Volgograd state medical university

Department of histology, embryology, cytology

MUSCLE TISSUE

Lecture for the 1 year
English medium students

Volgograd

THE OBJECTIVES:

1. To investigate morphological and functional differences and similarities between smooth, skeletal, cardiac muscle type.

2. To evaluate structural and size relationships of an entire skeletal muscle, fascicles, fibers, myofibrils and myofilaments.

3. To understand how arrangement of actin and myosin filaments create cross striations in cardiac and skeletal muscle.

4. To conceive sliding filament concept of contraction and how it applies to various muscle types.

5. To realize why skeletal muscles have the potential for partial regeneration while cardiac fibers do not.

MUSCLE TISSUE. GENERAL PROVISIONS

Muscle makes up much of the mass of the body and is present in many organs.

Terminology:

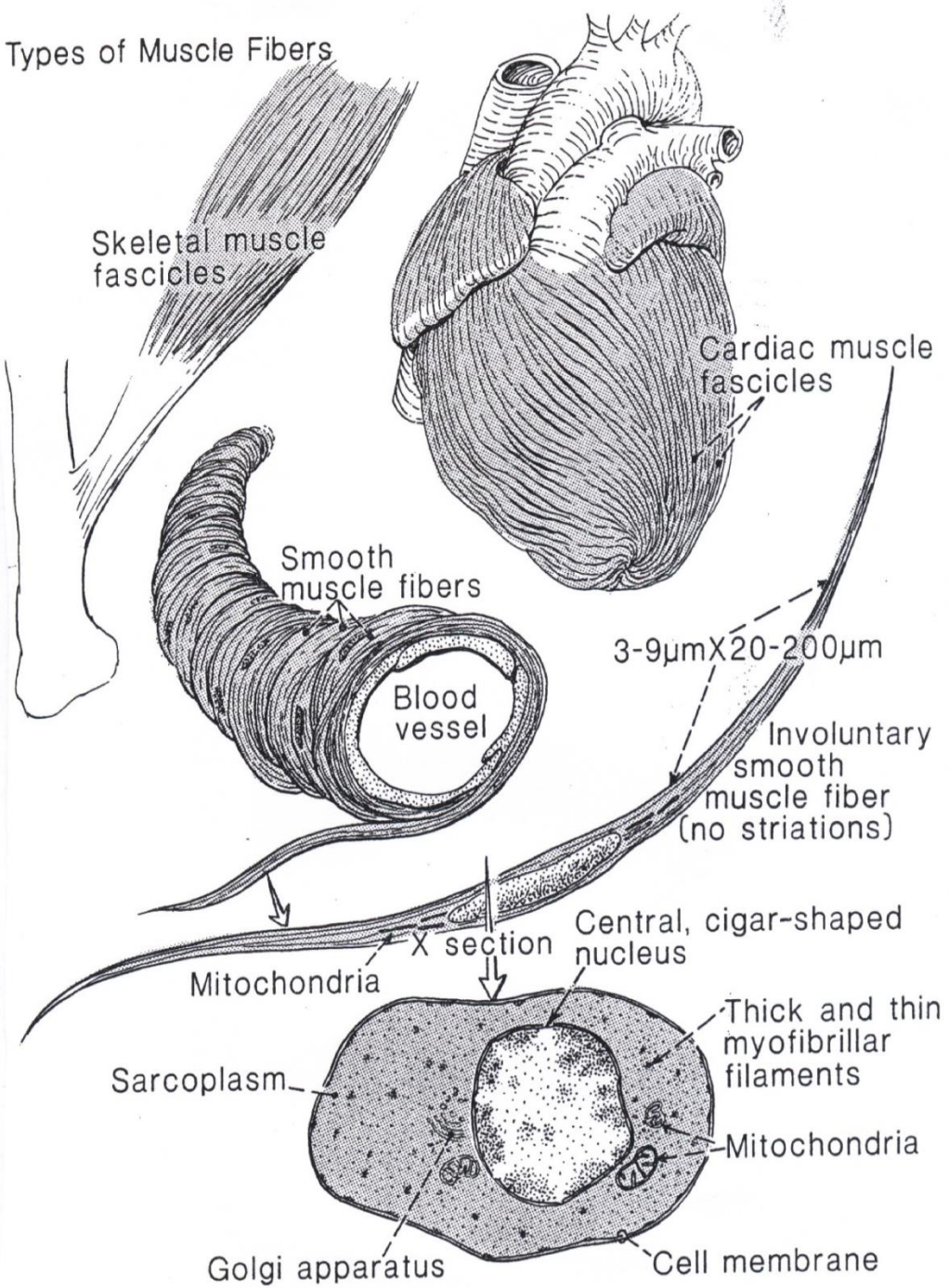
- muscle cell = muscle fiber (since muscle cells are much longer than they are wide),

- sarcoplasm = cytoplasm of the muscle fiber,

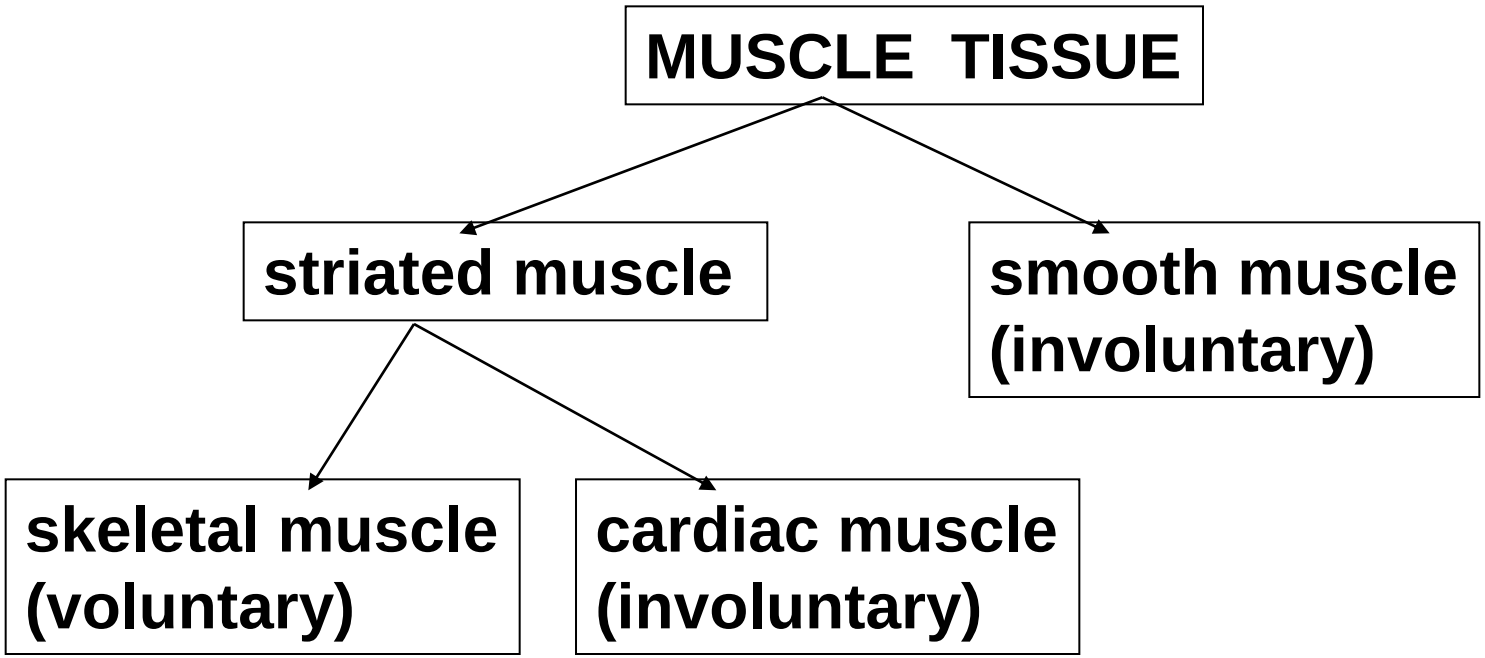
- sarcolemma = muscle fiber plasma membrane,

- sarcoplasmic reticulum = smooth endoplasmic reticulum of the muscle fiber.

THREE MAIN TYPES OF MUSCLE TISSUE

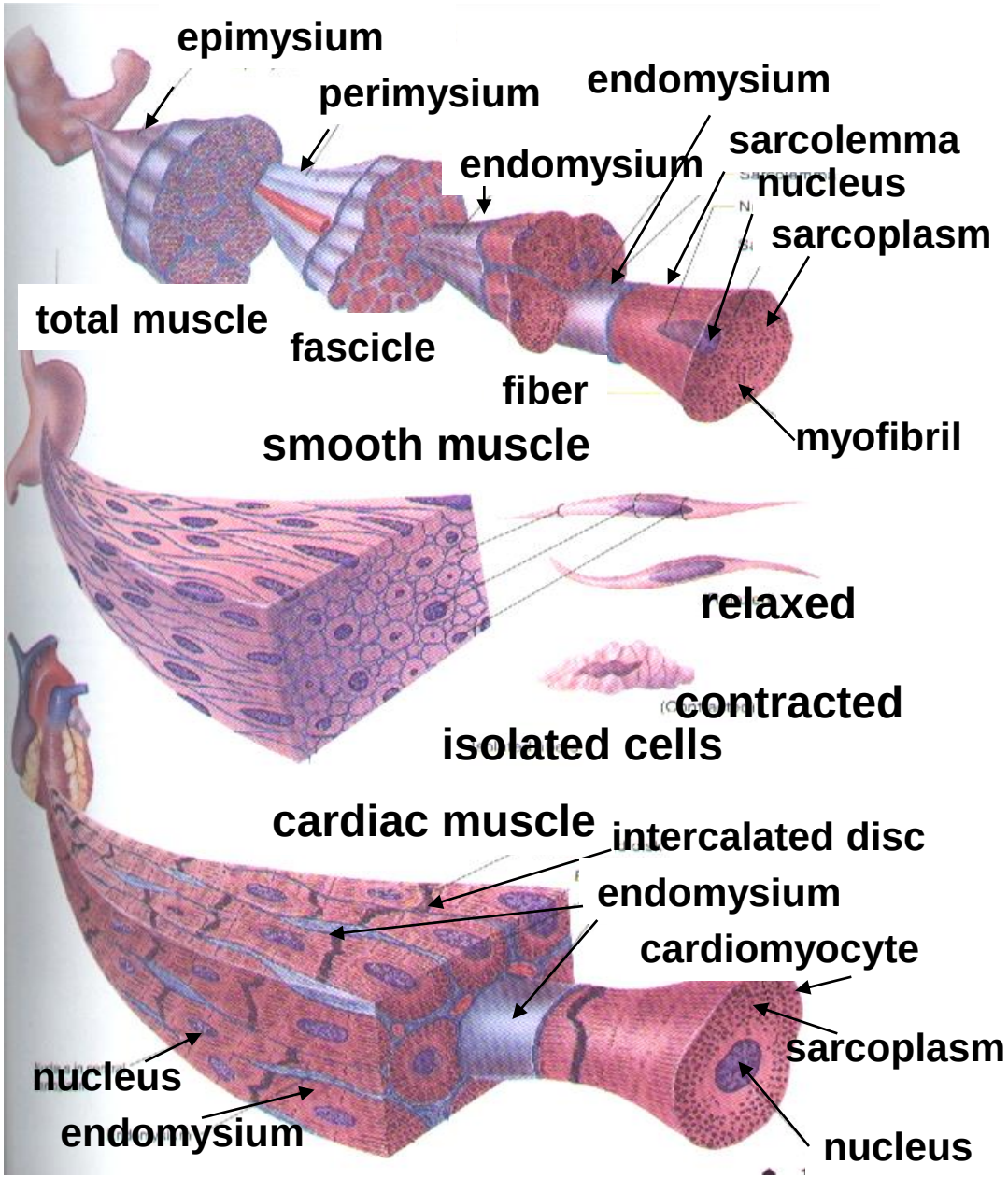


CLASSIFICATION OF THE MUSCLE TISSUE



skeletal muscle

MUSCLE TISSUE TYPES

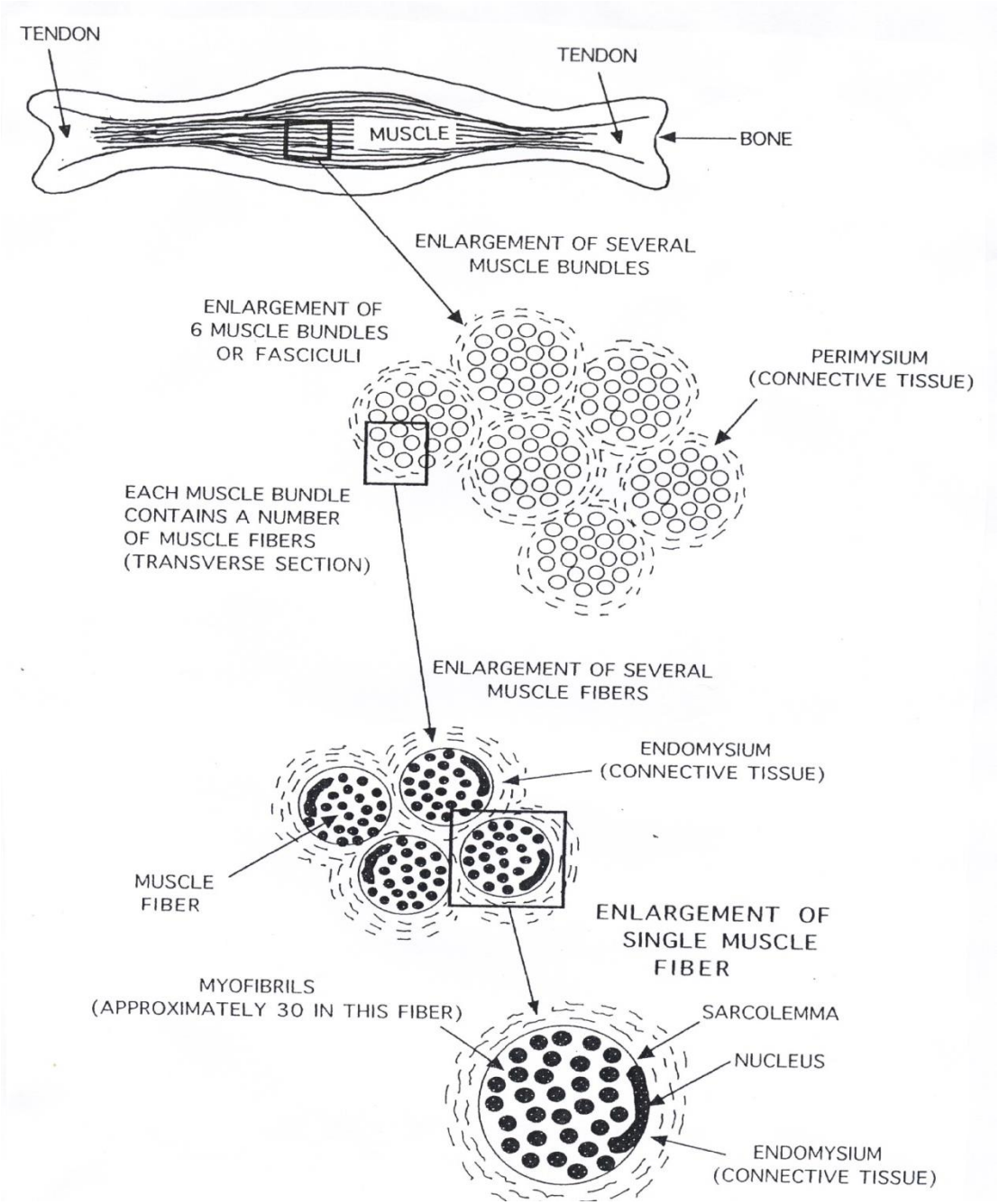


Three types of muscle tissue can be distinguished on the basis of morphologic and functional characteristics. Skeletal muscle is composed of bundles of very long cylindrical multinucleated cells that show cross-striations.

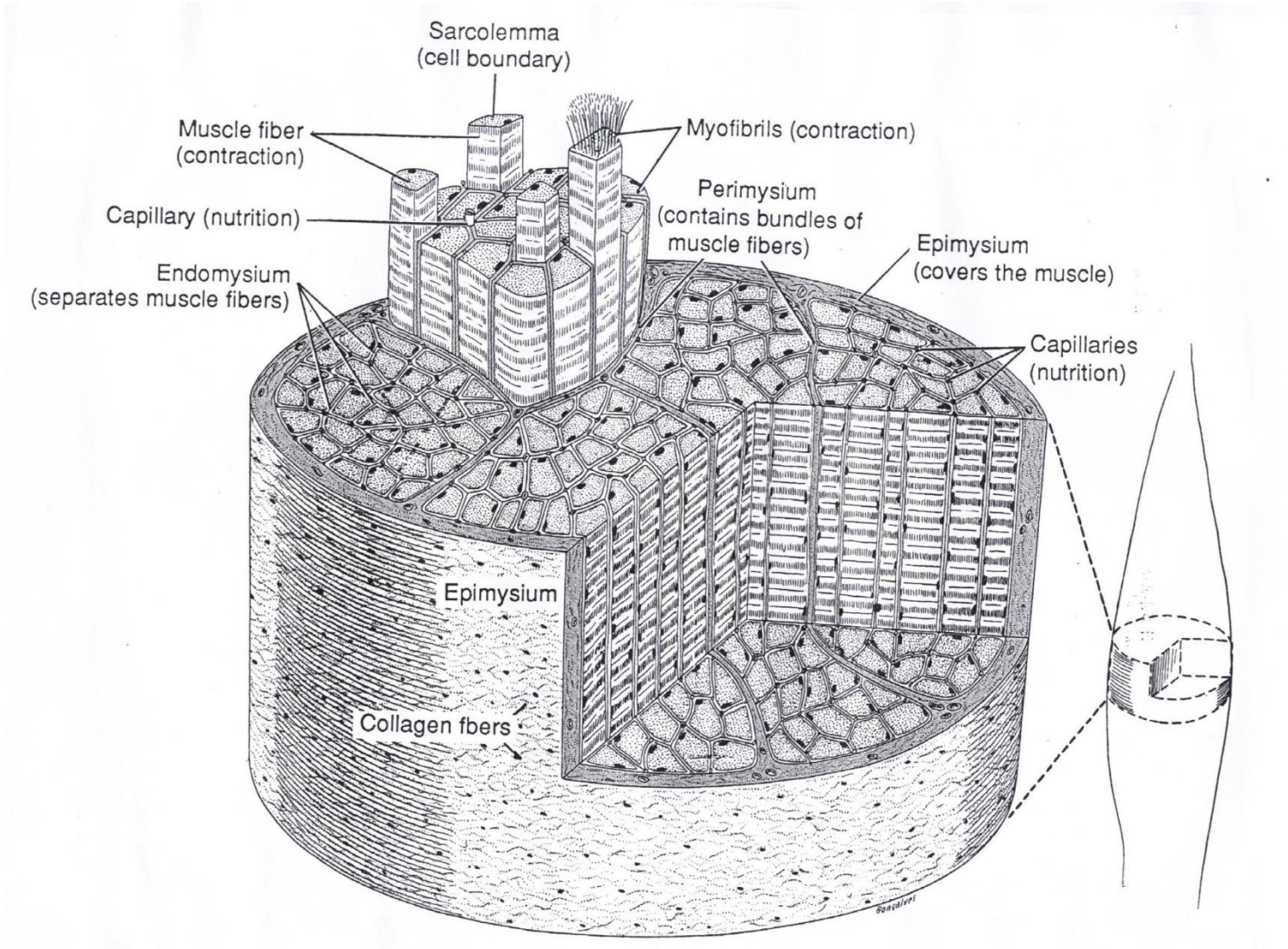
Cardiac muscle also has cross-striations and is composed of elongated branched cells that lie parallel to each other. At sites of end-to-end contact are the intercalated disks, structures found only in cardiac muscle.

Smooth muscle consists of collections of fusiform cells that do not show striation under LM. Their contraction process is slow and not subject to voluntary control.

SCHEMATIC RELATIONSHIP OF MUSCLE BUNDLES, MUSCLE FIBERS AND MYOFIBRILS



SCHEME OF SKELETAL MUSCLE TISSUE



Skeletal Muscle. General Provisions.

- Skeletal muscles is made of fasciculi,

- a fasciculus is made of muscle fibers,

- muscle fiber = muscle cell (multinucleated),

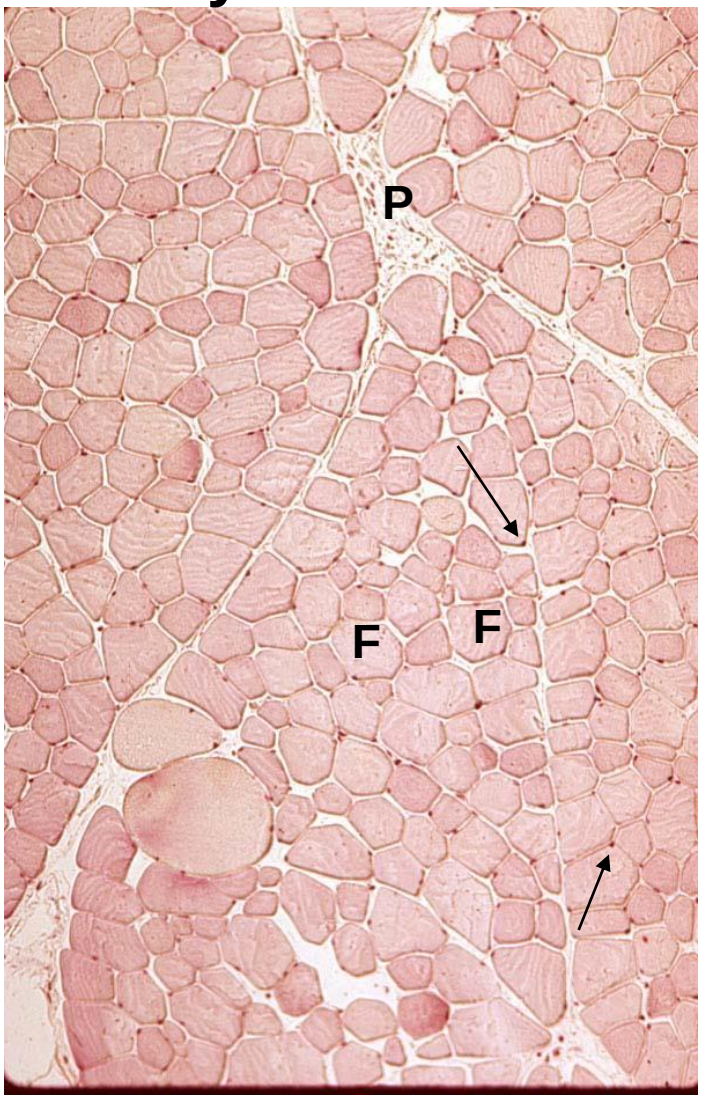
- muscle fibers are cylindrical and unbranched,

- muscle fibers are 1-30 mm long and are 10-100 mcm in diameter,

- multiple nuclei are located peripherally beneath sarcolemma,

- each fiber is surrounded by external basal lamina.

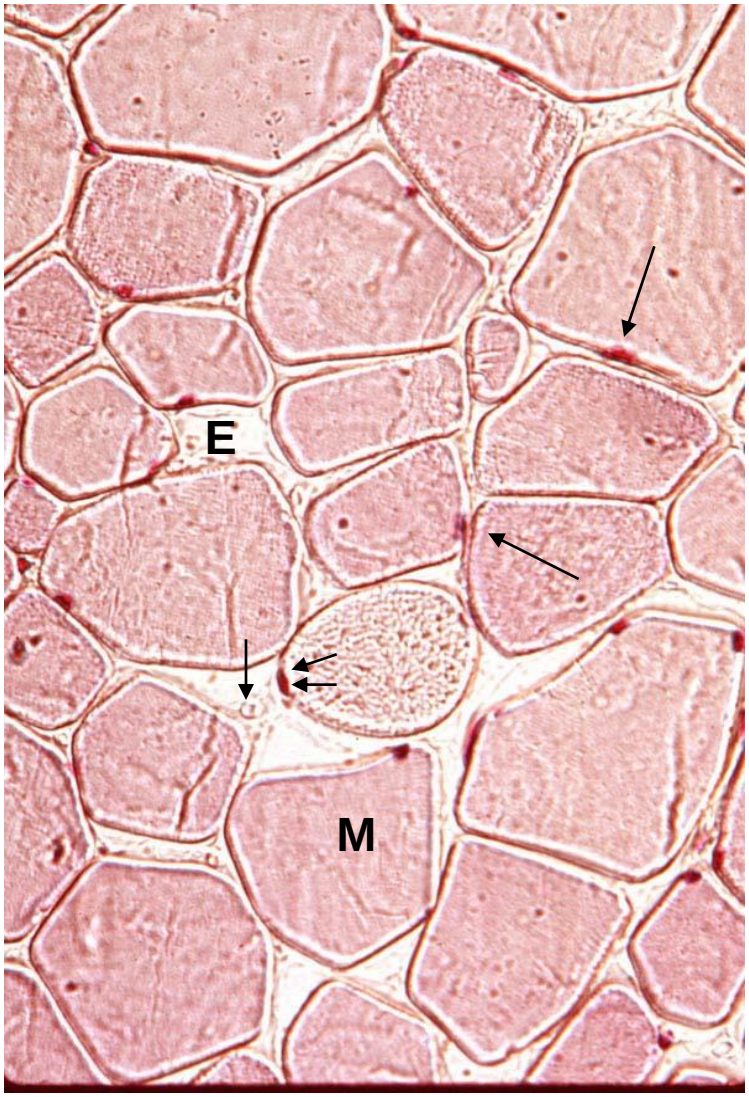
Skeletal muscle. x.s. Monkey. x 132.



Portions of a few fascicles are presented in this photomicrograph. Each fascicle is composed of numerous muscle fibers (F) that are surrounded by connective tissue elements, known as the perimysium (P), which house nerves and blood vessels supplying the fascicles. The nuclei of endothelial, Schwann, and connective tissue cells are evident as black dots in the perimysium.

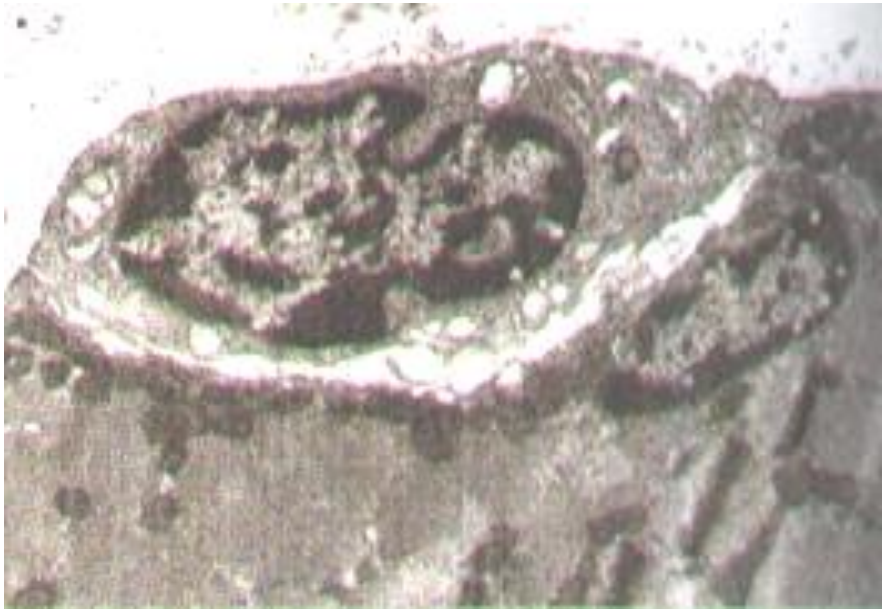
The peripherally placed nuclei (arrow) of the skeletal muscle fibers appear as black dots; however, they are all within the muscle cell. Nuclei of satellite cells are also present, just external to the muscle fibers, but their identification at low magnification is questionable.

Skeletal muscle. x.s. Monkey. x 540.



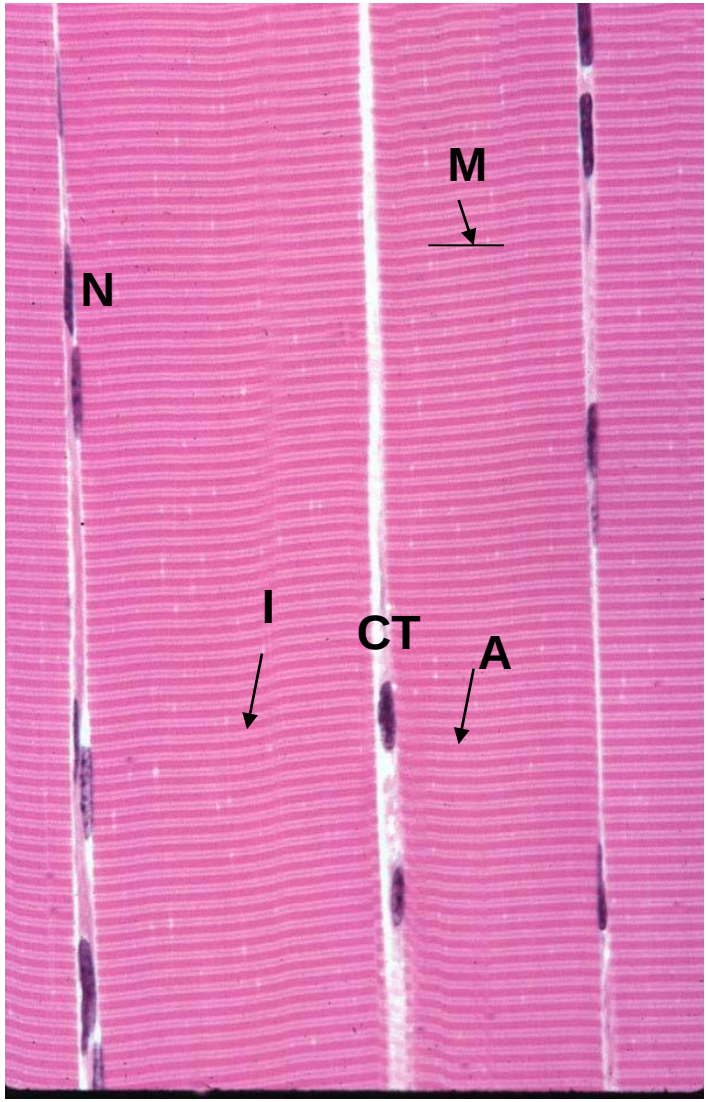
Transverse sections of several muscle fibers demonstrate that these cells appear to be polyhedral, that they possess peripherally placed nuclei (arrow), and that their endomysia (E) house numerous capillaries (short arrow). Many of the capillaries are difficult to see because they are collapsed in a resting muscle. The pale sarcoplasm occasionally appears granular, due to the transversely sectioned myofibrils (M). Occasionally, nuclei that appear to belong to satellite cells (double arrow) may be observed, but definite identification cannot be expected.

Satellite cell of the skeletal muscle. TEM.

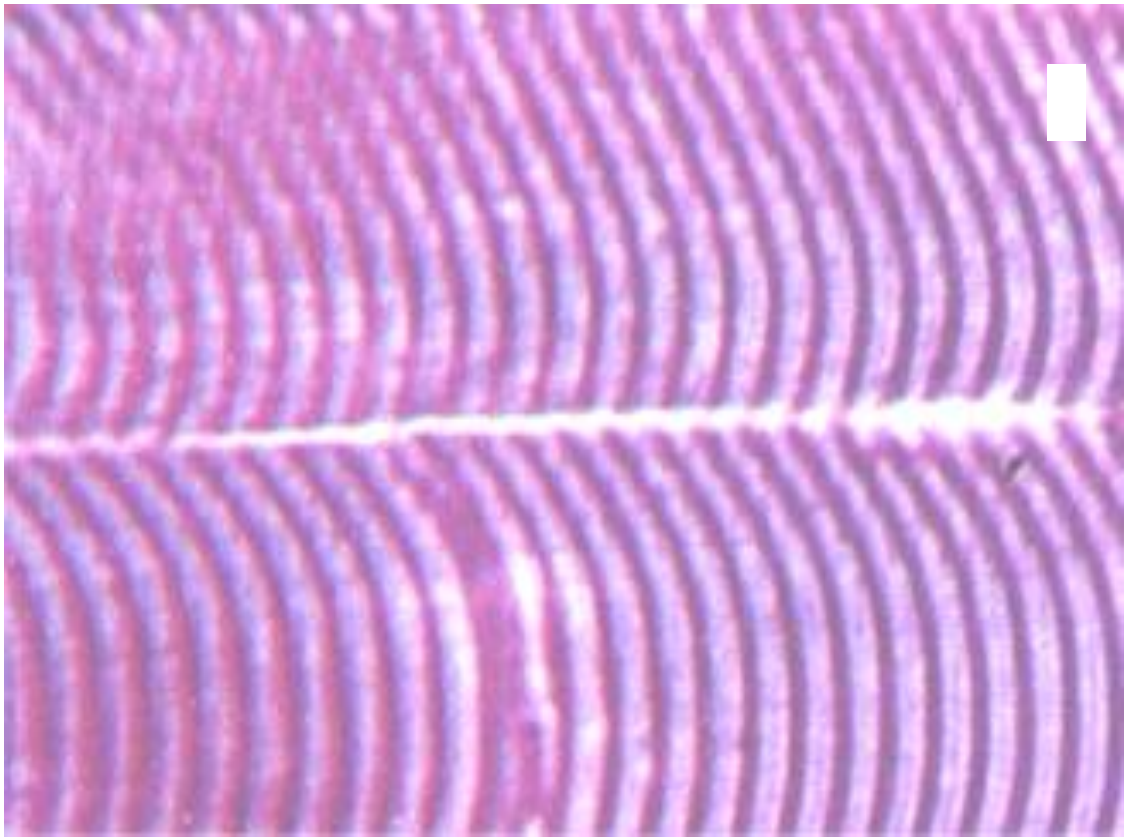


The cells is spindle-shaped, they are found immediately beneath the external lamina of a muscle fiber and act as stem cells in adult muscle.

Skeletal muscle. l.s. x 800



The numerous nuclei (N) of skeletal muscle cells are peripherally located. The intercellular space is occupied by endomysium, with its occasional connective tissue cells (CT) and reticular fibers. The longitudinal striations of skeletal muscle fibers represent myofibrils (M) that are arranged in almost precise register with each other. This ordered arrangement is responsible for the dark and light transverse banding.



MIOFIBRILS

Individual skeletal muscle cells appear to have cross-striations in longitudinal section due to the presence of stacks of myofibrils each of which is 1-2 mcm in diameter composed of alternating, overlapping zones of thick (dark-stained) and thin (light stained) filaments.

Skeletal Muscle. Structure.

- muscle fibers have cross-striations,

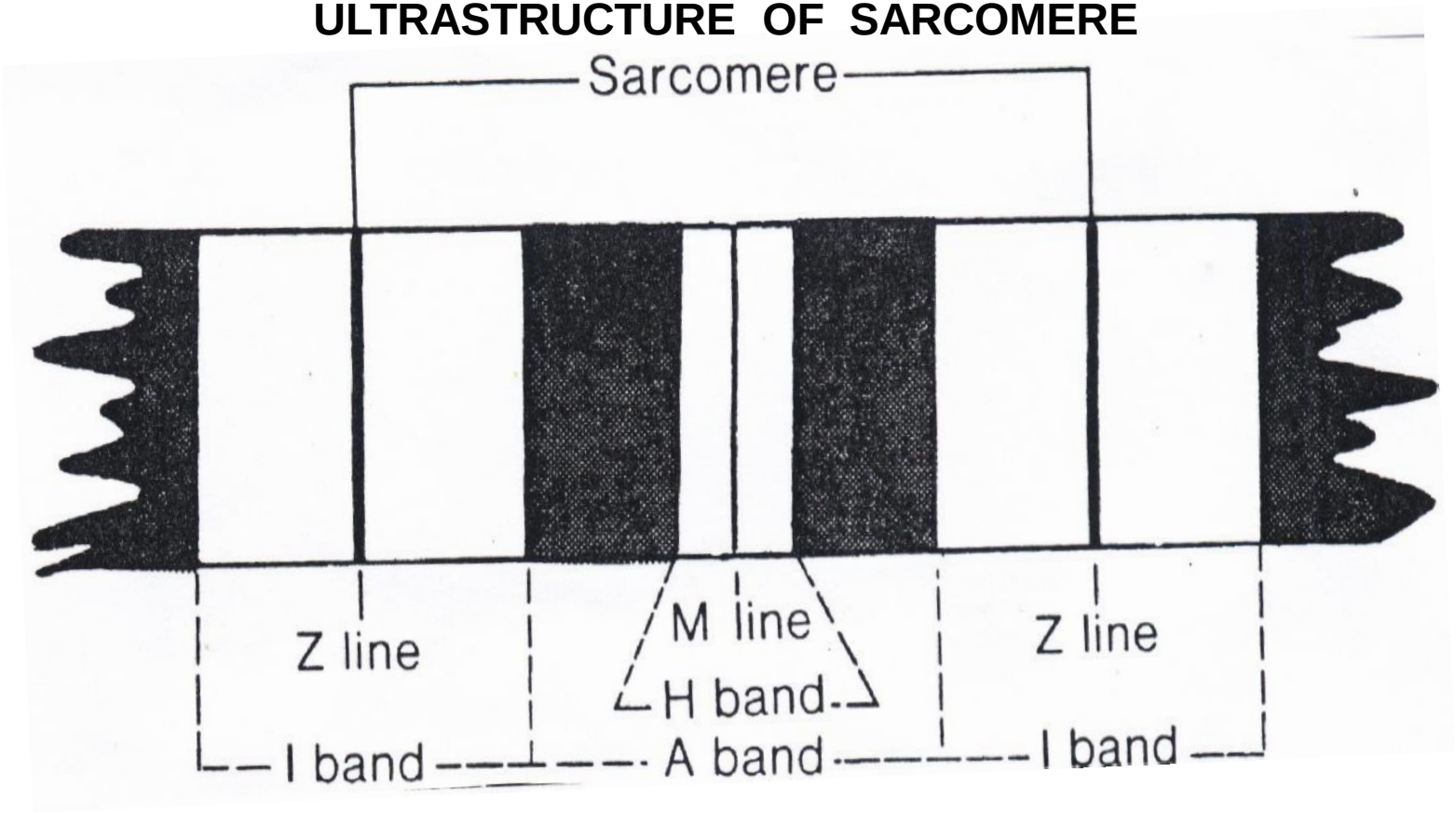
- muscle fibers contain dozens of myofibrils,

- each myofibril is composed of myofilament bundles (composed of contractile proteins and visible only under EM),

- fibers can increase in size but not in number,

- myofibrils are composed of a linear array of sarcomeres.

ULTRASTRUCTURE OF SARCOMERE

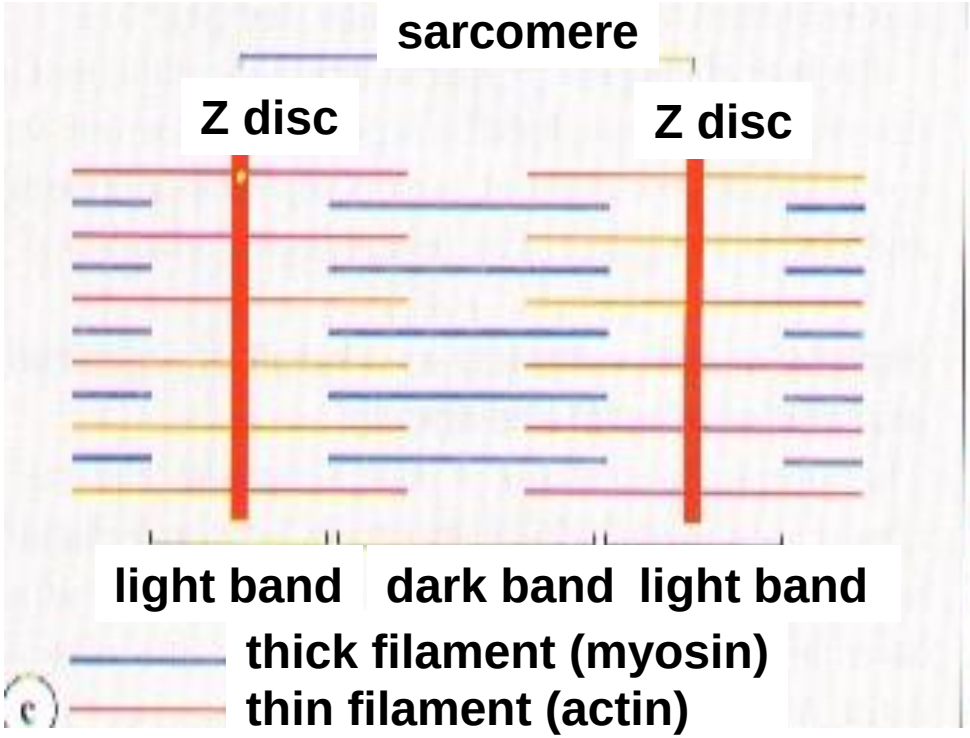


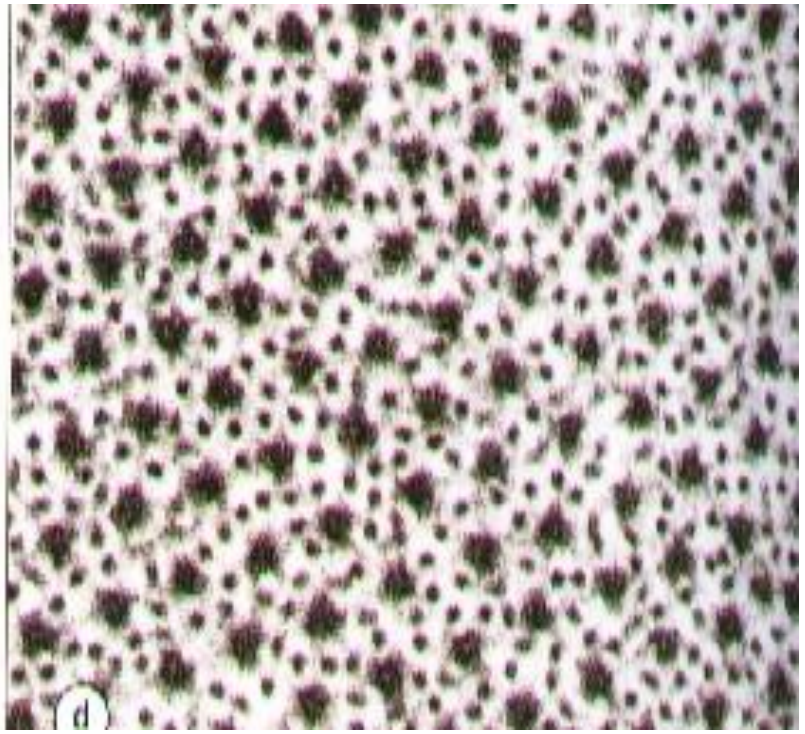
A precisely ordered collection of myofilaments (thin and thick filaments) comprise the basic contractile unit of the skeletal muscle cell - the sarcomere which is 2.5 mcm long..

Striations of skeletal muscle are resolved into A bands and I bands. I bands are divided into two equal halves by a Z-disc, and each A-band has a light zone, the H-band. The center of each A band is a dark M band. Adjacent myofibrils are secured to each other by the intermediate filaments desmin and vimentin.

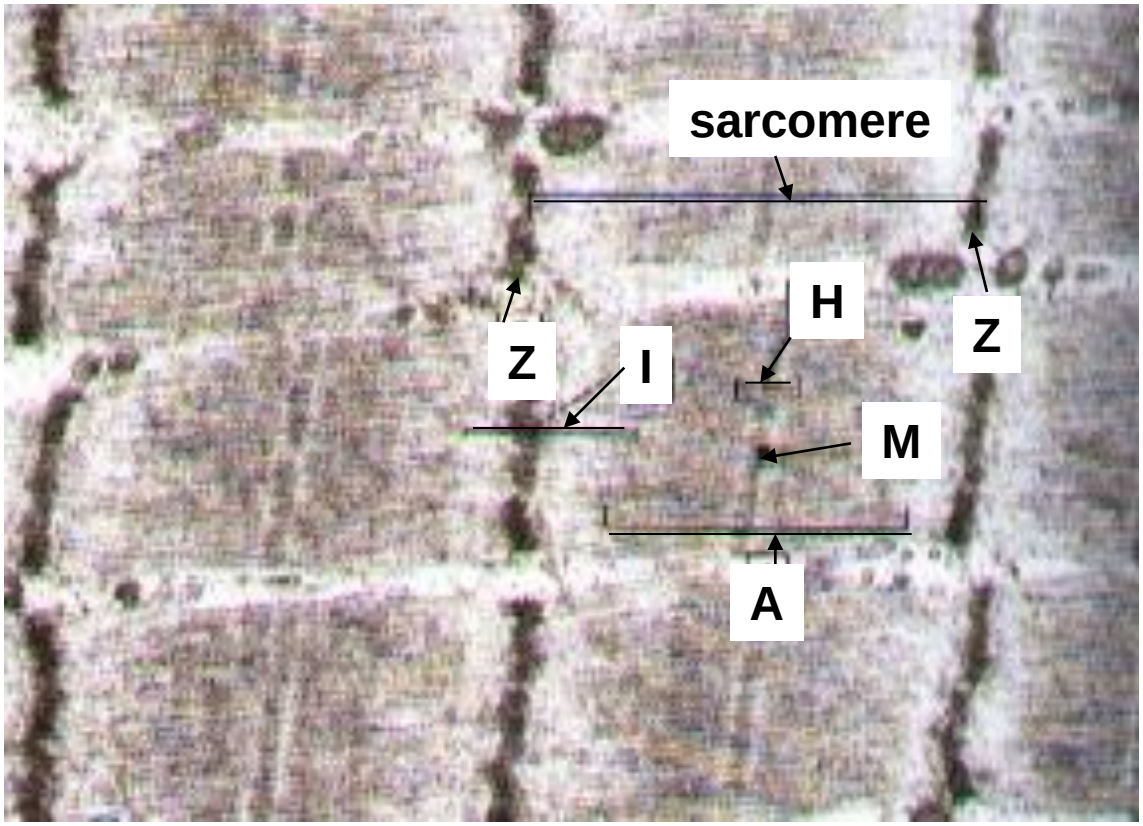
c) Diagram to show the arrangement of filaments in a sarcomere. The thin filaments are composed mainly of actin, the thick filaments mainly of myosin.

d) When viewed in cross-section at the level of overlap between the A and I bands each myofibril is seen to have a regular spaced arrangement of thick and thin filaments, such that each thick filament is surrounded by six thin filaments arranged in an approximately hexagonal lattice.





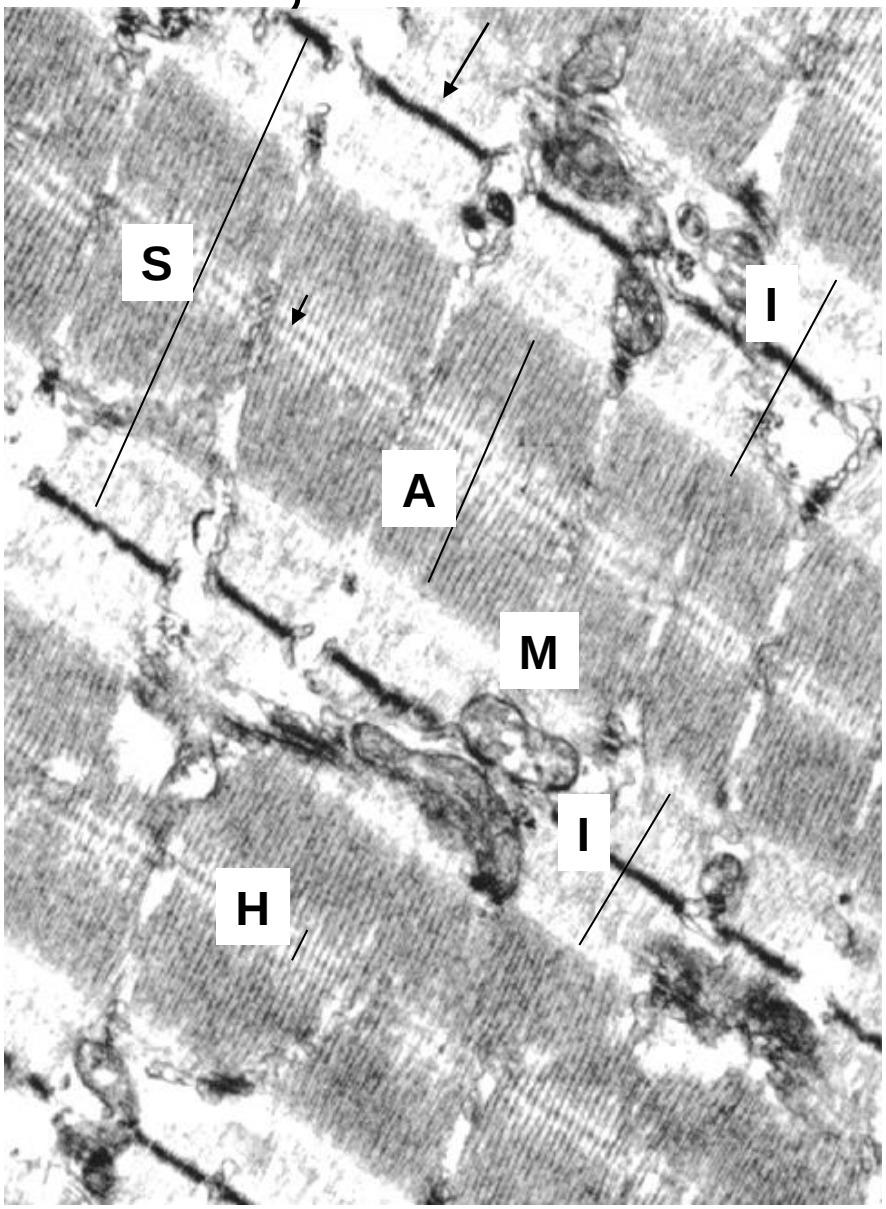
MYOFIBRILS



MIOFIBRILS

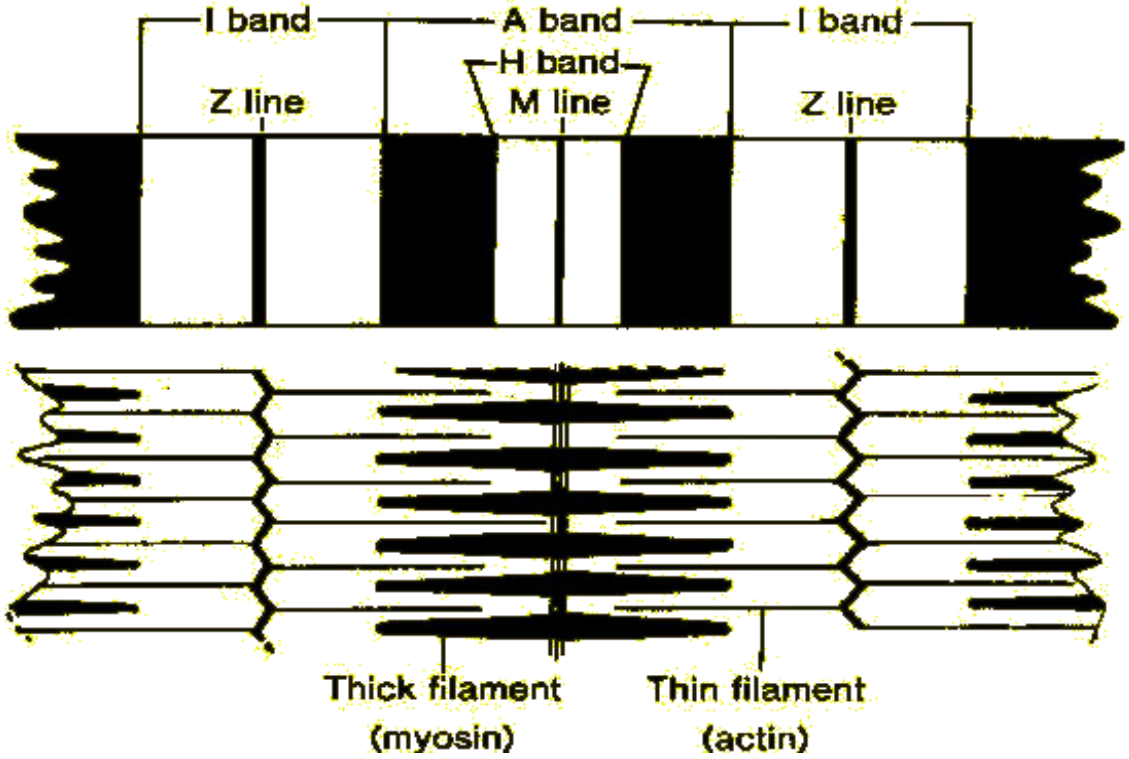
Ultrastructurally, several zones of staining can be discerned along myofibrils. The A (dark) band refers to the thick filament band and includes a zone where the thin filaments overlap the thick filaments. The I (light) band is the zone of thin filaments that does not overlap the thick filaments, the Z line is a dark band in the center of I band and the M line runs down the center of the H band. The unit deliniated between two Z disks is termed a sarcomere.

Skeletal muscle. EM. l.s. Rat. x 17,100



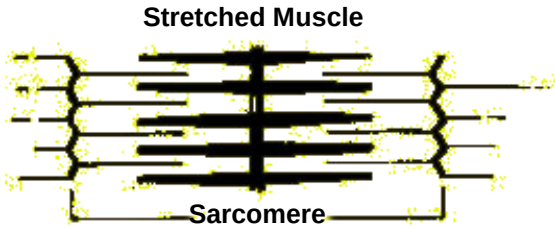
Perpendicular to the longitudinal axis of the fiber the dark and light cross-bandings are visible. The A band (A) is bordered by an I band (I) on either side. Each I band is traversed by a Z disc (arrow). The Z disc has the appearance of a dashed line because individual myofibrils are separated from each other by sarcoplasm. A sarcomere (S) extends from Z disc to Z disc and an almost precise alignment of individual myofibrils assures the specific orientation of the various bands within the sarcomere. The H zone (H) and the M disc (arrowhead) are clearly defined in this electron micrograph. Mitochondria are preferentially located occupying the region at the level of the I band as they wrap around the periphery of the myofibril.

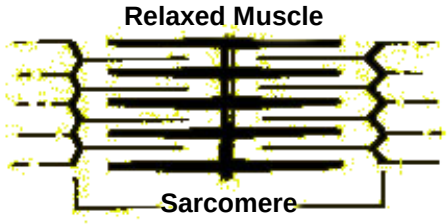
Relationship of Cross-Banding to the Arrangement of Thick and Thin Filaments

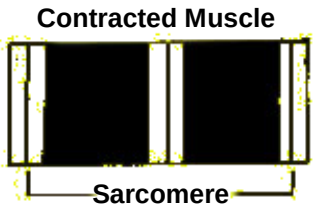


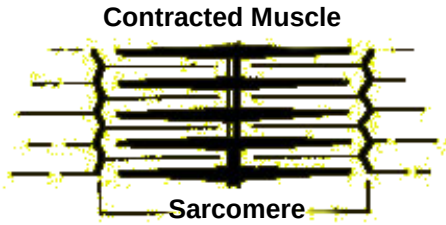
The structure and function of the contractile proteins in skeletal muscle is virtually the same as in cardiac muscle. The striated muscle fiber is represented by alternating A- and I-bands, I bands are bisected by dark transverse line called Z-line, the smallest repetitive subunit of the contractile apparatus - the sarcomere – extends from Z to Z line. Thin filaments originate at the Z disc and project toward center of the two adjacent sarcomeres thus pointing in opposite direction. Hence a single sarcomere has two groups of parallel arrays of thin filaments pointing toward its center.

BANDING PATTERN AND ARRANGEMENT OF THICK AND THIN FILAMENTS IN STRETCHED, RELAXED AND CONTRACTED MUSCLE



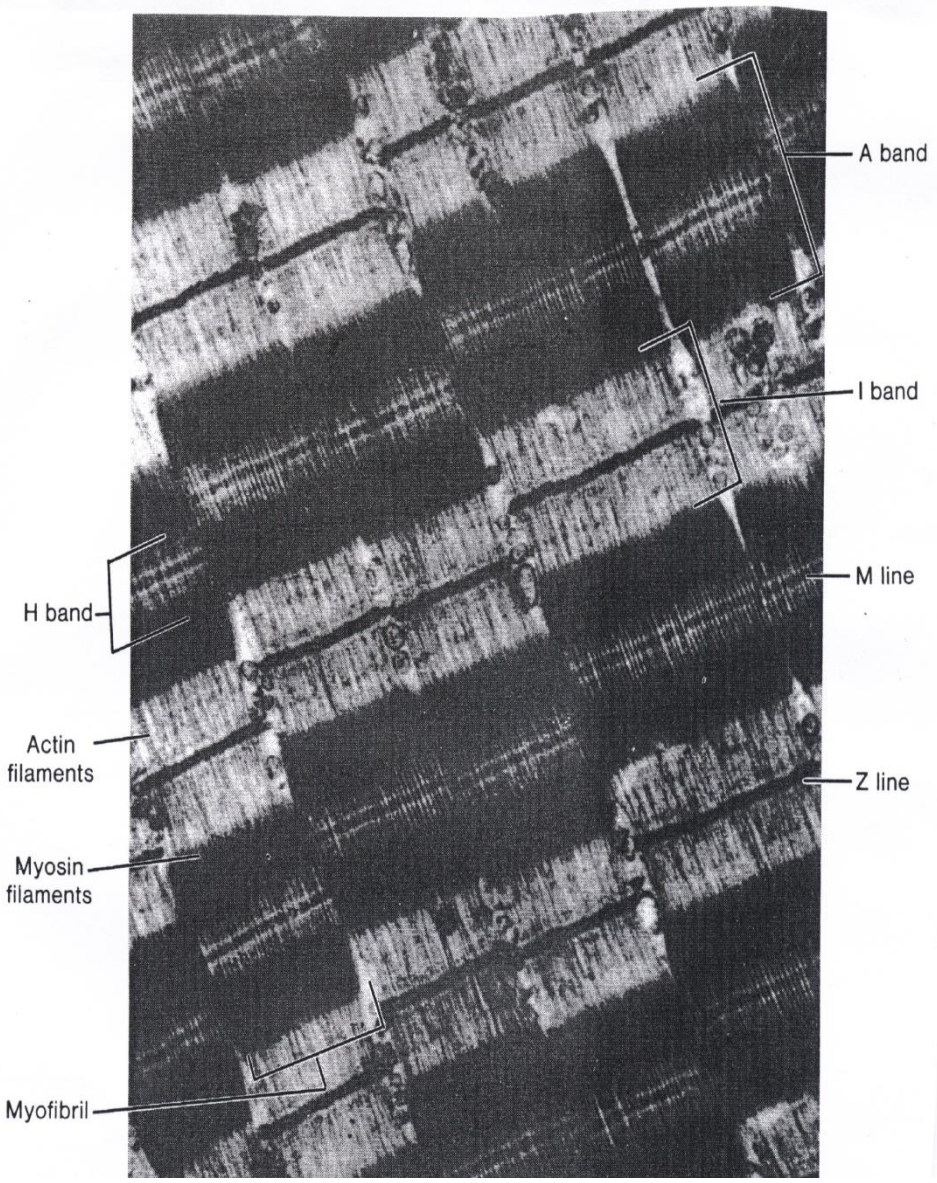






Thick (myosin) and thin (actin) filaments lie parallel to the long axis of the myofibrils in a symmetric pattern; thick filaments are 15 nm in diameter and 1.5 mc long, they occupy the A band, the central portion of sarcomere, while the thin filaments are 7 nm in diameter and 1.0 mcm long, they run between and parallel to the thick filaments and have one end attached to the Z-line; A-band is bisected by M-line – the site of lateral connection connections between adjacent thick filaments.

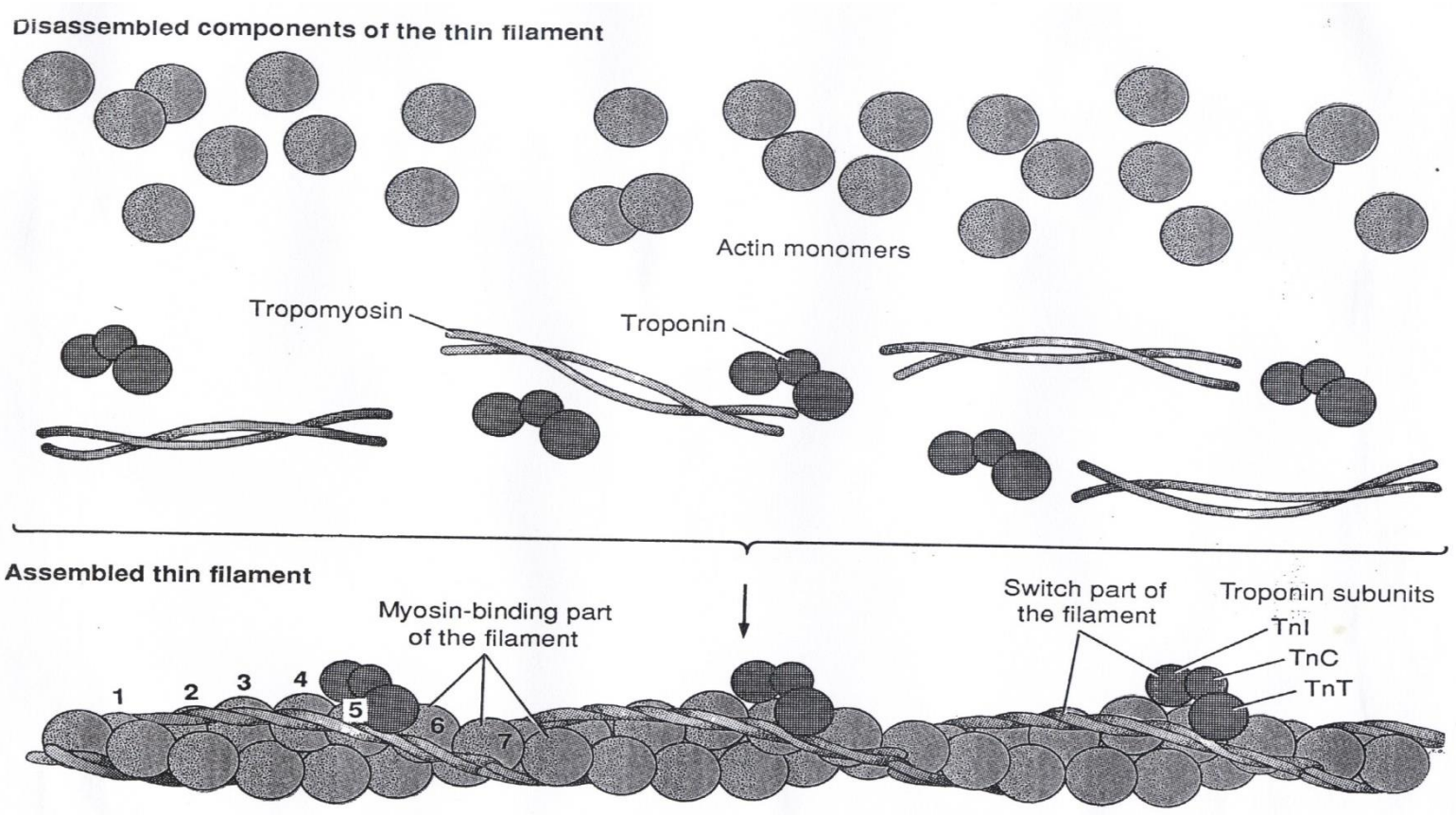
ULTRASTRUCTURE OF SARCOMERE



Banding pattern of each skeletal muscle fibril in the fiber.

Note that the light band (I) is bisected by a narrow dark line, the Z disc. The dark band (A) is also bisected, by the clear H zone. The center of the H zone is occupied by the M disc. The basic contractile unit of skeletal muscle is the sarcomere, extending from one Z disc to its neighboring Z disc. During muscle contraction, the myofilaments of each sarcomere slide past one another, pulling Z discs closer to each other. During this movement the width of the A band remains constant, while the I band and H zone disappear.

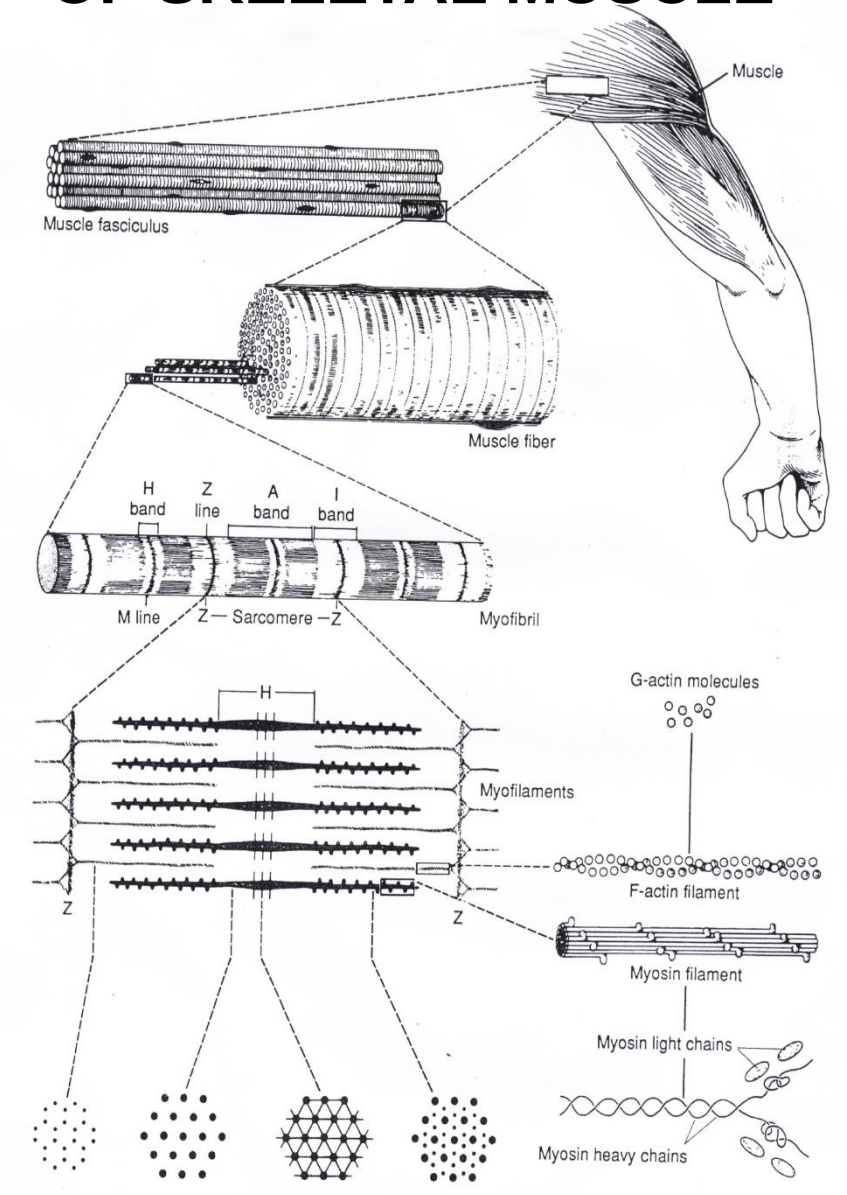
MOLECULAR BIOLOGY OF ACTIN MICROFILAMENT



Thin filaments are composed of the two chains of F-actin filaments wrapped around each other in association with tropomyosin and troponin.

The major component of each filament is F-actin, a polymer of globular G-actin units. The globular actin molecules (G-actin) are polarized and polymerize in one direction (F-actin). The filament is a special configuration of three major components – actin, tropomyosin and troponin.

HISTOPHYSIOLOGY OF SKELETAL MUSCLE



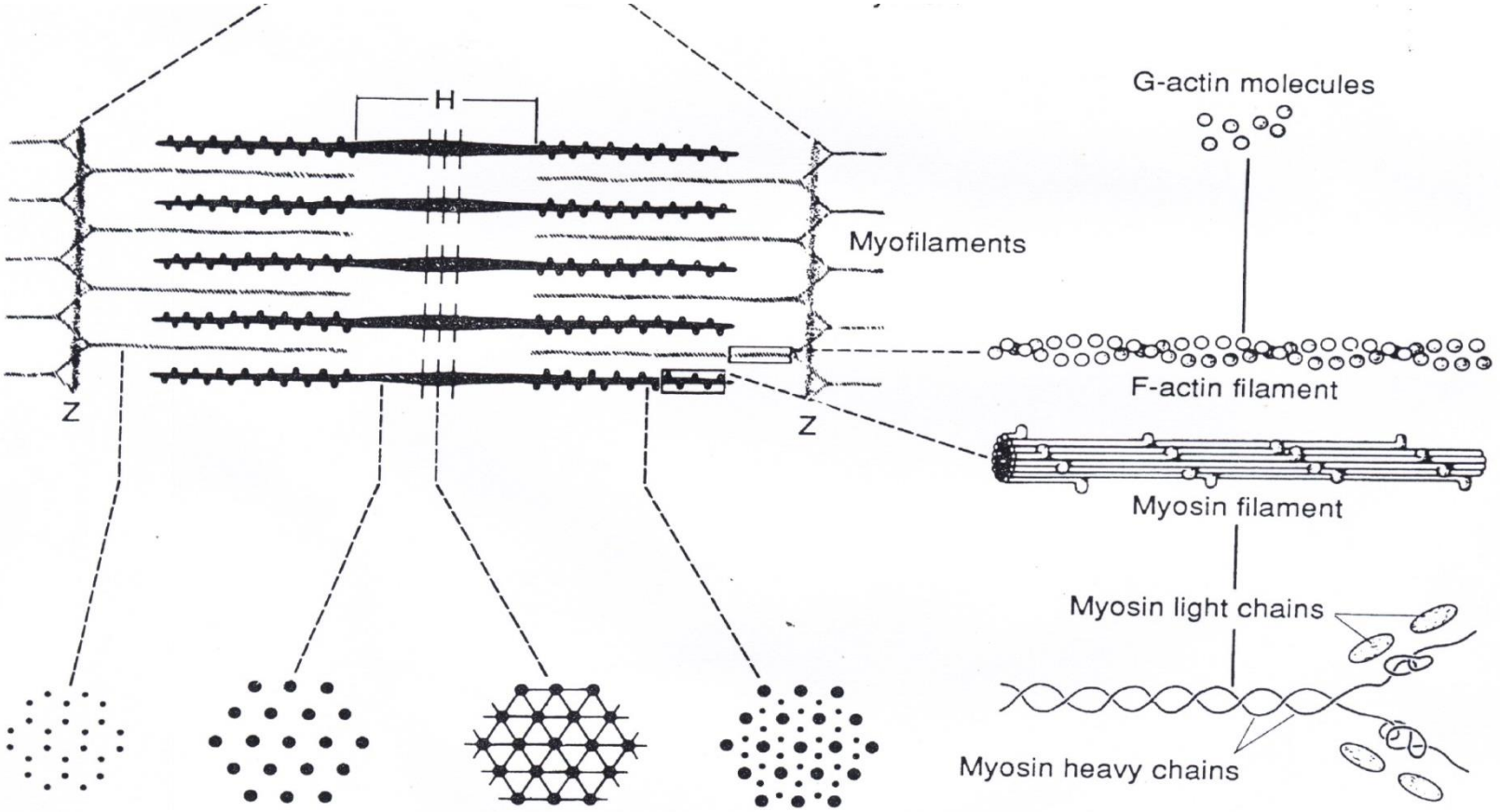
<u>Thin filaments are mainly formed from actin.</u>

Each thin filament is formed by polymerization of many single molecules of globular actin (G-actin). These actin filaments are polar, all G-actin molecules pointing in the same direction.

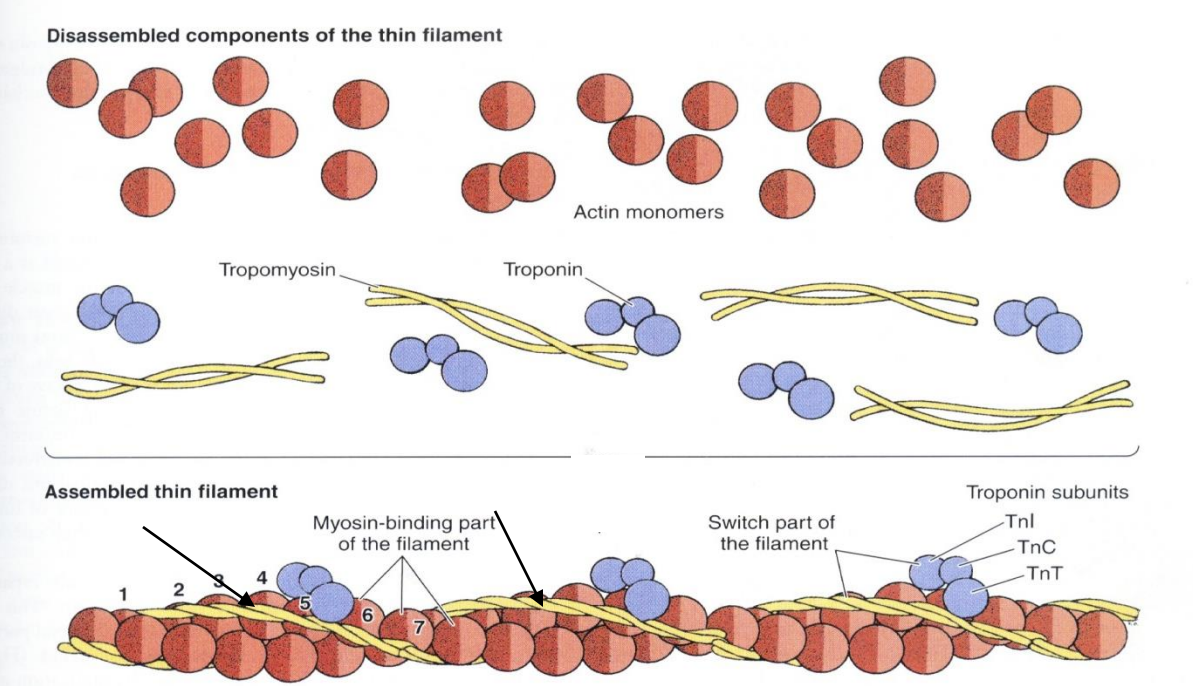
To form a complete thin filament, two actin filaments become attached by their tail ends to alpha-actinin in the Z-line so that they face in opposite direction (I.e. away from the Z line). Alpha-actinin and desmin are believed to tie adjacent sarcomeres together, thus keeping the myofibril in register.

HISTOPHYSIOLOGY OF SKELETAL MUSCLE

In a thin filament two strands of G-actin monomeres (F-actin) are twisted around each other in a double helix formation. Each G-actin monomer contains a binding site for myosin.



MOLECULAR BIOLOGY OF ACTIN MICROFILAMENT

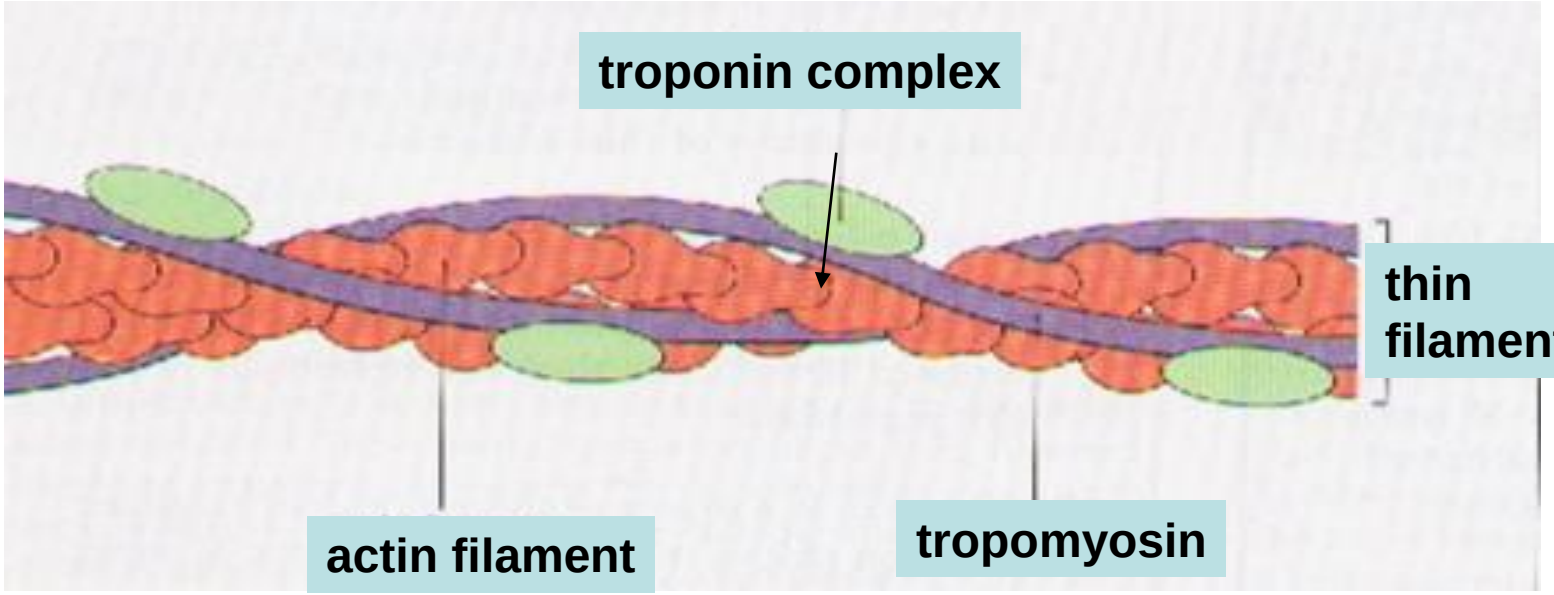


Tropomyosin is a long molecule (arrows) about 40 nm long containing 2 polypeptide chains. These molecules are bound head to tail forming filaments that run over the actin subunits alongside the outer edges of the groove between the twisted actin strands.

Troponin is a complex of 3 subunits: TnT, which strongly attaches to tropomyosin, TnC, which binds calcium ions, and TnI, which inhibits the actin-myosin interaction physically preventing myosin binding to actin.

In thin filaments each tropomyosin molecule spans 7 G-actin molecules and has one troponin complex bound to its surface.

CONTROL OF MUSCLE CONTRACTION



Tropomyosin is a long rod-like protein that winds around an actin filament to stabilize and stiffen it.

The troponin complex which regulates the binding of actin to myosin, is attached to tropomyosin and composed of three separate polypeptides termed troponin T, I and C. Troponin T binds complex to tropomyosin and positions the complex on the actin filament at the site where actin would bind to myosin. Troponin I physically prevents myosin binding to actin. Troponin C binds Ca++ ions which cause a confrontational change in the troponin complex, allowing myosin access to the actin filament.

ACCESSORY PROTEIN OF MUSCLE

Actinin holds actin filaments in a lattice arrangement in the Z disk. Other Z disk proteins include filamin, amorphin, and Z protein.

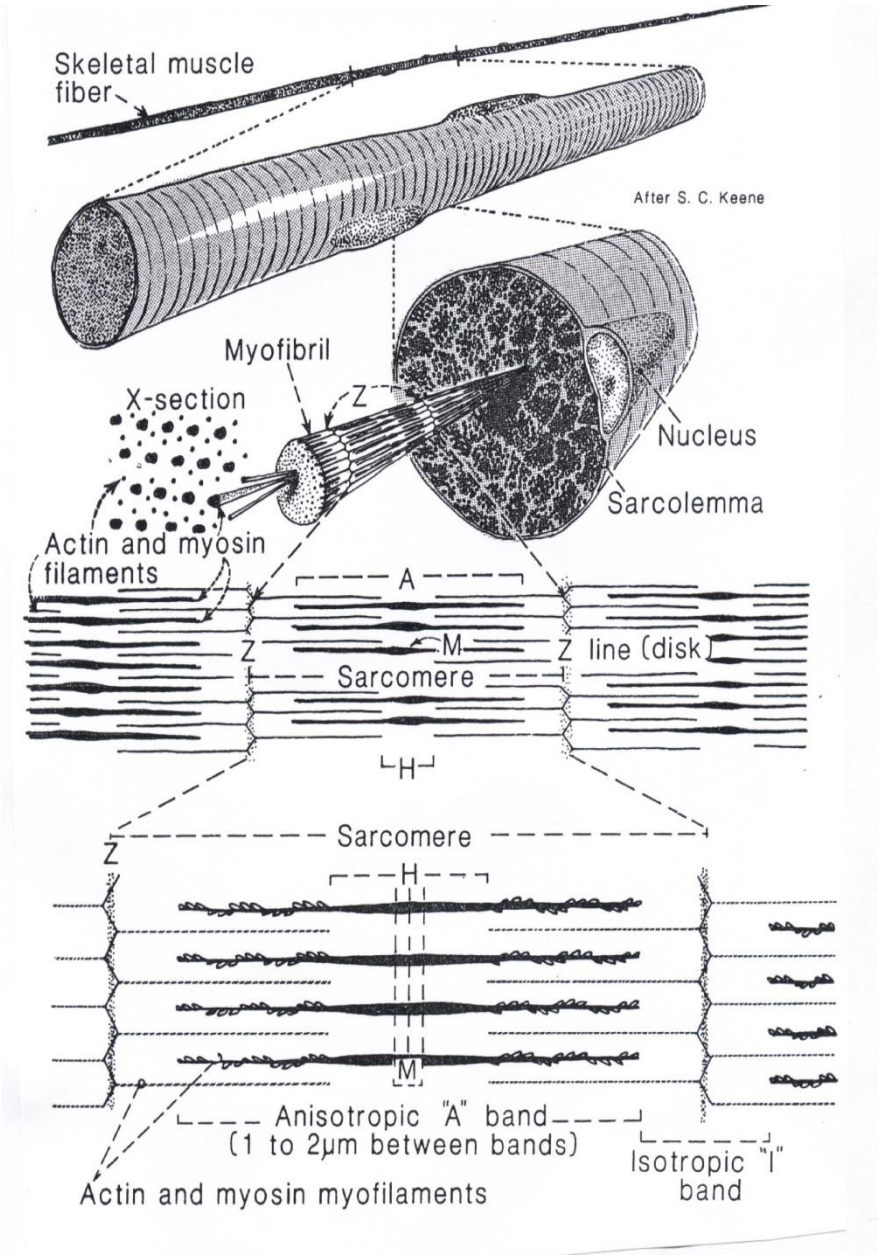
Myomesin holds myosin filaments in a lattice of arrangement in the region of the M line. Current models of the M line lattice suggest that additional, as yet uncharacterized proteins are also involved.

Titin (connectin) is an extremely long elastic protein, which runs parallel to the filament array and links the ends of the thick filaments to the Z disk, maintaining their ends in register with the lattice of thin filaments.

Desmin filaments (one of the class of intermediate filament proteins) link adjacent myofibrils to each other and maintain their register. In addition, they link myofibrils to the cell membrane.

C protein is a myosin-binding protein localized in seven stripes running parallel to the M band in the first half of the A band.

HISTOPHYSIOLOGY OF SKELETAL MUSCLE



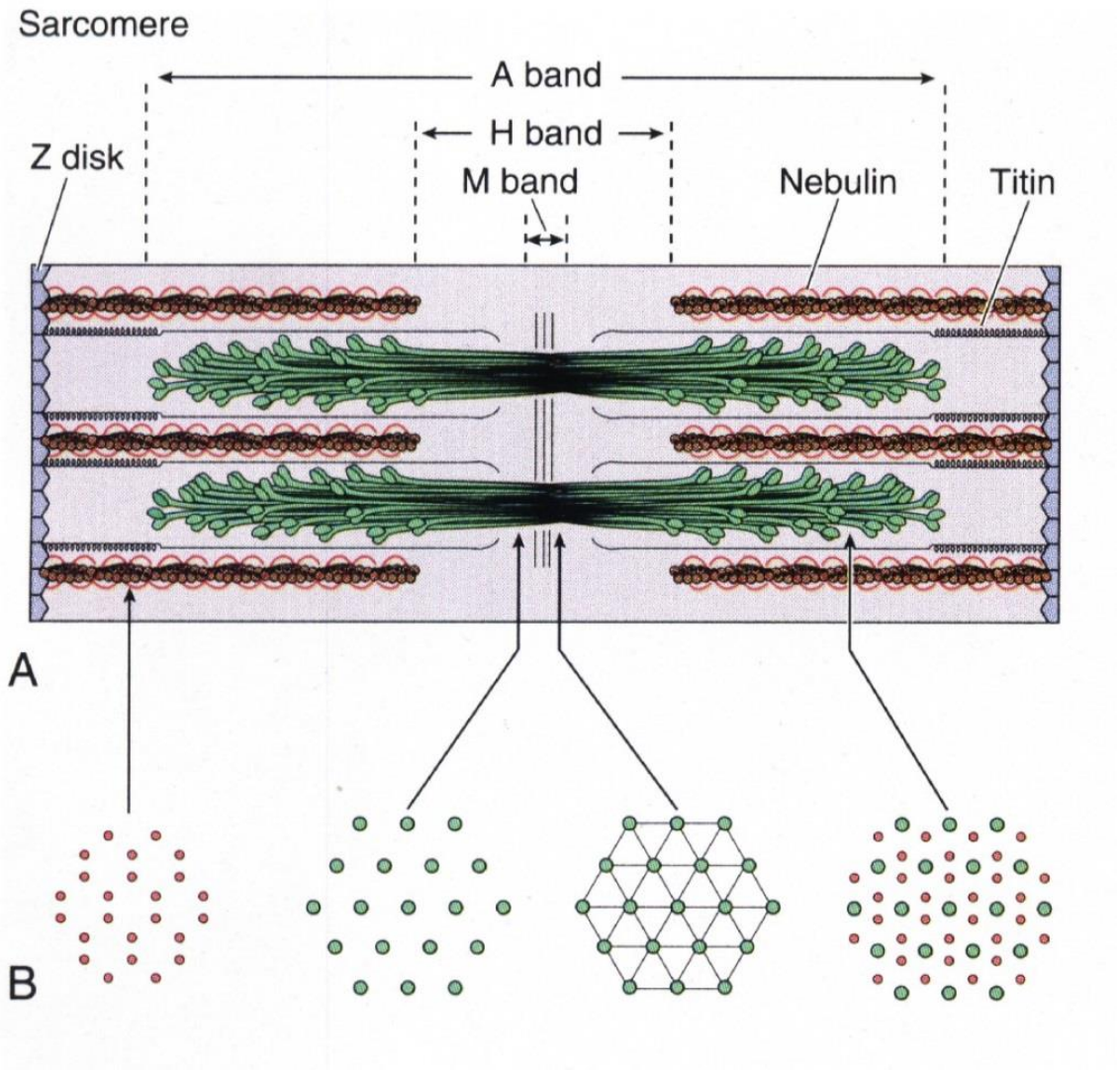
<u>Thick filaments are mainly formed from myosin.</u>

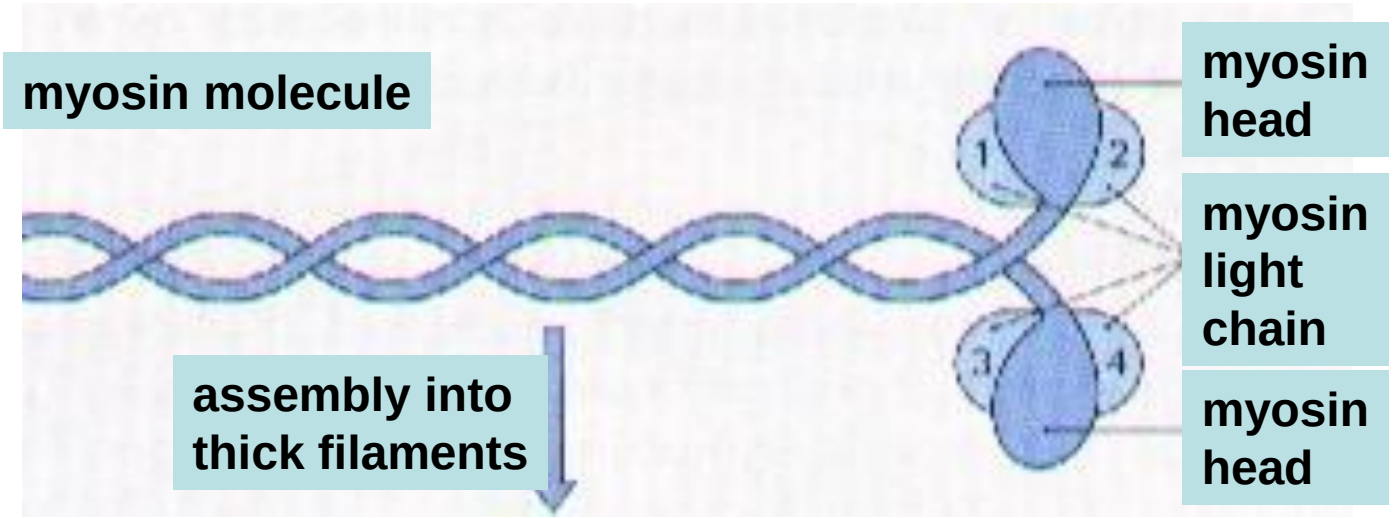
Thick filaments are composed mainly of the protein myosin.

Like actin filament, the myosin filament is polar. To form a complete heavy filament, two myosin filaments become attached by their tail ends so that they face in opposite direction (away from the M line).

Different molecular types (isoforms) of myosin are present in different types of skeletal muscle fiber.

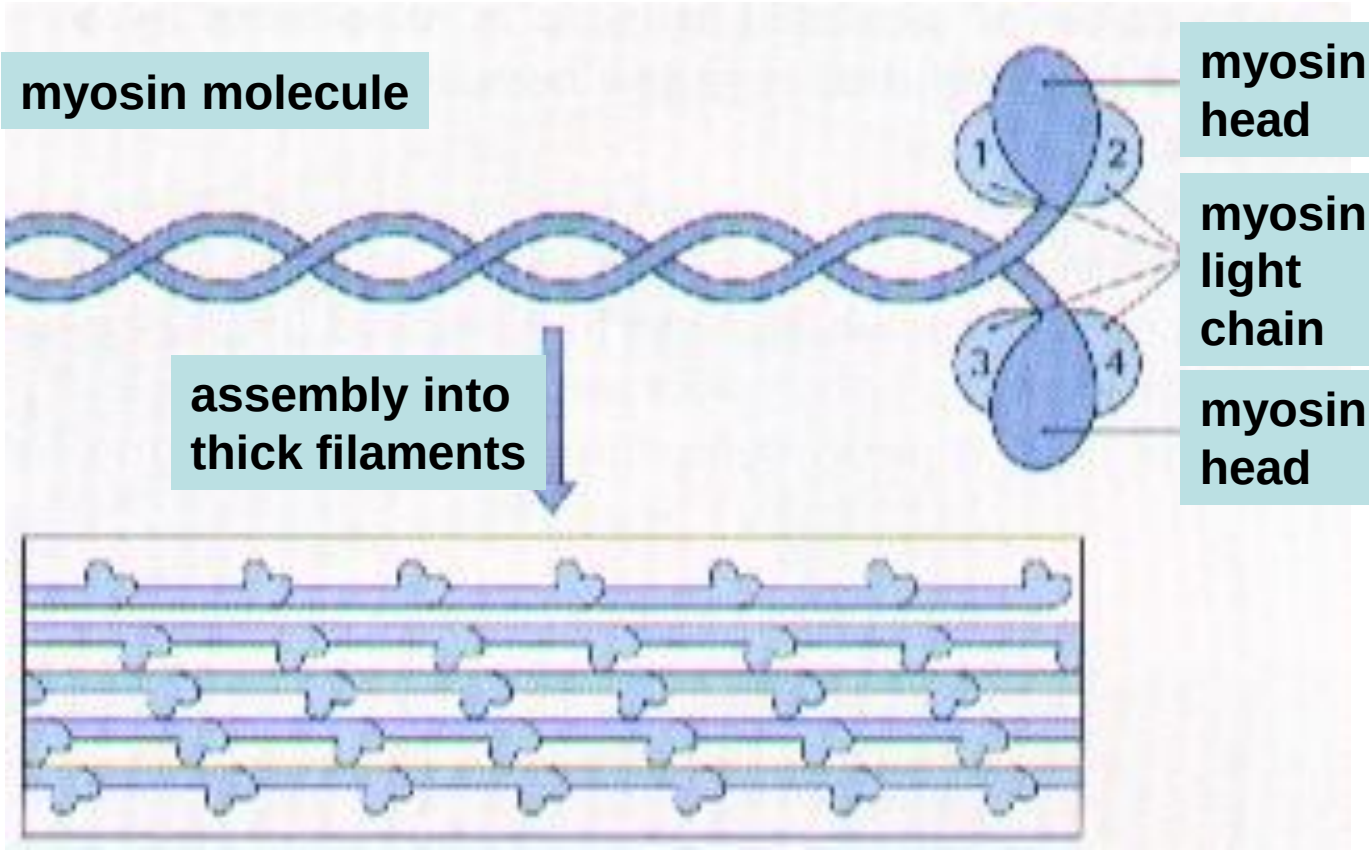
HISTOPHYSIOLOGY
OF SKELETAL MUSCLE





Myosin Molecule

Each myosin molecule is composed of two tad-pole shaped heavy chains, the tails of which coil around each other with four small light chains attached to the head portions. Thick filaments are composed of myosin molecules aligned end to end. Every thick filament consists of 200 to 300 myosin molecules.



Myosin Molecule

The coiled rod-like tail portion of many myosin molecules aggregate and pack together in a regular staggered array to form the filament, while the head portions project out in a regular helical pattern.

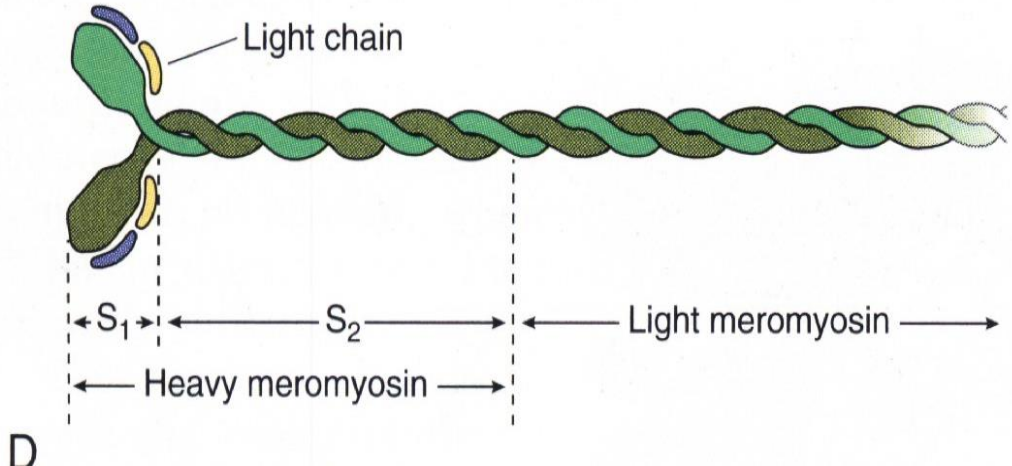
THICK FILAMENTS OF SKELETAL MUSCLE FIBER

Each myosin molecule is composed of two identical heavy chains and two pairs of light chains. The heavy chains resemble two golf clubs whose rod like polypeptide chains are wrapped around each other in an alpha-helix.

The heavy chains can be cleaved by tripsin into:

1.Light meromyosin, a rod-like tail composed of most of the two rod-like polypeptide chains wrapped around each other.
2.Heavy meromyosins, the two double heads with the attendant short proximal portions of the two rod-like polypeptide chains wrapped around each other.

The light meromyosin functions in the proper assembly of the molecules into the bipolar thick filament. Heavy meromyosin consists of two globular moieties (S1) and short helical rod-like segment (S2). S1 subfragment binds ATP and functions in the formation of cross-bridges between the thick and thin filaments. Light chains (not to be confused with light meromyosin) are of two types, and one of each type is associated with each S1 subfragment of myosin molecule. For each heavy chain therefore, there are 2 light chains, and a whole myosin molecule is composed of two heavy chains and four light chains.



MYOSIN MOLECULE

Myosin molecules are closely packed in a specific fashion in the thick filament. They are lined up in a parallel but staggered manner, spaced at regular intervals, lying arranged head to tail, so that the middle of each thick filament is composed solely of tail regions whereas the two ends of the thick filament consist of both heads and tail. The special orientation of the myosin molecules permits the heavy meromyosin portion to project from the thick filament at a 60-degree angle relative to neighboring heavy meromyosin, so that the head regions are always in register with the thin filaments.

Each myosin molecule appears to have two flexible regions, one at the junction of the heavy meromyosin with the light meromyosin, which permit each myosin molecule to contact the thin filament, and the other at the junction of the S1 and S2 subfragments, which enables the myosin molecule to drag the thin filament, incrementally, toward the middle of sarcomere.

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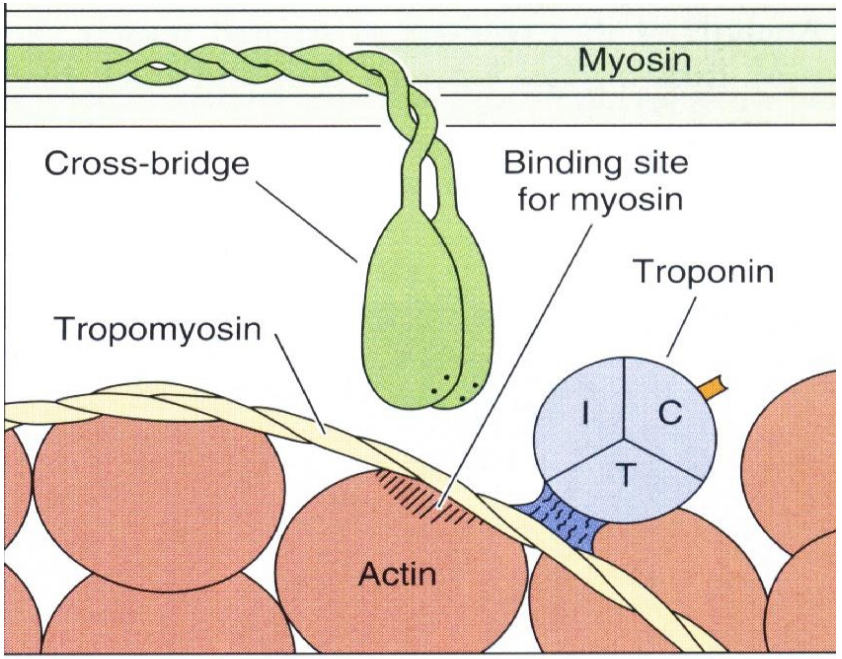
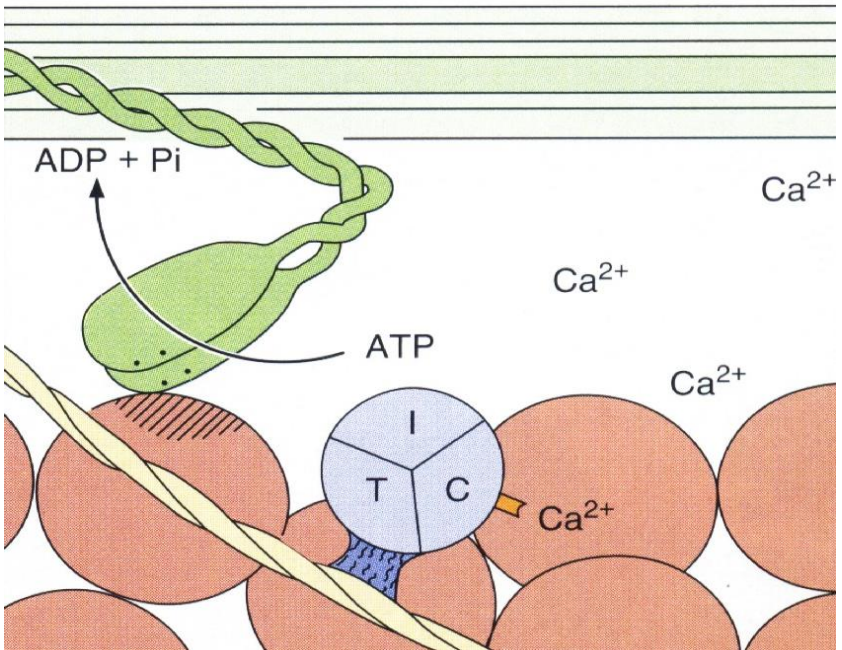
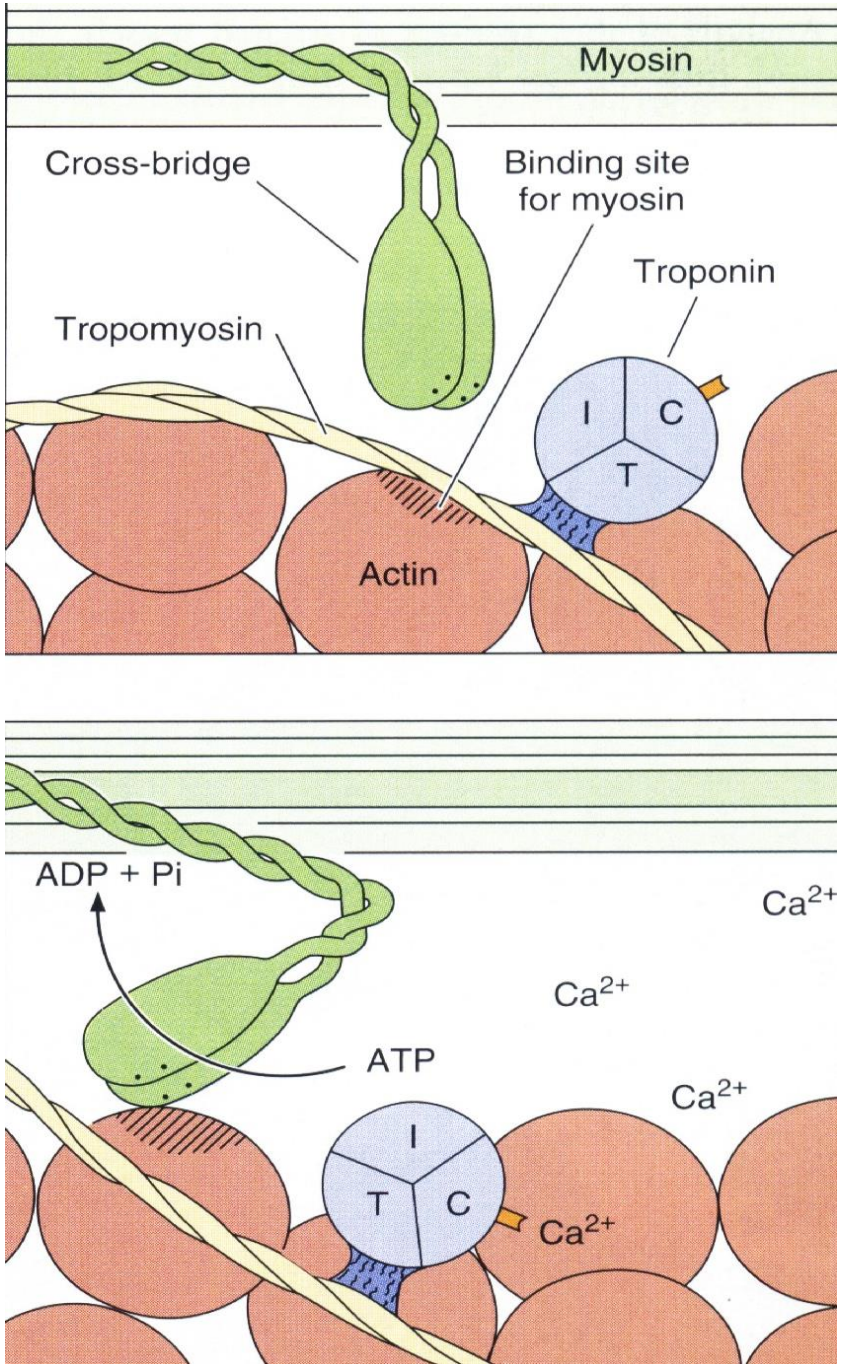


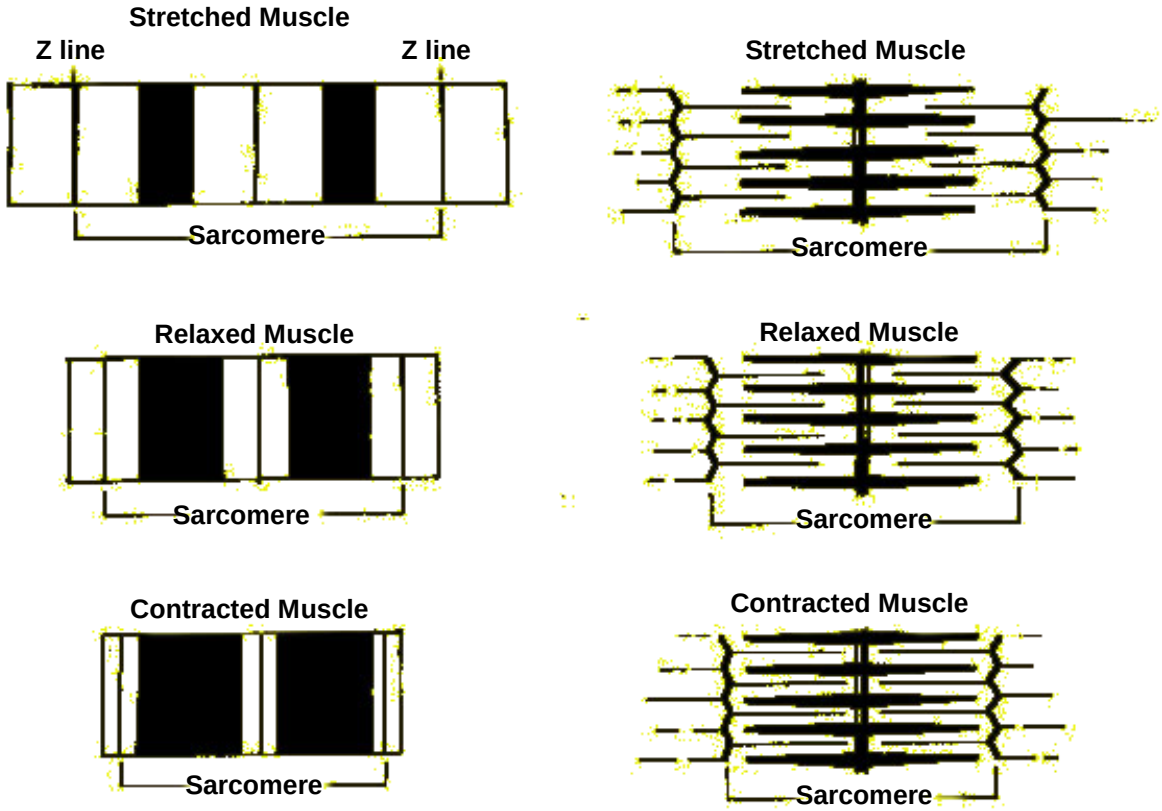


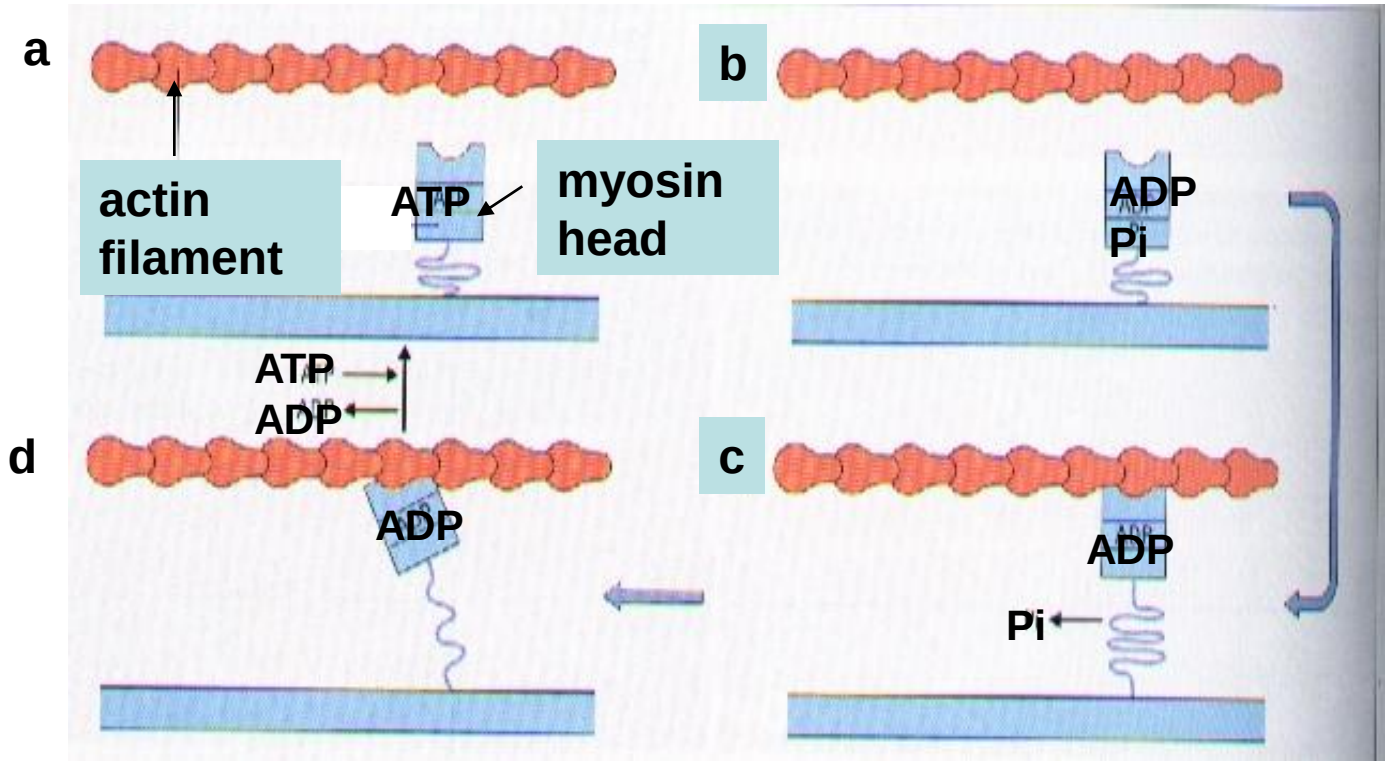
Muscle contraction is initiated by the binding of Ca++ to the TnC unit of troponin, which exposes the myosin binding site on actin (cross-hatched area). In a second step, the myosin head binds to actin and the ATP breaks down into ADP, yielding energy which produces a movement of a myosin head. As a consequence of this change in myosin the bound thin filaments slide over the thick filaments. This process which repeats itself many times during a single contraction leads to a complete overlapping of the actin and myosin and a resultant shortening of the whole muscle fiber.



MUSCLE CONTRACTION

During contraction individual thin and thick filaments do not shorten, instead the two Z-discs are brought closer together as the thin filaments slide past the thick filaments (Huxley's sliding filament theory). Thus when contraction occurs, the motion of the thin filaments toward the center of the sarcomere creates a greater overlap of between the two groups of filaments, effectively reducing the width of the I and H bands (deriving thin filaments in relaxed condition) without influencing the width of the A band.



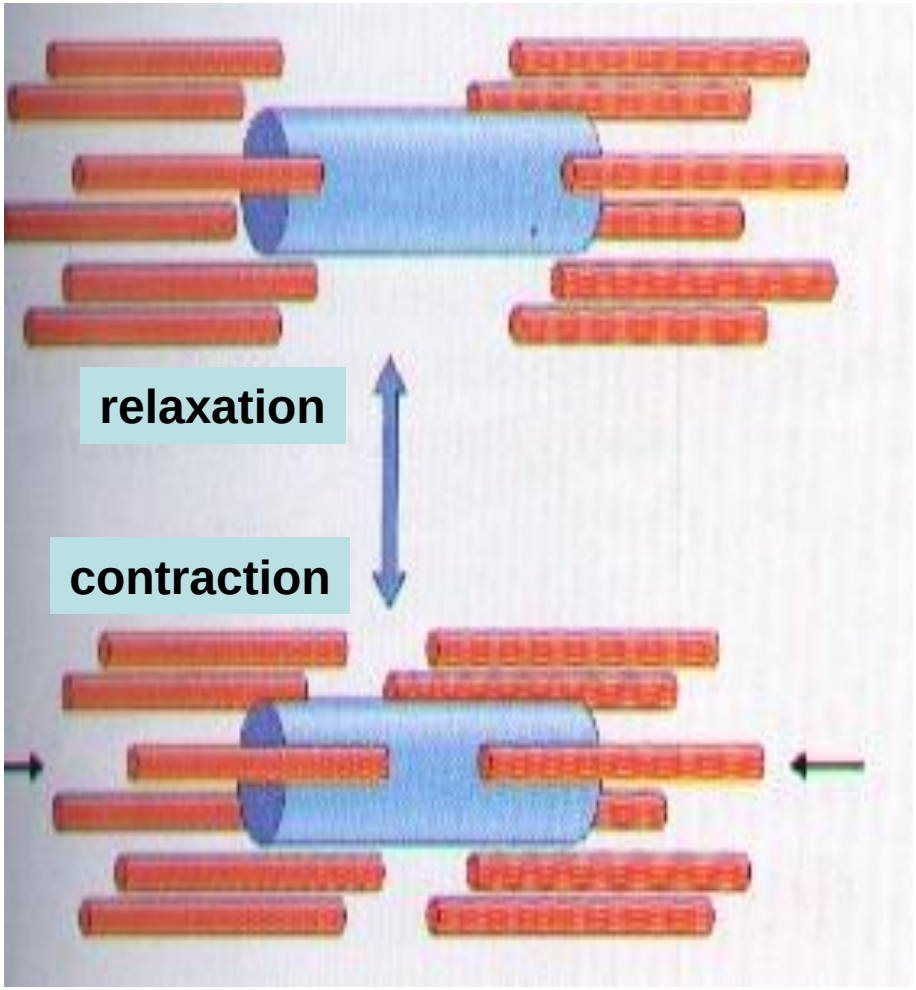


USE OF ATP BY MYOSIN BINDING TO ACTIN

A myosin molecule uses the energy of ATP to move along an actin filament.

a) **ATP bound to myosin is hydrolyzed to ADP and phosphate (Pi).**
b) **This causes myosin to bind loosely to actin.**
c) **Pi is released and myosin binds tightly to actin.**
d) **This binding initiates molecular folding of the myosin molecule to cause the movement of the molecule relative to the actin filament. ADP is released, fresh ATP binds, and the myosin returns to its non-attached state.**

The cycle repeats and the myosin head "walks" along the actin filament.



Muscle Contraction

During muscle contraction the thin filaments of the myofibrils slide over the thick filaments. This is reversed in muscle relaxation.

Contraction effectively reduces the resting length of the muscle fiber by an a amount which is equal to the sum of all shortenings that occur in all sarcomeres of that particular muscle fiber. According to the all-or-non law a single muscle fiber either contracts or does not as a result of stimulation.

The following sequences of events leads to contraction in skeletal muscle.

1. An impulse generated along the sarcolemma, is transmitted into the interior of the fiber via T-tubules, where it is conveyed to the terminal cisternae of the SR.
2. Ca++ ions leave the terminal cisternae through voltage-gate calcium release channels, enter the cytosol, and bind to the TnC subunit of troponin, altering its conformation.
3. Conformational change in troponin shifts the position of tropomyosin deeper into the groove, unmasking the active site (myosin binding site) on the actin molecule.
4. ATP present on S1 subfragment of myosin is hydrolyzed, but both ADP and inorganic phosphate remain attached to the S1 subfragment, and the complex binds to the active site on actin.
5. Inorganic phosphate is released, resulting not only in a greater band strength between the actin and myosin, but also in a conformational alteration of the S1 subfragments.
6. ADP is also released, and the thin filament is dragged toward the center of the sarcomere (“power stroke”).
7. A new ATP molecule binds to the S1 subfragment, causing the release of the bond between actin and myosin.

The attachment and release cycles must be repeated numerous times for contraction to be completed.

Each attachment and release cycle requires ATP for the conversion of chemical energy into mechanical energy of motion.

The force of muscle contraction is transmitted to the extracellular matrix by a series of link proteins.

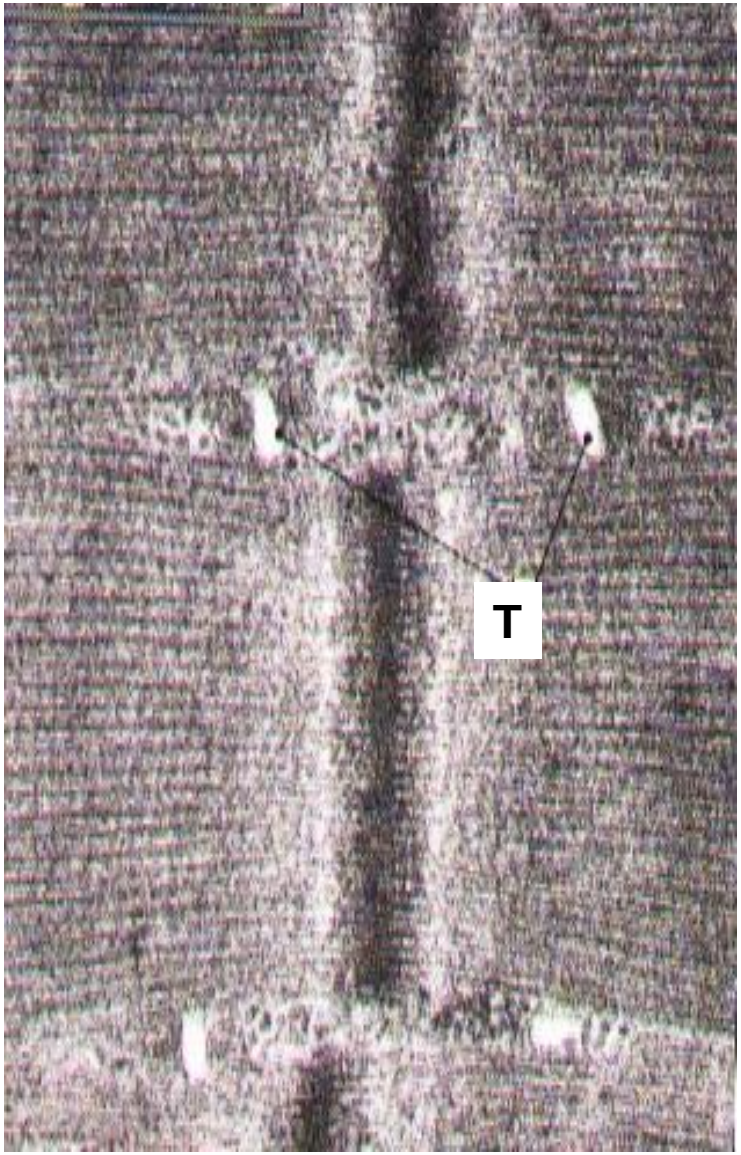
The cytoskeleton of each skeletal muscle fiber is linked to the external lamina by a series of link molecules.

Actin filaments inside the cell are linked to the protein distrophin. Distrophin then links with a complex composed of several glycoproteins that bridge through the muscle cell membrane to the cell surface. On the outer surface of the muscle cell the glycoprotein complex links to the protein merosin, which is a laminin component of the basement membrane. In this way forces generated inside the muscle are transferred to the extracellular matrix in the external lamina.

If there is a genetic absence of one of the linking proteins then muscle fibers are prone to undergo tearing on contraction and the affected person develops one of the many forms of muscular dystrophy.

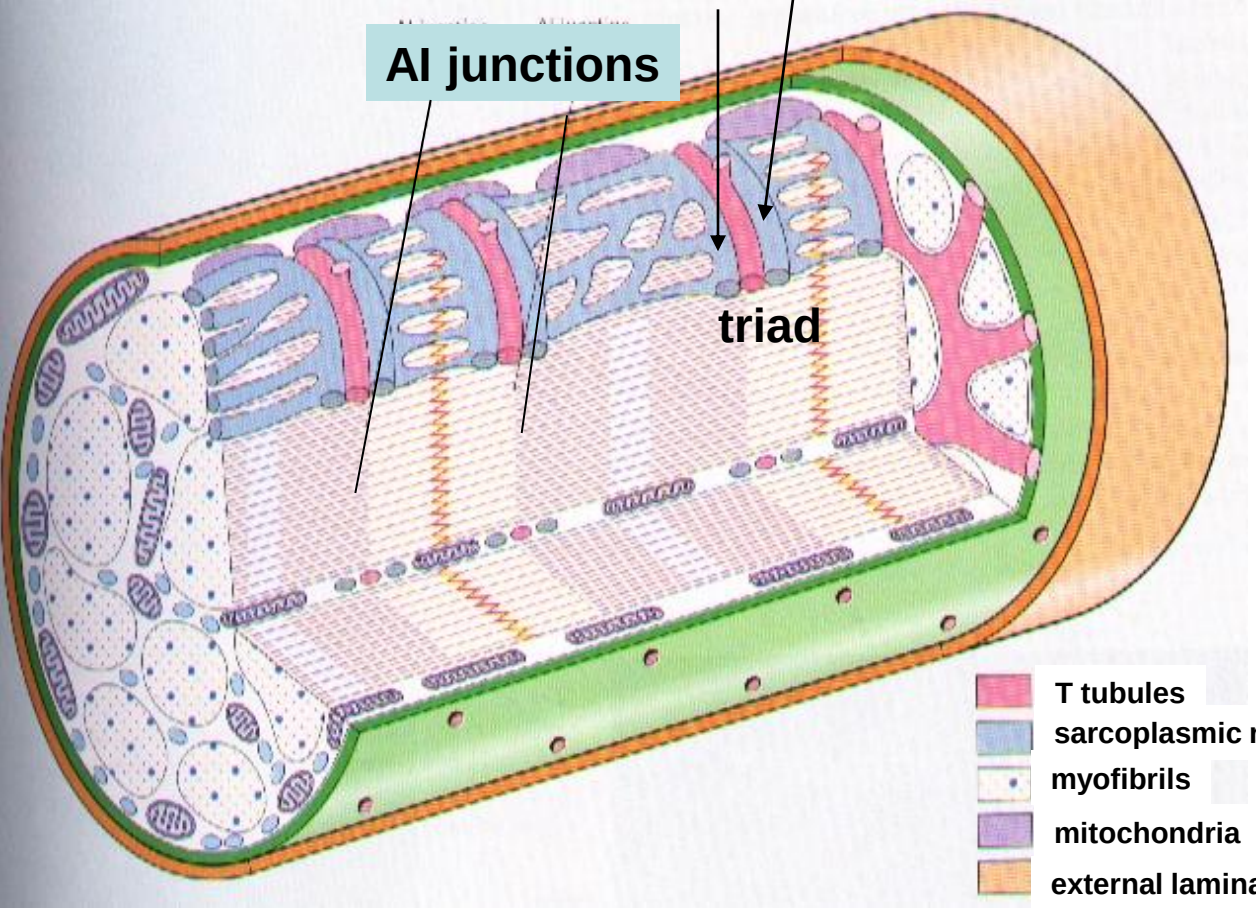
It is being increasingly recognized that the different form of muscular dystrophy can be related to defects in structural proteins in the muscle fibers, for example Duchenne dystrophy.

SKELETAL MUSCLE, TEM



Following a nerve signal, excitation of the muscle cell membrane is conveyed to the interior of the cell via a series of membranous channels (the transverse tubular system of T tubules) which extend from the muscle surface to surround each myofibril.

The T-tubule is seen as a small open tube (T) and on each side are extensions of sarcoplasmic reticulum. In humans SR contains electron-dense material making these relatively indistinct structures rather prominent.



MUSCLE CELL EXCITATION

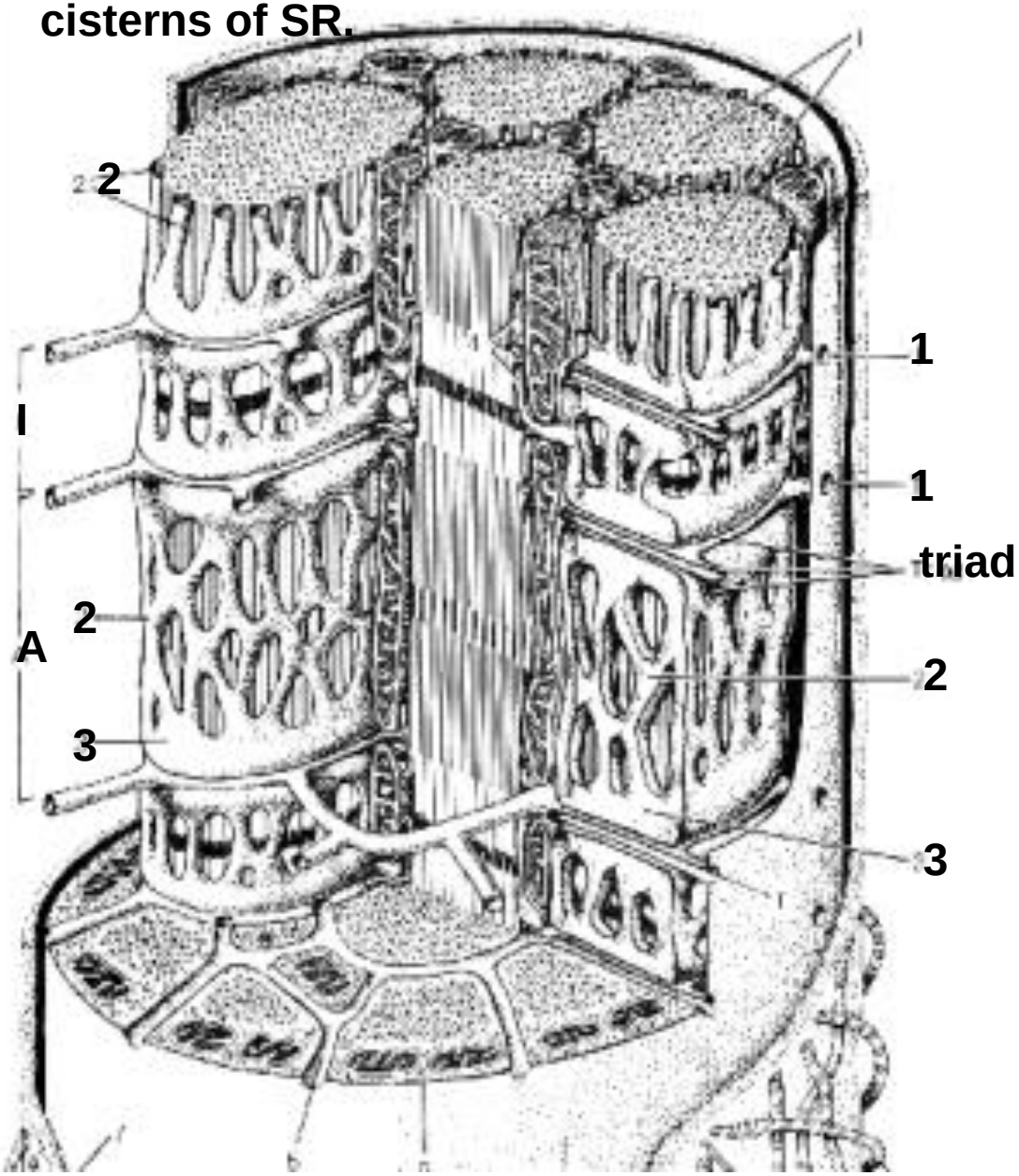
Running alongside each T tubule are two portion of SR, called terminal cisternae (arrows), which contain a high concentration of Ca++ ion channel and have electrically sensitive Ca++ ion channels in their wall. In human nuscle there is a membrane triad surrounding every myofibril in the AI junction region; thus there are two triads to each sarcomere.

Membrane excitation of the T tubule system causes these Ca++ ion channels to open, thus allowing Ca++ ions to flood in to sarcoplasm.

In resting state muscle cells have little intracellular free Ca++ ions, and a sudden increase in free cytosolic Ca++ ions initiates muscle contraction.

Membrane pumps (Ca++-ATPase) in the SR pump the Ca++ ions back into the SR rapidly (within about 30ms) and stop contraction. The close association of T tubules and SR form three tubules in cross-section (a membrane triad).

T-tubules run adjacent to the terminal cisterns of SR.



SKELETAL MUSCLE STRUCTURE

Coordination of contraction is achieved by invaginating T-tubules (1) of the sarcolemma that carry the depolarization to all the regions of the muscle nearly-simultaneously.

Tubular invaginations (T-tubules) of the muscle cell membrane penetrate deep into sarcoplasm and surround myofibrils in such a manner that at the junction of each A and I band these tubules become associated with the dilated terminal cisternae (3) of the sarcoplasmic reticulum (2) (smooth ER) forming triads.

Triads of two lateral cisterns flanking one T-tubule can be seen – this is where the depolarization of the sarcolemma triggers Ca++ release by the SR.

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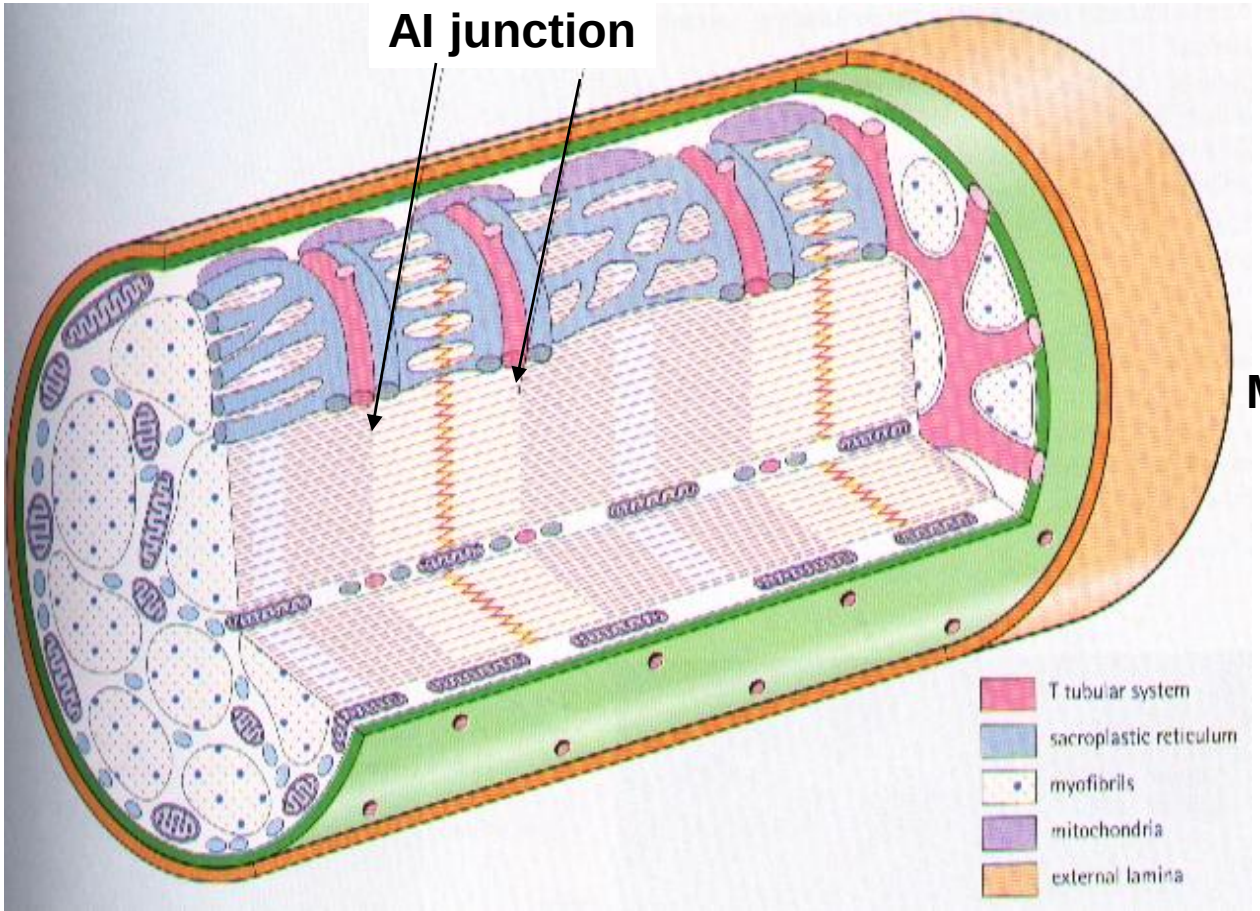
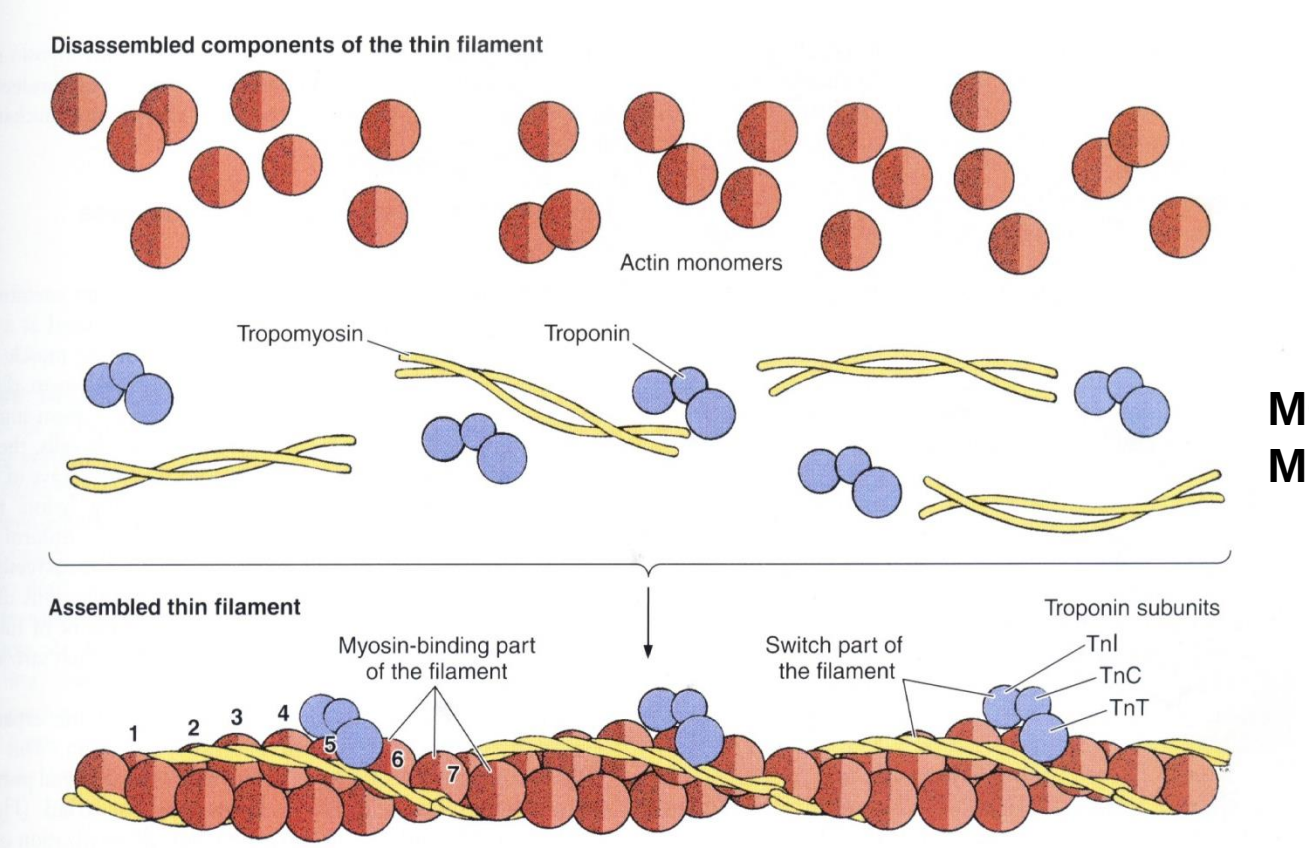


MUSCLE CONTRACTION

The following sequences of events leads to contraction in skeletal muscle.

3.Conformational change in troponin shifts the position of tropomyosin deeper into the groove, unmasking the active site (myosin binding site) on the actin molecule.



MOLECULAR BIOLOGY OF MUSCLE CONTRACTION

The following sequences of events leads to contraction in skeletal muscle.

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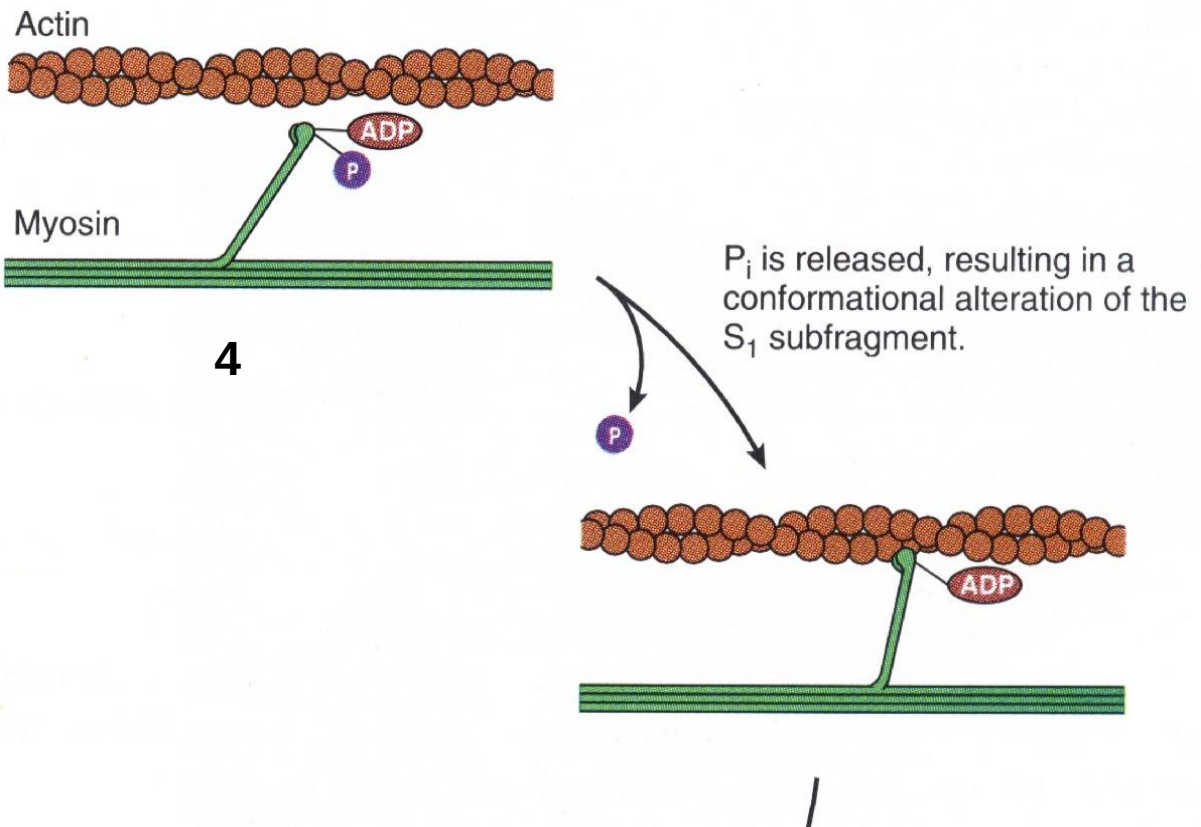
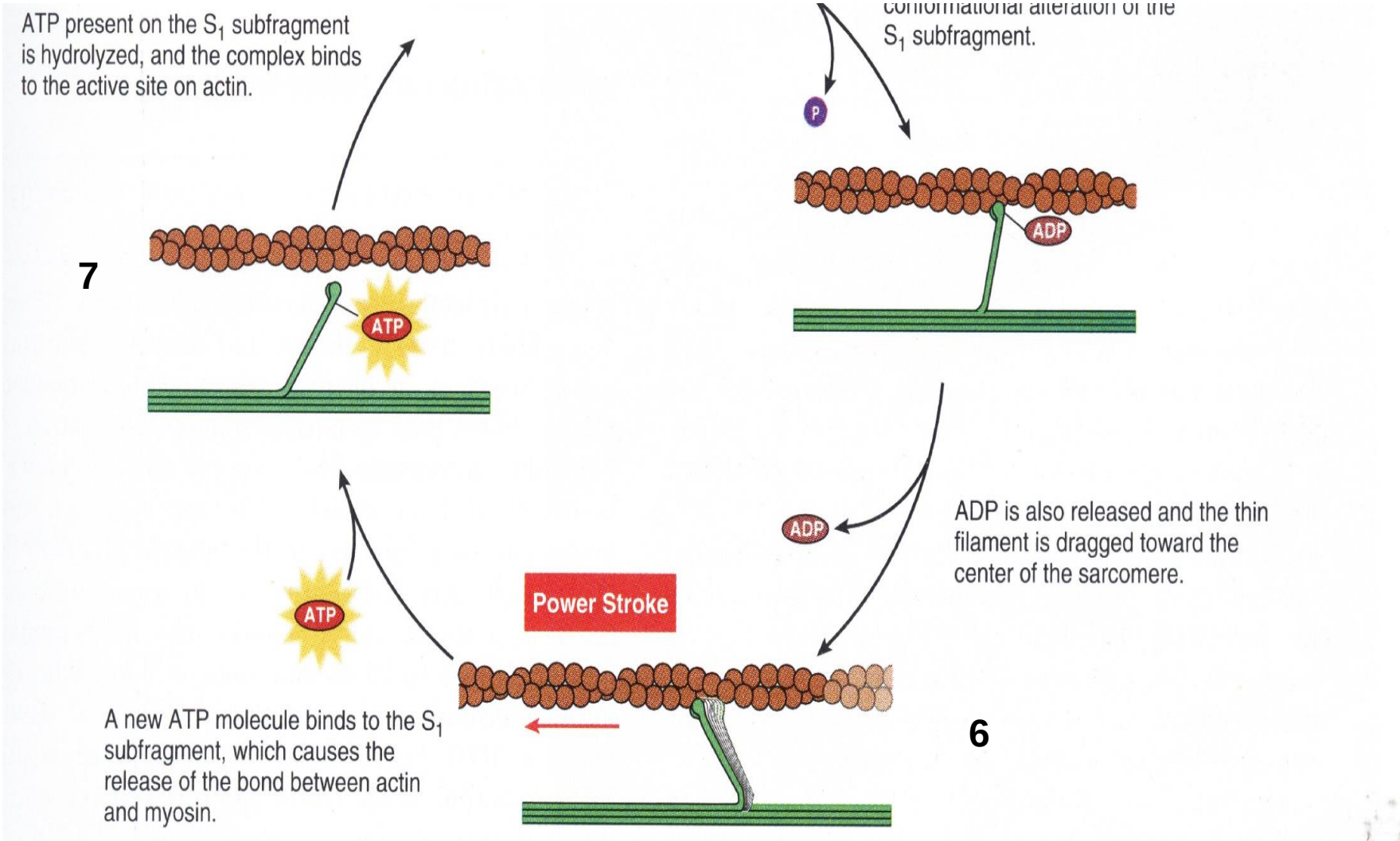
MOLECULAR BIOLOGY OF MUSCLE CONTRACTION



6.ADP is also released, and the thin filament is dragged toward the center of the sarcomere (“power stroke”).
7.A new ATP molecule binds to the S1 subfragment, causing the release of the bond between actin and myosin.

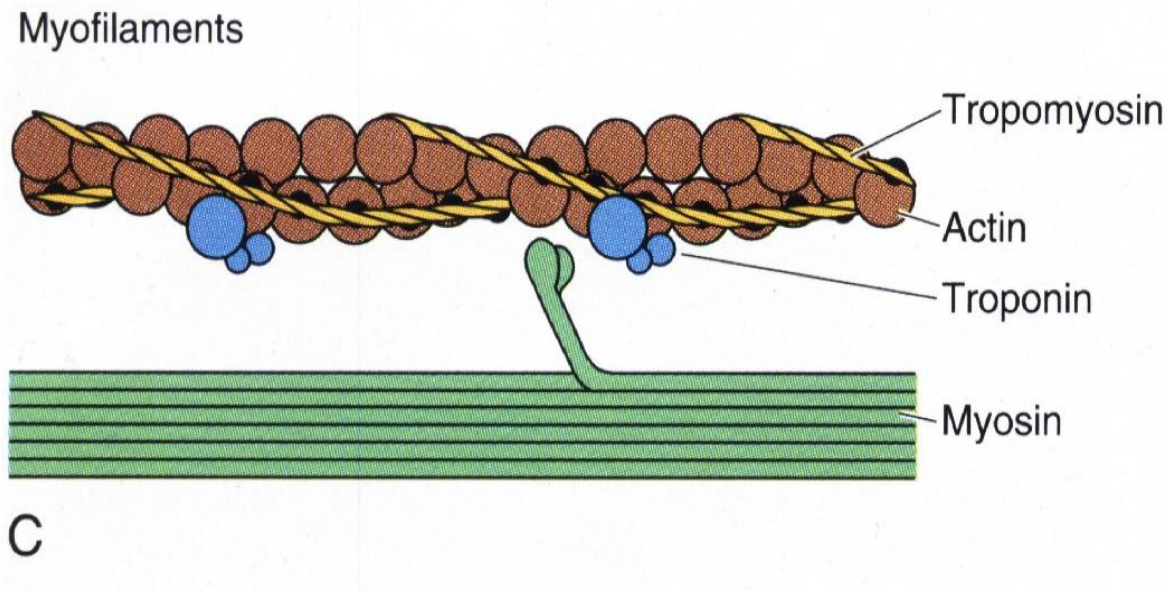
MOLECULAR BIOLOGY OF MUSCLE CONTRACTION



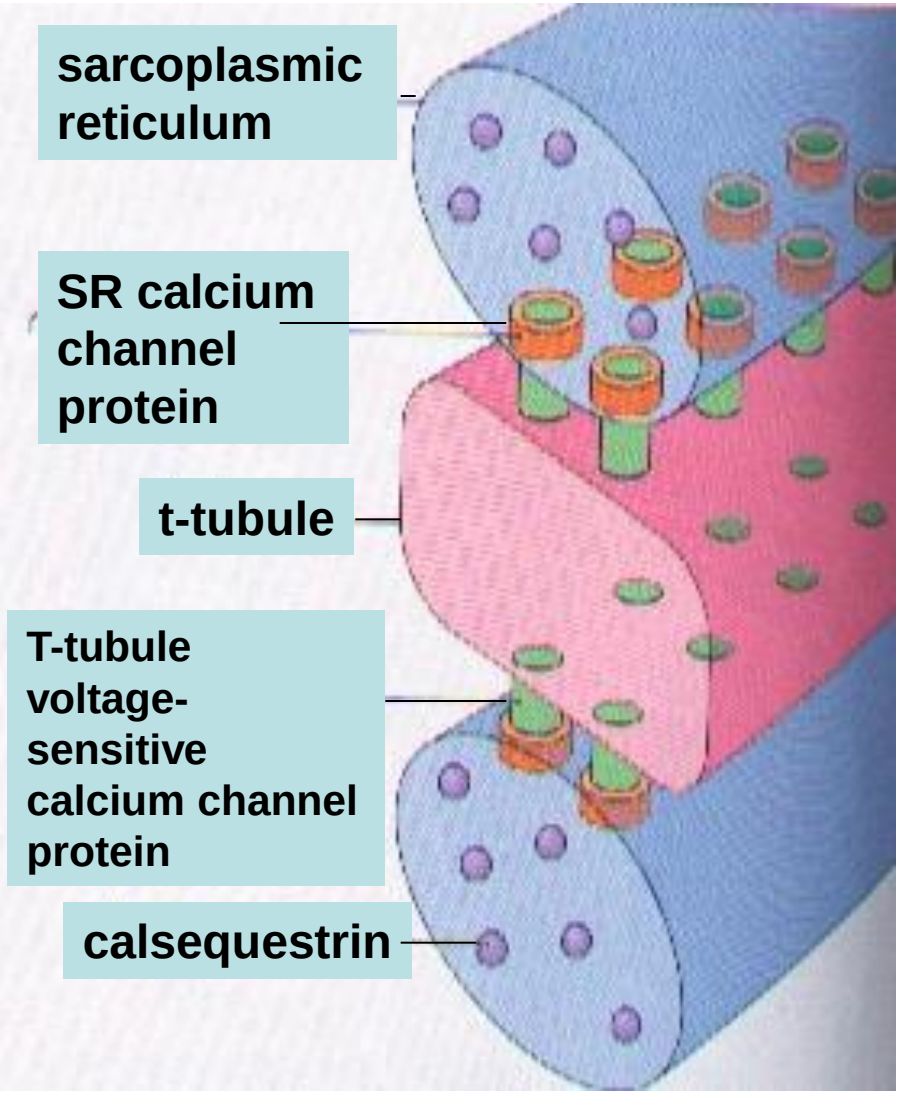
SKELETAL MUSCLE CONTRACTION

The attachment and release cycles must be repeated numerous times for contraction to be completed.

Each attachment and release cycle requires ATP for the conversion of chemical energy into mechanical energy of motion.



SKELETAL MUSCLE TRIAD



The SR Ca++ channel protein lines up with the Ca++ channel protein in the T-tubular system. Depolarization of the T-tubular system causes opening of the SR calcium channels. Calcium which is held in the SR lumen by calsequestrin, can then be released into the muscle cytoplasm.

SKELETAL MUSCLE:

- Each muscle fiber is surrounded by an external lamina.
- Striated muscle is based on close alignment of actin and myosin filaments.
- Actin is arranged as thin filaments anchored to the Z line.
- Myosin is arranged as thick filaments anchored to the M line.
- Membrane triads couple membrane excitation to calcium release into the cytoplasm.
- Cytosolic calcium regulates contraction.

TYPES OF SKELETAL MUSCLE FIBERS

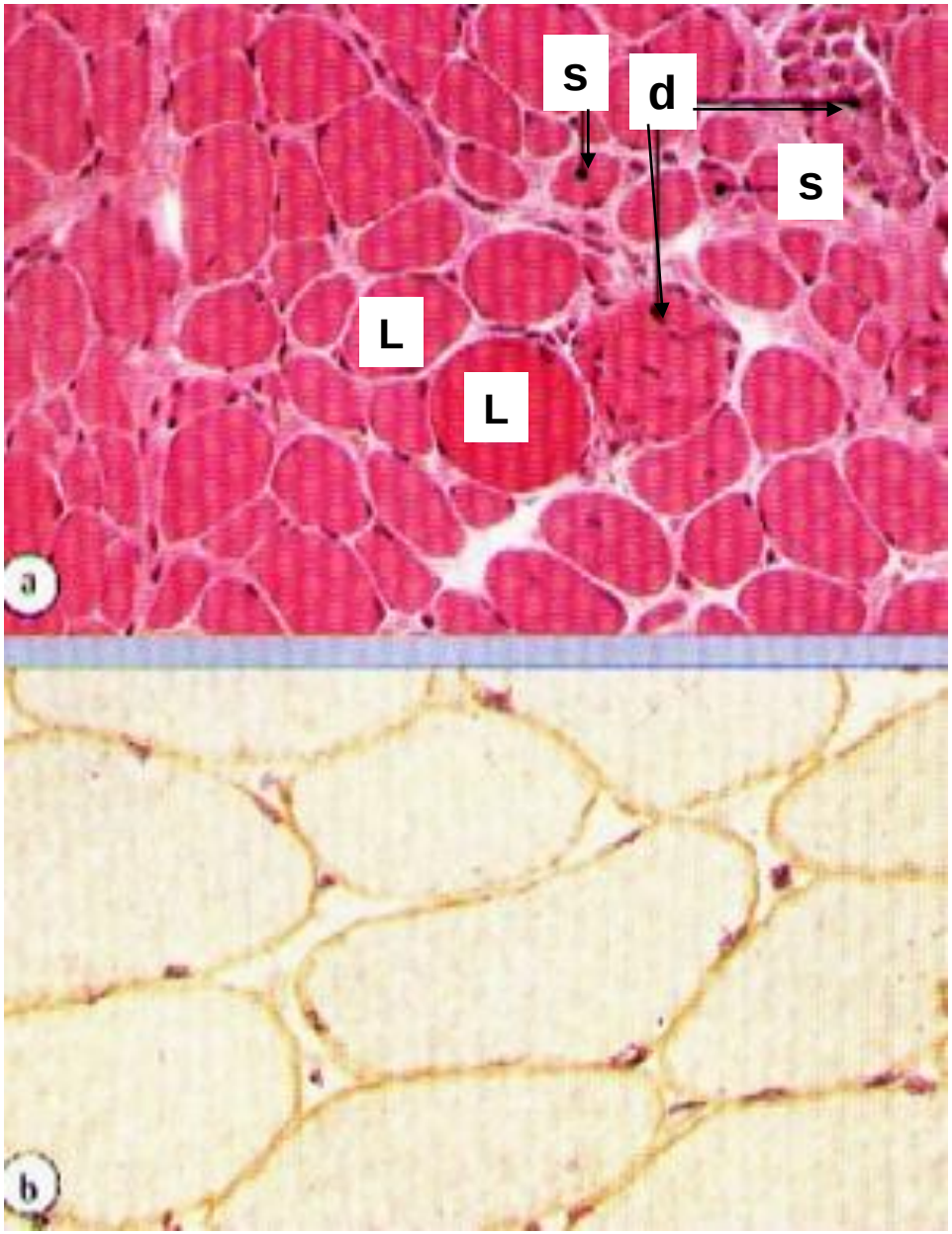
Distinguishing characteristics	*Type I (red or slow)*	*Type II (white or fast)*
Fresh gross appearance	Dark red due to rich blood supply, large amount of myoglobin, and abundant large mitochondria	Whitish grey color due to less blood, less myoglobin, and fewer mitochondria
Location	Perhaps in all muscles but predominate in slow-fatiguing, postural (antigravity) muscles, e.g., soleus m.	In all muscles; however, concentrated in easily fatigued, fast-acting muscles, e.g., gastrocnemius m.
Blood supply	Greater	Lesser
Average diameter	Smaller (27 μm rat diaphragm)	Larger (44 μm rat diaphragm)
Neuromuscular junctions	Smaller with shallow functional folds	Larger with deep functional folds
Myofibrils	Less numerous and poorly defined, cross striations less regular	More numerous and clearly defined, cross striations regular and prominent
Z lines	Thicker	Narrower (about half as wide)
Nuclei	Maybe scattered throughout fiber, not always hypolemmal in position	Hypolemmal in position
Sarcoplasm	Granular, large amount	Less granular, lesser amount
Mitochondria	Larger size and numbers, concentrated on periphery of fiber and between myofibrils; have closely packed, abundant cristae	Smaller, sparse; no pattern of accumulation; fewer cristae
Sarcoplasmic reticulum	Complex especially near H band	Simpler
Myoglobin	Abundant	Less abundant
Glycogen	Lesser amount	Greater amount
Oxidative enzymes	Abundant	Less abundant
Myofibrillar ATPase activity	Low	High
Maturation	Less mature	More mature
Respiratory activity	High	Low

DISEASES of MUSCLE

Several diseases of muscle have been attributed to special metabolic or structural abnormalities.

Duchenne muscular dystrophy is the most common inherited muscle disease and characteristically affects male children. Such individuals become unable to stand unaided in early childhood and develop progressive muscle weakness, becoming wheel-chair-bound by their midteens and typically dying in early adult life. The abnormality in Duchenne muscular dystrophy is due to a defect in the gene coding for a protein termed distrophin. This protein links actin to the external lamina, its absence leads to abnormal muscle fiber fragility.

CLINICAL CORRELATIONS



a) Skeletal muscle from a child showing the typical appearance of dystrophy, which is a congenital primary disorder of muscle. There is marked variation in fiber size, with some large fibers (L) and some abnormally small fibers (S). Some fibers are dead (D) and are being removed by phagocytic cells.

b) Normal skeletal muscle stained immunohistochemically for distrophin (which stains brown), showing its localization in the sarcolemma. In Duchenne muscular dystrophy this protein is absent.

SKELETAL MUSCLE

-Are composed of organized packets of striated muscle cells,
-Most muscles contain a mixture of different muscle cell types, according to the function of the muscle as a whole,
-Muscle cell types are type I (slow twitch), type 2A (fast twitch, fatigue-resistant), and type 2B (fast twitch, fatigue-sensitive),
-Individual muscle cells are incapable of regeneration by cell division, but a stem cell population of resting satellite cells is available partly to replenish muscles with functional contractile units after damage,
-Are dependent on nervous stimulation through motor end plates for contractile function and maintenance of structure.

SKELETAL MUSCLE FIBER TYPES

fiber type	metabolism	contractile behavior
I	oxidative	slow twitch
2A	oxidative & glycolytic	fast twitch, fatigue resistant
2B	glycolytic	fast twitch, fatigue sensitive

SKELETAL MUSCLE. FUNCTIUONAL CORRELATIONS.

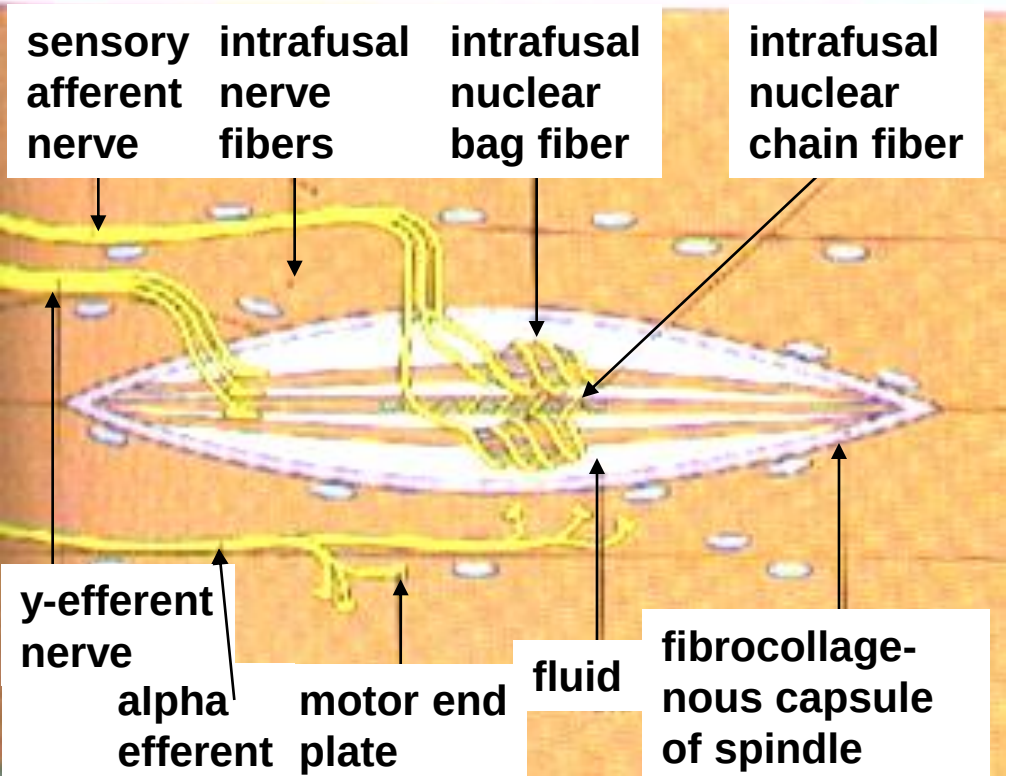
In skeletal muscle individual muscle cells are arranged into large groups to form anatomically distinct muscles. These are characterized by:

- **an orderly alignment of the constituent cells to generate a directional force following contraction,**
- **anchorage to other structures by highly organized fibrocollagenous support tissue,**
- **a rich blood supply reflecting high metabolic demands,**
- **innervation and control by specialized neurons (motor neurons) which terminate on muscle cells at specialized nerve endings (motor end plates);**
- **incorporation of specially adapted skeletal muscle cells into structures called spindles, to act as sensors of muscle stretch.**

Skeletal Muscle: Associated Structures

Muscle spindle:
-composed of highly modified skeletal muscle fibers located within the muscle near the tendon junction,
-regulate the degree of muscle tension,
-proprioception.

Golgi tendon organs:
-sensory structures located within tendons,
-prevent overextension by triggering contraction.



Sensory Innervation of Skeletal Muscle

Sensory innervation of muscle arises from two sources: encapsulated nerve endings in the tendons respond to stretch, and spiral nerve ending in muscle spindles sense stretch and tension.

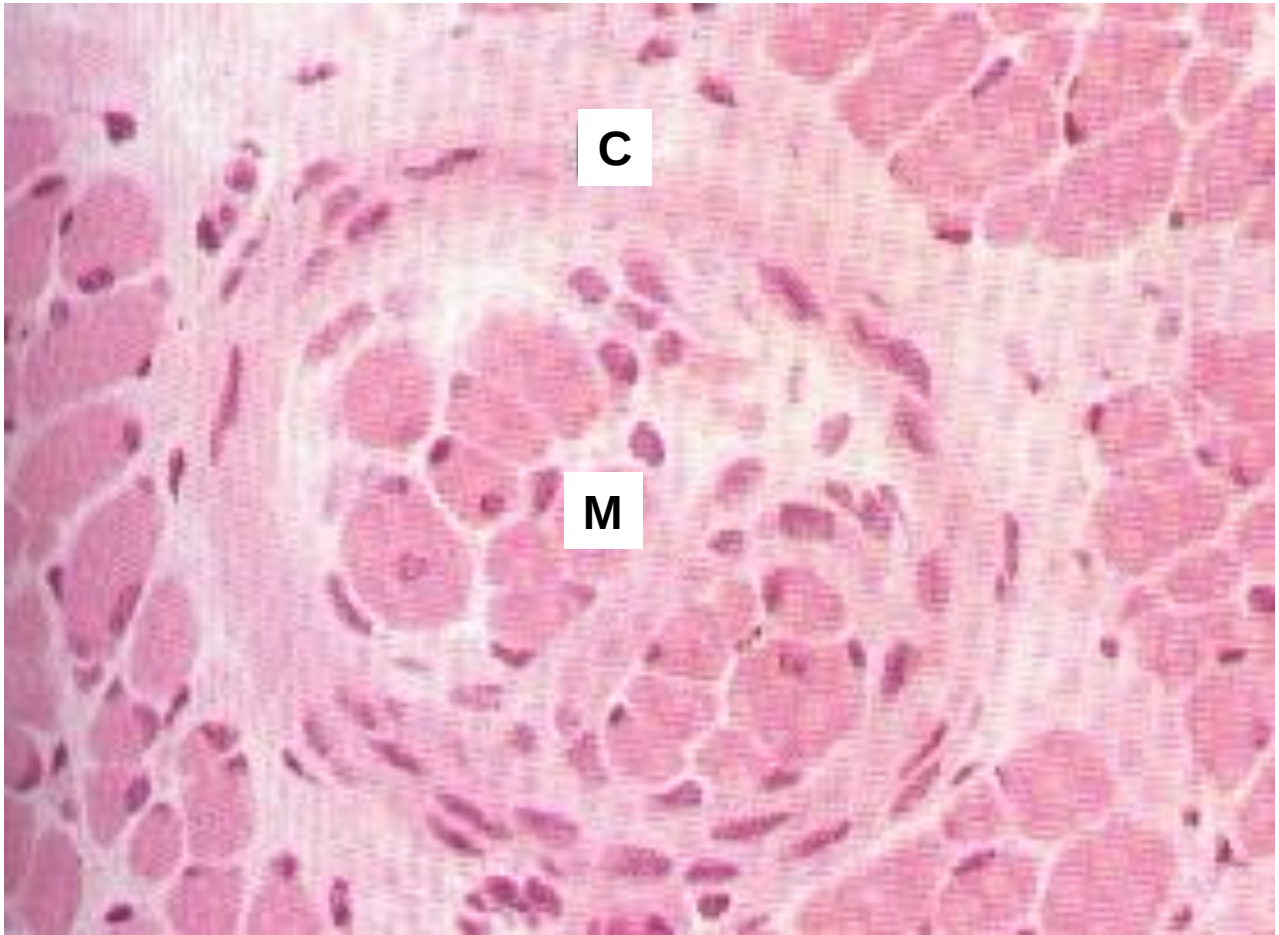
The muscle spindle is composed of fusiform capsule of fibrocollagenous tissue (continuous with perimysium) surrounding a group of 8-15 thin muscle fibers. These fibers are termed intrafusal fibers to distinguish them from normal skeletal muscle fibers (extrafusal fibers).

Two types of intrafusal fiber can be distinguished; those with a fusiform shape and central aggregate of nuclei (nuclear bag fibers) and those of uniform width with dispersed nuclei (nuclear chain fibers).

Specialized motor neuron fibers (y-efferent fibers) innervate the intrafusal fibers and adjust their length according to the state of muscle stretch, which is detected by spiral nerve endings. The latter are wrapped around the intrafusal fibers and from special sensory afferent fibers running back to the spinal cord.

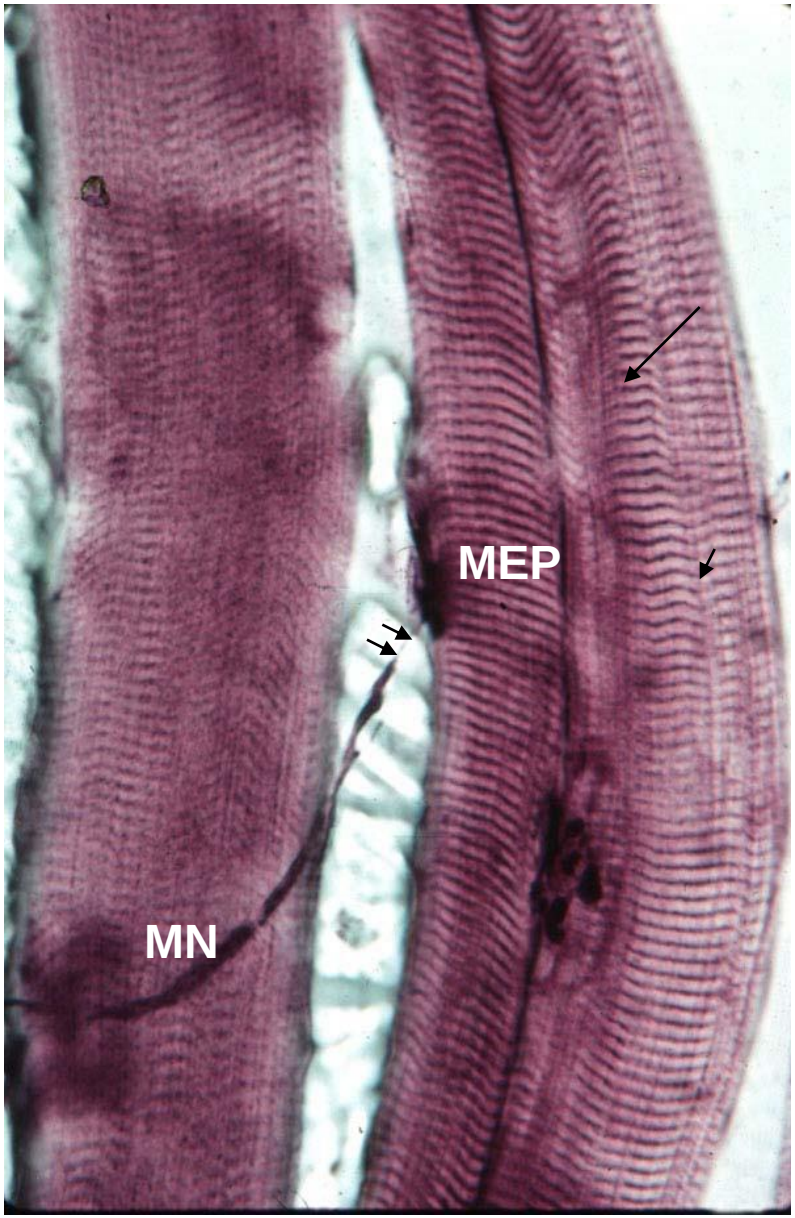
Sensory innervation of skeletal muscle

A muscle spindle may be identified by its circular fibrocollagenous capsule (C) and its content of intrafusal muscle fibers (M).

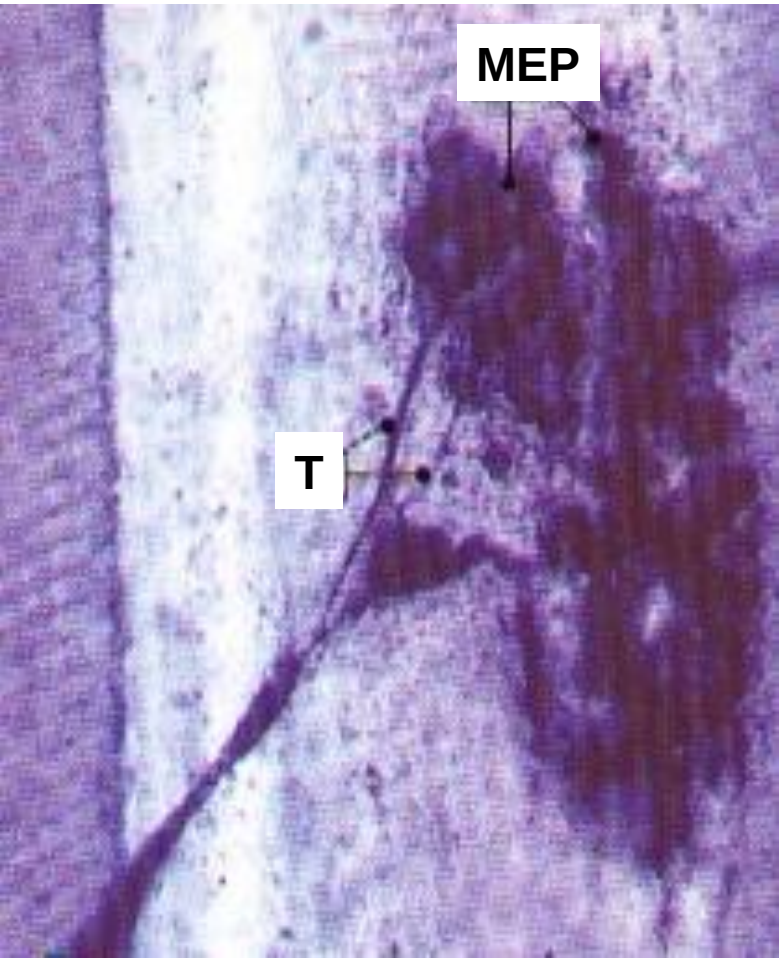


Muscle of a child, H & E

Myoneural junction. Lateral view. x 540.



The myelinated nerve fiber (MN) approaching the skeletal muscle fiber (SM). The A bands (arrowhead) and I bands (arrow) are well delineated, but the Z discs are not observable in this preparation. As the axon nears the muscle cell, it loses its myelin sheath and continues on as a nonmyelinated axon (double arrowhead) but retains its Schwann cell envelope. As the axon reaches the muscle cell, it terminates as a motor end plate (MEP), overlying the sarcolemma of the muscle fiber.



Several nerve twigs (T) branch from a single axon to innervate muscle fibers. There is a bulbous swelling (the motor end plate, MEP) at the end of each twig at the site of connection with the muscle. The group of fibers innervated by a single axon is a motor unit.

MOTOR INNERVATION OF SKELETAL MUSCLE, methylene blue staining

MOTOR INNERVATION OF SKELETAL MUSCLE

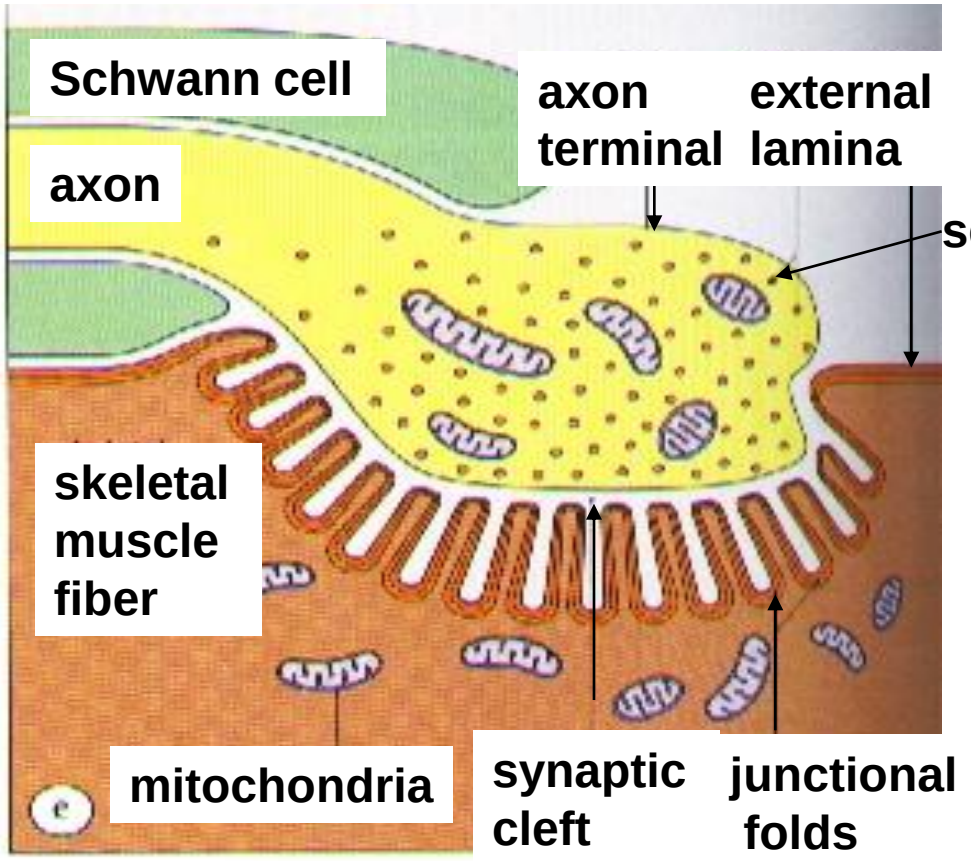
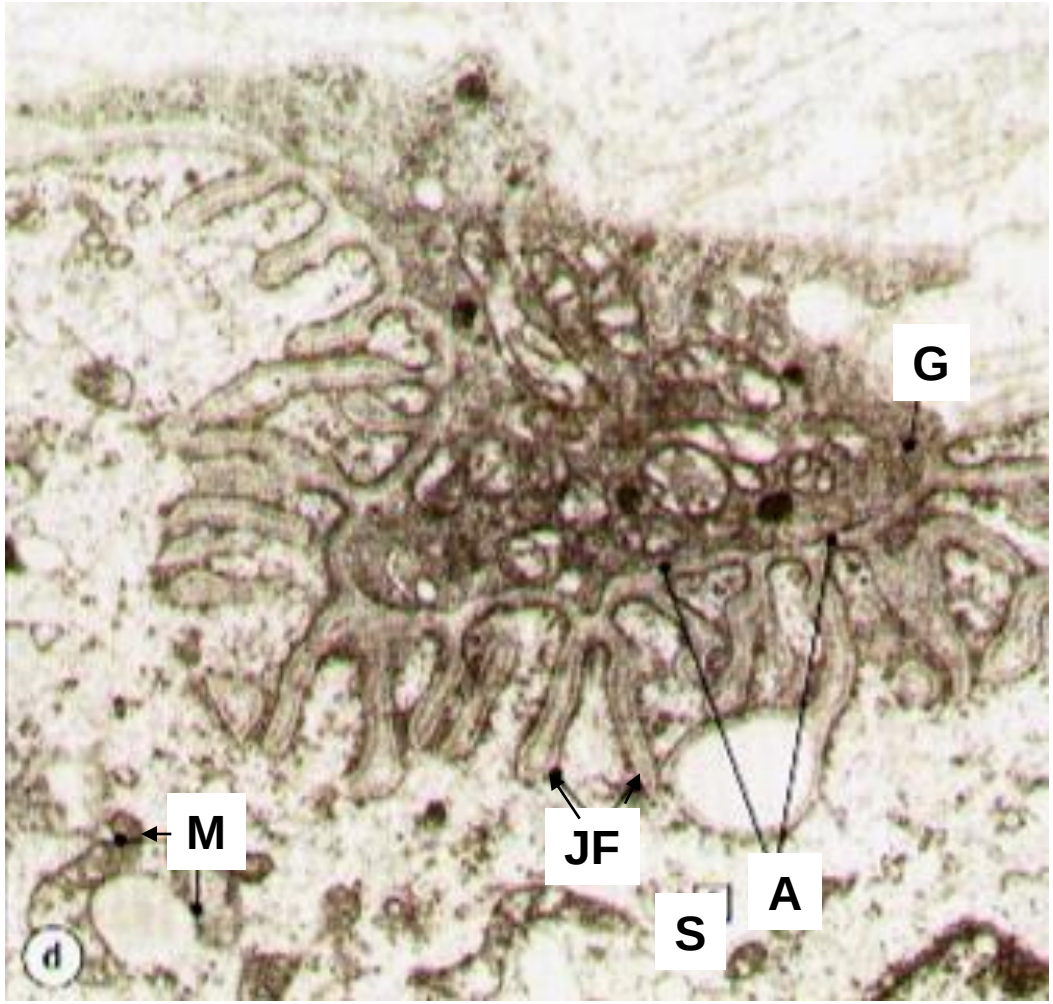


DIAGRAM OF THE MOTOR END PLATE

The sarcoplasmic membrane in the region the motor ends plate contains specialized receptors which, when activated by acetylcholine, permit muscle cell membrane depolarization.

MOTOR INNERVATION OF SKELETAL MUSCLE



THE MOTOR END PLATE, TEM

Cell membrane of the muscle fiber is thrown into a series of deep folds (junctional folds, JF), beneath which the sarcoplasm (S) contains numerous mitochondria (M). In the terminal swelling of the motor axon (A), neuro-secretory granules (G), containing the transmitter substance acetylcholine, and mitochondria are abundant.

MYASTHENIA GRAVIS

Myasthenia gravis is a disease caused by the formation of antibodies to the acetylcholine receptors and thereby prevent released acetylcholine from interacting with the receptors and causing depolarization.

Affected individuals develop tremendous muscle weakness manifest by fatigability, inability to lift the arms, failure to maintain an upright posture of the head, and drooping of the eyelids.

Treatment is by the administration of drugs (anticholinesterases) which inhibit the action of the enzyme acetylcholinesterase. This potentiates the action of released acetylcholine and allows it to bind to receptors not blocked by antibodies.

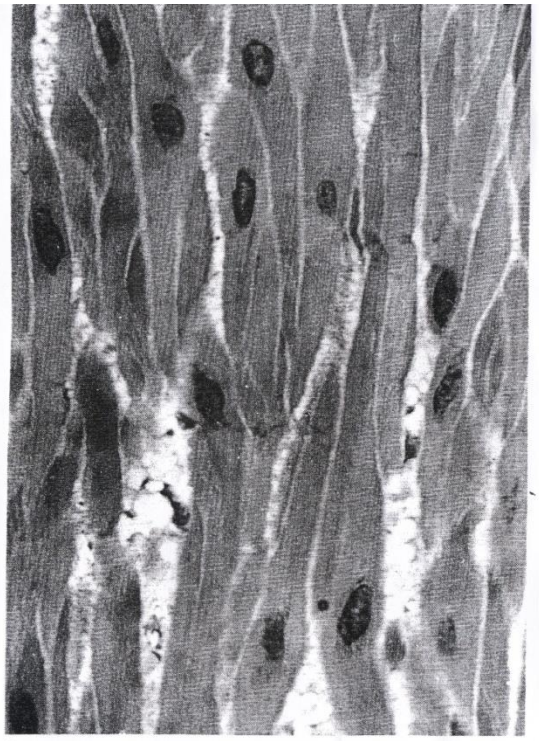
Myasthenia gravis is an autoimmune disease.

Smooth muscle cell is the main contractile cell in the walls of viscera and in blood vessels.

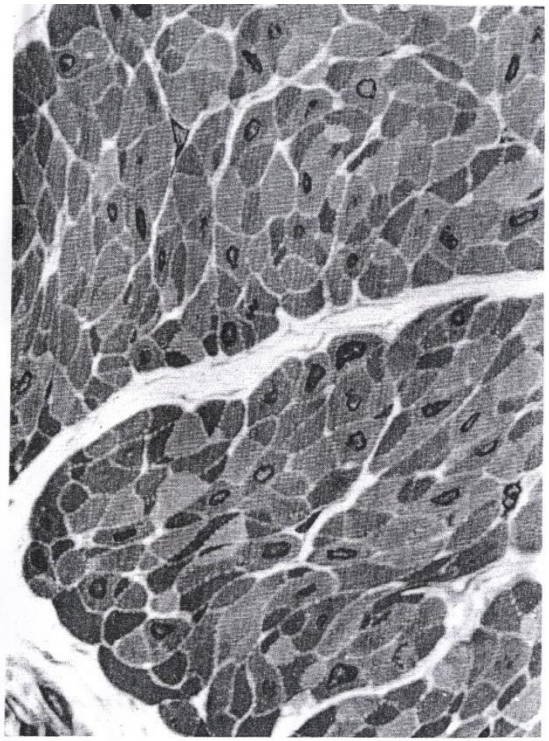
Smooth muscle cells have a much less organized system of contractile proteins than striated skeletal and cardiac muscle cells. Forming the contractile portions of the wall of the most hollow viscera (e.g. gut, urinary bladder and uterus), as well as the contractile elements in blood vessel walls and secretory gland ducts, smooth muscle cells are found in situations requiring sustained slow or rhythmic contractions not under voluntary control.

Contractile proteins are arranged in a criss cross lattice inserted circumferentially into a cell membrane, and contraction results in shortening of the cell.

SCHEME AND HISTOLOGICAL STRUCTURE OF SMOOTH MUSCLE TISSUE



A



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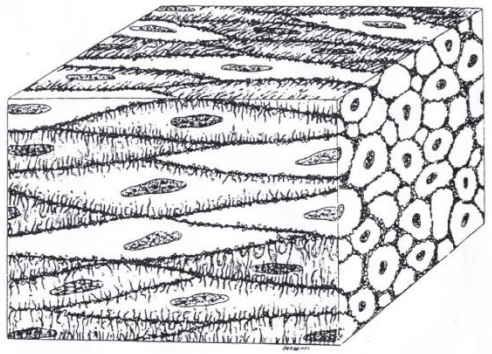
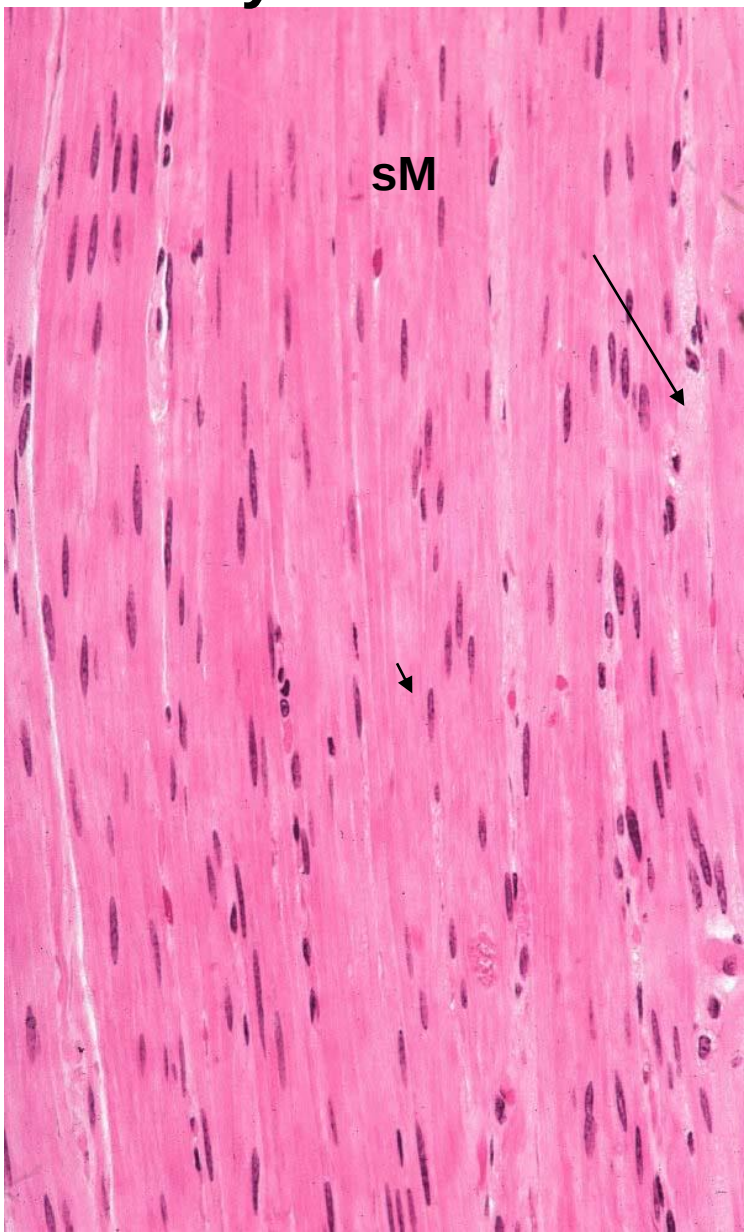


Figure Diagram of a segment of smooth muscle. All cells are surrounded by a net of reticular fibers. In cross section, these cells exhibit variable diameters.

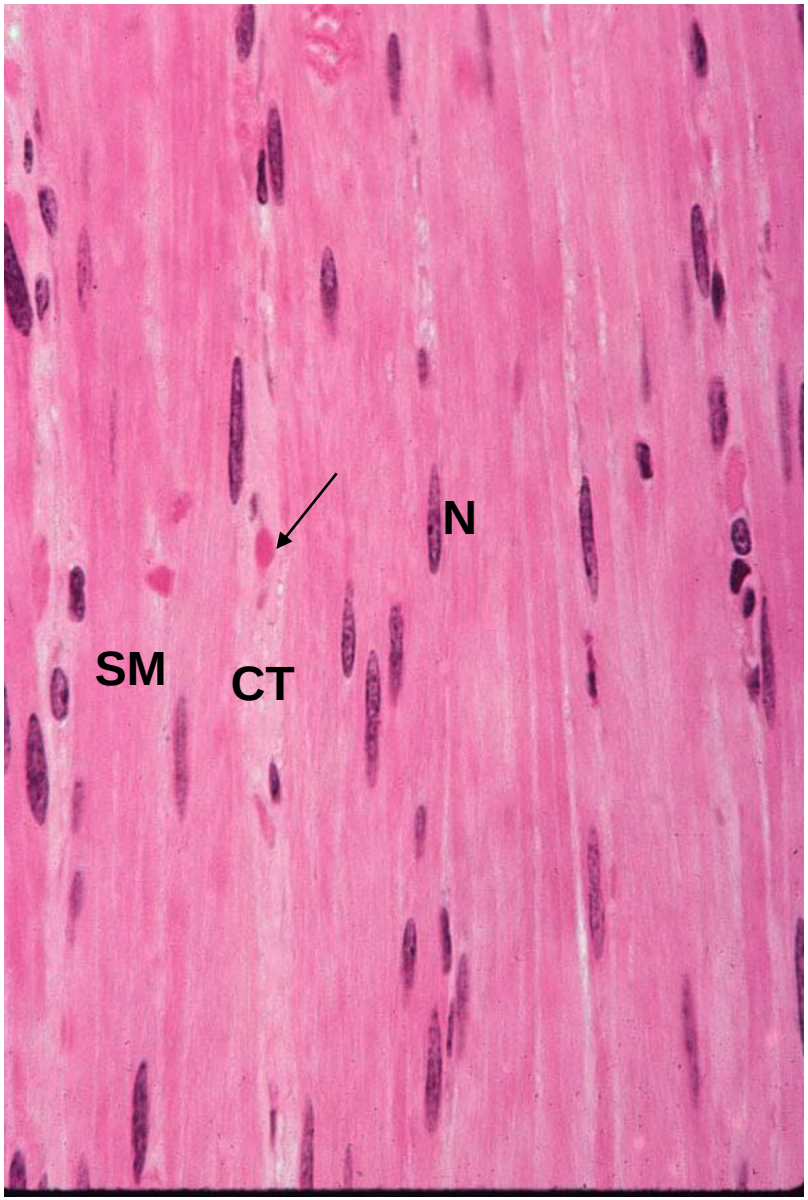
Urinary bladder. Smooth muscle cells sectioned longitudinally (a) and transversely (b). Diagram of a segment of smooth muscle. All cells are surrounded by a net of reticular fibers. In cross section these cells exhibit variable diameters. Each fusiform cell smooth muscle cell houses a single centrally placed nucleus, which becomes corkscrew shaped during contraction of the cell.

Smooth muscle. l.s. Monkey. x 270.

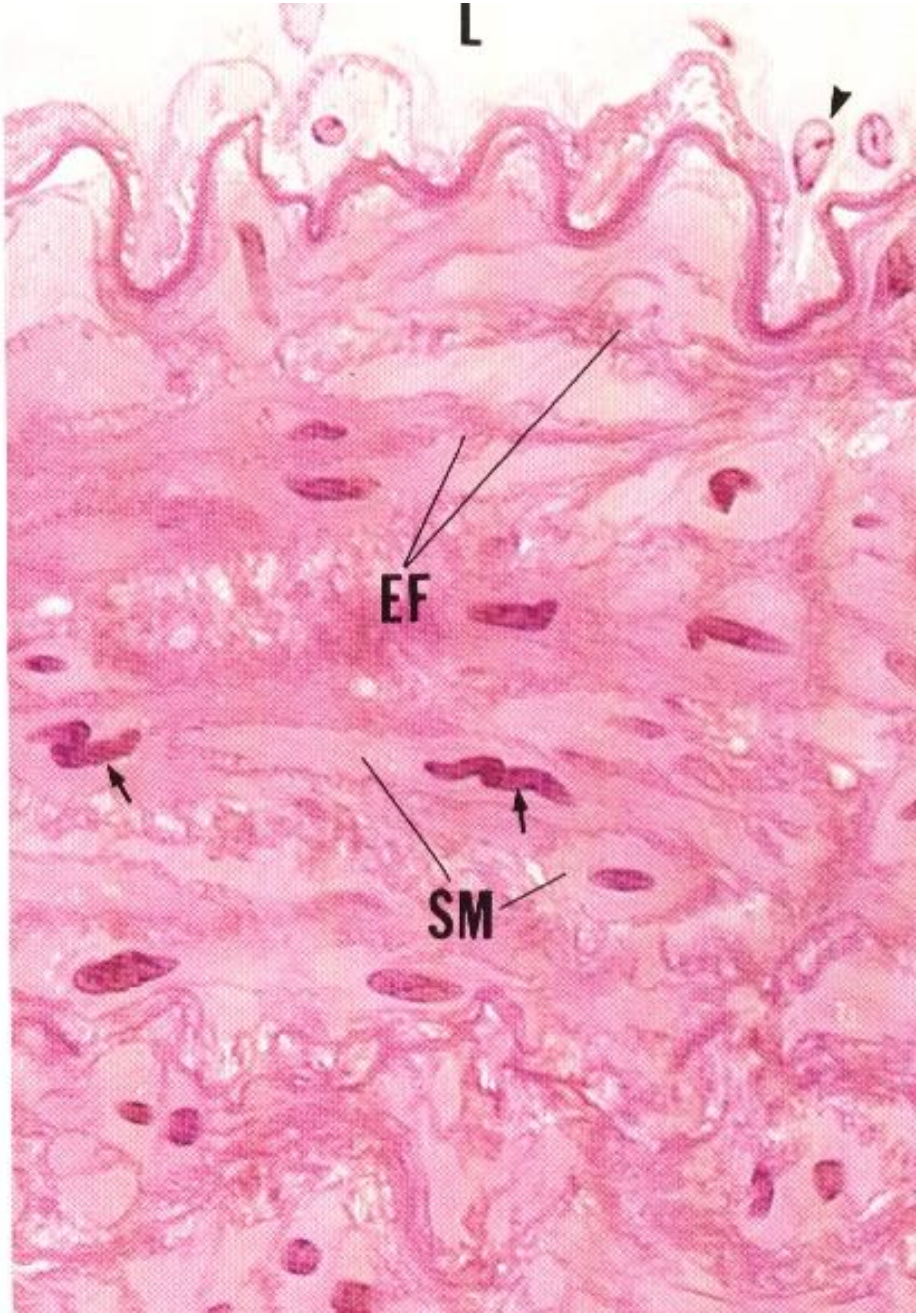


The longitudinal section of smooth muscle displays long fusiform smooth muscle cells (sM) with centrally located, elongated nuclei (arrowhead). Because the muscle fibers are arranged in staggered arrays, they can be packed very closely, with only a limited amount of intervening connective tissue (arrow). Utilizing hematoxylin and eosin, the nuclei appear bluish, while the cytoplasm stains a light pink. Each smooth muscle cell is surrounded by a basal lamina and reticular fibers, neither of which is evident in this figure. Capillaries are housed in the connective tissue separating bundles of smooth muscle fibers.

Smooth muscle. l.s. Monkey. x 540.



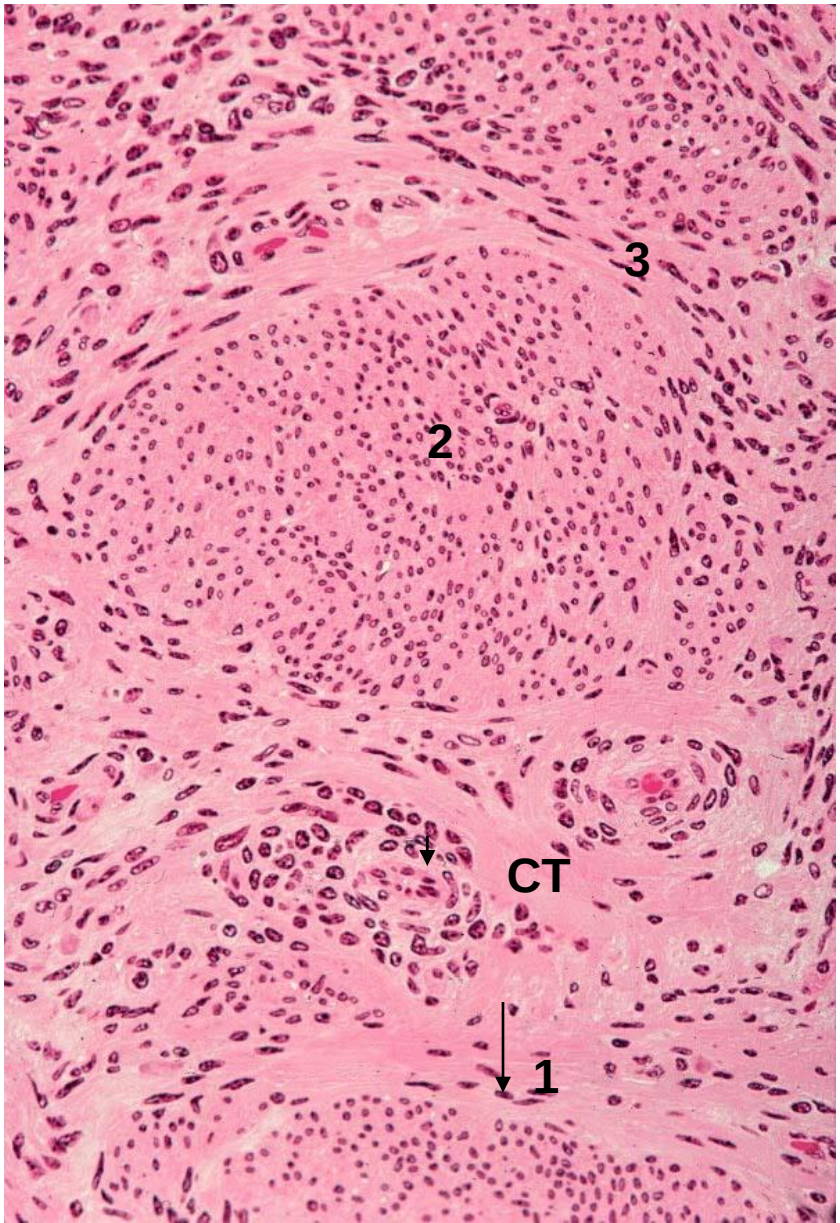
At a higher magnification the nuclei (N) of the smooth muscle fibers appear long, tapered structures located in the center of the cell. The widest girth of the nucleus is almost as wide as the muscle fiber. However, the length of the fiber is much greater than that of the nucleus. Note also that any line drawn perpendicular to the direction of the fibers will intersect only a few of the nuclei. Observe the difference between the connective tissue (CT) and smooth muscle (sM). The smooth muscle cytoplasm stains darker and appears smooth relative to the paleness and rough-appearing texture of the connective tissue. Capillaries (arrow) located in the CT elements between bundles of muscle fibers.



Smooth Muscle (Elastic Artery wall), H & E, x540

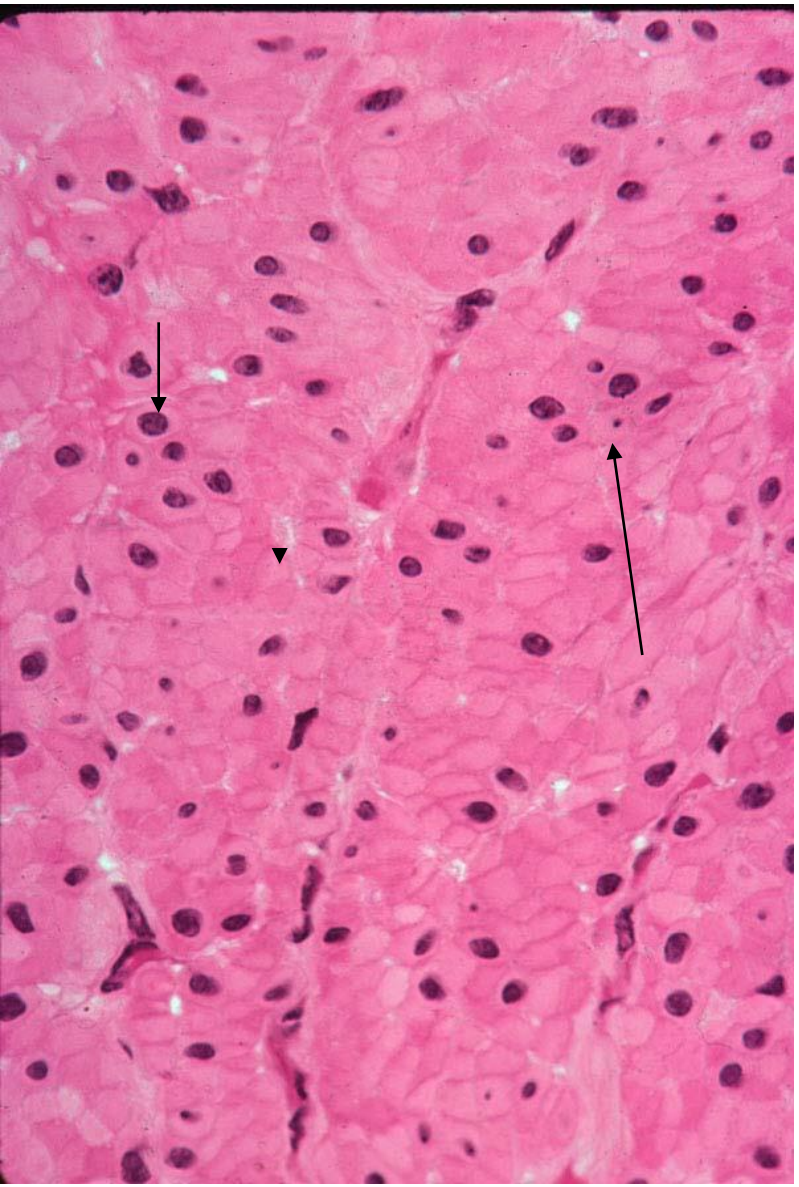
The tunica intima in the aorta houses many smooth muscle cells (SM) whose nuclei are corkscrew-shaped (arrows) indicative of muscle contraction.

Smooth muscle. Uterine myometrium. x.s. Monkey. x 270.



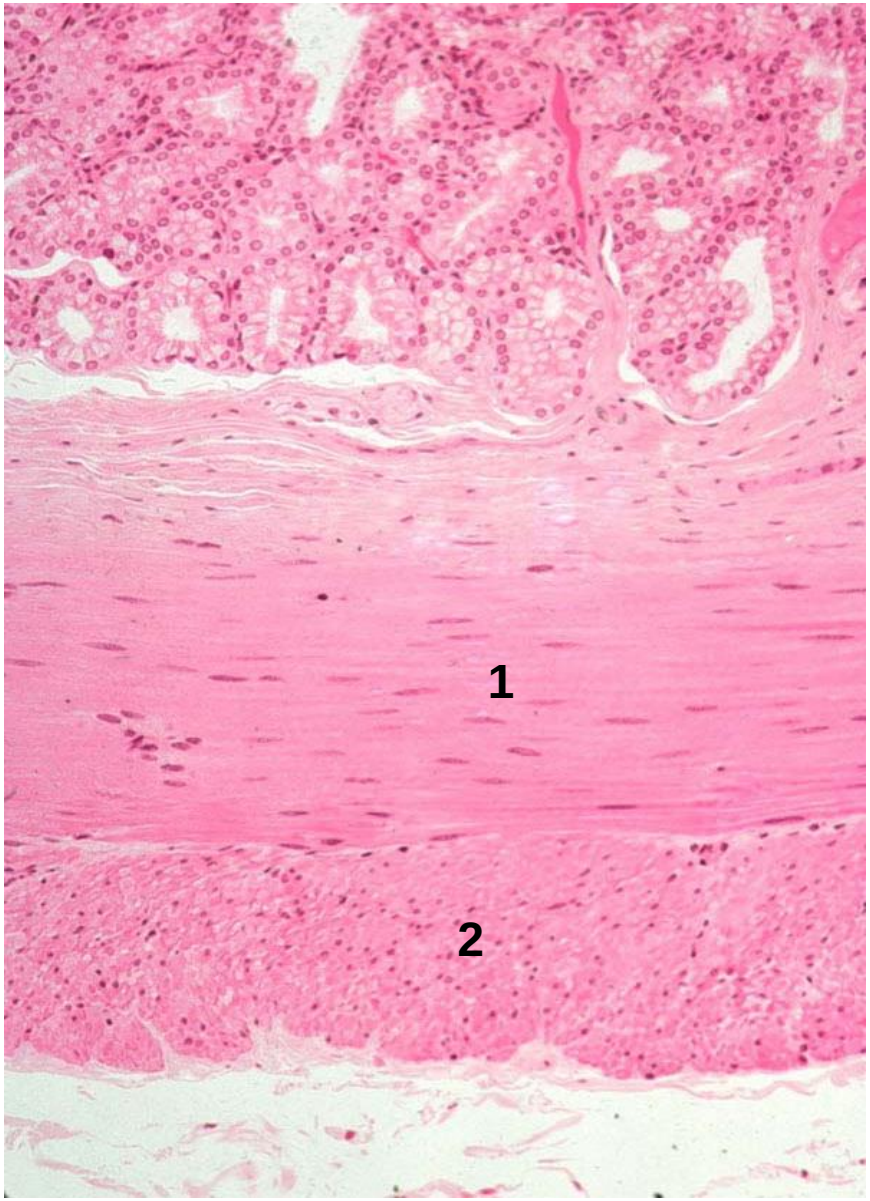
The myometrium of the uterus consists of interlacing bundles of smooth muscle fibers, surrounded by connective tissue (CT) elements. Note that some of these bundles are cut in longitudinal section (1), others are sectioned transversely (2), and still others are cut obliquely (3). At low magnifications, such as in this photomicrograph, the transverse sections present a haphazard arrangement of dark nuclei (arrow) in a lightly staining region. With practice, it will become apparent that these nuclei are intracellular and that the pale circular regions represent smooth muscle fibers sectioned transversely. Note the numerous blood vessels (arrowhead) traveling in the connective tissue between the smooth muscle bundles

Smooth muscle. x.s. Monkey. x 540.



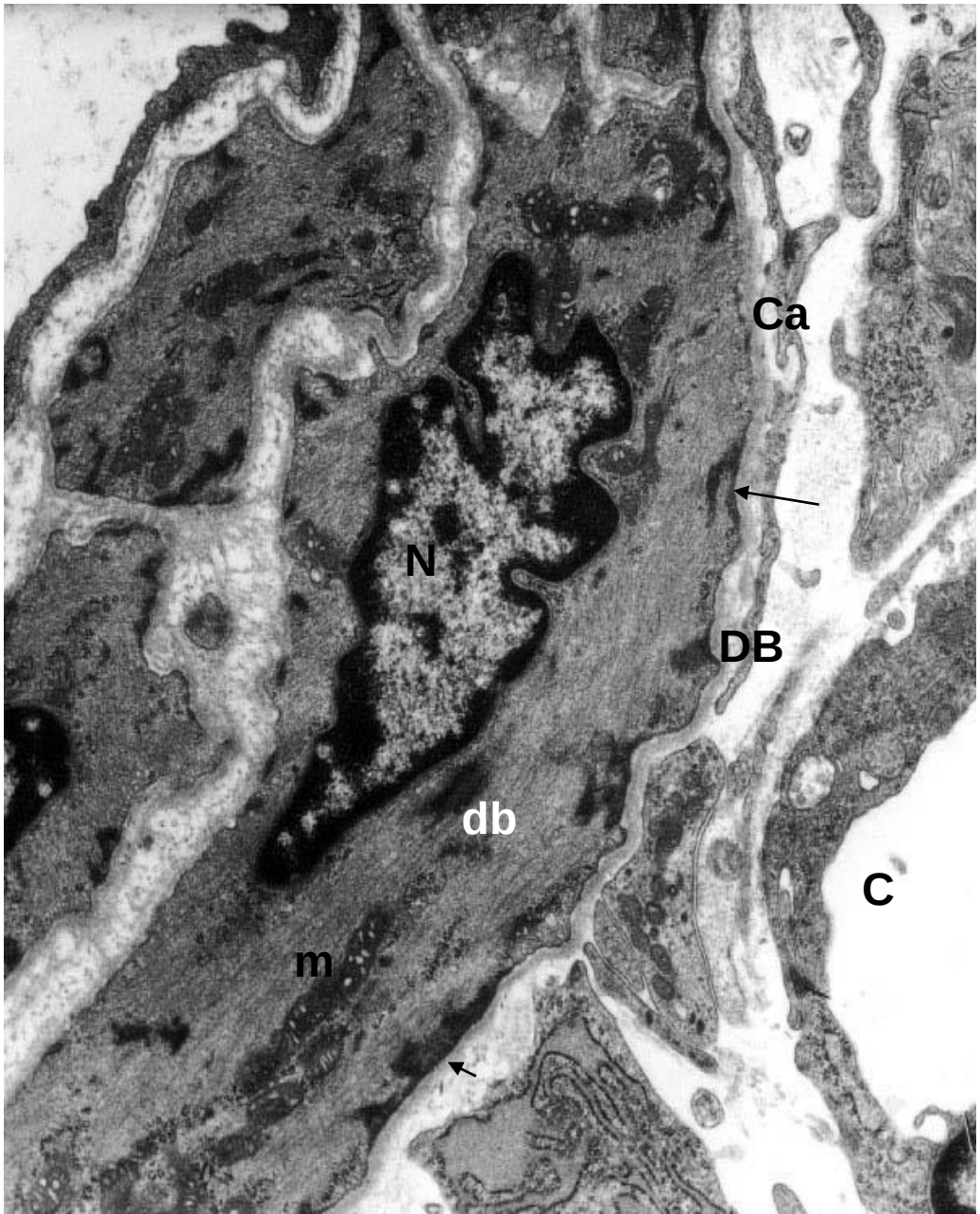
The muscle fibers are much longer than their nuclei and both structures are spindle-shaped, being tapered at both ends. Recall also that at its greatest girth, the nucleus is almost as wide as the cell. In transverse section this would appear as a round nucleus surrounded by a rim of cytoplasm (arrow). If the nucleus is sectioned at its tapered end, merely a small dot of it would be present in the center of a large muscle fiber (long arrow). Sectioned anywhere between these two points the nucleus would be of varied diameter in the center of a large muscle cell. Additionally, the cell may be sectioned in a region away from its nucleus, where only the sarcoplasm of the large muscle cell would be evident (arrowhead). Therefore, in transverse sections of smooth muscle one would expect to find only few cells containing nuclei of various diameters. Most of the field will be closely packed profiles of sarcoplasm containing no nuclei.

Smooth muscle. Duodenum. Monkey. x 132.



This photomicrograph of the duodenum demonstrates the glandular portion (G) with its underlying connective tissue (CT). Shown here are two smooth muscle layers in the intestines, which are at right angles to each other, so that once is cut in cross- and the other in transverse section (J).

Smooth muscle. EM. l.s. Mouse. x 15,120.



Observe that each smooth muscle cell is surrounded by an external lamina (arrowhead), which is similar in appearance to basal lamina of epithelial cells. The sarcolemma (arrow) displays the presence of numerous pinocytotic-like invaginations, the caveolae (Ca). The cytoplasmic aspect of the sarcolemma also displays the presence of dense bodies (DB), which are indicative of the attachment of intermediate filaments at that point. Dense bodies, composed of a-actinin (Z disc protein found in striated muscle), are also present in the sarcoplasm (db). The nucleus (N) is centrally located, and at its pole mitochondria (m) are evident. A small capillary (C) is evident in the lower right-hand corner.

Smooth muscle (J)

Occurrence – found as sheets forming the walls of hollow organs (except the heart), blood vessels and secretory ducts,

Cell structure:

-contains smallest fiber type (20 mcm in blood vessels to 500 mcm in uterus),

-cells are elongated with tapering ends (spindle shaped), non-branching,

-there are no cross striations or myofibrils,

-single, centrally placed nucleus, can appear spiraled or "corkscrew-shaped" in contracted state,

-external basal lamina is present to which cell membrane adhere,

-fibers are capable of hypertrophy and hyperplasia.

Instead of the rapid coordinated contractions performed by striated muscle, smooth muscle is specialized for prolonged, slow contraction. Therefore:

-there is no T-tubules in it as there is no strict coordination as in the striated muscle

-only a rudimentary SR is present because there is no need of massive contractions requiring large release of Ca++

Smooth muscle may be of two types:

1)Visceral Smooth Muscle (unitary type)

This type occurs in the wall of hollow organs (e.g. uterus).

-It generates its own level of rhythmic contractions which may also be stimulated by stretch and is transmitted from cell to cell through gap junctions.

- It has autonomous NS innervation which increases or decreases levels of spontaneous contraction rather than actually initiating it,

-Individual cells are coupled by gap junctions by which the nerve impulses (and accordingly contractions) are spread.

-Physiologically it is termed tonic smooth muscle.

-It is characterized by slow contraction, no action potential and low content of fast myosin.

2) Multiunit smooth muscle:

- Each cell has its own nerve supply, autonomic innervation precisely controls contraction.

- It is specialized for precise, graded contraction, e.g. Iris of the eye, vas deferens, large arteries.

- Physiologically it is called phasic smooth muscle.

- It is characterized by rapid contraction associated with an action potential and a high cell content of fast myosin.

SMOOTH MUSCLE FEATURES:

- spindle-shaped cells surrounded by external lamina

- main contractile cells of hollow viscera, blood vessels, and airways,

- contractile proteins inserted into focal densities around cell periphery,

-contraction modulated by neuronal and endocrine factors,

- two main types (tonic and phasic) characterized by arrangement and speed of contraction

SUPPORT CELL FUNCTION OF SMOOTH MUSCLE:

- Smooth muscle cells have to secrete elements of their extracellular matrix.

-Depending on the site, smooth muscle cells produce collagen, elastin, and other components of the extracellular matrix.

-Thus they have a support cell function as well as a contractile cell function. In most situations this support cell function is limited to manufacturing extracellular matrix to anchor the smooth muscle.

SMOOTH MUSCLE CONTRACTION

Thin filaments of actin (an isoform specific to smooth muscle) are associated with tropomyosin but, in contrast to striated muscle, there is no troponin.

The thick filaments are composed of myosin but of a different type to that in skeletal muscle and will only bind to actin if its light chain is phosphorylated; this phenomenon does not occur in skeletal muscle.

Although Ca++ ions in smooth muscle cells cause contraction as in striated muscle, the control of Ca++ ion movements is different. In relaxed smooth muscle free Ca++ ions are normally sequestered in sarcoplasmic reticulum throughout the cell. On membrane excitation, free Ca++ ions are released into the cytoplasm and bind to a protein called calmodulin (a calcium-binding protein). The calcium-calmodulin complex then activates an enzyme called myosin light- chain kinase, which phosphorylates the myosin light chain and permits it to bind to actin. Actin and myosin subsequently interact by filament sliding to produce contraction in a similar way to that for skeletal muscle.

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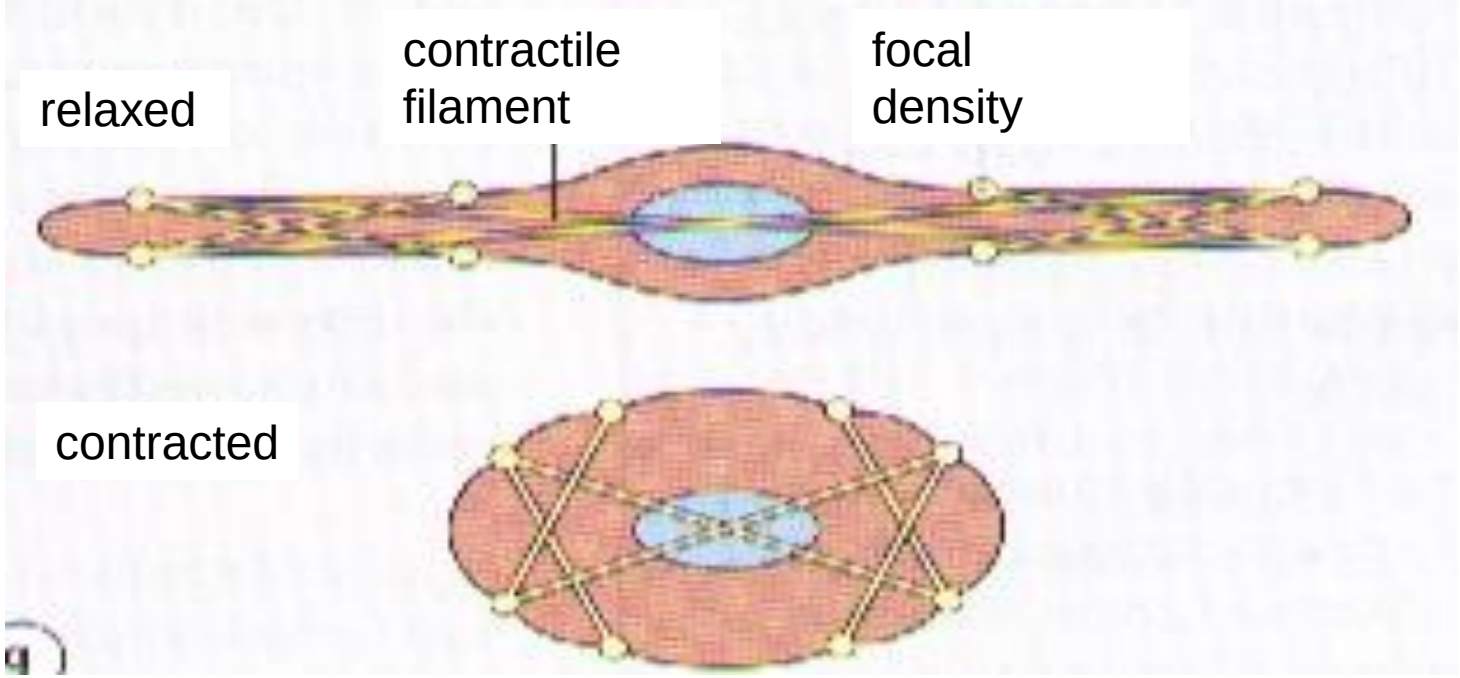
In the cell membrane of smooth muscle cells are calcium channels which can open and let calcium into the cell. Some of these channels are activated by hormones (ligand-gated channels) while others are activated by membrane depolarization(voltage-gated channels). These channels provide another mechanism for initiation or modulation of contraction.

Contraction of smooth muscle can be modulated by surface receptors activating internal secondary messenger systems. Expression of different receptors allows smooth muscle in different sites to respond to several different hormones.

Compared with skeletal muscle, smooth muscle is able to maintain a high force of contraction for very little ATP usage.



SMOOTH MUSCLE CELL CONTRAC-TION

Smooth muscle cells contain apparently haphzard arrangement of thick and thin filaments whose interdigitation is harnessed by an intermediate type of filament. These intermediate filaments form dense bodies where they cross each other and at points of attachment to the cytoplasmic aspect of the sarcolemma.

Contractile proteins are inserted into focal densities around the cell membrane. Focal densities are similar to adherent junctions and are studded around cell membrane. Tension generated by contraction is transmitted through the focal densities to the surrounding network of the external laminae, thus allowing a mass of SMC to function as one unit. The abundant intermediate filaments of smooth muscle, desmin, are also inserted into the focal densities. With contraction each cell assumes a short compact rounded shape.

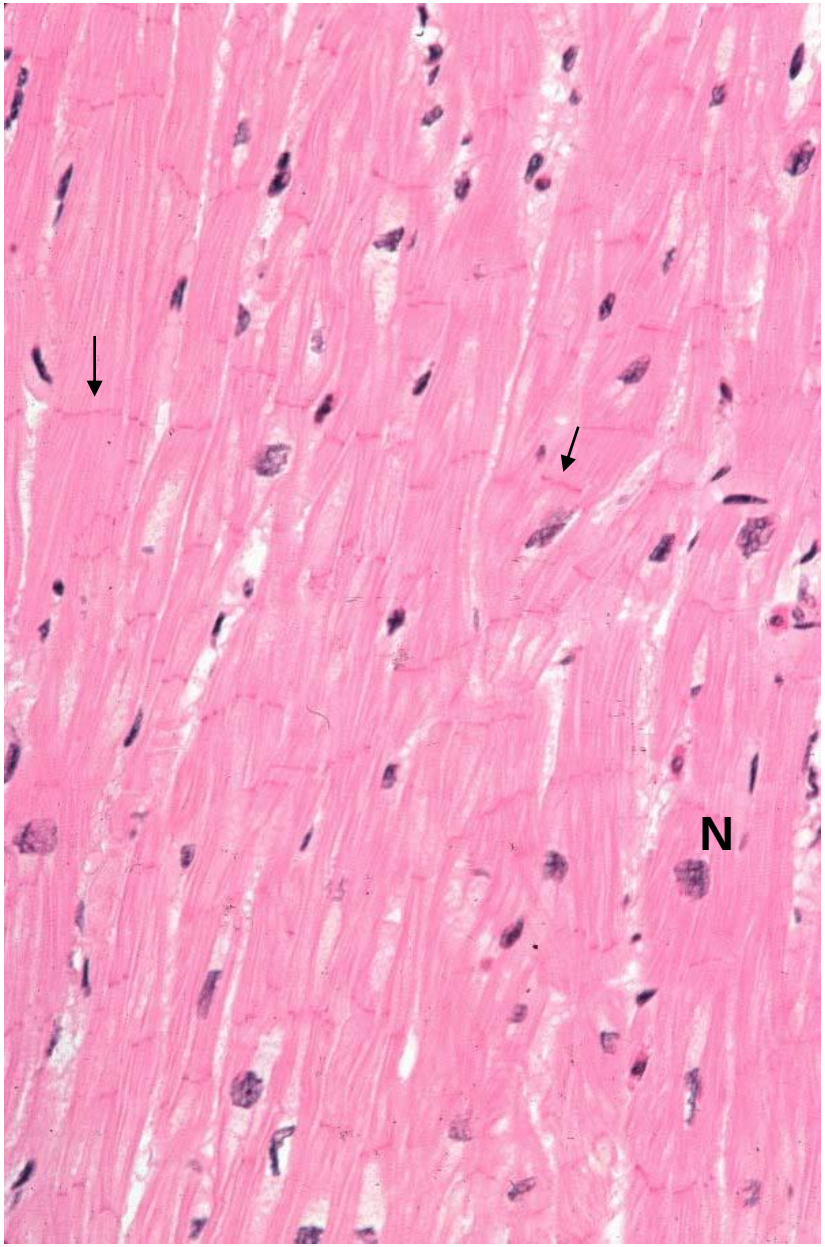
SMOOTH MUSCLE IN DISEASE

Smooth muscle is involved in several disease processes. The constriction of bronchi in asthma is caused by over-activity of smooth muscle cells in the walls of small airways. This can be reversed by administration of beta-agonist drugs which, acting on cell receptors, cause smooth muscle relaxation.

MYOFIBROBLASTS IN DISEASE

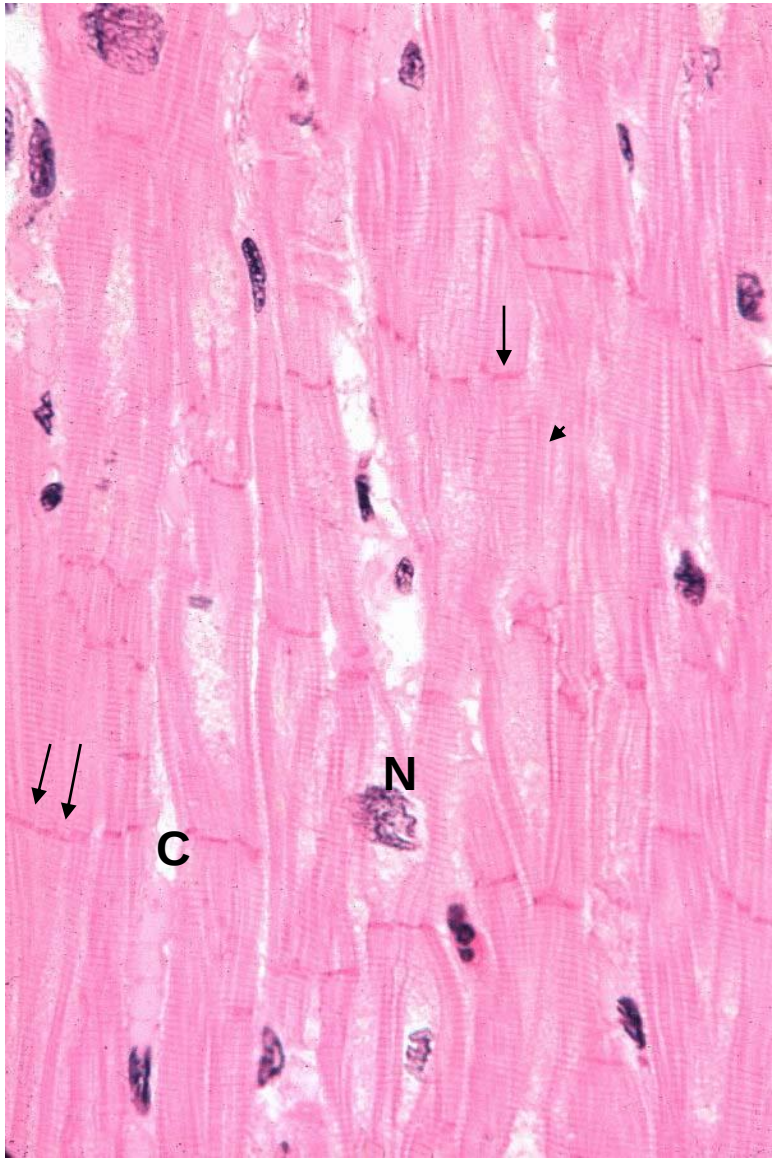
As well as being prominent in wound healing and in the normal process of repair, myofibroblasts are also found in several diseases characterized by fibrosis of tissues, for example fibrosis of the lung following damage by immune-mediated diseases, atheroma in the lining of arteries and cirrhosis of the liver. In these diseases the stimuli which cause myofibroblast proliferation are uncertain, but include local production of growth factors.

Cardiac muscle. l.s. Human. x 270.



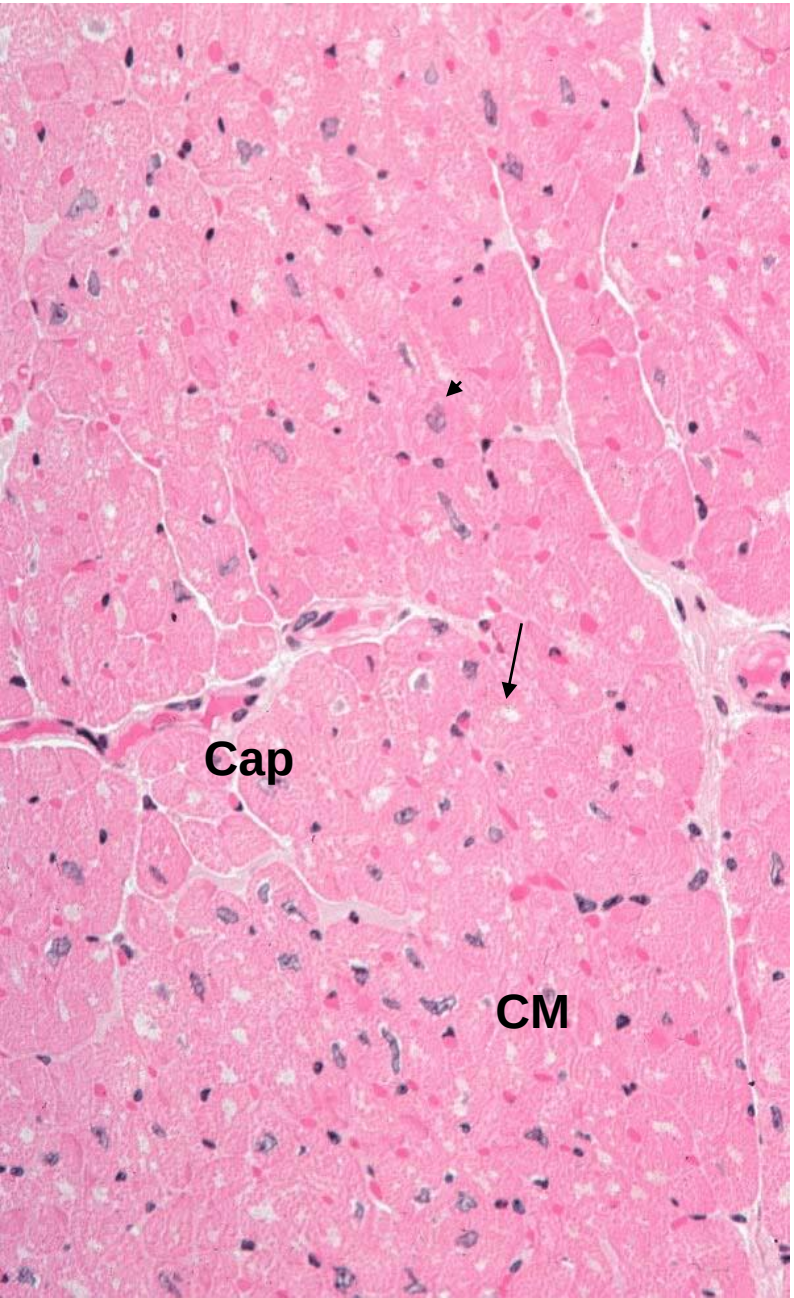
This low magnification of longitudinally sectioned cardiac muscle displays many of the characteristics of this muscle type. Each muscle cell possesses a large, centrally located oval nucleus (N), although occasional muscle cells may possess two nuclei. The intercalated discs (arrow), indicating intercellular junctions between two cardiac muscle cells, clearly delineated in this photomicrograph are not easily demonstrable in sections stained with hematoxylin and eosin. The intercellular spaces of cardiac muscle are richly endowed by blood vessels, especially capillaries. Recall that, in contrast to cardiac muscle, the long skeletal muscle fibers do not branch, their myofilaments parallel one another, their many nuclei are peripherally located, and they possess no intercalated discs.

Cardiac muscle. l.s. Human. x 540.



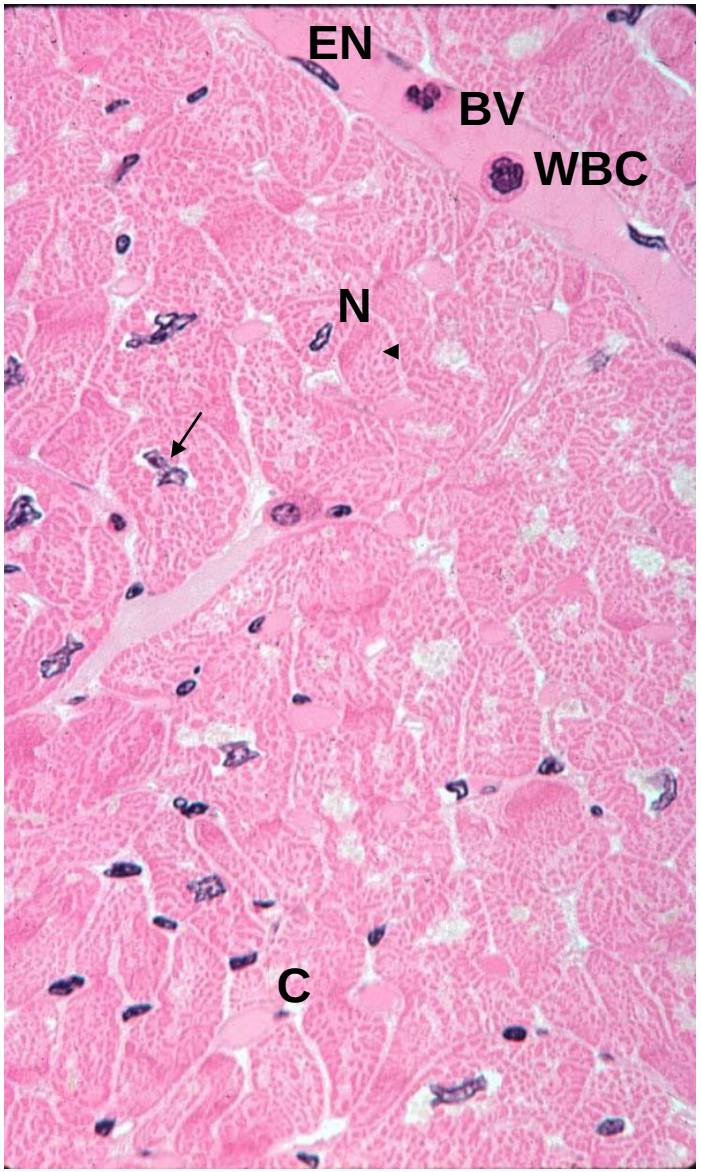
At a higher magnification the branching of the fibers (arrow) is evident, and the cross-striations, I and A bands (arrowheads), are clearly distinguishable. The presence of myofibrils (arrowhead) within each cell is well displayed in this photomicrograph, as is the "step-like" appearance of the intercalated discs (double arrow). The oval, centrally located nucleus (N) is surrounded by a clear area usually occupied by mitochondria. The intercellular areas are richly supplied by capillaries (C) supported by slender connective tissue elements.

Cardiac muscle. x.s. Human. x 270.



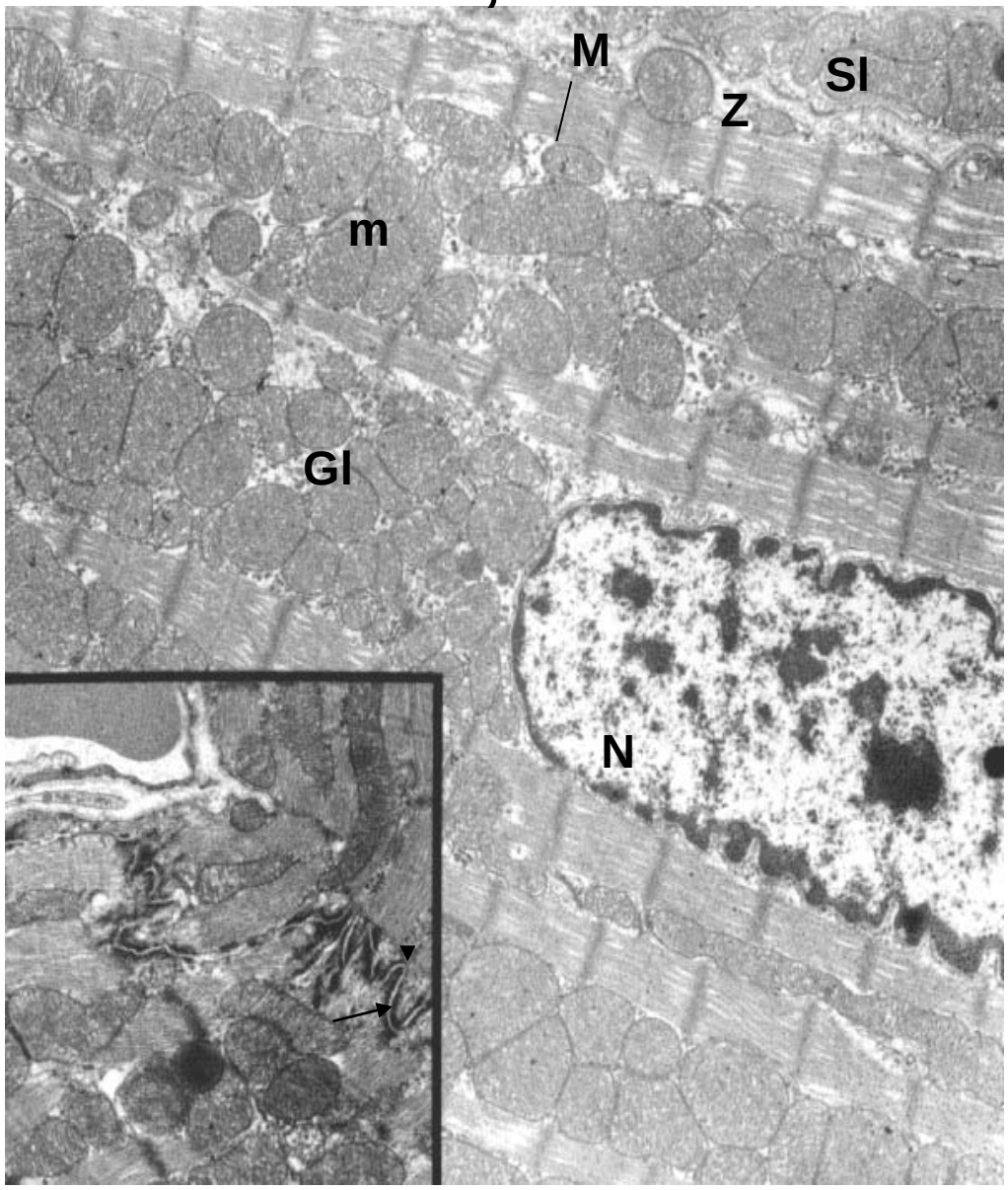
Cross-sections of cardiac muscle demonstrate polygon-shaped areas of cardiac muscle fibers (CM) with relatively large intercellular spaces whose rich vascular supply (arrow) is readily evident. Note that the nucleus (arrow) of each muscle cell is located in the center, but not all cells display a nucleus. The clear areas in the center of some cells (Cap) represent the perinuclear regions at the poles of the nucleus (arrow). These regions are rich in sarcoplasmic reticulum, glycogen, lipid droplets, and an occasional Golgi apparatus. The numerous smaller nuclei in the intercellular areas belong to endothelial and connective tissue cells. In contrast to cardiac muscle, cross-sections of skeletal muscle fibers display a homogeneous appearance with peripherally positioned nuclei. The connective tissue spaces between skeletal muscle fibers display numerous (frequently collapsed) capillaries.

Cardiac muscle. x.s. Human. x 540.



At high magnifications of cardiac muscle in cross-section, several aspects of this tissue become apparent. Numerous capillaries (C) and larger blood vessels (BV) abound in the connective tissue spaces. Note the endothelial nuclei (EN) of these vessels as well as the white blood cells (WBC) within the venule in the upper left-hand corner. Nuclei (N) of the muscle cells are centrally located, and the perinuclear clear areas (arrow) housing mitochondria are evident. Cross-sections of myofibrils (arrowhead) are recognizable as numerous small dots of varying diameters within the sarcoplasm.

Cardiac muscle. EM. l.s. Mouse. x 11,700.



The nucleus (N) of cardiac muscle cells is located in the center of the cell, as is evident from the location of the sarcolemma (Sl) in the upper part of this photomicrograph. The sarcoplasm is well endowed with mitochondria (m) and glycogen (Gl) deposits. Because this muscle cell is contracted, the I bands are not visible. However, the Z discs (Z) are clearly evident, as are the individual myofibrils (M). Inset. Cardiac muscle. Electron microscopy. l.s. Mouse. x 20,700. An intercalated disc is presented in this electron micrograph. Note that this intercellular junction has two zones, the transverse portion (arrow) composed mostly of desmosome-like junctions and a longitudinal portion that displays extensive gap junctions (arrowheads).

Cardiac muscle

Occurrence:

- Only in the myocardium and in the roots of large vessels where they join the heart

Cell structure:

- branching, cylindrical fibers around 100 mcm in size,

- usually one nucleus located centrally in the fiber,

- myofilaments organized into myofibrils identical to skeletal muscle, hence cross striations, although these are usually fainter,

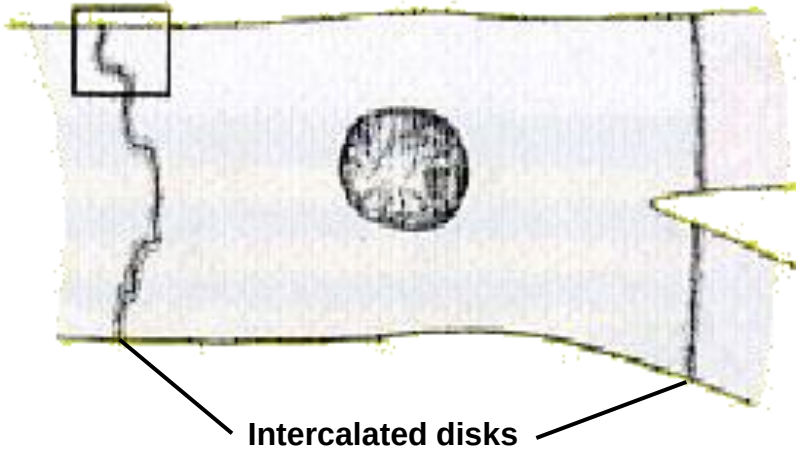
- fibers form interwoven bundles to produce contractions in all dimensions,

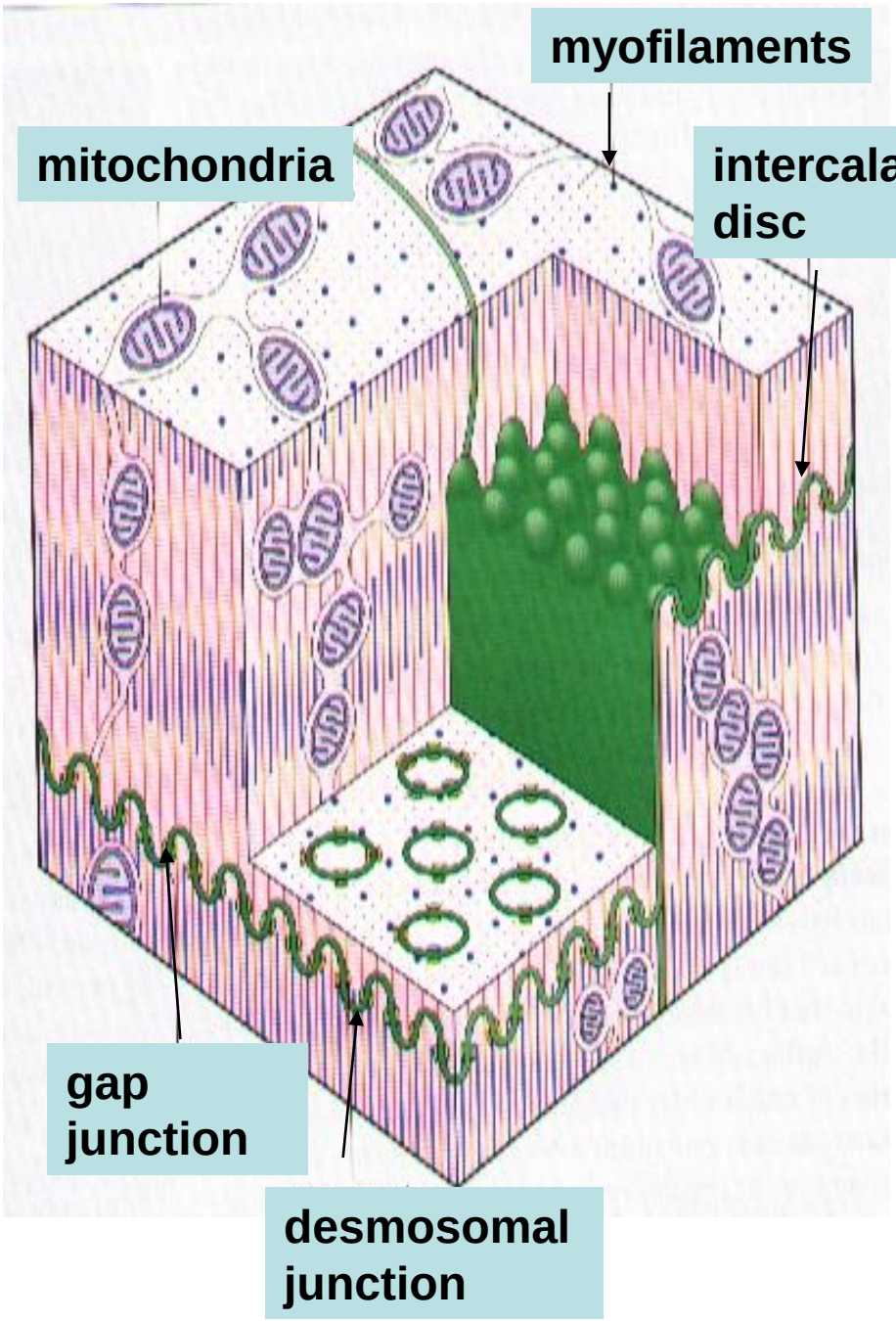
- fibers capable of hypertrophy, but not hyperplasia.

Cardiac muscle is a striated muscle but on the contrary to the skeletal muscle which is composed of bundles of long cylindrical multinucleated fibers, the cardiac muscle is composed of elongated branched individual cells – cardiomyocytes.

Banding pattern is very similar in skeletal and cardiac muscle. A unique and distinguishing characteristic feature of cardiac muscle is the presence of dark-staining transverse lines that cross the chains of the cardiac fibers at irregular intervals – the intercalated discs which represent junctional complexes found at the interface between the adjacent cardiac muscle cells.

Scheme of Cardiomyocyte





STRUCTURAL ARRANGEMENT OF ADJACENT CARDIAC MUSCLE CELLS

Cells are bound together by desmosomal junctions at interdigitating areas at the ends of adjacent cells to form the intercalated disc. Gap junctions facilitate transmission of the contractile stimulus between cells.

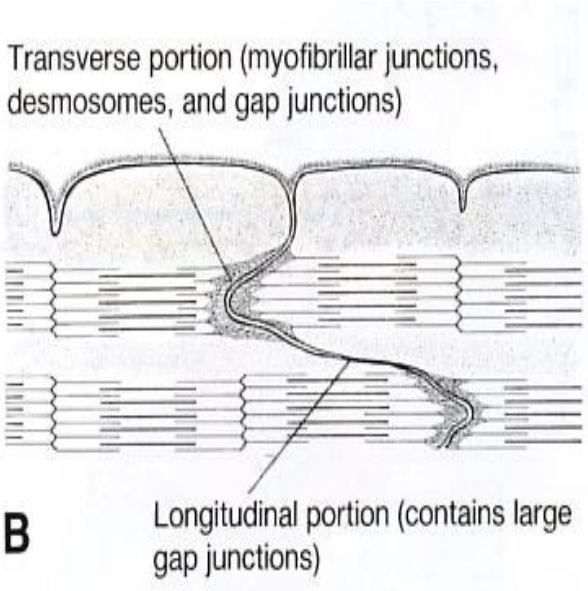
There are three main junctional specializations within the disc:

Fasciae adherentes – the most prominent membrane specialization in transverse portions of the disk, serve as anchoring sites for actin filaments of the terminal sarcomeres. They represent hemi-Z-bands.

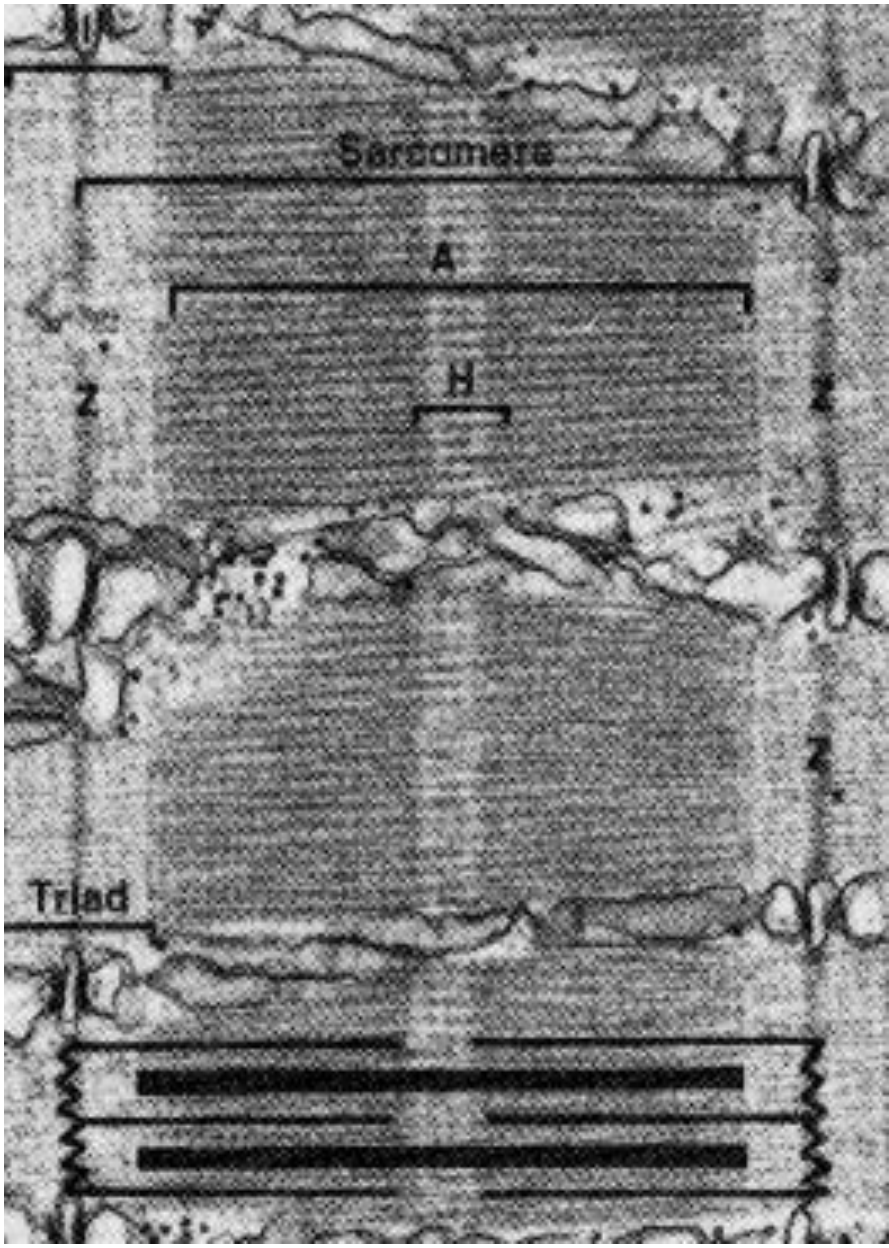
Desmosomes – also present in the transverse portion and bind the cardiac cells together to prevent their pulling apart under constant contractile activity.

Gap junctions - present on the lateral portions of the disc, they provide ionic continuity between adjacent cells. The significance of ionic coupling is that chains of individual cells act as a syncytium allowing the signal to contract to pass in a wave from cell to cell.

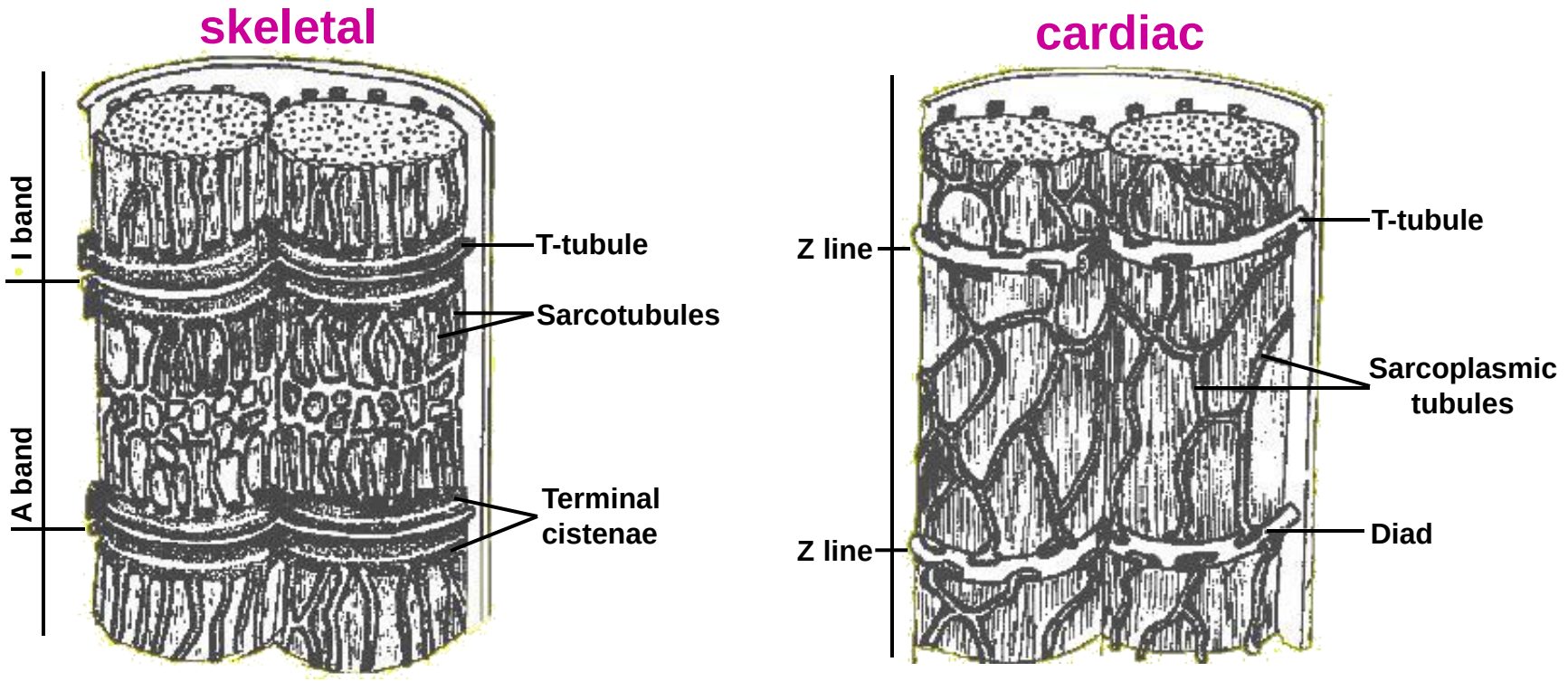
Junctional Specialization of the Intercalated Disc of the Cardiac Muscle



Striated Muscle: Cardiac and Skeletal (J)
Banding pattern:
-Contractile unit is the sarcomere
-Z line of alpha-actinin and desmin mark the border between sarcomeres
--the Z lines are contained in the light I bands made od actin
-Between the I bands is the A band made of myosin
--internal to A band is the H band, usually only visible under EM.



Diagrammatic Representation of the Sarcoplasmic Reticulum and System of T-tubules in Skeletal and Cardiac Muscle



The T-tubules are found at the level of the Z-band in cardiac muscle rather than at the A-I junction as in skeletal muscle; the sarcoplasmic reticulum is not as well developed and wanders irregularly through the myofilaments. Terminal cisterna (lateral expansions of the sarcoplasmic reticulum) are flattened and discontinuous leading to formation diads rather than triads of the skeletal muscle since the T-tubules are generally associated with only one sarcoplasmic cisterna.

COMPARISON OF MUSCLE TYPES

muscle	skeletal	cardiac	smooth
sarcolemma	Plasma membrane, basal lamina, and reticular fibers	Consists of plasma membrane, basal lamina, and reticular fibers	plasma membrane of cells & basal lamina,
Control of contraction	Neurogenic, contracts in response to impulse in motor end plates, voluntary	Myogenic, rate controlled by autonomous nervous system, involuntary	Impulses from sympathetic and parasympathetic nervous system, involuntary
innervation	Cerebrospinal nerves	Autonomous nervous system (sympathetic and parasympathetic)	Autonomous nervous system
Nature of contraction	Rapid, powerful	Moderately rapid, short intervals between contraction	Slow, rhythmic and sustained

COMPARISON OF MUSCLE TYPES

muscle	skeletal	cardiac	smooth
distribution	Skeletal muscles; sheets of abdominal muscle, middle ear ossicles	heart	Alimentary canal, urogenital, respiratory tubes; blood vessels, large ducts of glands, eye ciliary muscle, erector pili
pseudonyms	voluntary, striped, red and white fibers	heart	involuntary, non-striated
cell shape	cylindrical isodiametric	branched cylinders, rectangular cell units	fusiform, spindle-shaped
branching of fiber	no	yes	no
length of fiber	1-40 mm	<0.08 mm	0.02-0.5 mm
Diameter of fiber	10-40 mcm	15 mcm	8 mcm at widest part

KEY FEATURES OF MUSCLE TYPES

type	cell shape	nuclei	diameter	striations	other
smooth	small spindles	central, single	small with marked varia-tions	absent	packed tightly, little CT between the fibers
cardiac	short branching anasto-mosing cylinders	central, usually single, may be double	large, mode-rate variation	present	inter-callated discs
skeletal	long cylinders	peripheral, multiple	large, uniform	absent	