PATHOGENESIS OF SOME PROGRESSIVE MUSCULAR DISEASES

THESIS

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By

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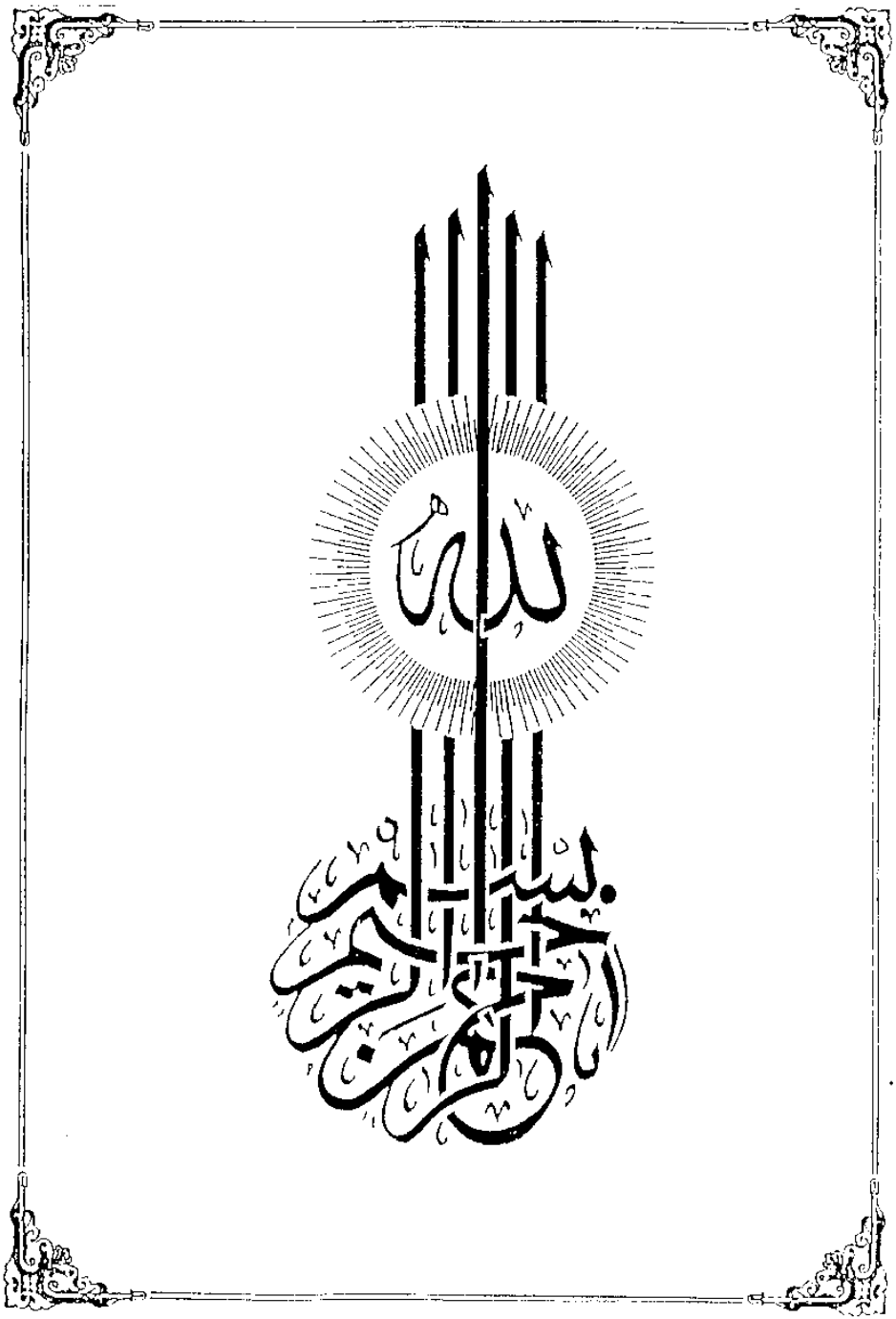

CONTENTS

INTRODUCTION AND AIM OF THE WORK

Neuromuscular diseases are generally divided into two categories : the neuropathies and the myopathies . Neuropathic disorders are those in which motor nerve cells or their processes are first affected resulting secondarily in atrophy of the muscle. Myopathic disorders are those in which the disease process involves the muscle directly without damaging its nerve supply.

Muscular dystrophies form a group of myopathies which have common features as their hereditary nature , their primary involvement of the voluntary muscles and the progressive tendency in most of them. Interest in the relationship between muscular dystrophy and neurogenic atrophy was awakened by Kugelberg and Welander (1956) who described some cases with spinal muscular atrophy closely resembling muscular dystrophy. This disorder proved to be a common cause of confusion and its existence necessitated careful clinical, electromyographic and histological examination to avoid errors in diagnosis. Then Drachman and associates (1967) revealed that in chronic denervating disorders, secondary myopathic changes may occur in muscle so that in advanced cases , primary myopathic and secondary neuropathic diseases

may be indistinguishable. A further twist to this already complex situation was added when Dubowitz (1969) suggested that the development of dystrophic changes in muscle might be under a neural influence. This was followed by numerous studies as those of McComas et al. (1971a,b), Marsh and Munsat (1974) and Dubowitz (1977a) which supported the neural theory.

However, another group of investigators as Mokri and Engel (1975) and Schotland et al. (1977, 1980) believed that the muscular dystrophies are due to a primary defect in the membrane of the muscle cell.

Thus it is obvious that the aetiology of the muscular dystrophies is still a matter of controversy. The importance of establishing the pathogenesis of this group of muscle diseases lies not only in the carrier detection but also in the possibility of finding some sort of treatment for the patients with muscular dystrophies.

The aim of the present work is to evaluate if the lesion is neuropathic or myopathic in origin. To achieve this evaluation, 100 cases with progressive muscular diseases were studied clinically and electromyographically. Their muscle biopsies were examined histologically, histochemically and histographically to detect the neurogenic or myopathic changes in the muscle. The results are discussed utilizing the available literature on the muscular dystrophies which is also reviewed.

HISTOGENESIS OF THE SKELETAL MUSCLE*

Skeletal, striated, or voluntary muscle arises in the embryo from mesodermal somites. The overlapping myoblasts or embryonic muscle cells are grouped in the form of 38 myotomes (3 occipital, 8 cervical, 12 thoracic, 5 lumbar, 5 sacral and 5 coccygeal). Each myotome receives a spinal nerve. Distinct skeletal muscles as recognized in the adult are formed by the process of migration and fusion of myoblasts from the myotomes. This reorganization is the basis for the multisegmental nerve supply to some muscles.

The histogenetic stages of muscle development have been subdivided into five overlapping phases:
1) differentiation into a primitive mononucleated muscle cell, the myoblast, 2) elongation and fusion of myoblasts into a multinucleated cell with the beginning of identifiable myofilaments and myofibers, the myocytes and myotubes (fused myocytes), 3) structural assembly of actin filaments, then myosin filaments, integration of thick and thin filaments and appearance of Z bands, onto which actin filaments are attached and appearance of the sarcoplasmic reticulum and transverse tubular system,

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* Adams (1975).

4) growth phase by fusion of myotubes, increase in number of myofilaments and migration of the nucleus to the sub sarcolemmal position, 5) innervation and organization of contractile function. This process occurs between the 4th and 16th week of gestation. Beyond this time and birth, muscle fibres enlarge in length and width but undergo no further structural changes. The multiplication of muscle fibres and growth of a muscle fasciculus seems to be accomplished by the multiplication and activation of reserve undifferentiated cells (satellite cells) that recapitulate the same process of maturation described above.

HISTOLOGY OF THE SKELETAL MUSCLE

- LIGHT MICROSCOPY *

Mature skeletal muscle cells are long and slender, ranging from 40 to 80 micrometers in diameter and from 1 to 50 milimeters in length. Since their length is much greater than their width, these cells are called fibres. Each muscle cell is surrounded by an electrically polarized membrane - the sarcolemma. The sarcolemma is bounded by delicate connective tissue called the endomysium. The entire muscle consists of a number of skeletal muscle bundles known as fasciculi. Fasciculi are bounded by a sheath, the perimysium which is visible to the naked eye. The perimysium is continuous with the course irregular connective tissue investing the whole muscle, the epimysium.

In routine light microscope preparations, the sarcoplasm (cell cytoplasm) is occupied mainly by longitudinal paralled columns of myofibrils about one micron in diameter. In cross section, these appear as dots, often grouped together with areas of clear sarcoplasm between the groups. Each muscle cell is multinucleated. The nuclei are ovoid, and usually peripherally situated. However, the extrinsic ocular muscles have some central nuclei.

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* Leeson and Leeson (1976).

Normal skeletal muscle fibres are polyhedral in cross section and appear of relatively equal diameter. Occasional small or large muscle fibres which have no pathological significance are seen in all muscles, they are the extracapsular parts of the intrafusal muscle fibres of the muscle spindles. Measurment of muscle fibre diameter requires accurate transverse sections. As muscle fibre sizes vary greatly with age, nutritional status and in different skeletal muscles, it is essential to know the normal variation in fibre size, for the particular muscle before interpreting any changes as being pathological. In muscles concerned with delicate movements e.g the lumbricals the fibre sizes are about 18 μ, while in large muscles concerned with coarse movements e.g tibialis anterior and vastus lateralis the fibre size ranges between 25 and 90 μ.

- ELECTRON MICROSCOPY*

The sarcolemma is too thin to be resolved clearly with the light microscope, but electron microscopy shows it to consist of the plasma membrane of the muscle cell covered by a fine extracellular basal lamina with which a few unit fibrils of collagen are associated. The plasma membrane shows a trilaminar structure. Associated with it usually are some micropinocytic vesicles.

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* Guyton (1982).

In the sarcoplasm, the mitochondria or sarcosomes are numerous and large each with closely packed cristae. This is to be expected in view of the high energy requirements for muscle contraction. Sarcosomes lie subjacent to the sarcolemma, concentrated near the poles of the nuclei and in parallel rows between the myofibrils.

Also, in a paranuclear position is a small Golgi apparatus. Ribosomes and a few small elements of granular endoplasmic reticulum also are present near the nucleus. A few lysosomes may be found in non fibrillar sarcoplasm. Glycogen particles are numerous and scattered throughout muscle cells, lipid vacuoles normally are present also and increase with age.

A. Sarcotubular System :

Electron photomicrographs show muscle fibrils to be surrounded by structures made up of membrane in the form of vesicles and tubules. These structures form two systems :-

- One consists of what are called T (for transverse) tubules which are actually invaginations of the membrane of the muscle fibre. The space between the two layers of the T system is an extension of the extracellular space.

- The second, the principal system, called the sarcoplasmic reticulum consists of tubules running parallel to the myofibrils. Each T tubule runs between a pair of sacs formed by fusion of the sarcoplasmic reliculum . These three transverse structures make up what is known as a triad. The triad is important functionally because although there is no open continuity between the sarcoplasmic reticulum and the T tubules at the triad, the close association of the two systems at this site enables the T tubules to function as a conduit for transmission of the electrical impulse, the normal muscle stimulus, to the sarcoplasmic reticulum. The arrival of the electrical impulse activates the release from the sarcoplasmic reticulum of calcium, the triggering agent for muscle contraction.

B. Striations :

By light microscopy, the cytoplasm of each striated muscle fibre in longitudinal section shows alternating thin bands of light and dark material, the dark bands being anisotropic and the light ones isotropic when seen with polarized light. Hence, the dark and light bands are called respectively "A" and "I" bands . The light I band is intersected by a thin dark line called "Z" line (from the German Zwischencheibe meaning between discs). It is customary to consider the muscle fibrils as

composed of structural units. Each unit extends between two adjacent Z lines and is termed sarcomere. Other bands in the myofibrils are visible occasionally. These are the pale H band (after Henson) bisecting the dark A band and within this there is a very fine dark M line (Middle).

The arrangement of thick and thin filaments is responsible for the striations of the skeletel muscle fibres. The thick filaments which are about twice the diameter of the thin filaments are made up of myosin. The thin filaments are made up of actin, tropomyosin and troponin. The thick filaments are lined up to form the A bands, whereas the array of thin filaments forms I bands. The Z line represents a structure to which the thin filaments are attached on either side. The lighter H bands in the center of A bands are the regions where, during relaxation of the muscle, thin filaments do not overlap the thick filaments. The M line is due to a central bulge in each of the thick filaments.

BLOOD AND LYMPH SUPPLY*

Arteries pierce the epimysium to reach the muscle to terminate as capillaries in the endomysium. The lymphatics lie in the epimysium and perimysium but not in the endomysium.

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* Leeson and Leeson (1976).

INNERVATION OF THE SKELETAL MUSCLE*

Motor Nerve Supply :

The muscular nerves are for the most part medullated and contain between 30 and 50 % of sensory fibres. After entering the sheaths of the muscle, the nerve breaks up into bundles of fibres which subdivide until a single motor nerve fibre joins each muscle fibre. The axon of a single motor anterior horn cell, by repeated branching, terminates on a group of muscle fibres averaging 100 - 200 in number. Each such group of structures is termed " motor unit ".

In large muscles such as the deltoid, motor units are large including more than 1000 muscle fibres whereas in small muscles such as those attached to the eye they may comprise only 10-15 muscle fibres.

The mode of distribution of muscle fibres of a given motor unit has been revised in the light of their physiological and biochemical properties. There is now general agreement that all of the muscle fibres within the domain of an alpha motor neuron are more diffusely scattered within a given region and further, that each motor unit is of one histochemical type e.g, phosphorylase - rich

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* Adams (1975).