THE MUSCULAR DYSTROPHIES
Edited by Alan E. H. Emery
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This book is timely. Although there have of course been substantial developments in all areas of genetic disease, there
can be few areas in which progress has been so rapid and has led to such fundamental shifts in practice, with respect to diagnostic strategy, and opinion with respect to the understanding of basic molecular mechanisms, than the muscular dystrophies. The clinically naive may note that these developments have not yet led to specific therapy and therefore doubt their importance, but their naivety blinds them to the enormous benefits of precise diagnosis.

The book’s editor, Alan Emery, is well known to all involved in the field of neuromuscular disease. He is one of those remarkable people who seem to have achieved as much in retirement as they did in their formal career. Following retirement, he set up the European Neuromuscular Centre and became its Research Director. The centre has now run over 100 workshops, each devoted to a specific neuromuscular disorder or an aspect of such diseases. The centre has acted as a remarkable focal point for clinicians and scientists from throughout Europe and other parts of the world. The output of those workshops is reflected in several of the contributions to the present volume.

The book has just under 30 contributors, from all corners of the globe, all acknowledged experts in their field. Tragically missing is Kiichi Arahata, a much loved and respected colleague who died during the preparation of the book, arguably at the peak of his career. Emery uses one of Kiichi’s own Haikus in tribute, and the chapter on Emery–Dreifuss muscular dystrophy is dedicated to his memory. There are 16 chapters, 10 devoted to specific conditions, or groups of conditions (e.g. congenital muscular dystrophies), and the remainder to various aspects of management (physical, surgical and medical). A single chapter covers prospects for gene and cell therapy.

Before reviewing the content, it is appropriate to consider for whom the book is written. Most patients with muscular dystrophy are likely to be under the care of a paediatric or adult neurologist. At some stage, further medical input may be required from a geneticist, cardiologist, respiratory physician, orthopaedic surgeon or rehabilitation specialist. All of these will find something of value in this book, not only with respect to immediate practical advice but also as a summary of the current state of knowledge (or rather our state of knowledge about a year ago, such is the pace of change) and as a concise source of reference. Physiotherapists, occupational therapists, family care officers, speech therapists and dietitians will find some of the science a little hard going, but will still find some useful information, particularly with respect to management issues.

The first chapter, ‘Muscular Dystrophy—An Evolving Concept’ is by the editor. It concludes with what may seem an odd sentence, ‘However, for the sake of tradition the currently accepted term ‘muscular dystrophy’ will be retained in the present text’. What other term could there possibly be? Well, it can be argued that the end product of the evolution of our concept of muscular dystrophy should be extinction of the term muscular dystrophy. Although Duchenne muscular dystrophy had been recognized for about a century, and facioscapulohumeral muscular dystrophy for only a little less, it was not until the 1950s, and the work of Walton and Nattrass, that a firm clinical concept of muscular dystrophy was established. This was coupled with advances in muscle histology and the view that certain common pathological changes (e.g. variation in muscle fibre size, fibre splitting, necrosis and regeneration, and replacement of fibres by fat and connective tissue) linked the clinically rather variable phenotypes. It was rather presumed that the next stage would be the identification of a specific gene defect, and thus absence or abnormality of a specific protein, in each of the clinically recognized forms of muscular dystrophy, and that this would provide a more logical classification of these disorders as well as providing insight into common molecular mechanisms.

There had been much evidence suggesting that Duchenne muscular dystrophy was due to a defect of membrane structure or function, and thus there was no great surprise when dystrophin was discovered and found to have a subsarcolemmal location. The subsequent identification of abnormalities of dystrophin-associated proteins in other forms of muscular dystrophy strengthened the membrane hypothesis. However, in a short period of time, other forms of muscular dystrophy were found to be due to defective proteins involved in calcium metabolism, the contractile apparatus, nuclear membrane structure, and intranuclear functions. Although some argue that there must be a single common pathway linking these apparently disparate proteins, such a pathway has not been found and may prove to be an over-simplistic concept. A further revelation was that different mutations in the same gene could cause markedly different phenotypes. Early on, it was learnt that different mutations in the dystrophin gene could produce either Duchenne muscular dystrophy, or a very mild variant of Becker muscular dystrophy, or sometimes just cardiomyopathy—but at least all involved muscle. Then came the realization that lamin A/C mutations could cause not only different forms of myopathy but also isolated cardiac conduction disease and a form of lipodystrophy. In these examples, there is generally some correlation between the specific mutation and the phenotype. More extraordinary was the subsequent realization that the same mutation could cause very different phenotypes. Thus, the same mutation in the caveolin-3 gene can cause either limb-girdle muscular dystrophy (LGMD), or isolated hyperCKaemia, or rippling muscle disease. The simple concept of one gene → one protein → one disease is no longer always tenable. Emery argues that we should now be moving towards classification based on the protein involved, giving rise to terms such as dystrophinopathy and emerinopathy, and abandonment of the term muscular dystrophy.

What of the other chapters? They are all of high standard and there is little unnecessary repetition between chapters. Some devote more space than others to historical aspects, and several play the game of challenging the appropriateness of the currently accepted eponymous title. For Duchenne,
Becker and Emery–Dreifuss respectively, read Meryon, Kostakow, and Cestan and Lejonne. Or preferably, as noted above, change to dystrophinopathies, emerinopathy and laminopathy. The chapter on congenital muscular dystrophies emphasizes the importance of clinical features in classification and helping to direct specific gene tests, such as the presence or absence of mental retardation, spinal rigidity and joint laxity. The clinical features of Duchenne and Becker muscular dystrophy are well known, but the considerable variability of Becker, and the commonness of cardiac involvement, are less well appreciated. Important differential diagnoses for Becker include LGMD and spinal muscular atrophy. The latter can be excluded easily, but LGMD still poses many challenges.

Bushby’s chapter on LGMD effectively updates her 1999 review for this journal. Shortly after her submission to the present book, a mutation affecting the fukutin-related protein was found to be the cause of LGMD type 2I, and it looks as if this may turn out to be one of the commonest, if not the commonest, form of LGMD in the UK—an indication of the pace of change in the field. She also emphasizes the importance to the patient of a precise diagnosis.

Facioscapulohumeral muscular dystrophy presents us with yet another challenge with respect to understanding genetic and molecular mechanisms. Having got used to the concept of nucleotide-repeat expansion disorders, along comes a condition in which there is contraction of a repeat sequence. Not only that, but there doesn’t seem to be a gene in the affected region and it appears that the molecular mechanism might be due to a positional effect on other genes. Two comments caused me anxiety. First, the view that penetrance is almost complete (>95%) by age 20 years is based on old clinical assessment data and recent DNA data shows that is figure is an over-estimate. This is a very important point for family ascertainment and genetic counselling. As Dubowitz has said recently, ‘the corner seems to be getting further away’. Remember, optimism with respect to the imminence of clinically useful treatments. If such researchers challenge this view, then they should come and sit in clinic and listen to the patients and their parents. We must be optimistic, but also realistic. When dystrophin was identified, it was felt/hoped that successful treatment was ‘just around the corner’ and such a view was conveyed to affected families. As Dubowitz has said recently, ‘the corner seems to be getting further away’. Remember, most of the boys who had a diagnosis of Duchenne muscular dystrophy at the time of the identification of dystrophin are now dead.

But, we must end on a more optimistic note. There is no doubt that the discoveries of the last 15 years have been of direct benefit to patients with muscular dystrophy and their families. The diagnostic process is more rapid and more accurate. Inappropriate therapies may be avoided and specific complications of a particular genetic disorder, such as cardiac involvement, may be sought and treated. Accurate genetic counselling is available. There is often more certainty with respect to prognosis. Appropriate management (e.g. cardiac, respiratory, surgical) may reduce disability and enhance quality of life. The pace of change has been extremely rapid. This book will bring you up to date, but watch out because the pace is likely to quicken even more in the next decade. We will shortly have identified most of the causative genes. The next stage in the process will be in trying to understand how a mutation in one gene, even sometimes the same mutation, can cause so much inter- and intrafamilial variability with respect to phenotype. The technologies to look out for will certainly
include DNA microarrays, that allow simultaneous visualization of the expression of many thousands of genes, and proteomics, which will look at protein structure and function, including post-translational effects and the modifying influence of environmental factors.

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