# HANDBOOK OF CLINICAL NEUROLOGY

*Edited by*

P. J. VINKEN and G. W. BRUYN

VOLUME 41

# DISEASES OF MUSCLE

## PART II

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*Edited by*

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# Foreword to volumes 40 and 41

*During the last two decades, interest in the structure and function of both normal and diseased muscle has increased exponentially. For some, the motivating force has been the quest to understand human athletic ability: how to maximize an individual's performance. For others, the goal has been at the other end of the continuum: the solution to the mystery of progressive muscle weakness.*

*These volumes are, therefore, timely and will provide the clinical neurologist with a comprehensive update of the field. The clinical descriptions of the muscular dystrophies, although refined and reclassified, have remained virtually unchanged since the first part of the nineteenth century when Charcot pointed out to his students, 'Duchenne discovered a disease that probably existed in the time of Hippocrates'. Sadly, despite the advances in our understanding of the molecular biology of myogenesis, the cause and treatment of the majority of neuromuscular diseases remains elusive. Although we are better able to detect the disease in its earliest stages and to define more accurately the pattern of inheritance, we do not fully comprehend the mechanisms of muscle failure nor effective methods of treatment.*

*The picture is not completely bleak. During the last ten years, a much greater understanding of the pathophysiology and treatment of myasthenia gravis has emerged. Many patients are no longer as incapacitated as they once were. Similar, although more modest, gains have been made in understanding many metabolic disturbances of muscle. The neurologist who today feels frustrated by the limited and palliative therapy available for the dystrophic patient can look forward to future advancements in this rapidly growing discipline.*

*The initial chapters of Volume 40 are to acquaint physicians with advancing technologic developments. Normal histochemistry and electronmicroscopy are described in detail as well as the pathologic reactions of skeletal muscles. The chapters on neuromuscular transmission, electro-diagnosis and human genetic analysis are developed to update the reader's basic sciences principles which will be called upon in later chapters as they relate to specific diseases.*

*Two chapters provide summaries of relevant experimental myopathies and human muscle culture. These two areas are highlighted on the one hand because of the scientific advancements that have been achieved during the last decade. On the other hand, they represent the bridge between pure research and research applied to the treatment of human disease. For example, experimental cross innervation has provided a better understanding of the role of the nervous system in maintaining the muscle. Muscle culture, too, has allowed the sequence of events from a single myoblast to a mature multinucleated, cross-striated muscle fiber to be defined accurately.*

*To be most useful to the clinical neurologist, the remaining chapters of these volumes are grouped according to a classification of diseases based primarily on clinical criteria. The nosology of disorders of the peripheral nervous system has undergone considerable change with the wide use of muscle histochemistry, electron-microscopy, and electrophysiological analysis. Diseases previously grouped because of their clinical distribution of weakness have on further analysis been found to be pathologically heterogeneous. Therefore, chapters describe limb girdle and facio-scapulohumeral syndromes rather than dystrophies. This delineation emphasizes, for example, that 'limb girdle' weakness can be caused by the dysfunction of the anterior horn cell, the peripheral nerve, or the muscle.*

*A summary chapter provides an overview of the major clinical presentations of muscle disease. The chapters which follow describe diseases which are similarly organized according to their predominant clinical feature such as myotonia or motor unit hyperactivity states. Certain diseases which are mentioned first according to clinical presentation may also be the subjects of entire chapters if major new developments have occurred, such as the X-linked dystrophies or myasthenia gravis. The chapters on endocrine and metabolic myopathies reflect the state of the art since the list of diseases grouped in this way will presumably grow as metabolic defects are elucidated for today's hereditary 'degenerative' disorders.*

*We have chosen not to repeat discussions of diseases which were thoroughly covered in recent volumes of the Handbook. The reader may wish to refer to Volumes 7 and 8 for discussions of diseases of the peripheral nerve and to Volume 22 for the anterior horn cell diseases and progressive external ophthalmoplegias. Contributors to this volume have attempted where appropriate to address the implications of recent evidence which suggests a neurotrophic influence as a factor in diseases previously thought to be primarily muscular in origin.*

*Since Duchenne first studied weak patients with his 'histologic harpoon' and 'faradic current', many other neurologists have contributed to our understanding of muscle in health and disease. Incidentally, it was a neurologist, Roger Bannister, who first broke the four minute mile barrier, emphasizing to all the potential of human performance when healthy. Perhaps in the near future, it will also be a neurologist who provides the cure for the less fortunate dystrophic child.*

*P.J.V.*
*G.W.B.*
*S.P.R.*

*Acknowledgement*

Several illustrations and diagrams in this volume have been obtained from other publications. Some of the original figures have been slightly modified. In all cases reference is made to the original publications in the figure caption. The full sources can be found in the reference lists at the end of each chapter. The permission for the reproduction of this material is gratefully acknowledged.

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# Contents

CHAPTER 1

# Congenital myopathies

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A congenital myopathy is a condition causing muscle weakness at birth in which the central and peripheral nervous systems are presumed to be intact and the primary pathological lesions are seen in muscle tissue. The diseases discussed in this chapter produce rather pathognomonic changes in muscle from which their names are derived. One must not infer that because the primary lesions are seen in muscle that the process is, necessarily, a primary myopathy. It is for this reason that some authors choose to avoid the designation 'myopathy' and refer to these conditions as 'congenital neuromuscular diseases'. This distinction becomes even more important when the results of newer techniques show that, indeed, some of these conditions may be due to subtle defects in innervation rather than a problem within the muscle tissue.

As a group, the congenital myopathies have certain characteristics which are of special interest not only to those interested in abnormal muscle function but also to those concerned with basic mechanisms of normal muscle development and function. The conditions tend to be rather benign when compared to other conditions causing weakness at birth in that they are typically relatively slowly progressive or static in nature despite the fact that they may be rather severe at birth with marked weakness and hypotonia (the so-called 'floppy infant syndrome'). Clinically, they may be indistinguishable from conditions such as infantile spinal muscular atrophy (Werdnig–Hoffmann disease) which carries a grave prognosis.

Due to the fact that each disease affects only one aspect of muscle structure without the diverse degenerative changes that accompany the non-specific myopathies, they represent rather 'pure' situations in which to study normal and pathological mechanisms of muscle function and give information as to possible etiological factors in other more common myopathies.

As will become obvious, these congenital myopathies are not easily detected with routine histological techniques but invariably require the use of histochemical and electron microscopic analysis for accurate diagnosis. Since the conditions are named for their pathological appearance, there is disagreement among investigators as to the proper terminology for each condition. Many of them have originally been given rather exotic names which are easily remembered. When other investigators gave alternative (presumably more accurate) names, the result was several names for the same condition. In this chapter, the original names will be used since they are in most common usage despite the fact that they are often misnomers. The discussion will be limited to those congenital neuromuscular diseases with characteristic muscle biopsy findings. Other con-

*References, p. 23*

ditions causing muscle weakness at birth, such as congenital muscular dystrophy, myasthenia gravis, polymyositis, myotonic dystrophy, acid maltase deficiency and mitochondrial myopathies will be discussed in other chapters.

*History*

The first clinical description of the hypotonic infant was presented by Hoffmann in 1893 who reported seven patients in four different families who were found to be extremely hypotonic in the first year of life after a relatively normal neonatal period, and in whom the condition progressed to cause death. Autopsy showed a reduced number of anterior horn cells, so the condition was thought to be on a spinal basis and later became known as infantile spinal muscular atrophy or Werdnig–Hoffmann disease.

In 1900, Oppenheim described a series of patients which were born extremely hypotonic and had a paucity of movements with reduced to absent deep tendon reflexes; he coined the term 'amyotonia congenita' to describe them. Despite a rather limited follow-up and lack of pathological confirmation, he presumed that these patients ran a benign course with general improvement, thus differentiating them from cases of infantile spinal muscular atrophy. He presumed that the disease resulted from disordered development of muscles rather than a central nervous system abnormality.

Ever since Oppenheim's report, there has been considerable controversy in the literature as to what is the nature of the pathology in hypotonic infants and how to predict which ones have a benign non-progressive condition, as opposed to a more malignant fatal disease. The most likely explanation for the controversy is that many of the case reports are on patients with inadequate follow-up or with no pathological confirmation of their conditions. As pointed out by Brandt (1950), Oppenheim's original cases were poorly documented and not followed-up so that what appeared to be non-progressive in many cases was actually infantile spinal muscular atrophy with a fatal progressive course.

In 1903, Batten first suggested that cases with infantile amyotonia may have a myopathic condition. Subsequently, he considered Oppenheim's disease a form of congenital dystrophy called the 'simple atrophic type', characterized by lack of tone and power but without atrophy or hypertrophy of muscles (Batten 1910) Unfortunately, Batten did not include pathological material in his study.

In 1905, Spiller did a necropsy study on a case fitting Oppenheim's original description and found the muscle fibers to be uniformly small. The anterior horn cells and the rest of the CNS were normal, thus differentiating this condition from true infantile spinal muscular atrophy. This was followed in 1909 by a report by Lereboullet and Baudouin of a case of amyotonia congenita who died at age 11 months and had non-specific myopathic changes on muscle biopsies, with variation in fiber size, increased sarcolemmal nuclei and increased connective tissue.

In 1927, Greenfield and Stern took the opposite point of view from Batten, concluding that the diseases amyotonia congenita and infantile spinal muscular atrophy were identical and that the benign cases represented remissions that could occur for up to two years.

Although the conclusions of Greenfield and Stern were well accepted for several years, Turner (1940) reported a family with six of 13 sibs affected by a non-progressive form of congenital muscle weakness whose biopsies showed myopathic changes (degeneration of fibers with phagocytosis). A follow-up of this family 50 years later confirmed the relatively non-progressive nature of the condition, although Shy and Magee (1956) point out that there may well have been some progression in at least one family member.

A significant change in thinking about infantile hypotonia then occurred in 1956, when Shy and Magee reported a family in which there appeared to be a dominantly transmitted condition causing severe weakness at birth which was non-progressive so that the children eventually improved in function. They found that the muscle fibers of all affected family members had a consistent unusual appearance in that the central region of many of the fibers was disrupted. This, then, was the first example of a *specific* pathological change in muscle which could be used to define the disease process. Subsequent to this study, the

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muscle biopsy has become the most effective means of differentiating spinal muscular atrophy from a group of rather benign neuromuscular diseases.

In 1957, shortly after Shy's original report on central core disease, Walton reviewed the subject of the 'floppy' or hypotonic infant. At that time, he defined a category called 'benign congenital hypotonia' which included infants born extremely hypotonic but who subsequently improved and had no evidence of central or peripheral nervous system disease nor of any other primary metabolic, dystrophic, or inflammatory conditions. Muscle biopsy was normal in these infants. Walton predicted that the application of newer techniques would define more specific disease states into which these conditions could be categorized. In the past two decades, a large number of specific disease entities have been defined and suggested through use of histochemistry and electron microscopy. These conditions are the subject of this chapter.

## CENTRAL CORE DISEASE

This was the first of an increasingly large list of neuromuscular diseases which affect infants in the neonatal period and which are associated with rather specific pathological changes in the skeletal muscle fibers.

In 1956, Shy and Magee reported a family in which the affected members (four males and one female) had weakness which was present at birth and did not progress to any appreciable degree. The muscle biopsy showed a very specific abnormality in that the central region or 'core' of almost every fiber had a disrupted myofibrillar pattern. Subsequently (Greenfield et al. 1958), this condition was called 'central core disease' due to this characteristic abnormality. Prior to Shy and Magee's paper, no muscle pathology had ever been convincingly demonstrated in a case of congenital non-progressive weakness. As opposed to the non-specific myopathic changes associated with myopathies in general, this was highly unusual. No destruction of muscle fibers was seen and no replacement of connective tissue but rather a specific structural abnormality. The pattern of inheritance suggested an autosomal dominant. The typical clinical features of the disease are summarized as: congenital weakness, most severe in the lower extremities but present proximally in the upper extremities as well; occasional facial weakness, delay in walking, a non-progressive pattern, hypotonia during childhood, normal deep tendon reflexes and no evidence of muscle wasting or sensory disturbances.

Subsequent to Shy's original report, a wide variety of clinical and inheritance patterns has been reported in patients exhibiting central cores in their muscle biopsies (Bethlem et al. 1971). In one family, the affected infants did not have hypotonia and the patients had the unusual feature of cramps after exercise (Bethlem et al. 1966). In another, there was focal muscle wasting in the right shoulder as the only clinical manifestation (Dubowitz and Platts 1965). One case with typical central core lesions was normal at birth but had a severe progressive myopathy starting at age one year with features resembling facioscapulohumeral dystrophy (Bethlem et al. 1971). Osteoarthritic deformities are frequently associated with this condition, such as congenital hip deformities and pes cavus (Armstrong et al. 1971; Telerman-Toppet et al. 1973). EMG is usually 'myopathic' with small motor units of short duration, and creatine phosphokinase (CPK) is usually normal (Bethlem et al. 1971). Most reported cases are transmitted as autosomal dominant but some are sporadic and one (Dubowitz and Platts 1965) may have been an autosomal recessive. As far as carrier detection is concerned, clinically normal relatives of affected patients have not revealed any abnormalities on muscle biopsy (W. K. Engel et al. 1961; Bethlem et al. 1971). In some sporadic cases, EMG abnormalities have been found in both parents (Dubowitz and Roy 1970; Bethlem et al. 1971).

An interesting and important condition associated with central core disease is malignant hyperthermia. This is a severe, potentially fatal, hyperthermic reaction to general anesthesia, usually halothane and/or succinylcholine, but occasionally with other agents. It is sometimes accompanied by severe muscle rigidity (Gordon et al. 1973). This syndrome has been reported in three families with central core disease (Denborough et al. 1973; Isaacs et al. 1974; W. K. Engel 1977); both

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conditions are quite rare, thus making the association more likely than would be expected by chance.

The abnormal central core region of the muscle fibers is easily overlooked on routine paraffin-embedded material consisting only of a relatively amorphous-staining central region. Histochemical stains highlight the abnormal region since it appears unstained with oxidative enzyme reactions, as opposed to the normally staining peripheral region (Fig. 1). This change reflects the electron microscopic observation that the central region is devoid of mitochondria. The amorphous appearance is due to the streaming of Z bands and disruption of myofibrils in this region (W. K. Engel et al. 1961) (Fig. 2). The cores are usually round or oval and run the length of the fiber. They are not always *central* and more than one core may exist in the same fiber (Dubowitz and Pearse 1960). The cores appear to involve selectively Type I fibers (Dubowitz and Pearse 1960; Dubowitz and Platts 1965), although they have been seen in Type II fibers as well (Dubowitz and Brooke 1973b). In addition to selective Type I fiber involvement by cores, there is commonly a marked predominance of Type I fibers or paucity of Type II fibers (Dubowitz and Pearse 1960; Dubowitz and Platts 1965; W. K. Engel 1977). In regions where there is a marked predominance of Type I fibers, there is a normal distribution of Type I fiber subtypes and single fiber electromyography shows no increase in motor unit density (W. K. Engel 1977). These findings indicate that there may well be a Type II fiber paucity, possibly resulting from a defective innervational pattern by type II motor neurons, since it is known that fiber type and, probably, fiber subtype are determined by innervation. Also of relevance is a report of a family in which a mother and two children had non-progressive congenital muscle weakness but only the mother

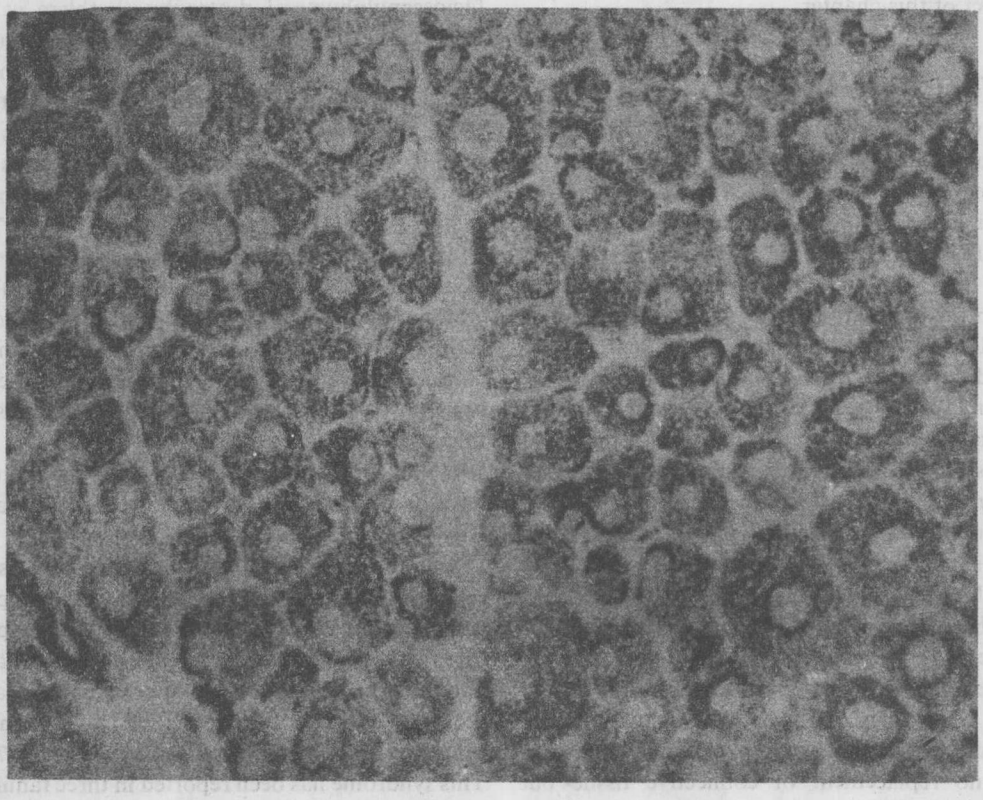

Fig. 1. Central core disease. There is a discrete punched-out region in the center of nearly every fiber in the field NADH-TR reaction, ×200.

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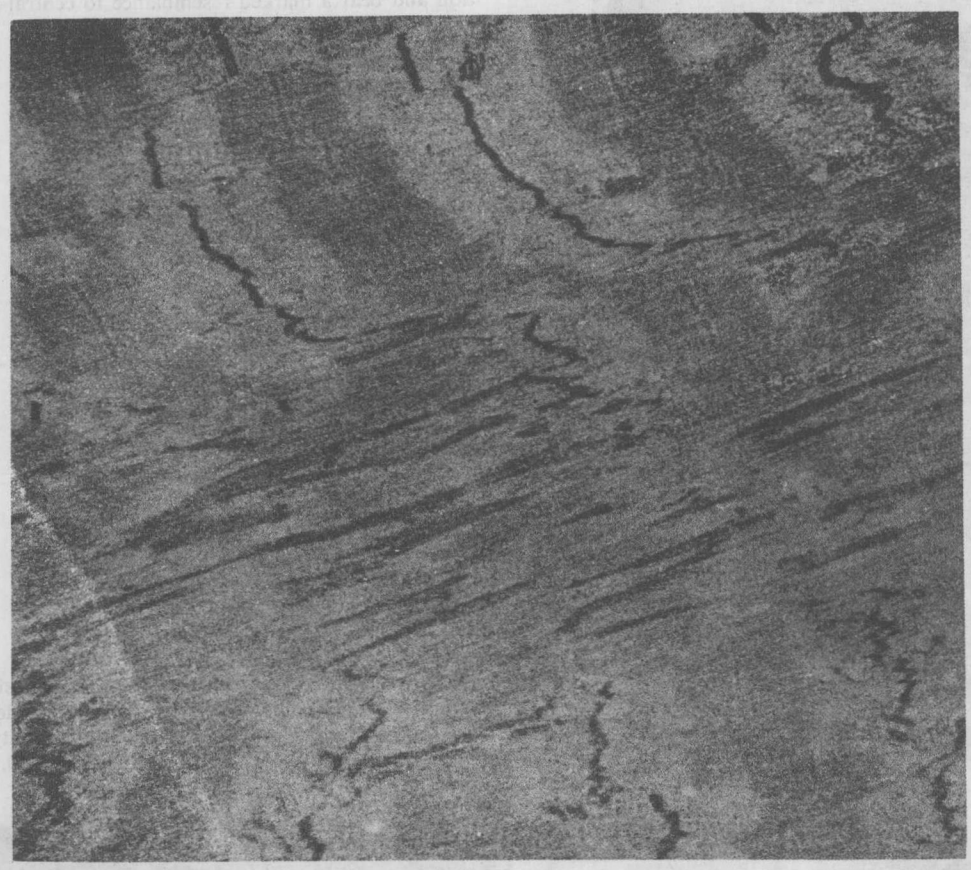

Fig. 2. Central core disease. The central region shows disruption of the myofibrillar pattern typical of an 'unstructured' core. Electron micrograph, × 10,600.

had central core lesions in her muscle biopsy. The two children had marked Type I fiber predominance suggesting that the gene has various means of expression and that the central core lesions may not be primarily responsible for the weakness (Morgan-Hughes et al. 1973). Another observation supporting a possible defect in innervation is that central core fibers bear a marked resemblance to 'target' fibers (Fig. 3) which are thought to be characteristic of chronic denervation (W. K. Engel 1961, 1962). The target lesion is also found in Type I muscle fibers and consists of three zones rather than the two seen in cores; the third zone consisting of increased numbers of mitochondria is between a normal zone and a zone where mitochondria are absent. The three-zoned appearance resembles a target. Target lesions run only part of the length of a fiber, while central cores appear to run the entire fiber length (Schotland 1969). Central core-like (two-zoned) lesions can be produced experimentally following tenotomy (W. K. Engel et al. 1966) and following intoxication with triethyltin sulfate (Graham et al. 1976). These structures also occur selectively in Type I fibers and bear a marked resemblance to similar structures produced by denervation. Also, target-like three-zoned lesions are seen occasionally in typical cases of central core disease (Dubowitz and Roy 1970) (Fig. 4). In one study, an attempt was made to differentiate 'structured' from 'unstructured' cores based upon the ultrastructural appearance. In some patients' biopsies there was marked disorganization of the myofibrils in the central region while in others there was rather well-preserved myofibrillar structure but reduced mitochondria in the central region

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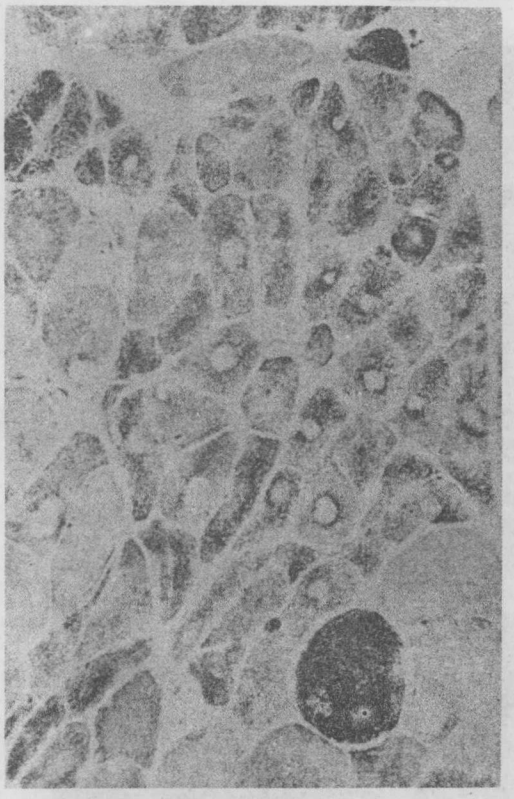
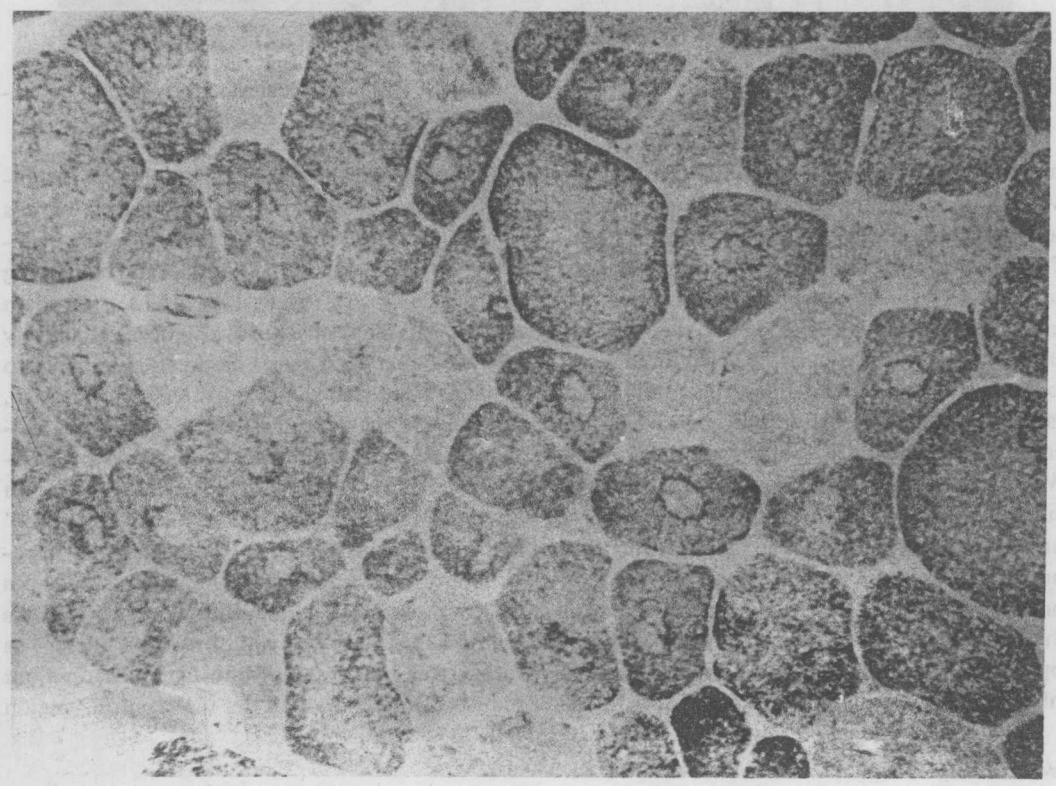


Fig. 3. Target fibers. These are seen in chronic denervation and bear a marked resemblance to central core lesions. NADH-TR reaction.

Fig. 4. Central core disease. In this case, the core lesions in the dark (Type I) fibers have three zones with a dense rim around the central region. Note the similarity to the target lesions. NADH-TR reaction, ×240.



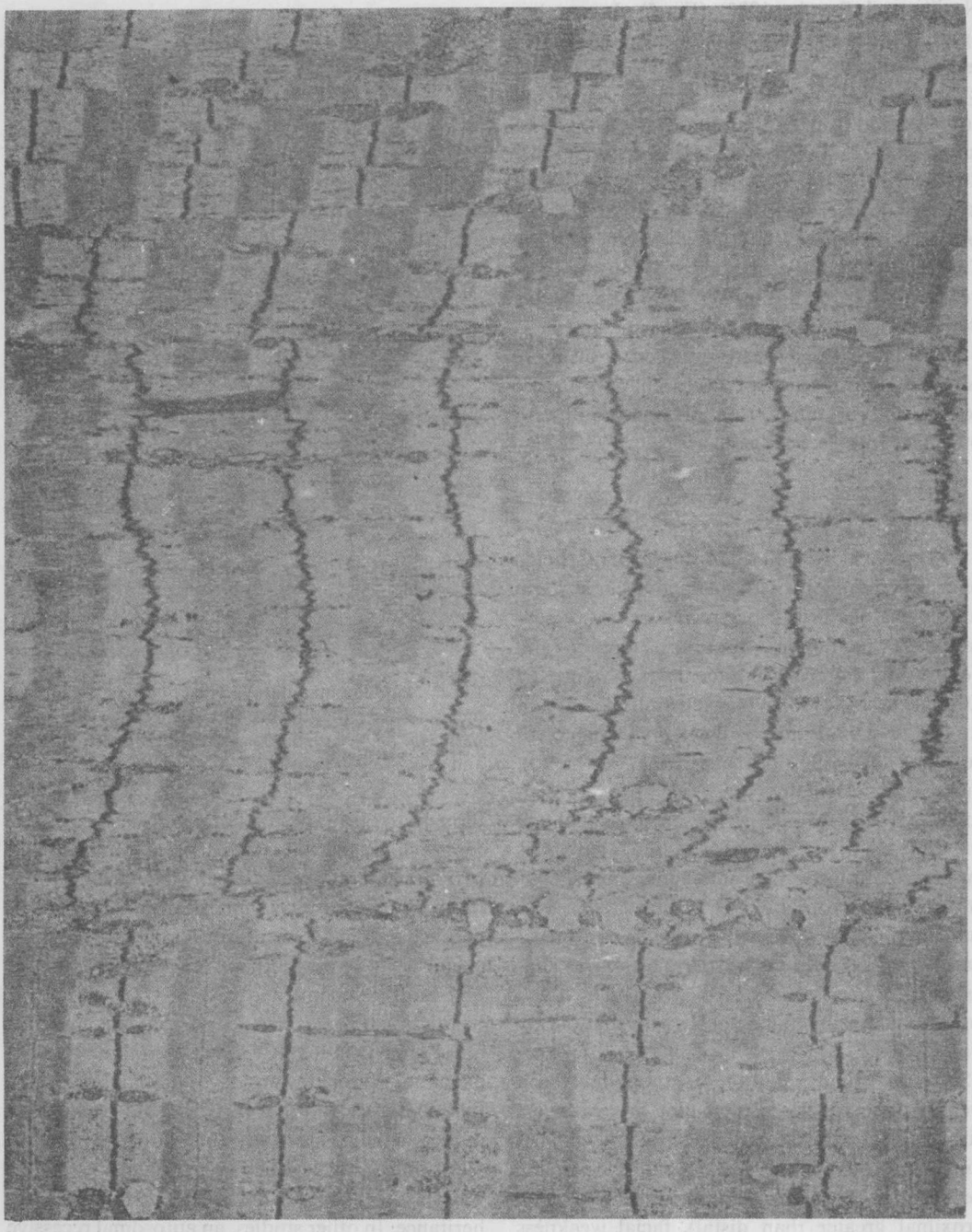


Fig. 5. Central core disease. A 'structured' core. Note the better preservation of the myofibrillar pattern in the central region where mitochondria are absent. Electron micrograph. × 7,200.

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(Neville and Brooke 1973) (Fig. 5). In another report, both structured and unstructured cores were found in the same patient (Telerman-Toppet et al. 1973), thus making the distinction possibly more quantitative than qualitative. It should be emphasized that structured cores would be extremely difficult to detect without histochemical and electron microscopic techniques. Also, there appears to be no correlation between the number of fibers containing central core lesions and the progression or clinical severity of the disease (Bethlem et al. 1971). Nevertheless, the disease is confirmed by the marked prevalence of these lesions in the absence of other changes in the biopsy, and in the setting of non-progressive congenital muscle weakness.

## NEMALINE MYOPATHY

In 1963, Shy et al. described the second specific congenital myopathy with distinctive clinical and pathological features. Four members in two generations of a family were born 'floppy' and showed slow motor development which improved with time. Muscle biopsy showed multiple 'thread-like' forms within muscle fibers which suggested the name 'nemaline' (Greek: nema = thread). They were originally presumed to represent 'coiled' structures but in the same original paper, they are referred to as 'rod-like' aggregates thus originating the alternate name for the condition: 'rod myopathy' (W. K. Engel and Resnick 1966). A third name for the abnormal structures in this condition, 'myogranules', was suggested by Cohen et al. 1963) in a paper which appeared almost simultaneously with that of Shy et al. (1963).

Since the original case report, there have been over 30 case reports of nemaline myopathy. A fairly typical clinical pattern has emerged as summarized by Hopkins et al. (1966). The patients are born with hypotonia, generalized weakness, (proximal greater than distal), facial weakness (Fig. 6), high-arched palate, frequent skeletal deformities, reduced or absent tendon reflexes and a 'myopathic' EMG. As in central core disease, the course is usually either very slow or non-progressive.

The inheritance of nemaline myopathy is

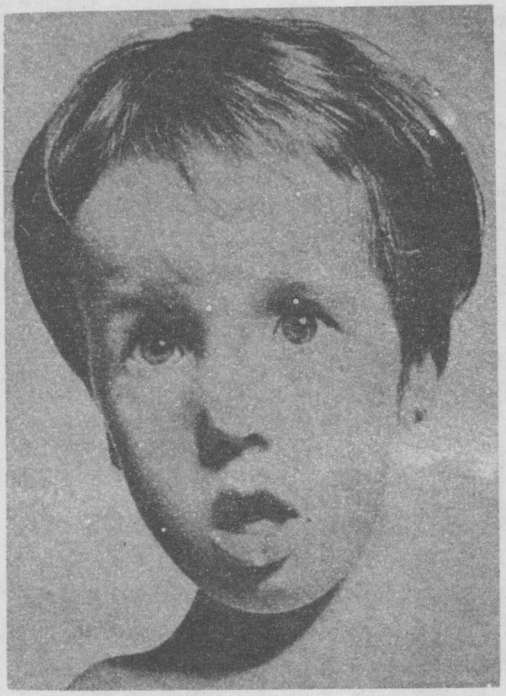

Fig. 6. Nemaline myopathy. The child has the typical facies associated with this and other congenital myopathies. The face is narrow and the mouth is held open and drooling (the so-called 'fish-mouth' appearance).

thought to be autosomal dominant. Shy's original report suggested this pattern, since a mother and two daughters were clinically affected, yet the mother's biopsy was normal despite a 'myopathic' EMG. No mention is made of histochemistry on the mother's muscle biopsy. The first biopsy-documented case of transmission of the disease through two generations was by Spiro and Kennedy (1965). Of note is that familial cases affecting two generations have all been transmitted by the mother and that there is a 2:1 preponderance of female cases (Shy et al. 1963; Price et al. 1965; Spiro and Kennedy 1965; Shafiq et al. 1967). This is suggestive of a sex-linked dominant inheritance. In other studies, an autosomal recessive inheritance is suggested since siblings are affected but not parents (Nienhuis et al. 1967; Shafiq et al. 1967; Neustein 1973). Alternatively, such cases could be dominantly transmitted with variable penetrance.

As in the other congenital myopathies, excep-

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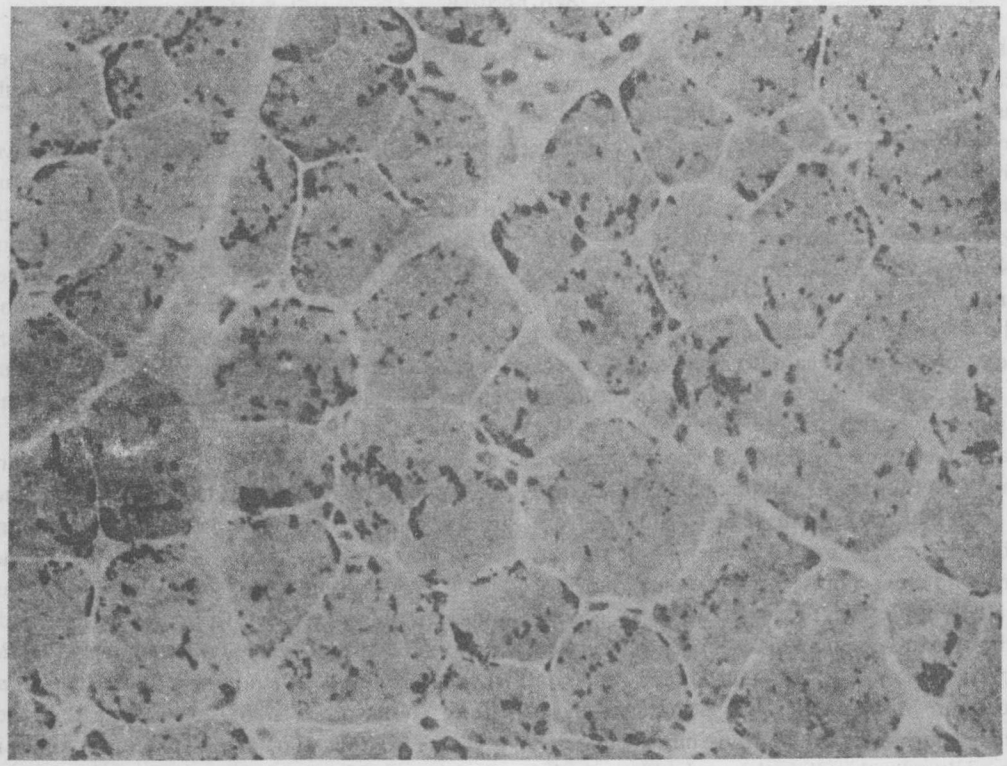

Fig. 7. Nemaline myopathy. The small rod bodies are seen in every fiber and tend to form clusters. Modified Gomori trichrome stain, × 600.

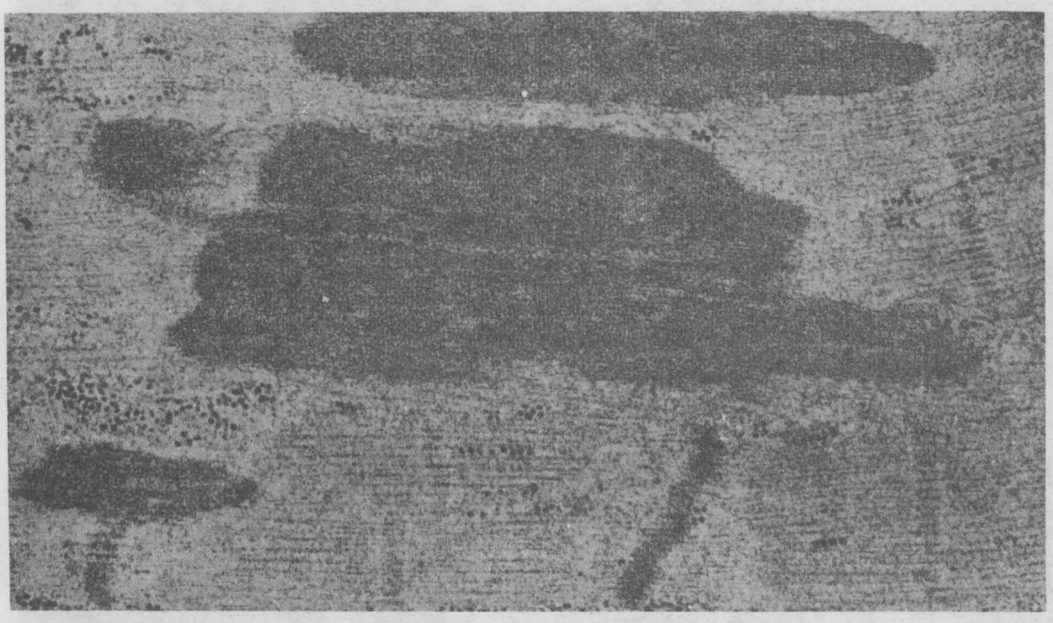

Fig. 8. Nemaline myopathy. The characteristic rod bodies are approximately the length of a sarcomere. The small one at the lower left is seen in relation to the Z band from which it presumably originated. Electron micrograph, × 32,000.

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