PATHOLOGY ANNUAL: NINETEEN SEVENTY-EIGHT

PART 2

series editors SHELDON C. SOMMERS
PAUL PETER ROSEN

PATHOLOGY ANNUAL

PART 2

VOLUME 13

1978

APPLETON-CENTURY-CROFTS/New York

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78 79 80 81 82/10 9 8 7 6 5 4 3 2 1

Library of Congress Catalog Card Number: 66-20355

Prentice-Hall International, Inc., London
Prentice-Hall of Australia, Pty. Ltd., Sydney
Prentice-Hall of India Private Limited, New Delhi
Prentice-Hall of Japan, Inc., Tokyo
Prentice-Hall of Southeast Asia (Pte.) Ltd., Singapore
Whitehall Books Ltd., Wellington, New Zealand

PRINTED IN THE UNITED STATES OF AMERICA
CASEBOUND 0-8385-7752-0
PAPER 0-8385-7754-7

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CONTENTS

SKELETAL MUSCLE IN DENERVATION

VERNON W. ARMBRUSTMACHER

Recent advances in histopathologic techniques in the areas of histochemistry and immunopathology applied to the study of normal and abnormal skeletal muscle have added greatly to our understanding of the pathophysiology of denervating disease and the complex interrelationship between the lower motor neuron and the skeletal muscle fiber. Before considering the pathologic findings of denervating disease it is appropriate to review the embryogenesis of skeletal muscle, its normal microscopic anatomy, and the techniques used to study the muscle biopsy specimen. At the present time, the study of a skeletal muscle biopsy specimen is the best morphologic method of evaluating the condition of the lower motor neuron. In general, this is more productive than examining a biopsy specimen from nerve, which of clinical necessity must be an "expendable" sensory nerve rather than a motor nerve.

EMBRYOGENESIS

Skeletal muscle is derived from the mesodermal layer of the embryo. The first morphologic evidence that an undifferentiated cell is predestined to become a skeletal muscle fiber is the accumulation of myosin and actin filaments in the cytoplasm (Fig. 1); they appear shortly after the myoblast becomes postmitotic.[1] Physiologic studies have shown that at about the same time the cell membrane is already irritable and capable of depolarization, although the cell cannot contract because myofibrils are lacking.[2] Very shortly after these myoblastic features appear, the cells acquire the ability to fuse with each other. This ability distinguishes skeletal muscle cells from smooth muscle and cardiac muscle.

The resulting multinucleated elongated cell is called an *early myotube,* and it is characterized by rapid synthesis of myosin and actin (Fig. 2). At this stage we see the beginnings of the orderly arrangement of myosin within hexagonal

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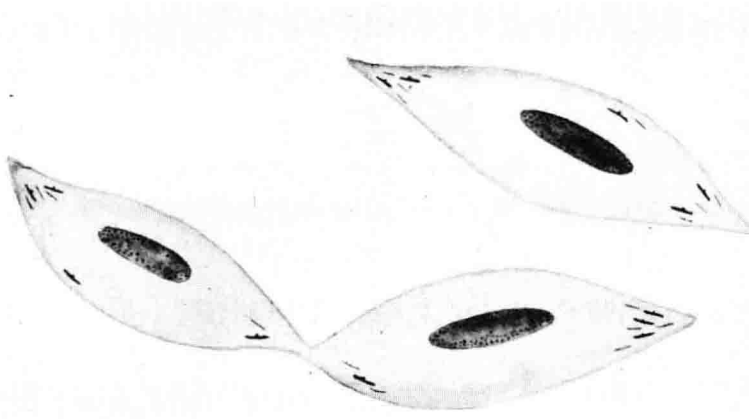

Fig. 1. Myoblasts. Spindle-shaped cells recognized by the presence of myosin and actin filaments. They soon become postmitotic and begin to fuse. (AFIP 77-5174-3)

arrays of actin filaments. The Z-band does not appear until the myofilaments are aggregated near the periphery of the cytoplasm.[3] After the appearance of the Z-band the myofilaments grow in length as new sarcomeres are added to the ends, thus forming myofibrils.[4] The nuclei, containing prominent nucleoli, tend to occupy the center, and the earliest myofibrils accumulate peripherally. In the late myotube stage there is a single central row of nuclei, first surrounded by an area of relatively clear sarcoplasm and then by a zone of progressively more densely packed myofibrils that have a characteristic pattern of cross striations (Fig. 3).

Other organelles in the developing myotube are the mitochondria, ribosomes, and sarcoplasmic reticulum. At first the mitochondria are oval, have straight, stubby cristae, and are located in the clear central area of the cytoplasm. Later they become elongated and have folded complex cristae. Free ribosomes are scattered throughout the cytoplasm, whereas polyribosomes are related to the myofilaments.[5] The transverse tubules are invaginations of the sarcolemma and are

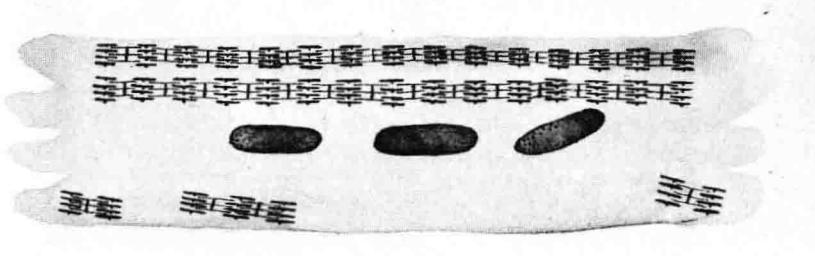

Fig. 2. Early myotube. Fusion results in an elongated, multinucleated cell. Myofilaments (actin and myosin) are aligning, and myofibrils are forming. (AFIP 77-5174-1)

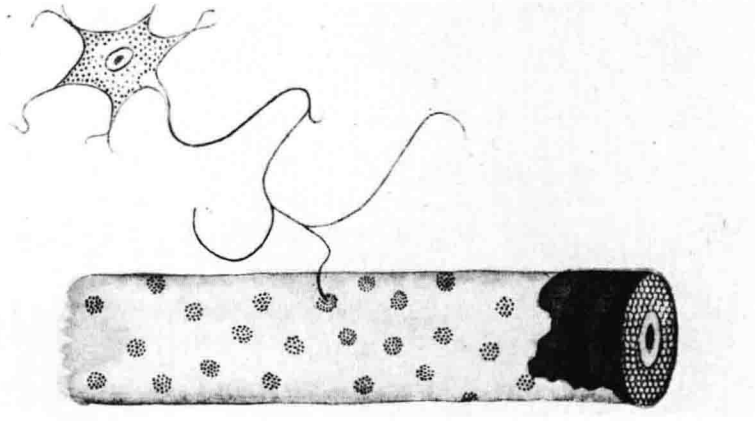

Fig. 3. Late myotube. The nuclei lie centrally, and myofibrils are packed peripherally. Receptor sites (represented as clusters of dots) have spread over the surface of the myotube. A single motor end-plate will form at the site of the nerve ending. (AFIP 77-6832)

continuous with the extracellular space. At first they are parallel to the long axis of the developing myofibrils, but later they assume a transverse position. The sarcoplasmic reticulum is derived from the smooth endoplasmic reticulum.[6]

The late myotube begins to synthesize acetylcholine receptor protein in large amounts. The protein appears diffusely on the sarcolemmal surface, and at this stage of maturity the myotube seems to have an attracting influence on the lower motor nerve endings growing through the area.[7, 8] As a result of this attraction, synaptic contact is made between one of the myotubes and one of the nerve endings.[2] The development of this contact (the motor end-plate) somehow informs the cell to eliminate all other receptor protein (extrajunctional receptor, EJR) from its surface, and receptor protein is confined to the point of the motor end-plate in a very concentrated focus.[2] The disappearance of the EJR protein results in no further innervation of that myotube by other nerve endings. Thus we have the normal situation, in which a single muscle fiber is innervated by a single nerve ending with a single motor end-plate.[9, 10]

Only after the motor end-plate has formed is the myotube capable of developing to full maturity. Without this neurotrophic influence the muscle fiber would remain at the myotube stage indefinitely.[11, 12] Since by this time mitosis and fusion are complete, the individual will not develop any new muscle fibers.

The mature muscle fiber (Fig. 4) is a multinucleated cell of varying length in which the nuclei are in a subsarcolemmal position. These nuclei are small, cigar shaped, and quite hyperchromatic, with no obvious nucleolus. The sarcoplasm is packed with myofibrils, and the sarcolemma is covered with a basement membrane. At one point on the muscle fiber there is a motor end-plate, which is the communication of the muscle fiber with the nervous system. One fiber contains one motor end-plate, but one motor neuron may innervate multiple muscle fibers. The motor neuron, with all of the muscle fibers it innervates, is called the *motor unit*.

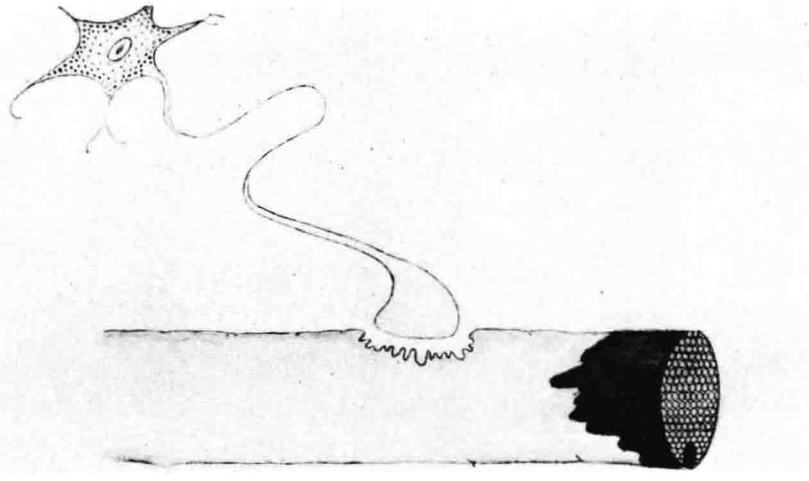

Fig. 4. Mature muscle fiber. It is innervated by one nerve ending and is covered by a basement membrane. The EJR has disappeared. The nuclei have been displaced to a subsarcolemmal position, and the sarcoplasm is packed with myofilaments. (AFIP 77-6833)

NORMAL MICROSCOPIC ANATOMY

Motor End-Plate

The motor end-plate is a key region in the muscle fiber. It can be easily demonstrated with esterase techniques and is visible with the light microscope. It has an irregular configuration and ranges from 2 to 10 μm in diameter. With ultrastructural techniques one can see that the nerve fiber, as it approaches the muscle fiber, loses its myelin sheath and that the axon swells and becomes irregular in its configuration as it lies upon the surface of the muscle fiber. At the nerve endings there are concentrations of mitochondria and multiple synaptic vesicles (Fig. 5) containing quanta of acetylcholine. The sarcolemma opposite the nerve ending is thickened and thrown into complex folds, greatly increasing its surface area. The basement membrane of the muscle fiber follows the synaptic cleft throughout these folds.

The receptor sites can be directly visualized by means of a remarkable agent, alpha-bungarotoxin. Alpha-bungarotoxin is one of the peptides present in the venom of the poisonous serpent *Bungarus multicinctus*. It has the very convenient and helpful property of binding specifically and irreversibly to nicotinic receptor proteins for acetylcholine.[13] This polypeptide can be tagged with agents such as iodine-125, fluorescein, or peroxidase.[14] Thus the distribution of receptor site protein and its metabolism can be studied directly. It has been shown that these receptors are located mostly on the crowns and upper surfaces of the folds in the postsynaptic membrane.[14, 15] In almost all preparations there is some labeling of the presynaptic membrane, and there is disagreement as to whether this represents artifact or the presence of presynaptic receptor protein.[14, 15] As the electrical

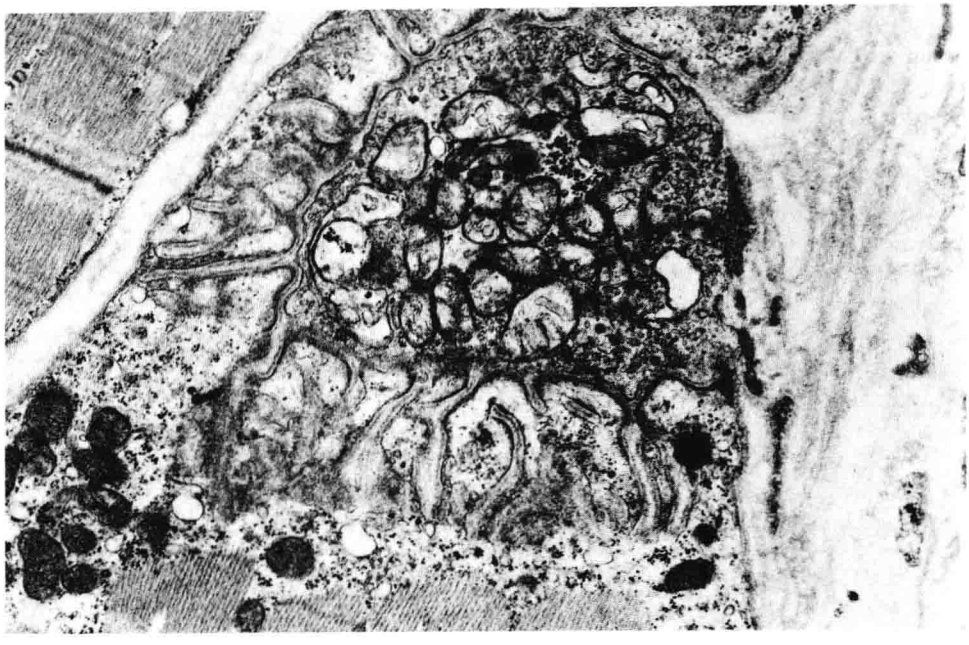

Fig. 5. Motor end-plate. The nerve ending is packed with mitochondria and synaptic vesicles. Adjacent sarcolemma is thickened and folded, and the basement membrane is deposited throughout the synaptic cleft. × 11,600. (AFIP 17073)

impulse travels to the nerve ending, vesicles containing acetylcholine are delivered to specific points on the presynaptic membrane and release their quanta of acetylcholine. The latter diffuses across the synaptic space and attaches itself to the receptors, causing changes in the permeability of sodium and potassium. Thus, if enough acetylcholine is released, a depolarization wave is triggered and spreads along the surface of the muscle fiber, resulting in contraction. Also present, free in the synaptic space and in the depths of the synaptic folds, is the enzyme acetylcholinesterase. This immediately breaks down the acetylcholine, reexposing the receptor site so that it can again be available for depolarization.

Mature Skeletal Muscle

Mature skeletal muscle functions by receiving an electrical signal, rapidly spreading it throughout its internal environment, and converting it to a chemical signal by causing the release of calcium in the sarcoplasmic reticulum. Calcium activates the chemical events that cause actin and myosin to slide past each other, resulting in contraction.

Let us review some aspects of the morphology of skeletal muscle prior to considering the pathologic reactions to denervation. If a skeletal muscle is sectioned across its belly and examined under very low magnification, it is seen that the

muscle fibers are divided in a fairly orderly way by various layers of connective tissue. The outermost layer of the connective tissue, which we would call the *fascia* grossly, is the *epimysium*. Internally the connective tissue subdivides the muscle fibers into numerous fascicles or small groups of fibers of various sizes. The layers surrounding these fascicles are the *perimysium*. The blood vessels and nerves tend to distribute themselves internally via these connective tissue septa. The thickness of the septa varies considerably within the muscle, and for this reason the prominence of this connective tissue is of little significance in the interpretation of pathologic changes. Around individual muscle fibers is a very scanty, delicate arrangement of collagenous connective tissue called the *endomysium*. The amount of endomysium in a muscle biopsy specimen is normally constant but varies considerably with various pathologic conditions, and its appearance is important in the interpretation of muscle biopsy specimens.

An individual muscle fiber, viewed longitudinally under high magnification, is composed of a regular arrangement of cross striations. The nucleus is pressed to a subsarcolemmal location because the fiber is packed with myofibrils composed of myofilaments. In a properly fixed specimen the myofibrils are aligned

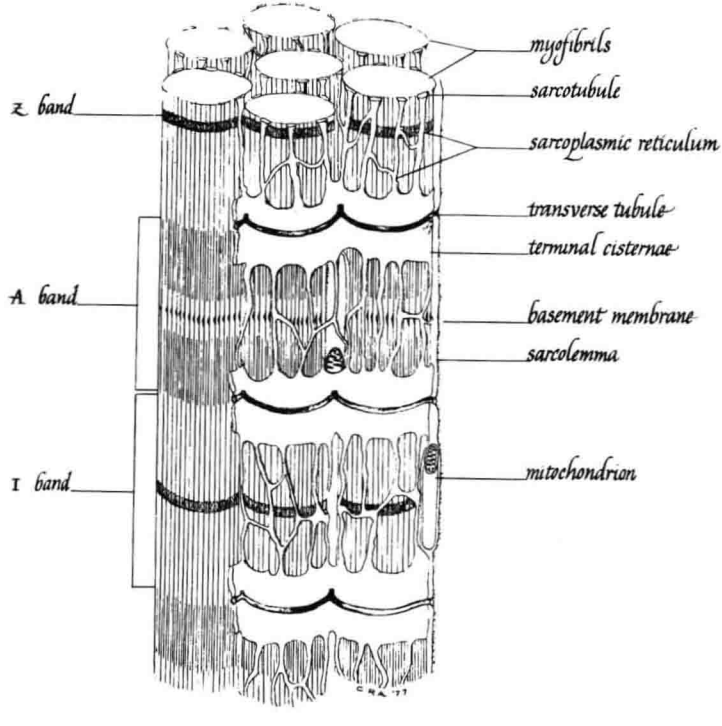

Fig. 6. Portion of a muscle fiber. The sarcomeres of the myofibrils are in register. Myofibrils are intimately surrounded by sarcoplasmic reticulum and mitochondria. It is these membranous organelles that are red with MGT stain and dark with NADH-TR reaction. The sarcoplasmic reticulum is closely related to the transverse tubules, which arise from the sarcolemma. A basement membrane covers the fiber. (AFIP 77-5174-7)

with each other, thus making the cross striations apparent. These cross striations will be described in greater detail later.

The internal organization of the muscle fiber (Fig. 6) reflects several interesting specializations that allow the fiber to receive the electrical signal and to contract. The sarcolemma communicates diffusely with the interior by forming transverse tubules, the lumina of which are continuous with the extracellular space. If one mentally erases all other organelles from the inside of the muscle fiber and leaves only the transverse tubular system, one would see a transverse network of interconnecting tubules that looks like chicken wire. The transverse plane of this array of tubules is slightly inclined, resulting in a continuous spiral arrangement of these tubules. The transverse tubular system is intimately associated with the sarcoplasmic reticulum, which in turn wraps itself extensively around each myofibril. The electrical signal is carried internally via the transverse tubular system, which communicates very closely with the dilated regions (the cisterns) of the sarcoplasmic reticulum. A transverse section across the tubule demonstrates the triad of a sacule of dilated sarcoplasmic reticulum on each side of a distinct tubule. In a given species the triads are related consistently to a portion of the sarcomere. In some species the triads are adjacent to the Z-line, while in most mammals, including man, the triads are adjacent to each junction between the A- and I-bands. Mitochondria are scattered between individual myofibrils and in the subsarcolemmal space.

Individual myofibrils are composed of numerous myofilaments consisting of

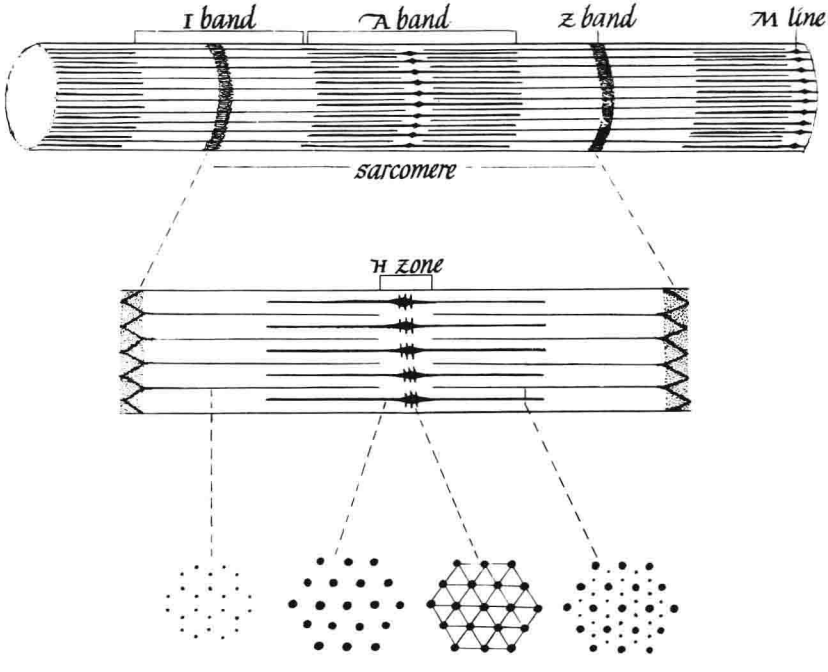

FIG. 7. Arrangement of the myofilaments, resulting in the striated pattern. (AFIP 77-5174-10)

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