.

Precision in prognosis is important also in trials of treatment. Here the need to compare outcomes in treated patients and controls, using the smallest effective numbers and the shortest effective period of follow-up, makes an understanding of the natural history of the untreated disease, in all of the subjects in the trial, very important. A preceding period of repeated careful functional

measurement makes it much easier to match cases and controls properly. With this in mind, many muscle clinics make regular measurements of their patients' speed of walking or running, of climbing stairs, and of rising from the floor or from a standard chair. More elaborate functional testing, including the use of multiple standard tasks or the direct measurement of the power of individual muscles, are rarely used, except during the course of treatment trials.

References

1. Erb, W. H. (1891) Dystrophia muscularis progressiva: Klinische und pathologis-chanatomische Studien. *Deutsche Zeittschrift fur Nervenheilkunde* **1,** 13.
2. Bell, J. (1943) On pseudohypertrophic and allied types of progressive muscular dystrophy, in *Treasury of Human Inheritance, vol. 4,* Cambridge University Press, London, pp.
3. Walton, J. N. and Nattrass, F. J. (1954) On the classification, natural history and treatment of the myopathies. *Brain* **77,** 169.
4. Walton, J., Karpati, G., and Hilton-Jones, D. (eds.) (1994) *Disorders of Voluntary Muscle*. 6th ed. Churchill Livingstone, Edinburgh.
5. Duchenne, G. B. (1872) *De l'Electrisation Localisee et de son Application a la Pathologie et a la therapeutique*. 3rd ed. Bailliere, Paris.
6. Gowers, W. R. (1886–1888) *Manual of Diseases of the Nervous System*, vols. 1 and 2 Churchill, London.