CHAPTER 1: CLINICAL PERSPECTIVE: PHENOTYPIC EXPRESSION IN MUSCULAR DYSTROPHY

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My assignment is to introduce molecular biologists and developmental biologists to the clinical concept of muscular dystrophy, and to provide a brief summary of previous studies of possibly significant primary gene expression in these inherited diseases of muscle.

The failure thus far to discover an abnormal gene produce in these diseases stems from the difficulty of identifying the initial disturbance in a cascade of effects leading to almost total degeneration of muscle. Nevertheless, there is some information and I shall try to review the essentials. There have been several reviews and conferences on related topics in the past decade (1-6).

Muscle weakness can arise from a disturbance in the motor nerve, the peripheral nerve, or from muscle itself. The idea that separate diseases can affect primarily one of these three anatomic structures was first suggested by neuropathologists of the 19th century. Assignment of the source of the trouble is accomplished through clinical neurologic examination; electromyography and measurement of nerve conduction velocity; morphologic study of muscle biopsy; and biochemical study of blood and muscle. When it is determined that the patient's symptoms are due to dysfunction of muscle in the absence of clinical or laboratory evidence of altered neural function, the disorder is classified as a myopathy.

A muscular dystrophy is a myopathy with four special characteristics: (1) It is inherited. (2) Symptoms consist solely or primarily of weakness. (3) The weakness is progressive. (4)
The morphologic changes imply degeneration and regeneration of muscle, with no evidence of abnormal storage of a metabolic product within muscle fibers (although fat and connective tissue accumulate to replace the degenerated muscle).

Not all inherited myopathies are classified as muscular dystrophies. For instance, some heritable myopathies are manifest by myoglobinuria (appearance of the muscle pigment in the urine) and there may not be any muscle weakness between attacks of myoglobinuria. Other disorders are manifest by myotonia, without weakness, and some by symptoms similar to cramps. Although inherited, these conditions are not called dystrophies. In other conditions, there is weakness but, unlike the dystrophies, the weakness does not become progressively more severe; instead the weakness may be episodic and occur in attacks, as in familial periodic paralysis, or the weakness may be fixed, never getting worse, as in some congenital myopathies. Finally, there are conditions that may resemble muscular dystrophies clinically but differ because there is abnormal storage of lipid or glycogen within the muscle fibers. These and other closely related metabolic myopathies will be reviewed later in this volume by Miranda.

Within the category of muscular dystrophy there are many different diseases that can be differentiated on clinical and genetic grounds. To take just two examples (Table 1), the Duchenne and facioscapulohumeral (FSH) types differ in pattern of inheritance (expression in boys alone or both sexes); age at onset; first symptoms in pelvic girdle or shoulder girdle muscles; whether the face is affected; presence of pseudohypertrophy; rate of progression and ultimate effect on life expectancy; serum content of sarcoplasmic enzymes; and severity of necrosis and regeneration in muscle. Limb-girdle dystrophy, probably heterogeneous, differs from both Duchenne and FSH. These clinical and biologic differences all imply different abnormalities of different genes and different gene products. Duchenne dystrophy itself provides little evidence of heterogeneity; within limits of the rate of progression, the clinical picture is homogeneous. Attempts to identify subtypes by the association with mental retardation have not, to my mind, been successful because there is no uniform association with retardation within families and because the retardation, unlike the myopathy, is not progressive.

On the other hand, Becker dystrophy has always seemed to clinicians as though it ought to be allelic with Duchenne dystrophy because it is similar in all respects except for the age at onset and rate of progression. In contrast to Duchenne dystrophy, almost all boys with Becker dystrophy are still walking by age 12 and they may live long after age 30. Evidence from molecular genetics suggests that the two disorders are, in fact, allelic (7).