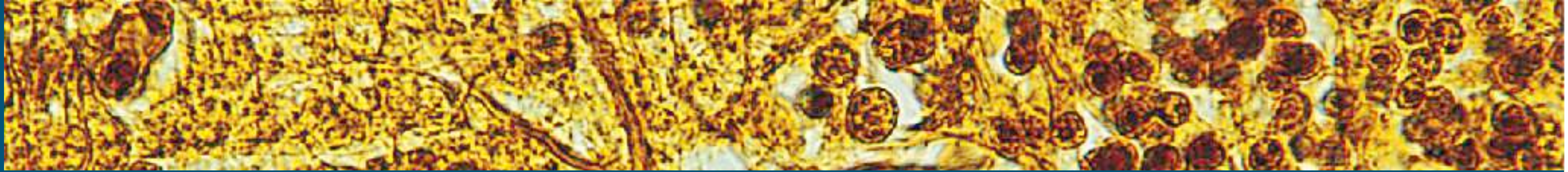


# Muscle Tissue

Histology

Textbook of Histology, 4th ed.

# Learning Objectives

1. Be able to identify the three types of muscle at the light microscope level, including distinctive features of each, such as the intercalated disk of cardiac muscle.

2. Be able to describe the structural basis of muscle striation.

3. Know the structural elements that harness muscle contraction (i.e., the shortening of myofibrils) to the movement of a body part as well as the mechanism by which muscle cells contract.

4. Understand the function and organization of the connective tissue in skeletal muscle (endo-, peri-, and epimysium).

5. Be familiar with the regenerative potential of each muscle type.

# Muscle Tissue

**Striated Muscle**

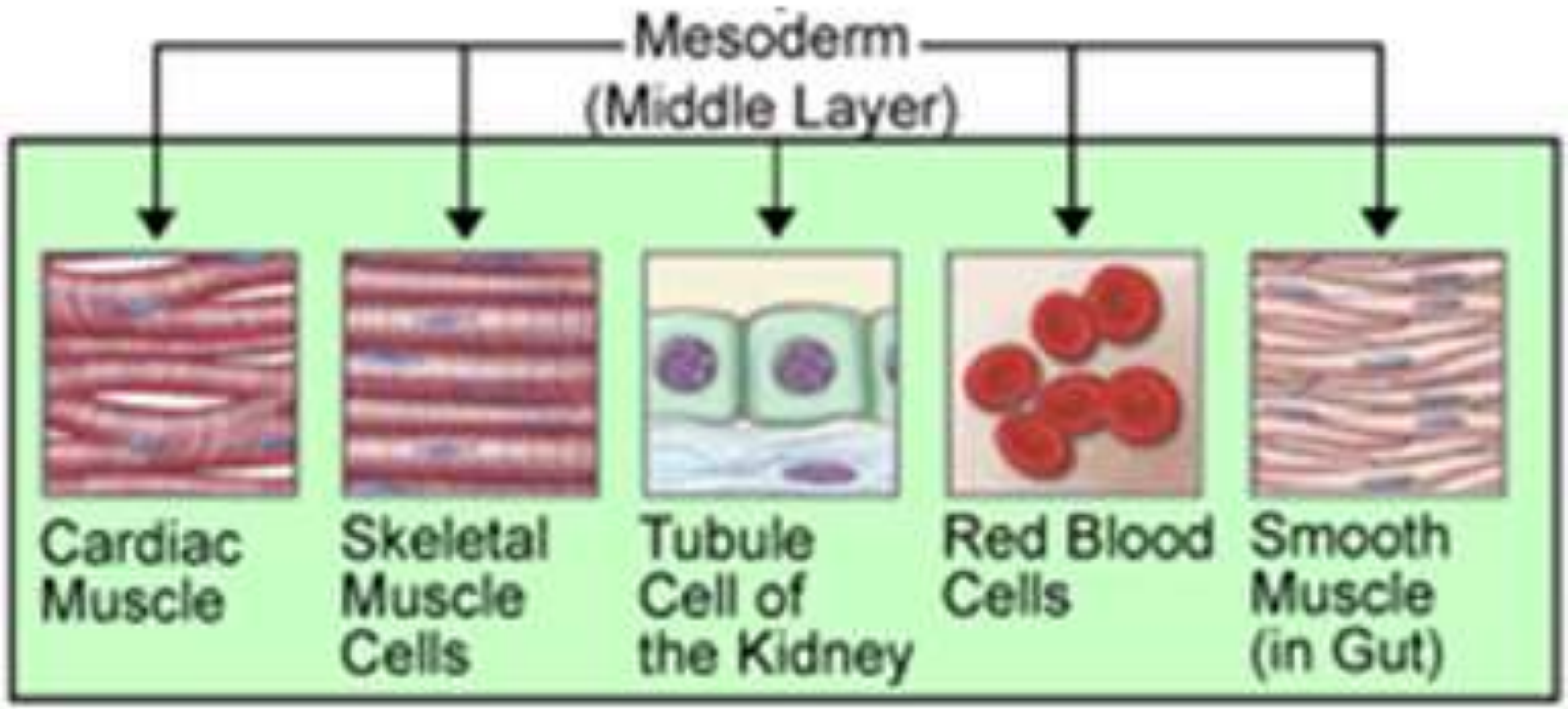
- Skelateal Muscle
- Cardiac Muscle

**Non – Striated**

Smooth Muscle

# Muscle Tissue

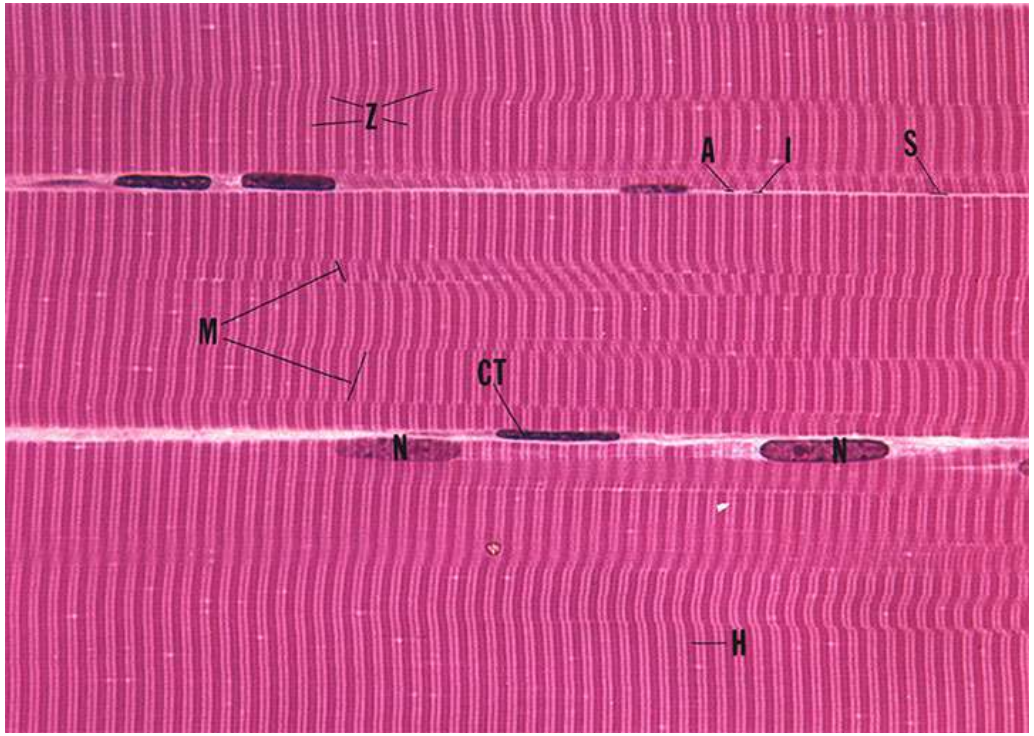
Muscle tissues develop from the **mesoderm**,
including cardiac muscle, skeletal muscles cells and smooth muscle in gut.



# *Skeletal Muscle*

**Striated Muscle** - *regularly arranged contractile units*

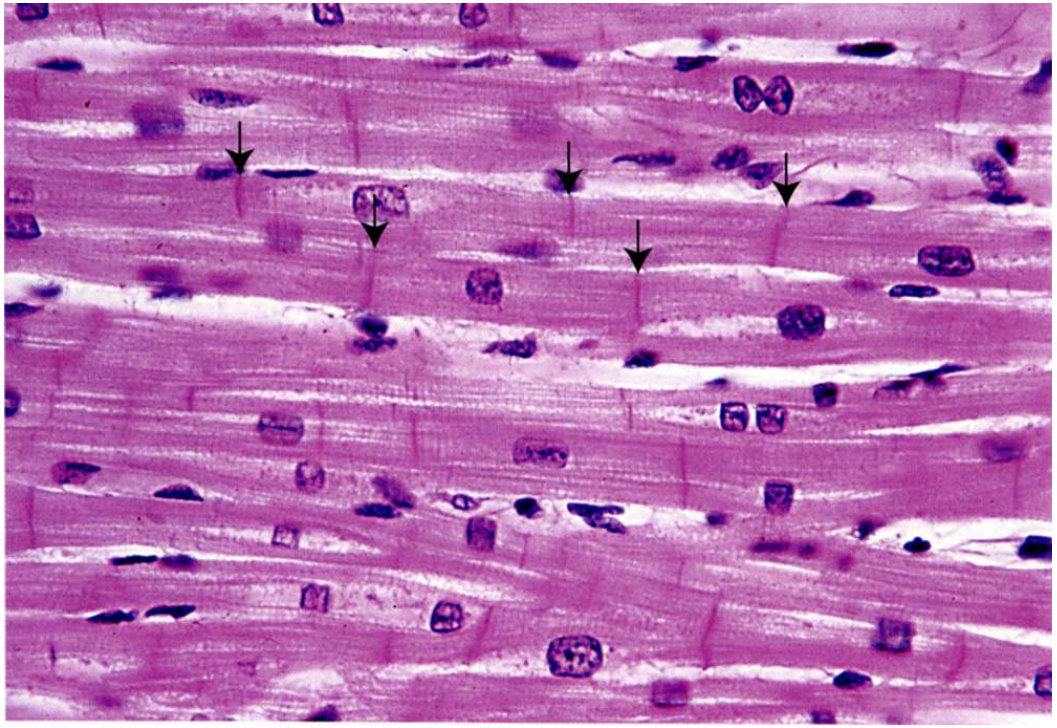
*Skeletal Muscle* - long, cylindrical multinucleated cells with peripherally placed nuclei. Contraction is typically quick and vigorous and under voluntary control. Used for locomotion, mastication and phonation.



# Cardiac Muscle

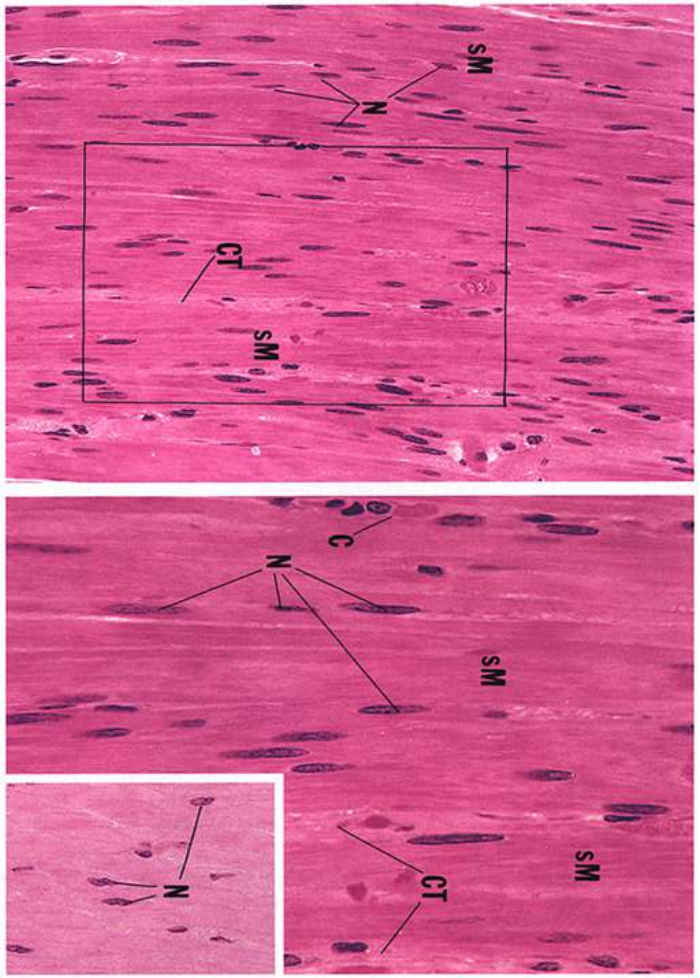
**Striated Muscle** - *regularly arranged contractile units*

*Cardiac Muscle* - elongated, branched cells with a single centrally placed nucleus and intercalated discs at the ends. Contraction is involuntary, vigorous, and rhythmic.

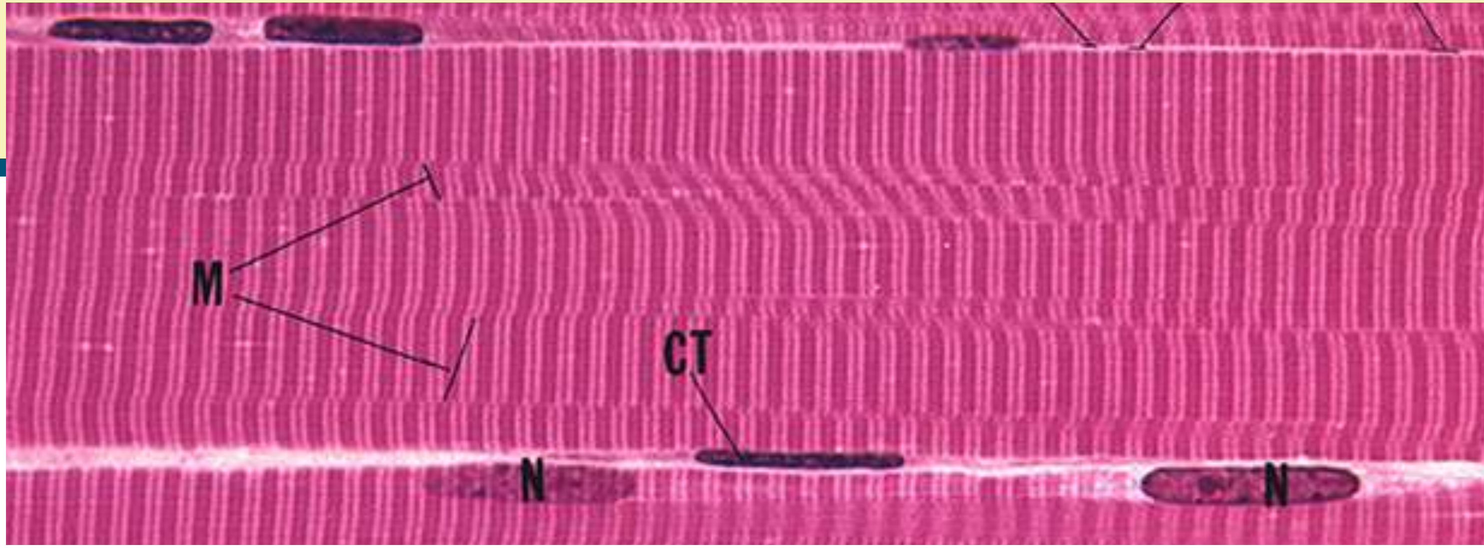


# Smooth Muscle

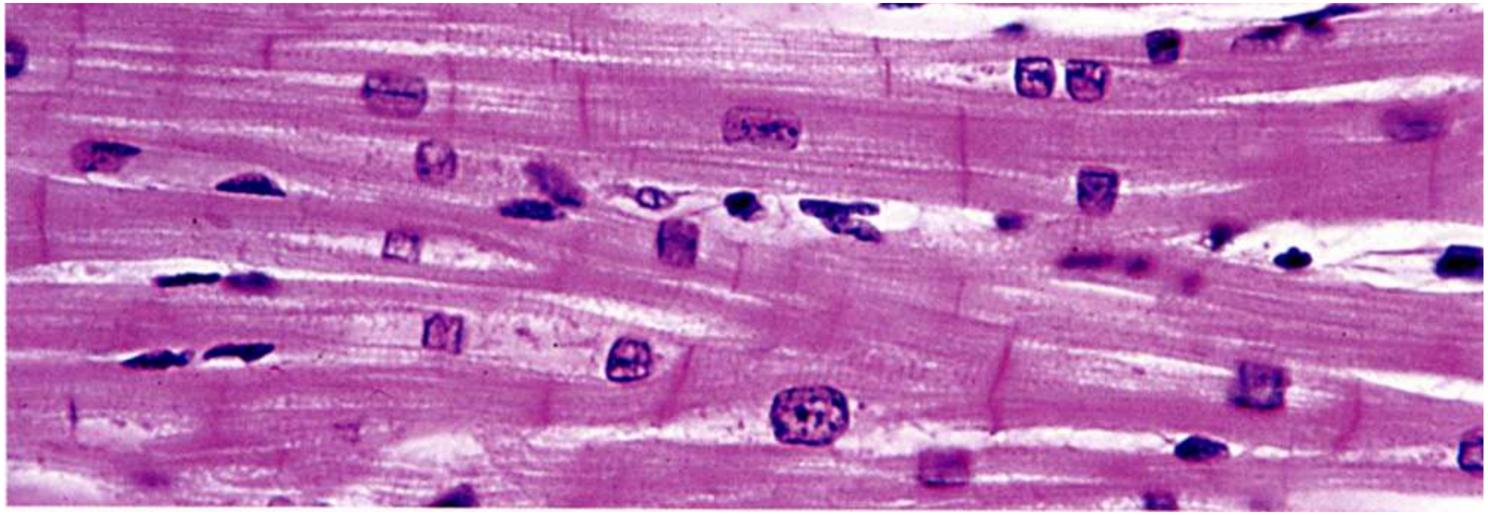
**Smooth Muscle** - possesses contractile machinery, but <u>it is irregularly arranged</u> (thus, non-striated). Cells are fusiform with a central nucleus.  Contraction is involuntary, slow, and long lasting.



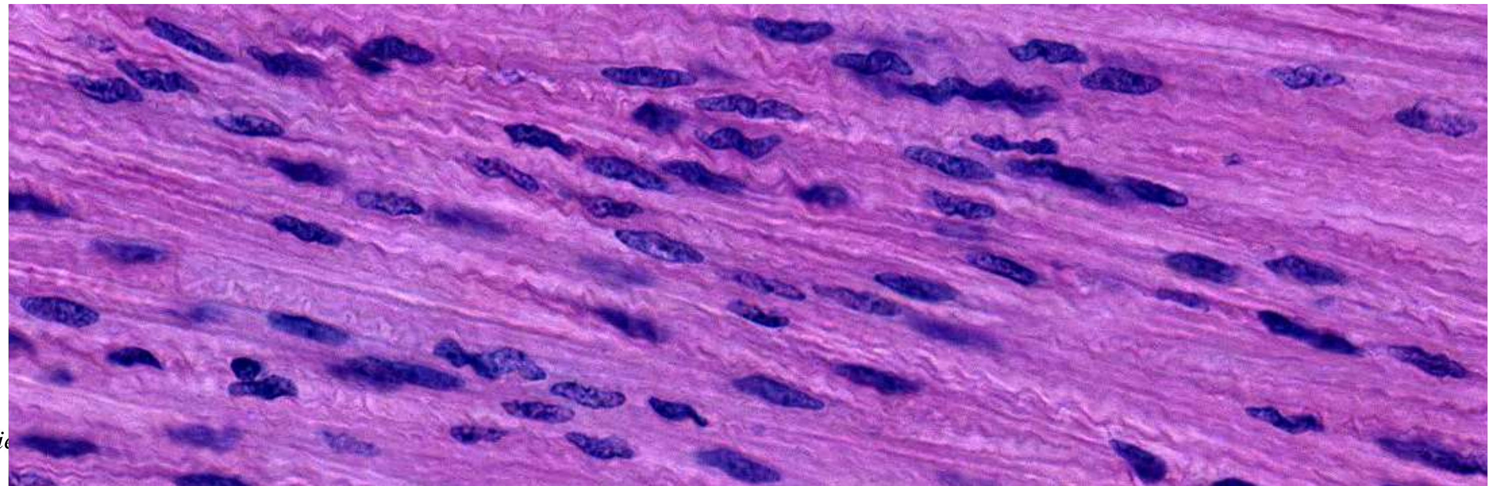
Skeletal Muscle



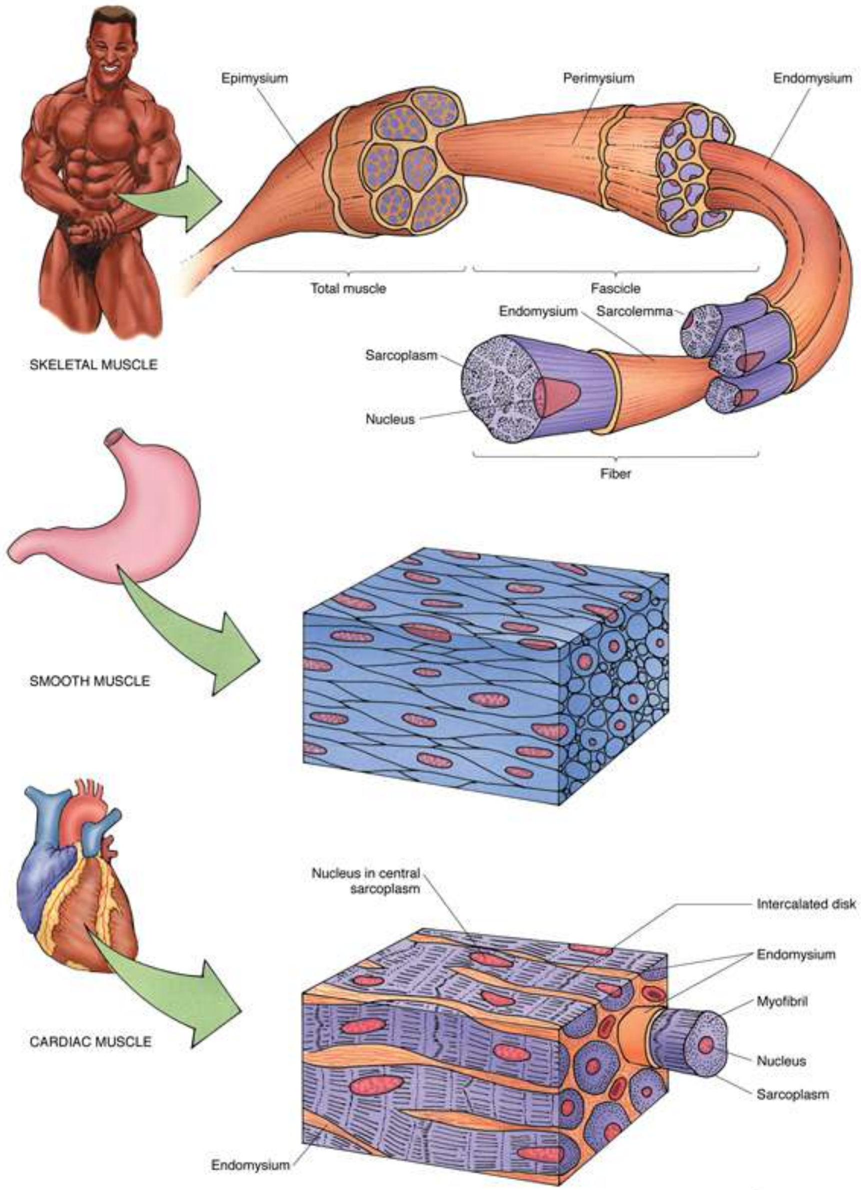

Cardiac Muscle



Smooth Muscle



# Muscle Tissue

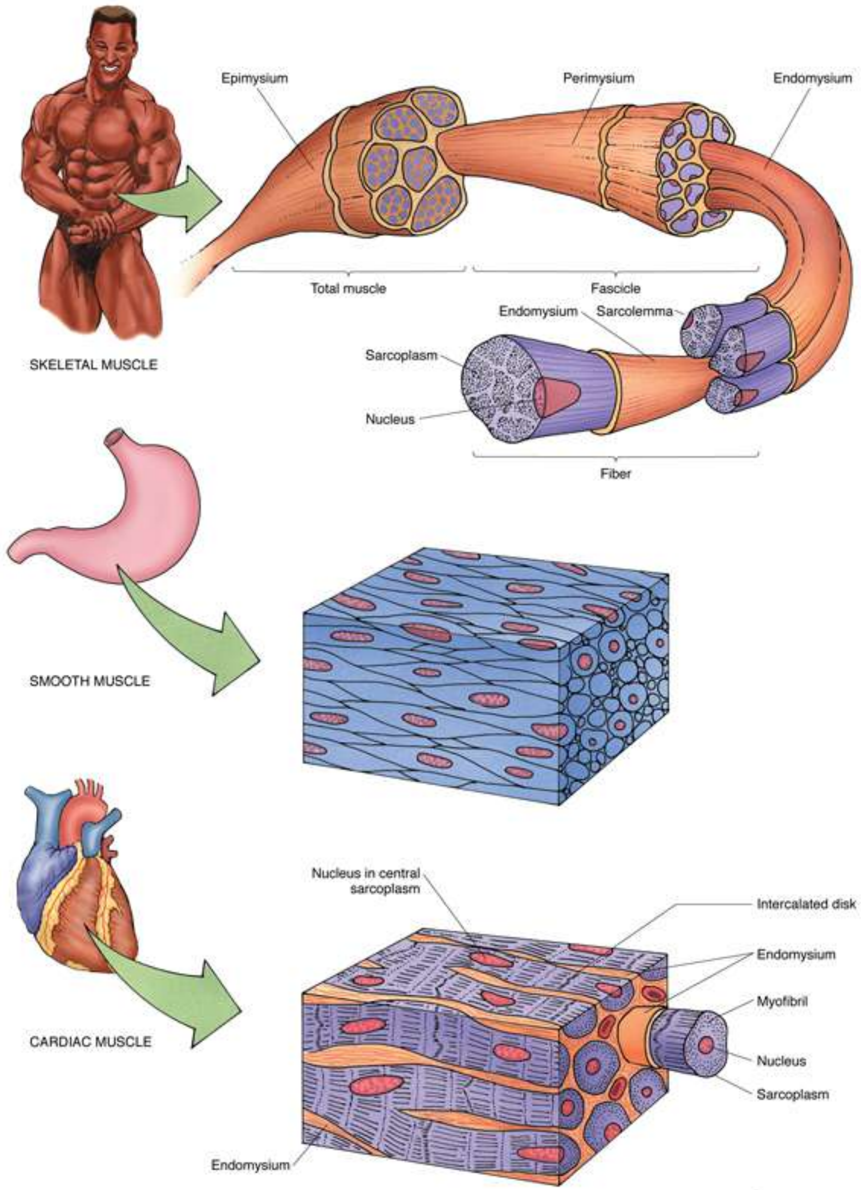



Three types of muscle. *Top,* Skeletal muscle; *center,* smooth muscle; *bottom,* cardiac muscle.

**Striated** muscle displays characteristic alternations of **light and dark cross-bands**, which are absent in smooth muscle.

There are two types of striated muscle: **skeletal,** accounting for most of the voluntary muscle mass of the body, and involuntary **cardiac** muscle, limited to the heart.

# Muscle Tissue




Three types of muscle. *Top,* Skeletal muscle; *center,* smooth muscle; *bottom,* cardiac muscle.

**Smooth muscle** is located in the walls of blood vessels and the viscera as well as in the dermis of the skin.

# Muscle Regeneration and Growth

## Skeletal Muscle

- Increase in size (hypertrophy)
- Increase in number (regeneration/proliferation)
  - Satellite cells are the source of regenerative cells

## Heart Muscle

- Increase in size (hypertrophy)
- Formerly thought to be non-proliferative
  - Post-infarction tissue remodeling by fibroblasts (fibrosis/scarring)
  - New evidence suggests mitotic cardiomyocytes and regeneration

## Smooth Muscle

- Increase in size (hypertrophy)
- Increase in number (regeneration/proliferation)
  - Smooth muscle cells are proliferative
  (e.g. uterine myometrium and vascular smooth muscle)
  - Vascular pericytes can also provide source of smooth muscle

# Function of Muscle Tissue

- Produce Movement
- Maintain posture
- Stabilize joints
- Thermogenesis

**Cachexia**, is loss of weight, muscle atrophy, fatigue, weakness

# Properties of Muscle Tissue

**Excitability**

- Respond to chemicals released by nerve cells
- Ability to generate electrical signals

**Contractility**

- Ability to shorten and generate force

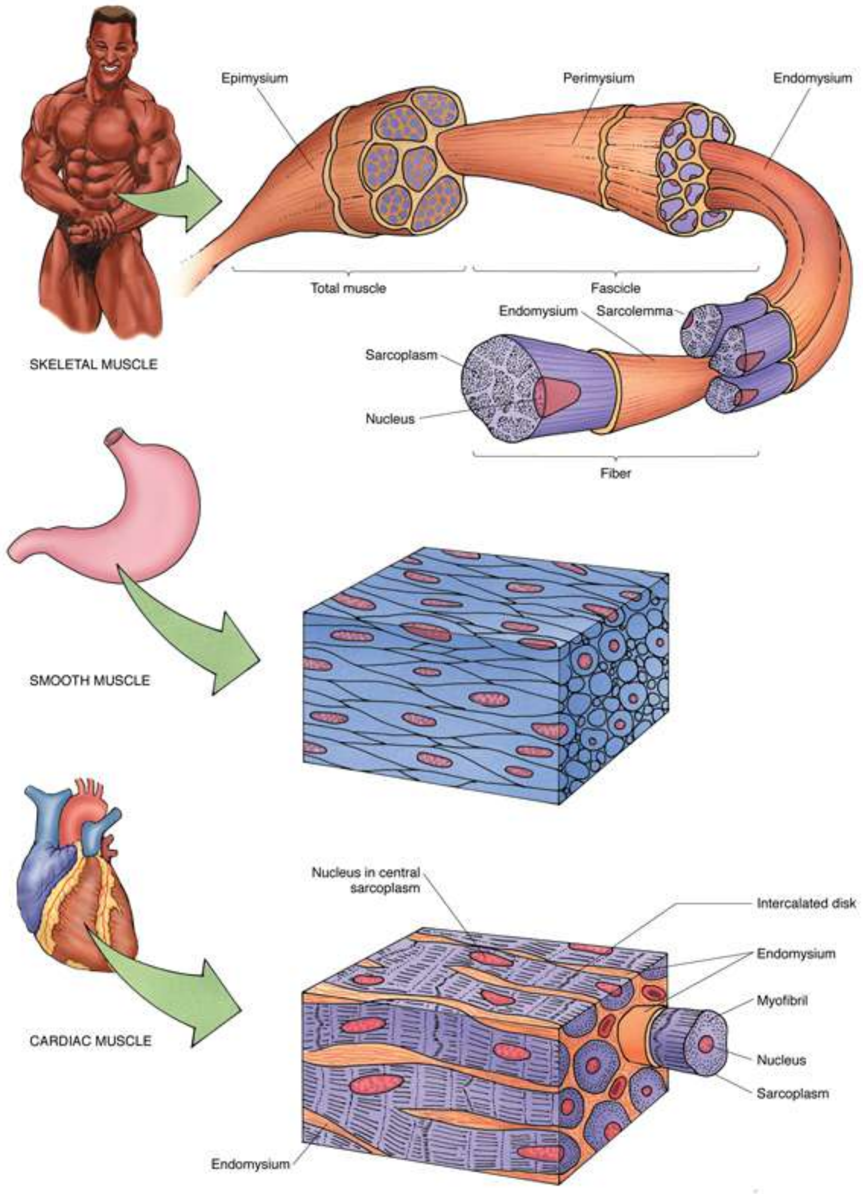
**Extensibility**

- Ability to stretch

**Elasticity**

- Ability to return to the original shape

# Muscle Tissue




Three types of muscle. *Top,* Skeletal muscle; *center,* smooth muscle; *bottom,* cardiac muscle.

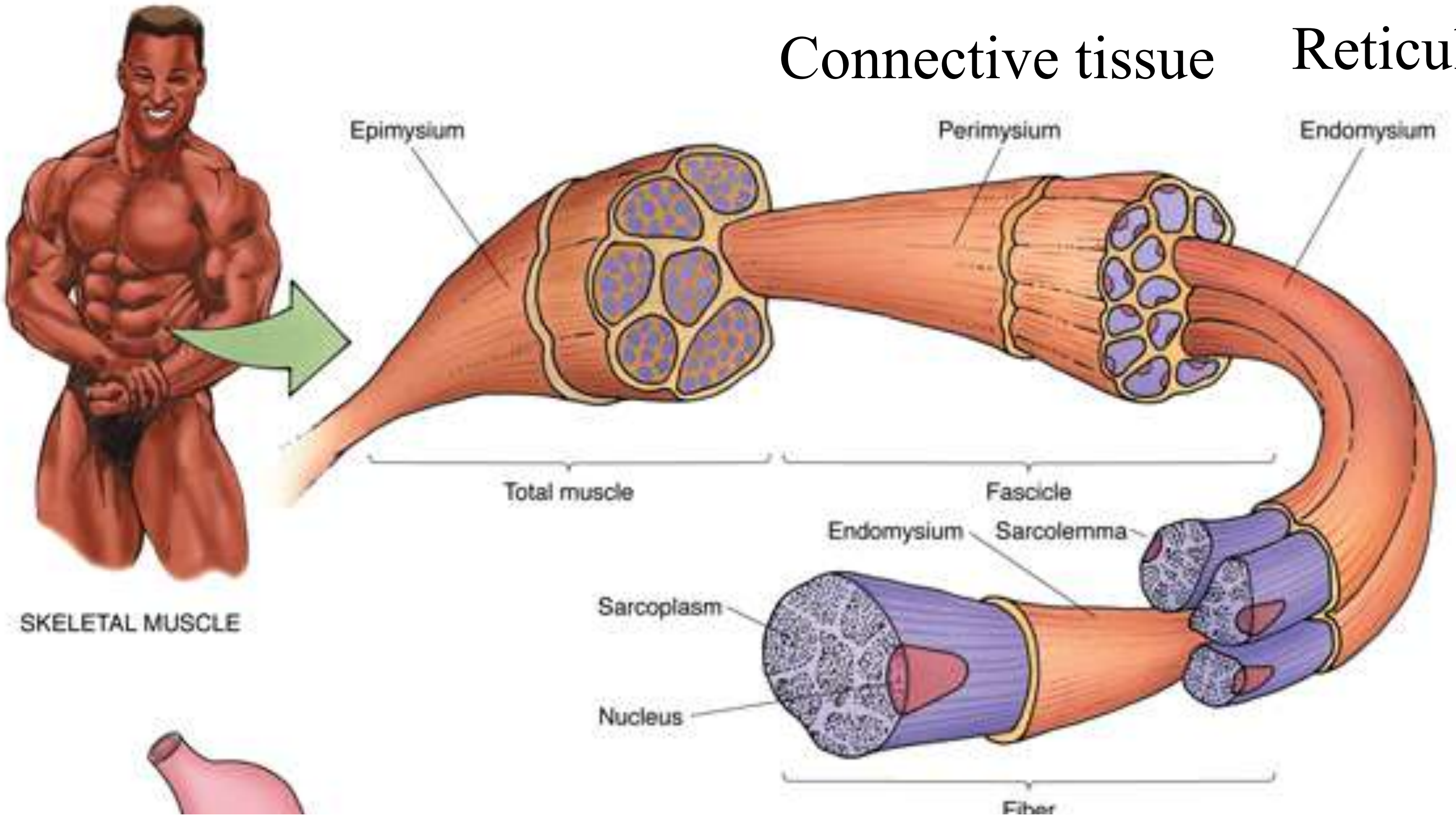
Cells of muscle are elongated and are called **striated** or **smooth** muscle, depending on the respective presence or absence of a regularly repeated arrangement of <u>myofibrillar contractile proteins, **the myofilaments**.</u>

Unique terms are often used to describe the components of muscle cells.

- Thus, muscle cell membrane is referred to as **<u>sarcolemma</u>;**
- the cytoplasm, as **sarcoplasm;**
- the smooth endoplasmic reticulum, as **sarcoplasmic reticulum;**
- and occasionally, the mitochondria, as **sarcosomes.**

# Muscle Tissue

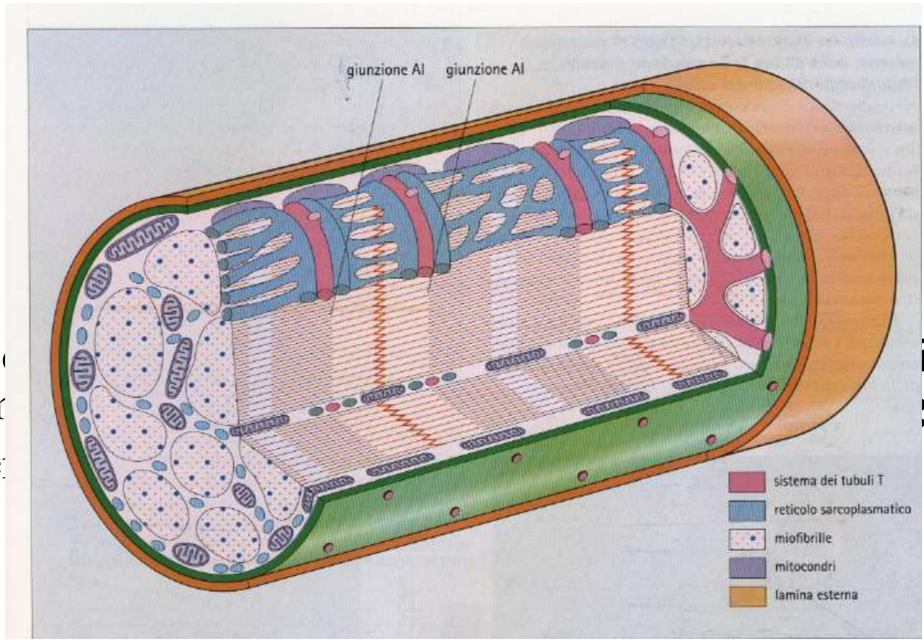
Connective tissue Reticular fibers

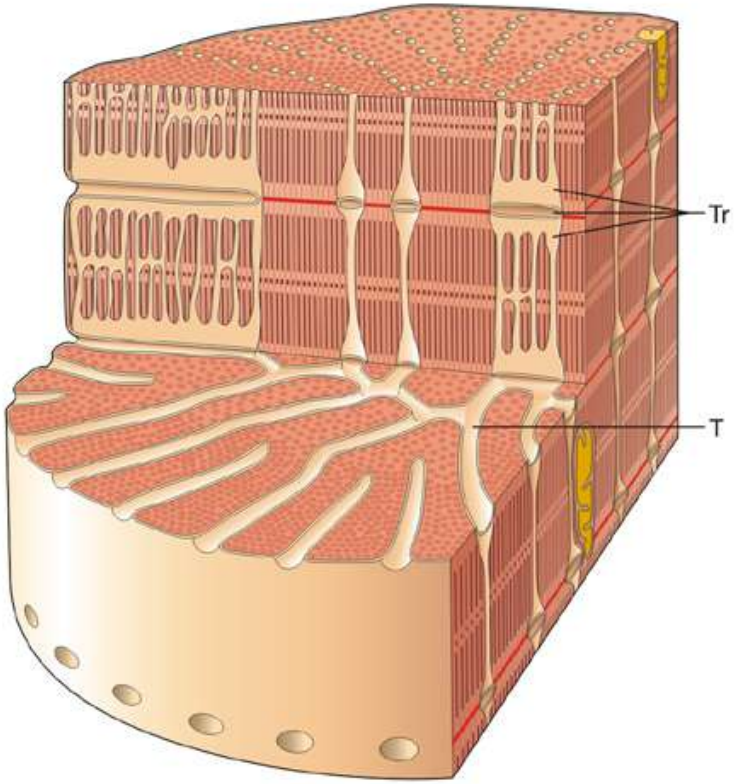



Because they are much longer than they are wide, muscle cells frequently are called **muscle fibers**.

# Scheletal Muscle Fiber Organization

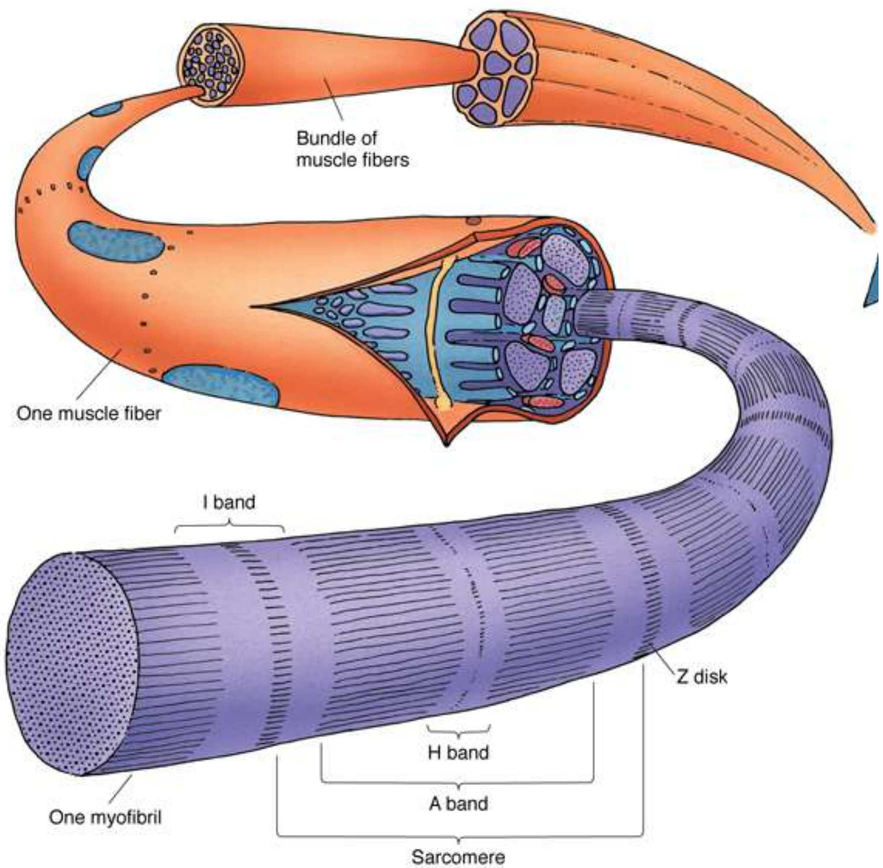
- Size from few mm up to 10 cm lenght
  10-100 um width
- **Sarcolemma**




- **Sarc** … iculum well
  the m … *ganized in n*
- Seve … the striatio

# Skeletal Muscle

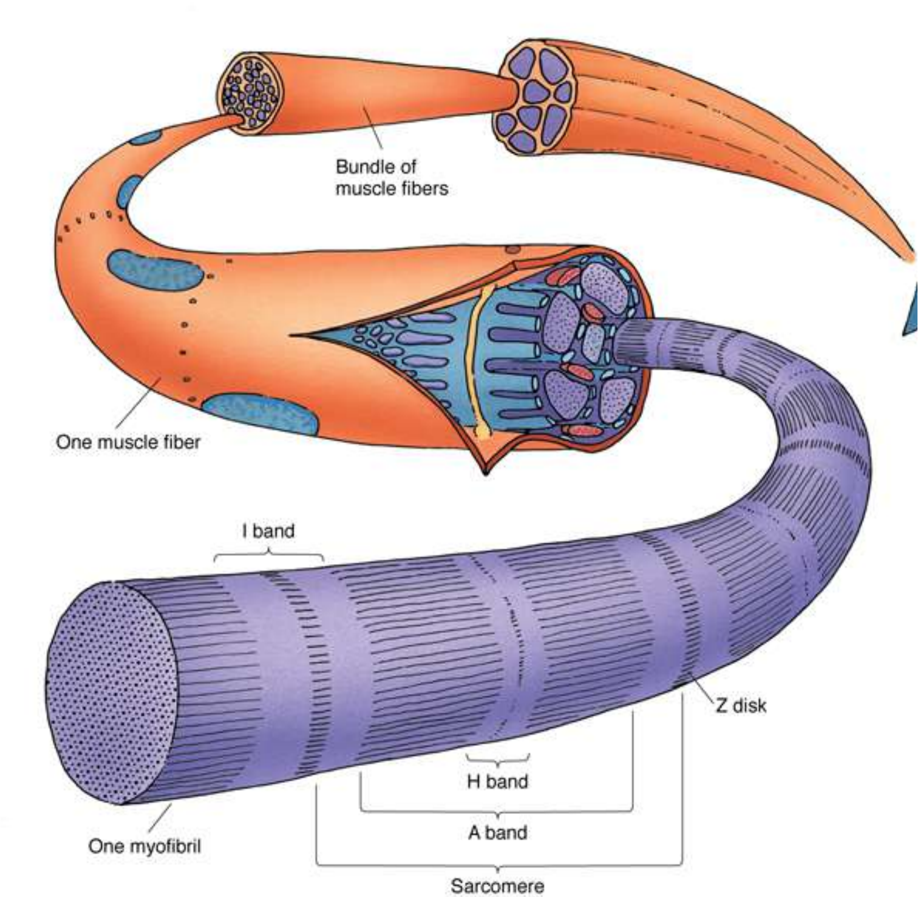



Much of the skeletal muscle cell or muscle fibers is composed of longitudinal arrays of cylindrical **myofibrils,** **<u>each 1 to 2 μm</u>** in diameter.

They extend the entire length of the cell and are aligned precisely with their neighbors.

<u>This strictly ordered parallel arrangement of the myofibrils is responsible for the cross-striations of light and dark banding that are</u> characteristic of skeletal muscle viewed in longitudinal section.

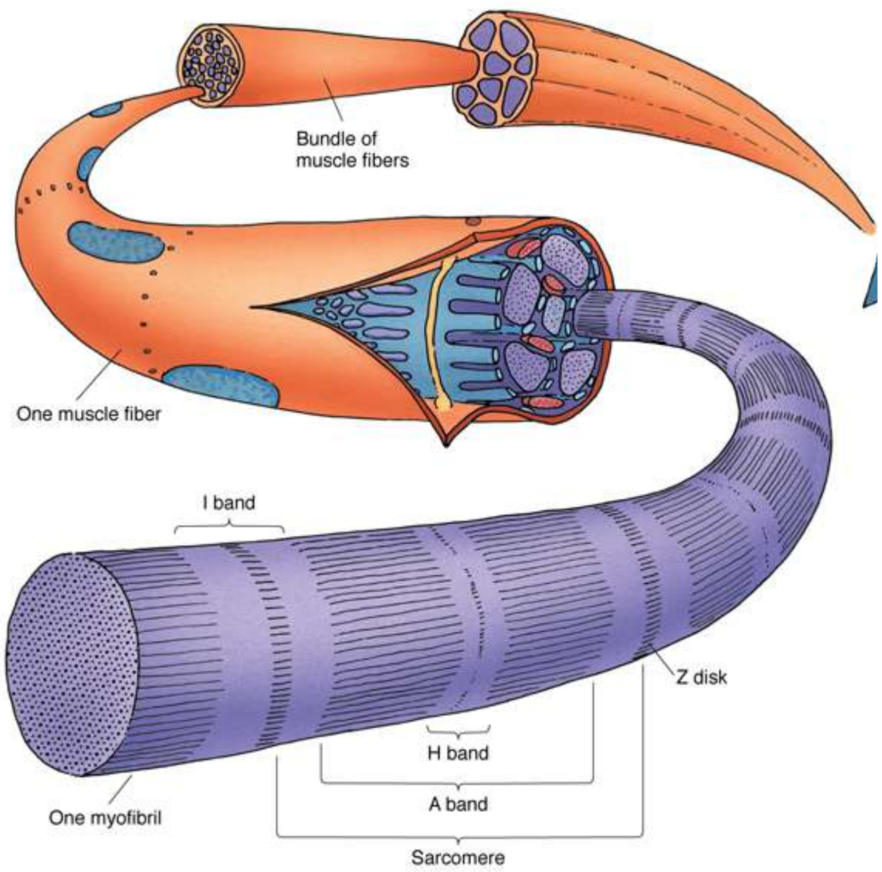
# Skeletal Muscle




Skeletal **muscle fibers** are multinucleated cells, with their numerous nuclei peripherally located just beneath the cell membrane (sarcolemma).

Each cell is surrounded by **endomysium**, whose fine reticular fibers intermingle with those of neighboring muscle cells.

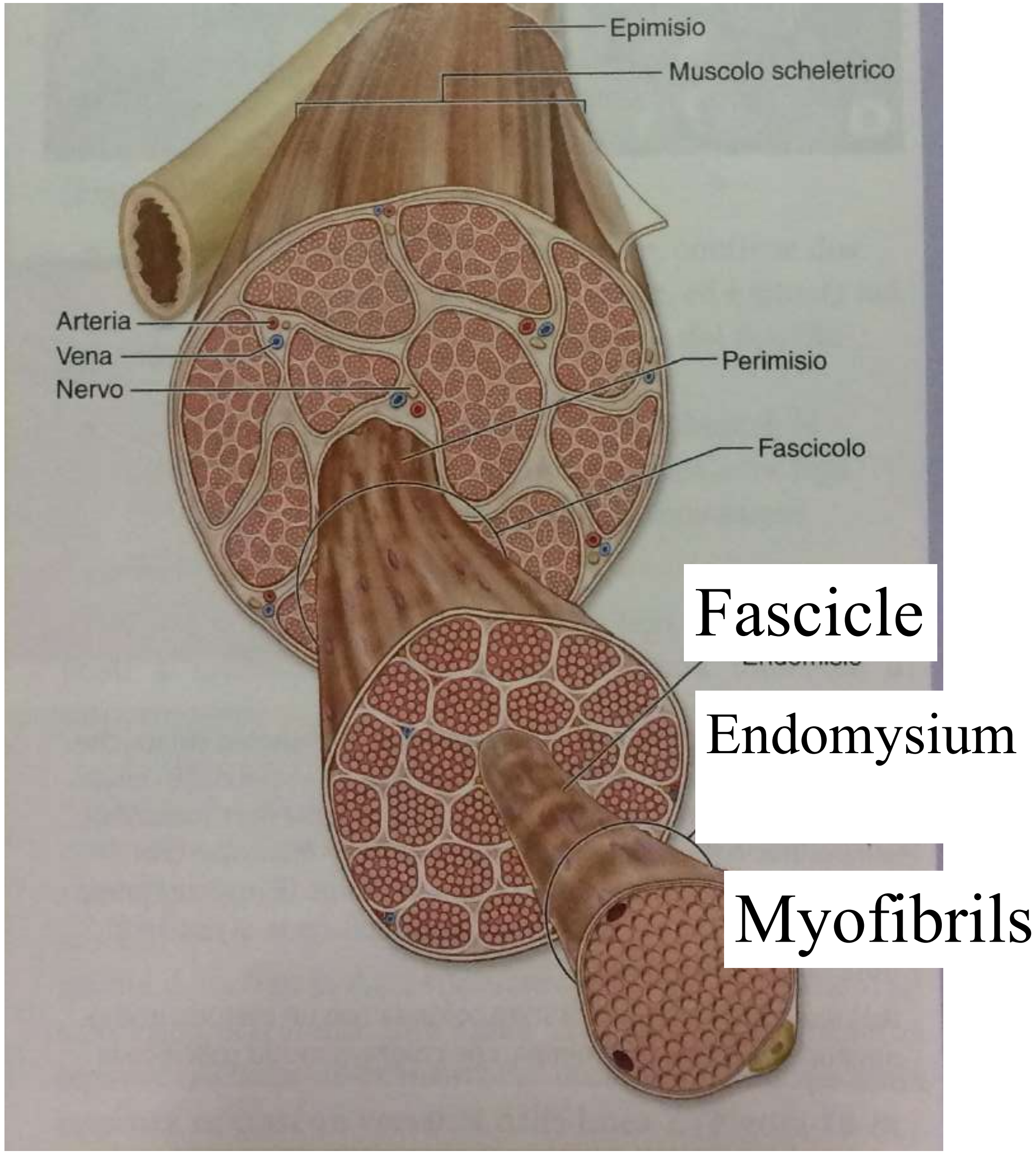
# Skeletal Muscle




The entire gross muscle is surrounded by a **thick connective tissue investment**, known as the **epimysium**.

Individual skeletal muscle fibers possess a sarcolemma that has tubular invaginations (T tubules) that course through the sarcoplasm and are flanked by terminal cisternae of the sarcoplasmic reticulum.

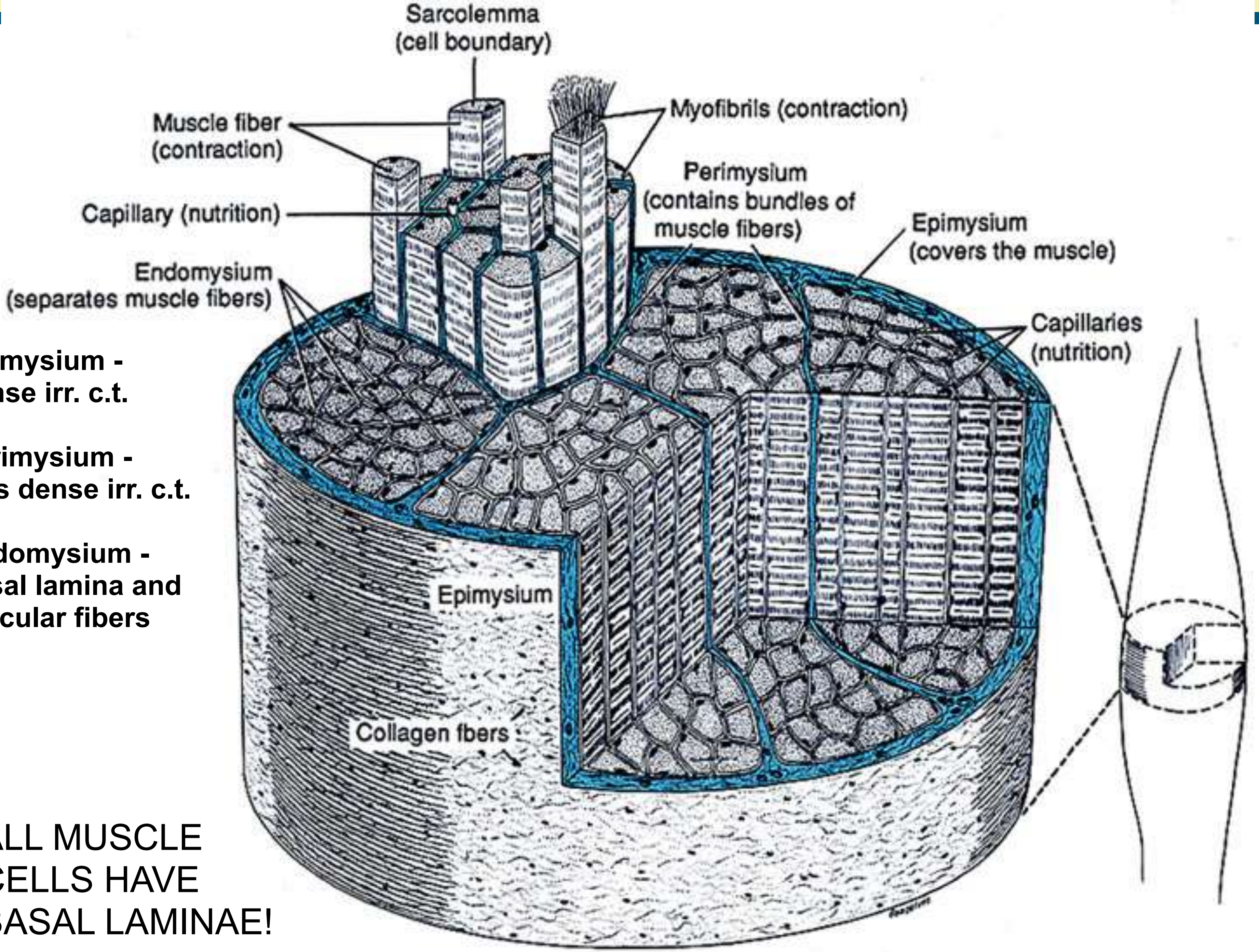
# Skeletal Muscle




The contractile elements of the skeletal muscle fiber are organized into discrete cylindrical units called myofibrils.

Each myofibril is **composed of thousands of sarcomeres** with their characteristic A, I, and H bands and Z disk.

# Skeletal Muscle Investments



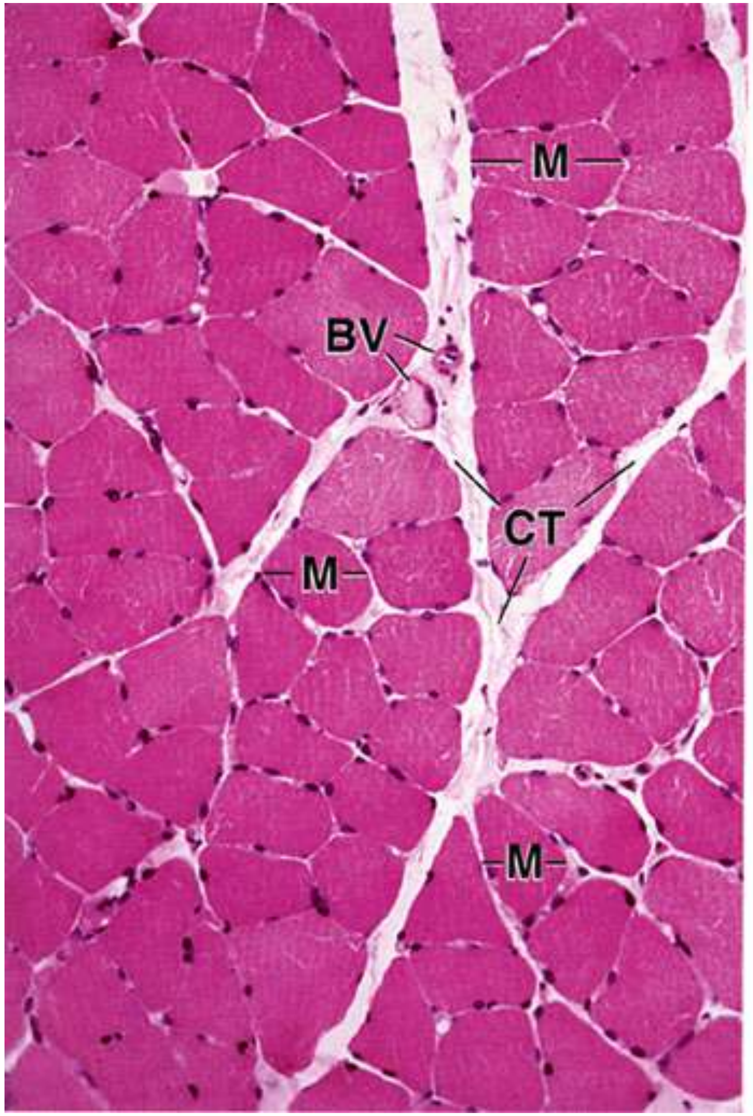

**Epimysium - dense irr. c.t.**

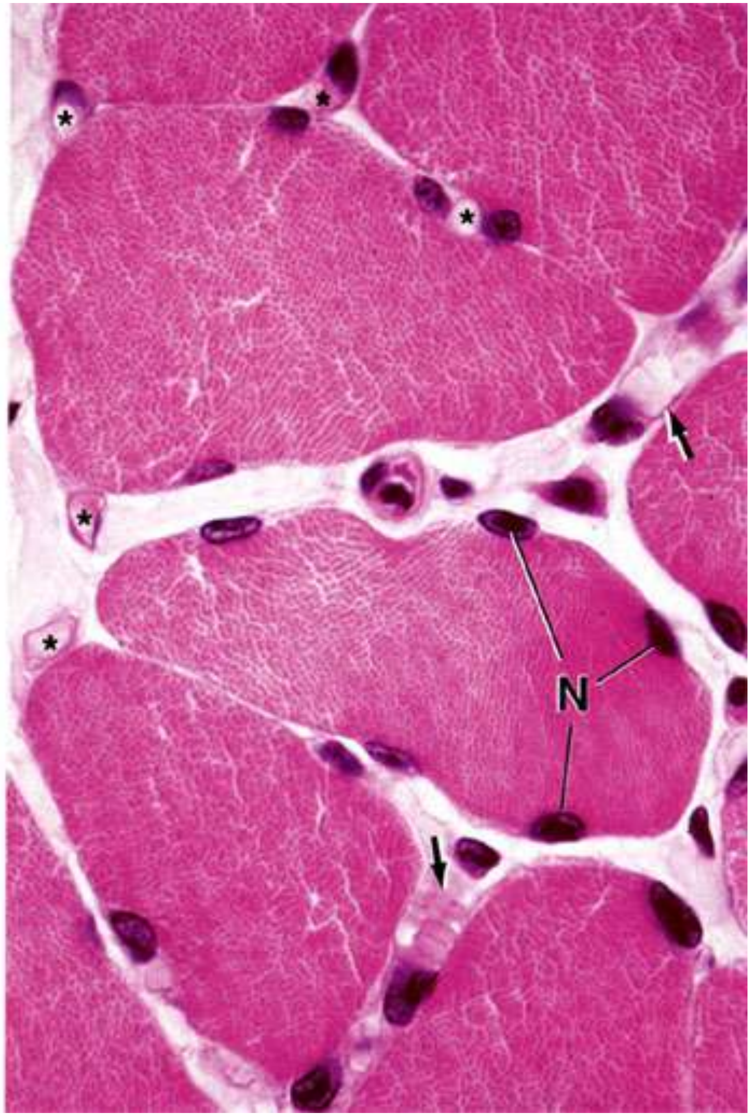
**Perimysium - less dense irr. c.t.**

**Endomysium - basal lamina and reticular fibers**

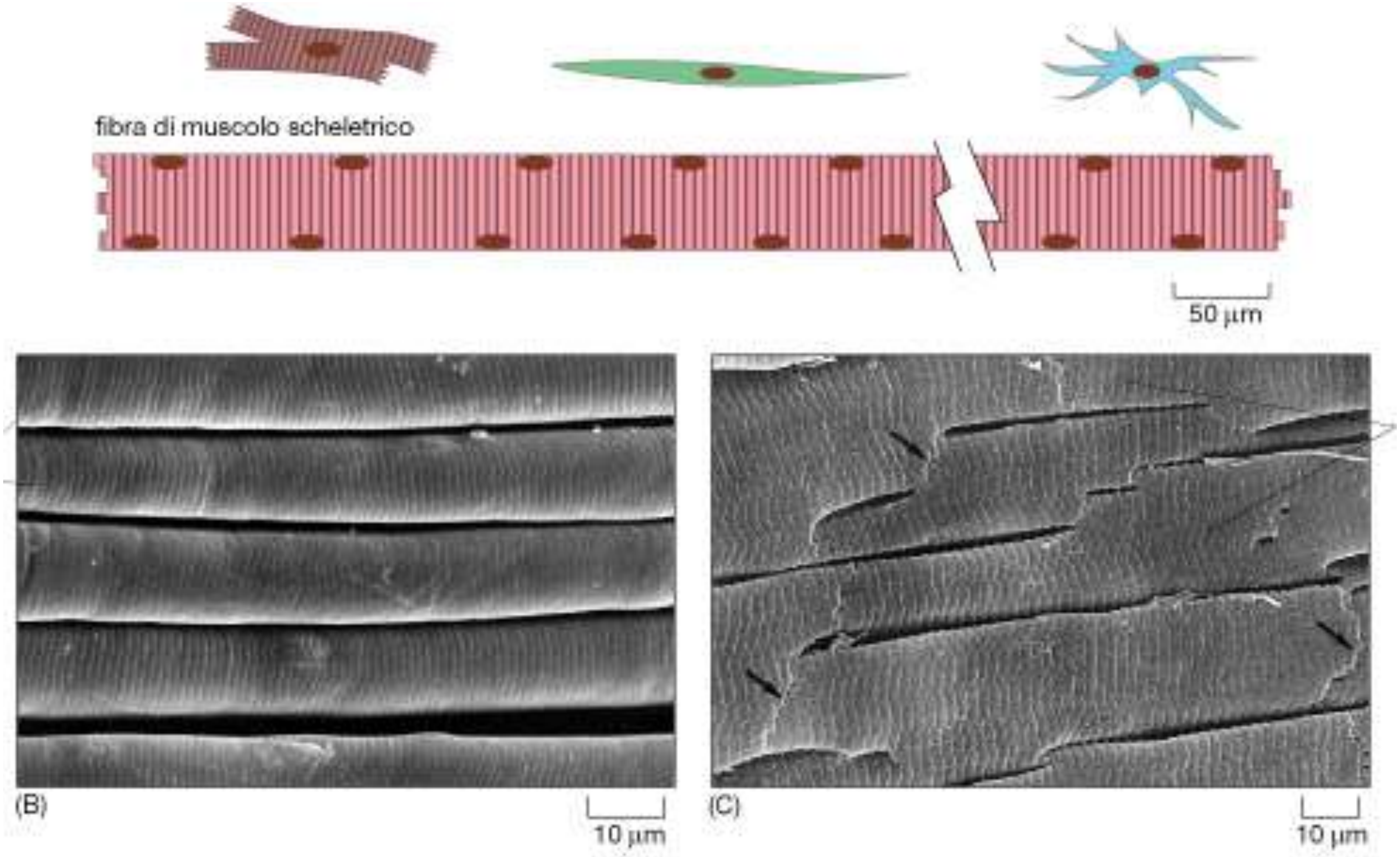
ALL MUSCLE CELLS HAVE BASAL LAMINAE!

## Skeletal Muscle as seen in transverse/cross section in the light microscope

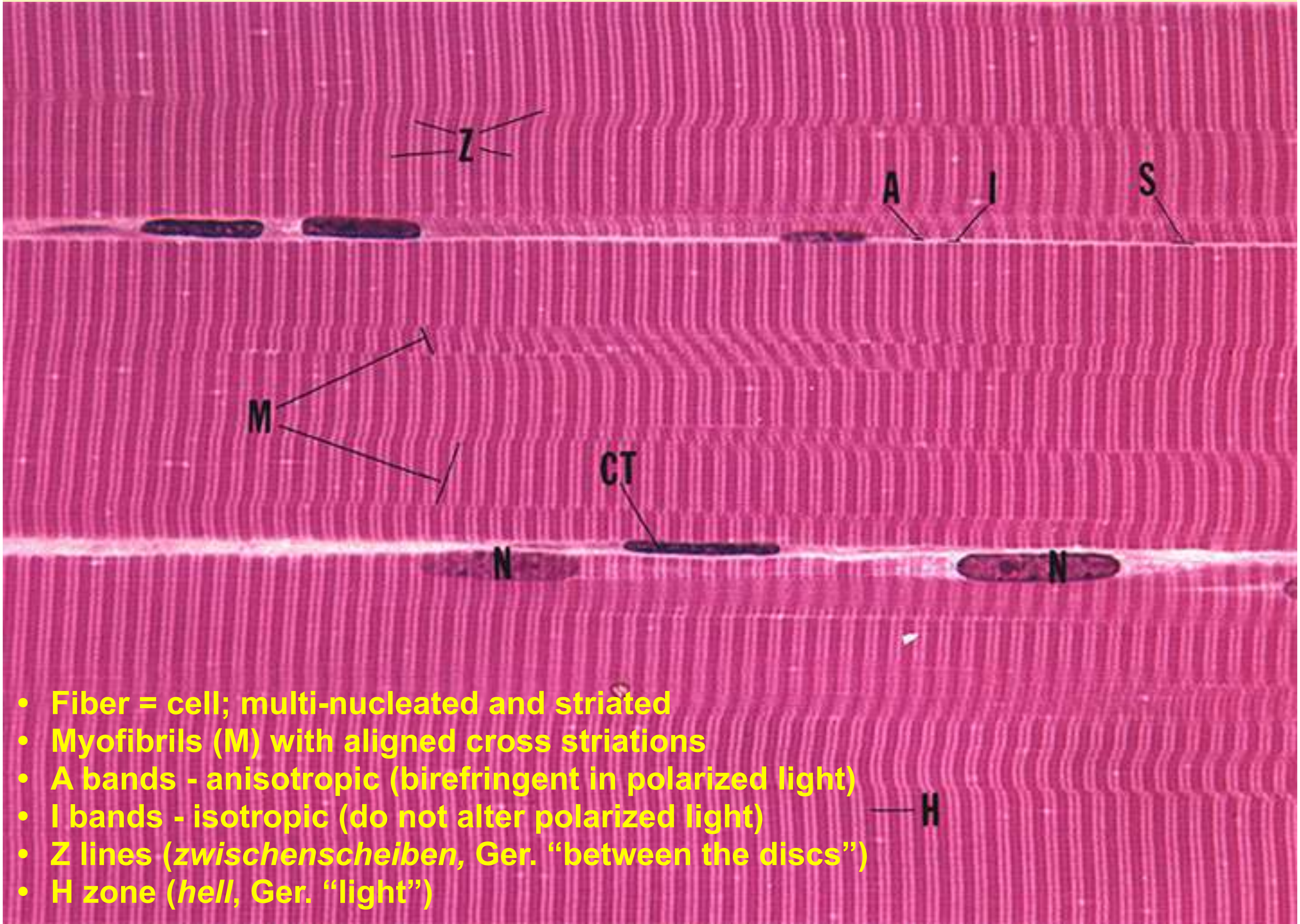


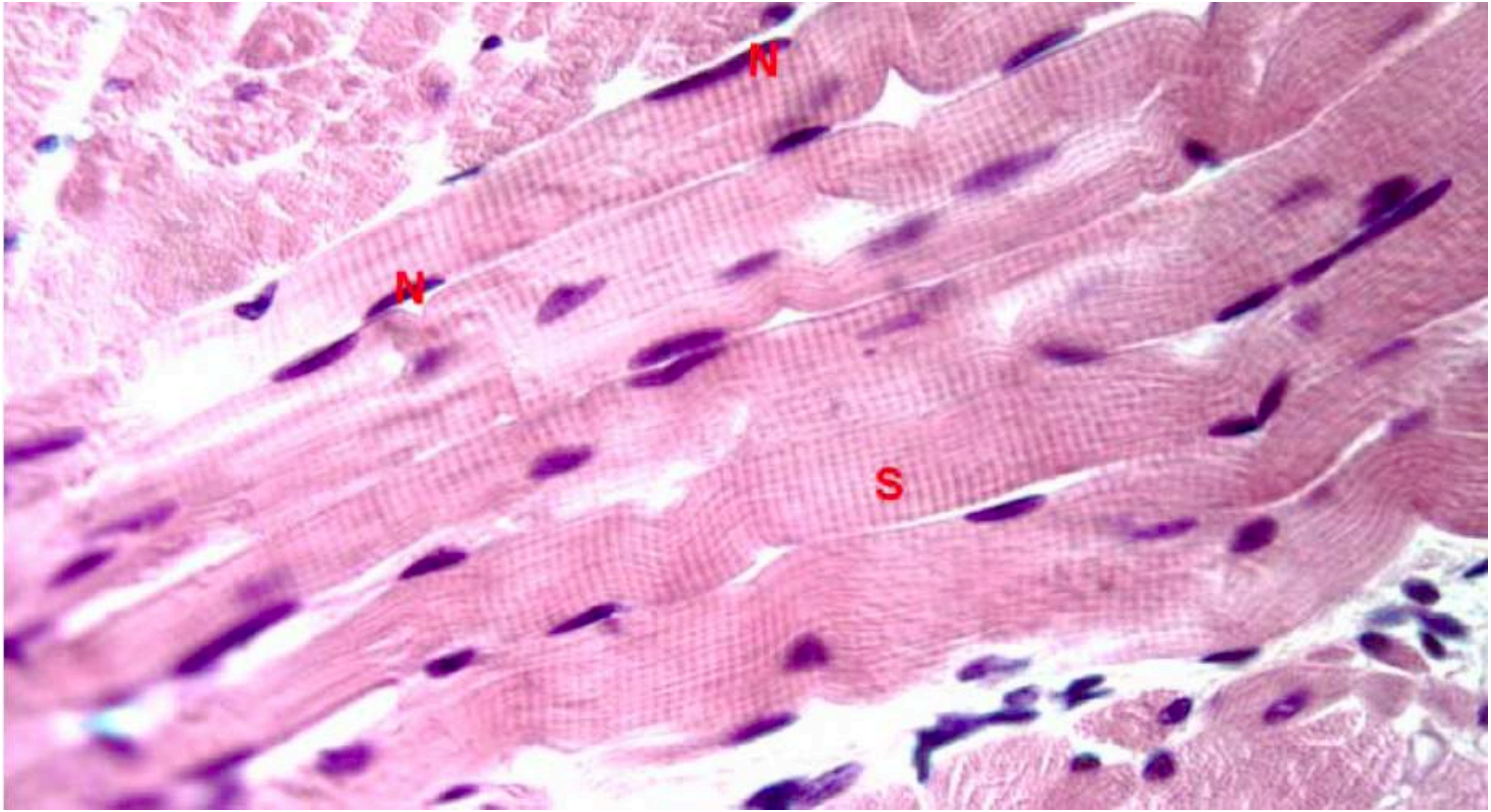

Identify endo, epi or perimysium


fibra di muscolo scheletrico
50 µm
(B)
10 µm
(C)
10 µm

# Skeletal Muscle as seen in longitudinal section in the light microscope




- Fiber = cell; multi-nucleated and striated
- Myofibrils (M) with aligned cross striations
- A bands - anisotropic (birefringent in polarized light)
- I bands - isotropic (do not alter polarized light)
- Z lines (*zwischenscheiben,* Ger. "between the discs")
- H zone (*hell*, Ger. "light")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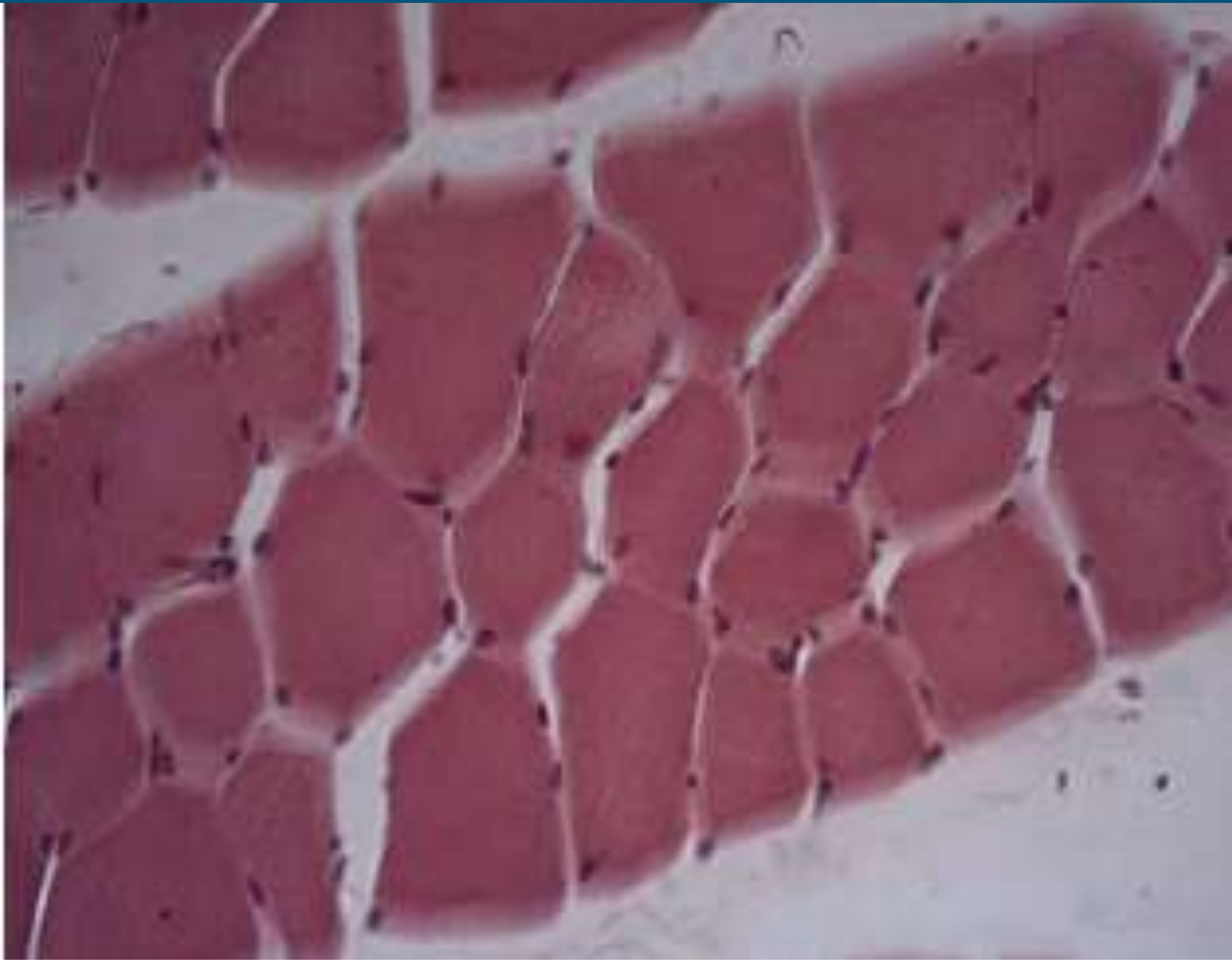
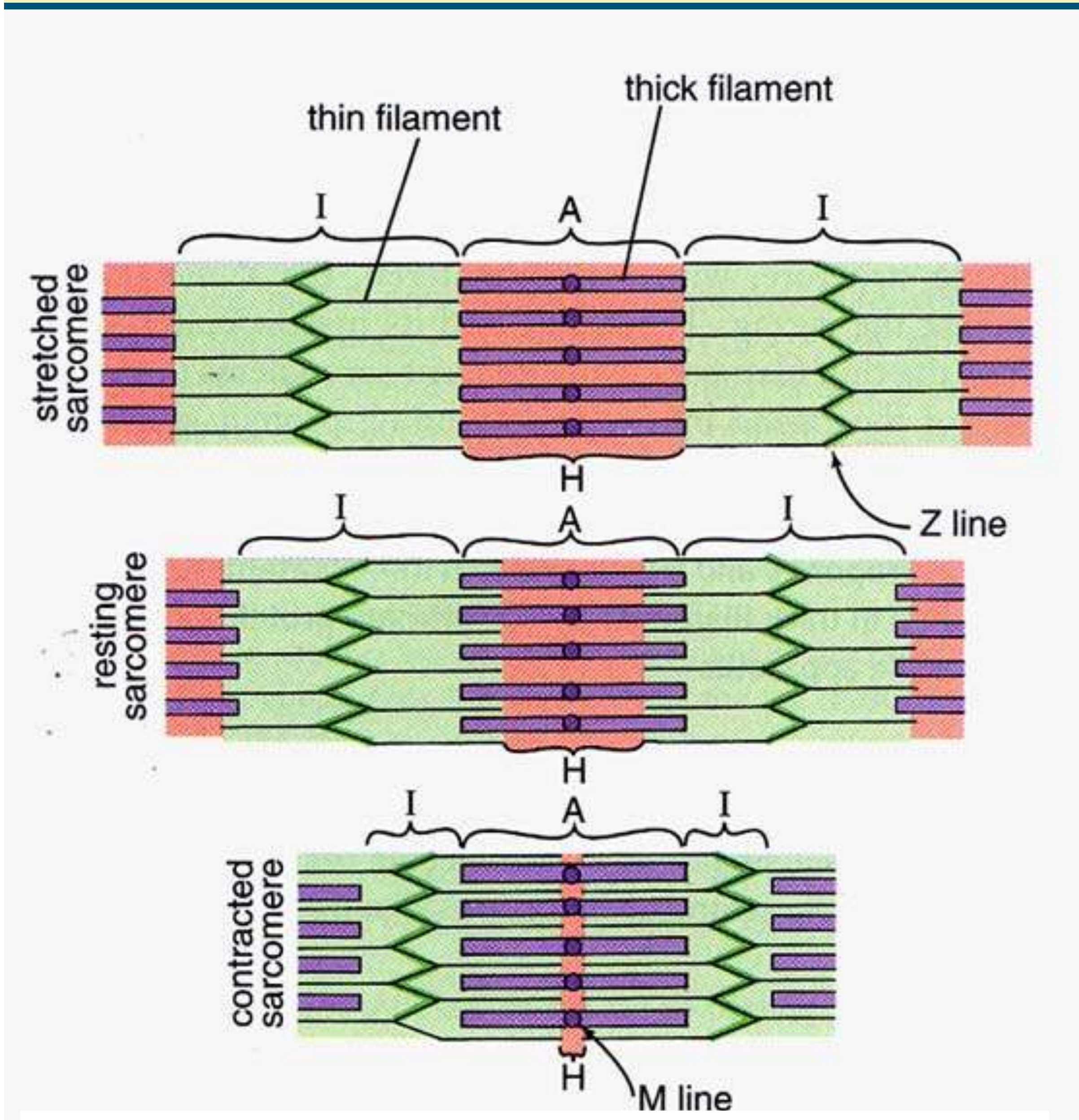
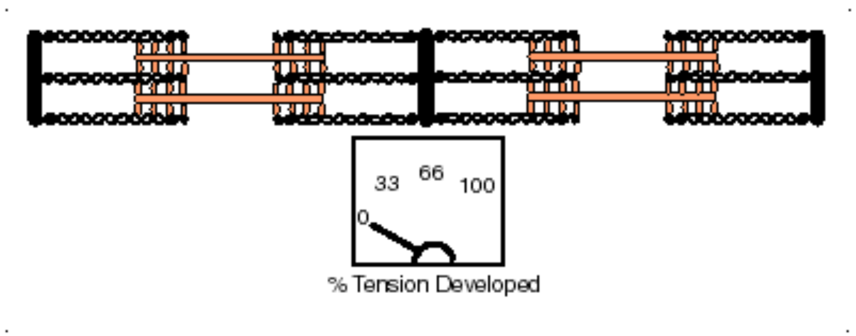


# Sarcomere structure



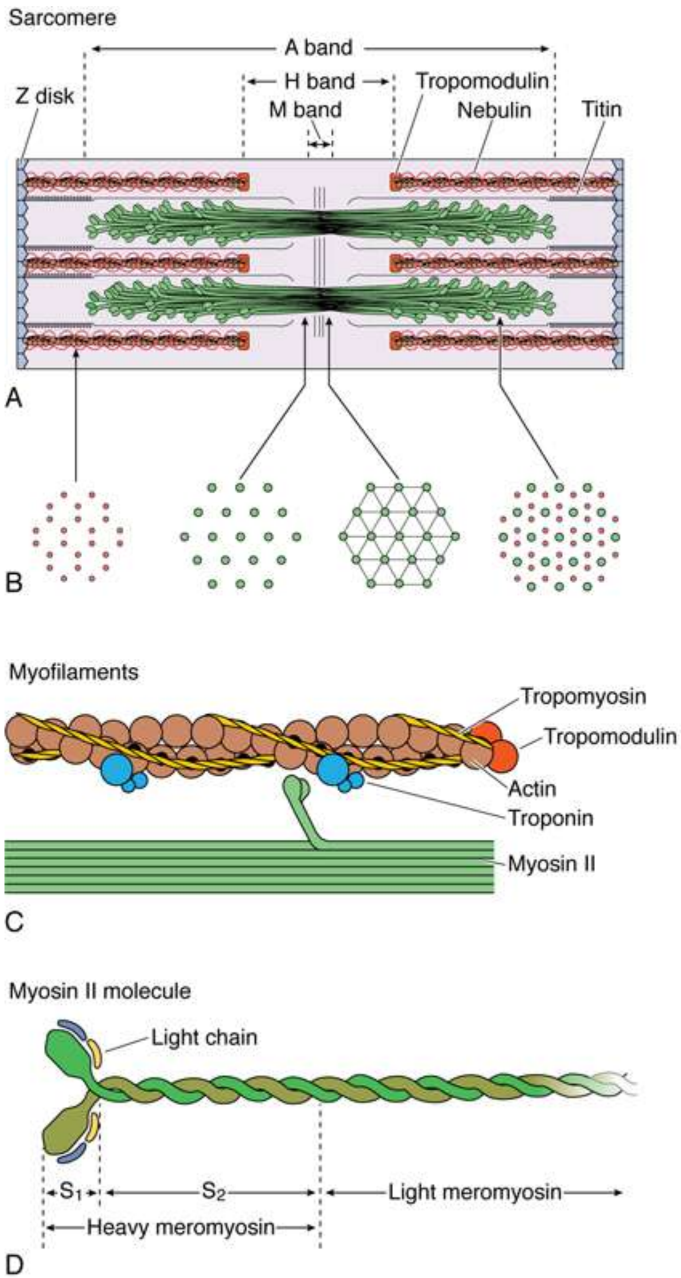

***<u>Muscle fibers are composed of many contractile units (sarcomeres)</u>***

Changes in the amount of overlap between thick and thin filaments allows for contraction and relaxation of muscle fibers

Many fibers contracting together result in gross movement

<u>Note</u>: **Z lines** move closer together; I **band** and **H band** become smaller during contraction

# Myofilaments




Electron microscopy reveals the presence of parallel, interdigitating, rod-like **thick myofilaments** and **thin myofilaments.**

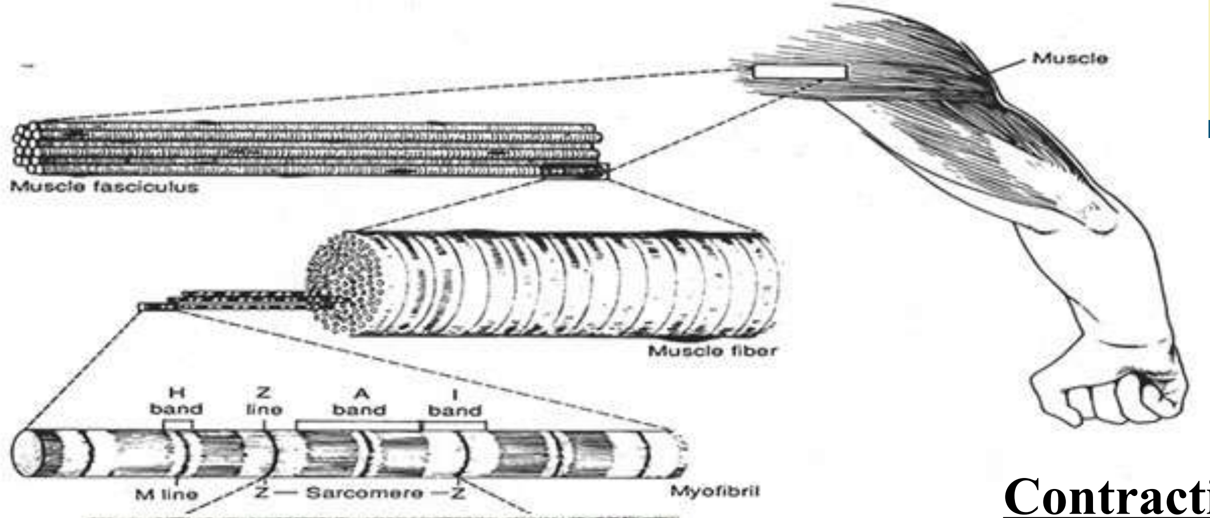
The **thick filaments** (15 nm in diameter and 1.5 µm long) are composed of **myosin,** whereas the **thin filaments** (7 nm in diameter and 1.0 µm long) are composed primarily of F-**actin.**

**Thin filaments originate at the Z disk** and project toward the center of the two adjacent sarcomeres, thus pointing in opposite directions.

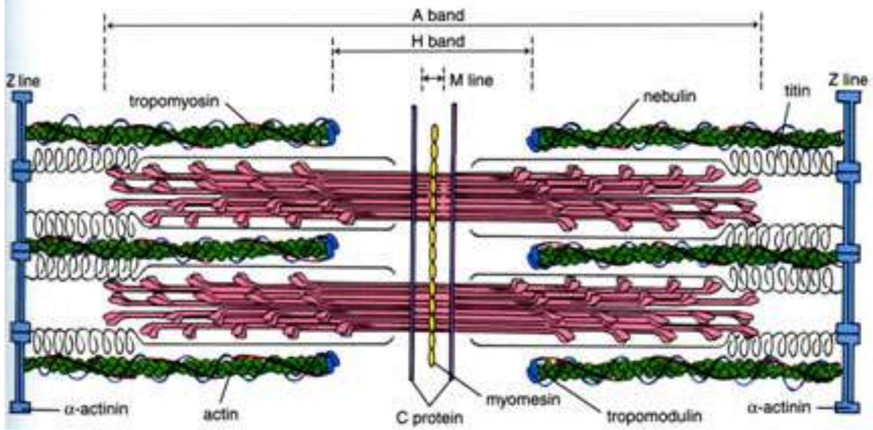
Hence, a single sarcomere has two groups of parallel arrays of thin filaments, each attached to one Z disk, with all the filaments in each group pointing toward the middle of the sarcomere.

Thick filaments also form parallel arrays, interdigitating with the thin filaments in a specific fashion.

# Sarcomere structure










**<u>Contractile unit of striated muscle</u>**

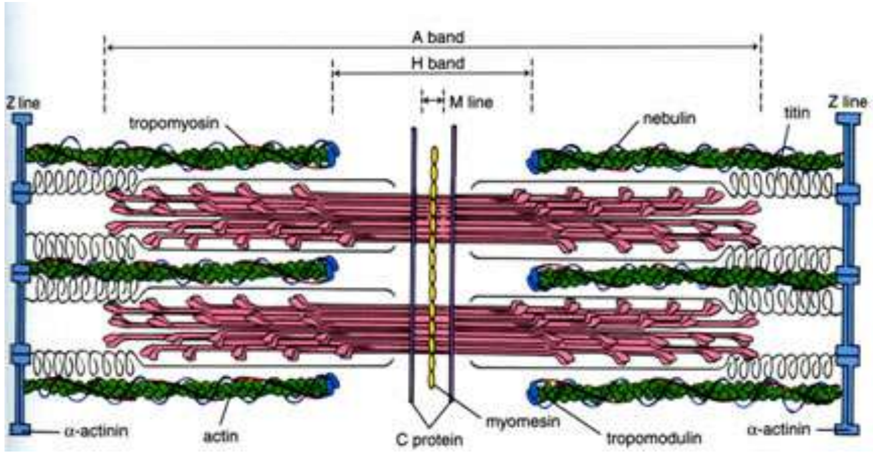
Structures between Z lines

- 2 halves of Isotropic (I) bands
- Anisotropic (A) band
- M line (*mittelscheibe,* Ger. "middle of the disc")
- Myofilaments
  - Actin and troponin
  - Myosin

Other structural proteins

- Titin
- Nebulin
- Desmin (Z line)
- Vimentin (Z line)

# Sarcomere structural proteins






**Nebulin** is a giant protein (600–900-kd) associated with thin (F-actin) filaments; it inserts into the Z disk and acts as a **stabilizer** required for maintaining the length of F-actin.

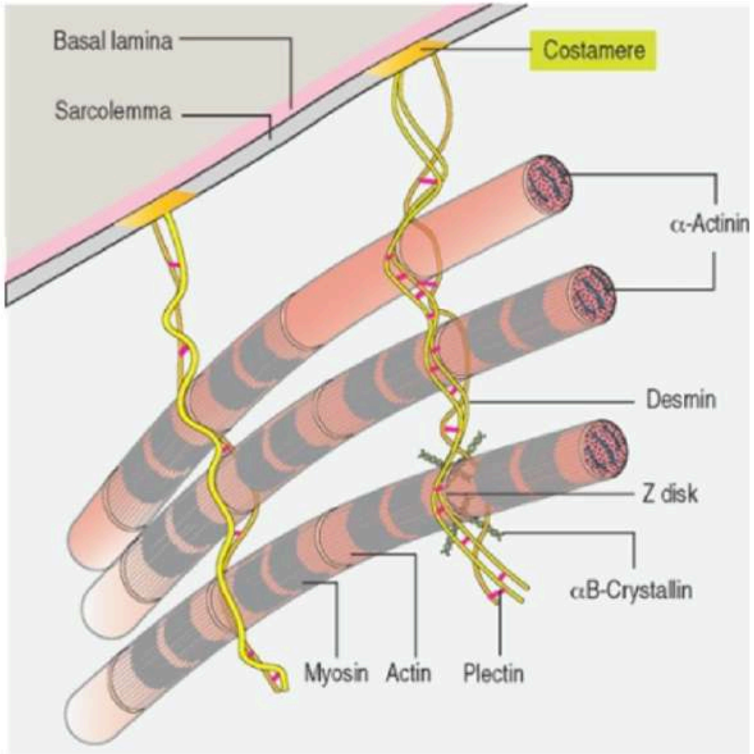
**Titin** is a very large protein with a molecular mass in the range of millions determined by about 34,000 amino acids. Each molecule associates with **thick (myosin) myofilaments** and inserts into the Z disk, extending to the bare zone of the myosin filaments, close to the M line.

Titin has the following functions:

1.It controls the assembly of the thick myofilament

2. It regulates sarcomere elasticity by establishing a spring-like connection between the end of the thick myofilament and the Z-disk

# Sarcomere structural proteins



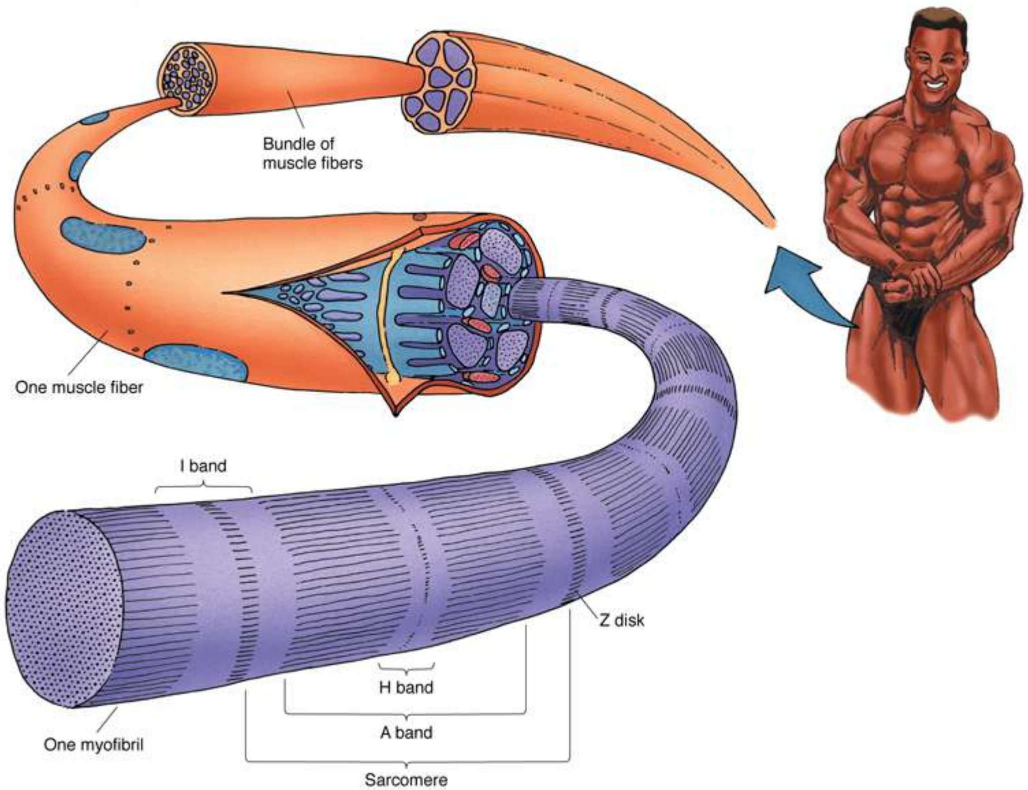

**Desmin** is (10-nm) filaments protein essential for the maintenance of the integrity of the contractile apparatus in the muscle:

**1.** Desmin stabilizes myofibrils. Desmin filaments encircle the Z disks of myofibrils and are linked to the Z disk and to each other by **plectin** filaments. Desmin filaments extend from the Z disk of one myofibril to the adjacent myofibril. Desmin filaments also extend from the sarcolemma to the nuclear envelope.

**2.** Desmin links myofibrils to the sarcolemma. Desmin inserts into specialized sarcolemma-associated plaques, called **costameres.** Costameres, acting in concert with the dystrophin-associated protein complex, transduce contractile force from the Z disk to the basal lamina, maintain the structural integrity of the sarcolemma and stabilize the position of myofibrils in the sarcoplasm.

**3.** Desmin determines the distribution and function of mitochondria in skeletal and cardiac muscle. In the absence of desmin, proper mitochondrial positioning is lost and mitochondrial function is compromised, leading to cell death by either energy deprivation or release of proapoptotic cytochrome c.

# Skeletal Muscle




Organization of myofibrils and sarcomeres within a skeletal muscle cell. Note that the entire gross muscle is surrounded by a thick connective tissue investment, known as the epimysium, which provides finer connective tissue elements (the perimysium) that surround bundles of skeletal muscle fibers. Individual muscle cells are surrounded by still finer connective tissue elements, the endomysium. Individual skeletal muscle fibers possess a sarcolemma that has tubular invaginations (T tubules) that course through the sarcoplasm and are flanked by terminal cisternae of the sarcoplasmic reticulum. The contractile elements of the skeletal muscle fiber are organized into discrete cylindrical units called myofibrils. Each myofibril is composed of thousands of sarcomeres with their characteristic A, I, and H bands and Z disk.

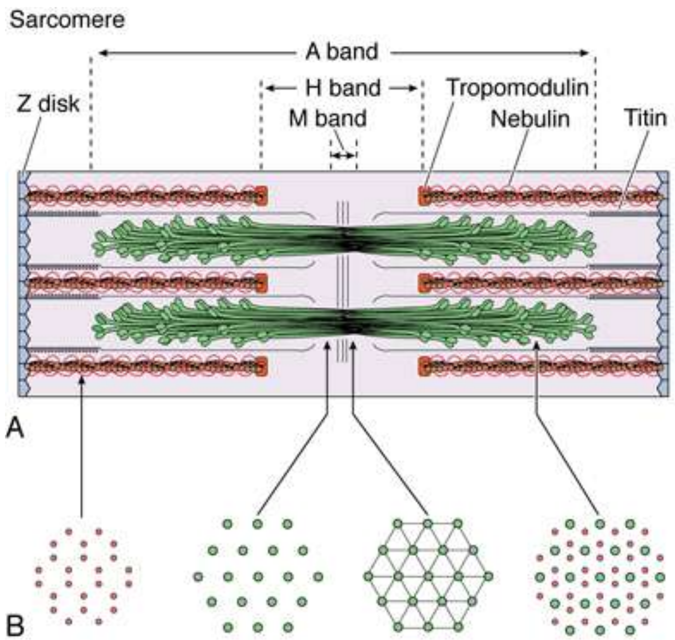
The dark bands are known as **A bands** and the light bands as **I bands**.

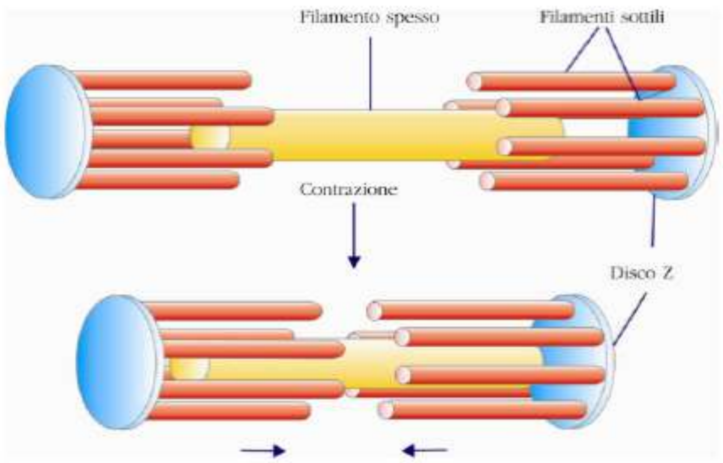
The center of each A band is occupied by a pale area, the **H band,** which is bisected by a thin **M line.**

Each I band is bisected by a thin dark line, the **Z disk (Z line).**

The region of the myofibril between two successive Z disks, known as a **sarcomere,** is 2.5 μm in length and is considered the contractile unit of skeletal muscle fibers. During muscle contraction, the I band becomes narrower, the H band is extinguished, and the Z disks move closer together (approaching the interface between the A and I bands), but the width of the A bands remains unaltered.

# Huxley's **sliding filament theory**




In a relaxed skeletal muscle fiber, the <u>**thick filaments**</u> <u>do not extend the entire length</u> of the sarcomere and the thin filaments projecting from the two Z disks of the sarcomere do not meet in the midline.

Therefore, there are regions of each sarcomere, on either side of each Z disk, where only thin filaments are present.

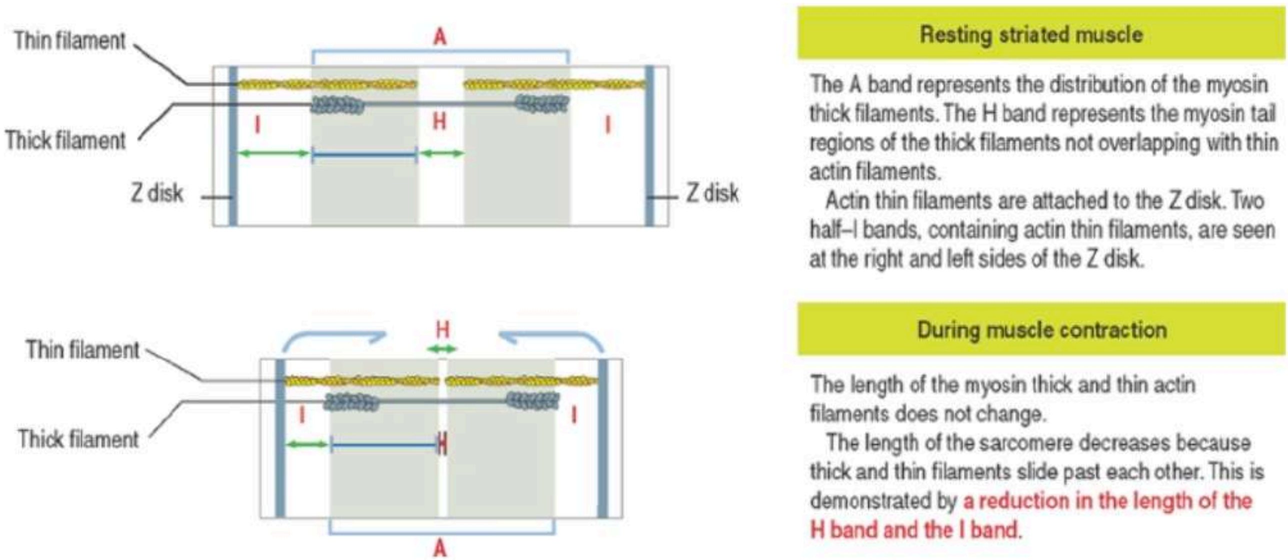
<u>During contraction, individual thick and thin filaments do not shorten; instead, **the two Z disks are brought closer** together as the thin filaments slide past the thick filaments</u> **(**Huxley's **sliding filament theory).**

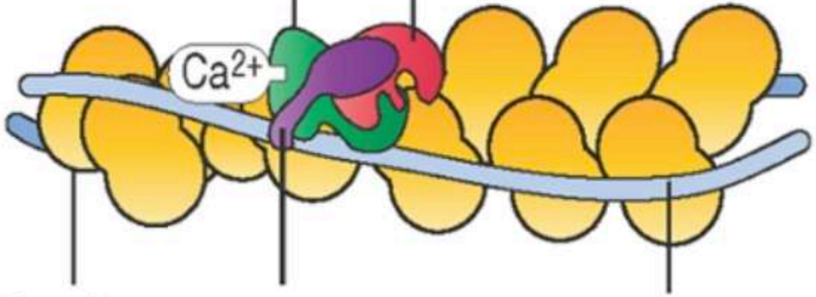
Thus, when contraction occurs, the motion of the thin filaments toward the center of the sarcomere creates a greater overlap between the two groups of filaments, effectively reducing the widths of the I and H band

# Sarcomere changes during muscle contraction

During muscle contraction, the muscle shortens about one-third of its original length. The relevant aspects of muscle shortening are the following:

- The **length** of the thick and thin filaments **does not change** during muscle contraction (the length of the A band and the distance between the Z disk and the adjacent H band are constant).
- The **length of the sarcomere decreases** because thick and thin filaments slide past each other (the size of the H band and I band decrease).
- The force of contraction is generated by the process that moves one type of filament past adjacent filaments of the other type.






**Tropomyosin**, the **troponin complex** and **$Ca^{2+}$ levels** in the cytosol (sarcoplasm) control muscle contraction. How is muscle contraction controlled?

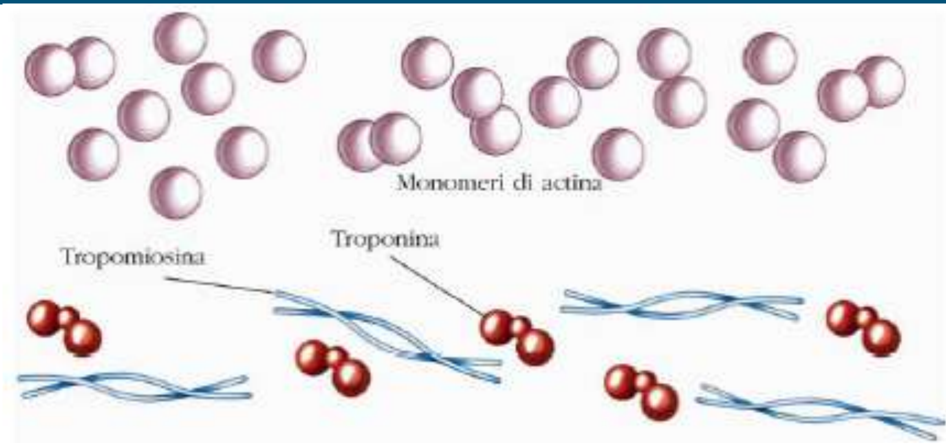
**Tropomyosin** consists of two α-helical rods twisted around each other. The rods are located in a groove along F-actin, near the myosin head. **Troponin (Tn)** is a complex of three proteins: **TnI**, **TnC** and **TnT**. TnC binds to $Ca^{2+}$, TnI binds to actin and TnT binds to tropomyosin. TnC is found only in striated muscle.

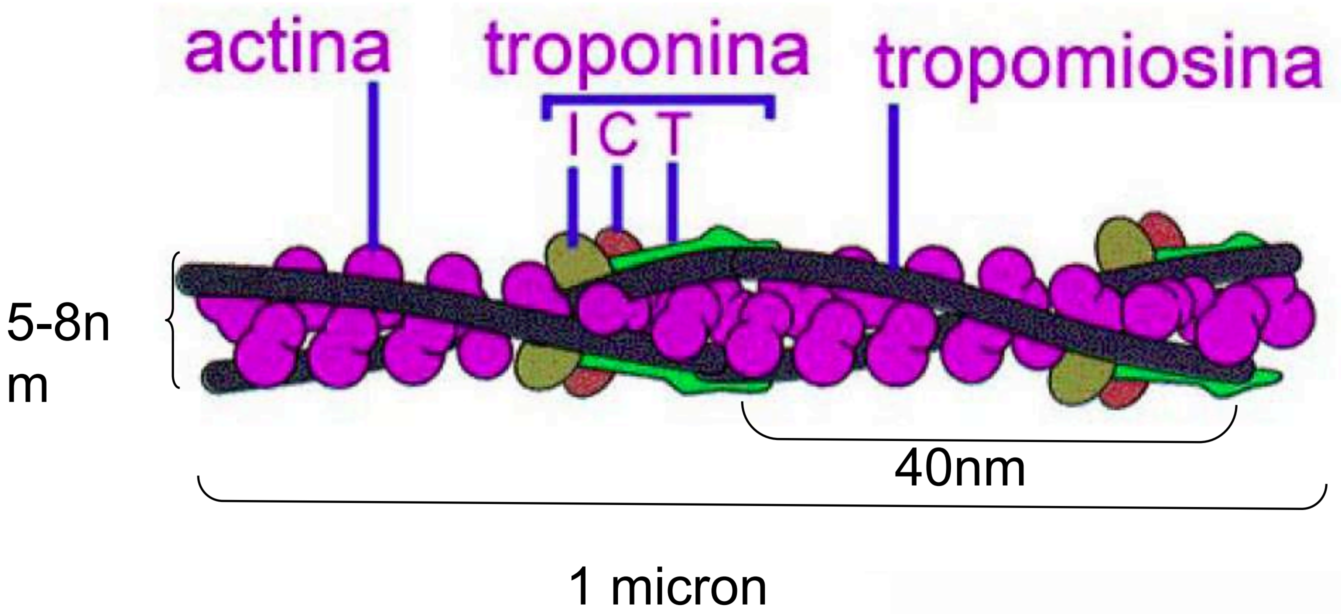
When the muscle is **resting**, $Ca^{2+}$ is bound to only the high-affinity site of TnC, enabling tropomyosin to block the interaction of F-actin with myosin.

During **muscle contraction**, $Ca^{2+}$ levels increase (see 7-13). Then, $Ca^{2+}$ occupies the low-affinity site of TnC and the previously occupied high-affinity site becomes empty. Consequently, TnC changes its configuration that is transmitted to TnI, TnT and tropomyosin. As a result, F-actin can now interact with the myosin head to elicit muscle contraction.

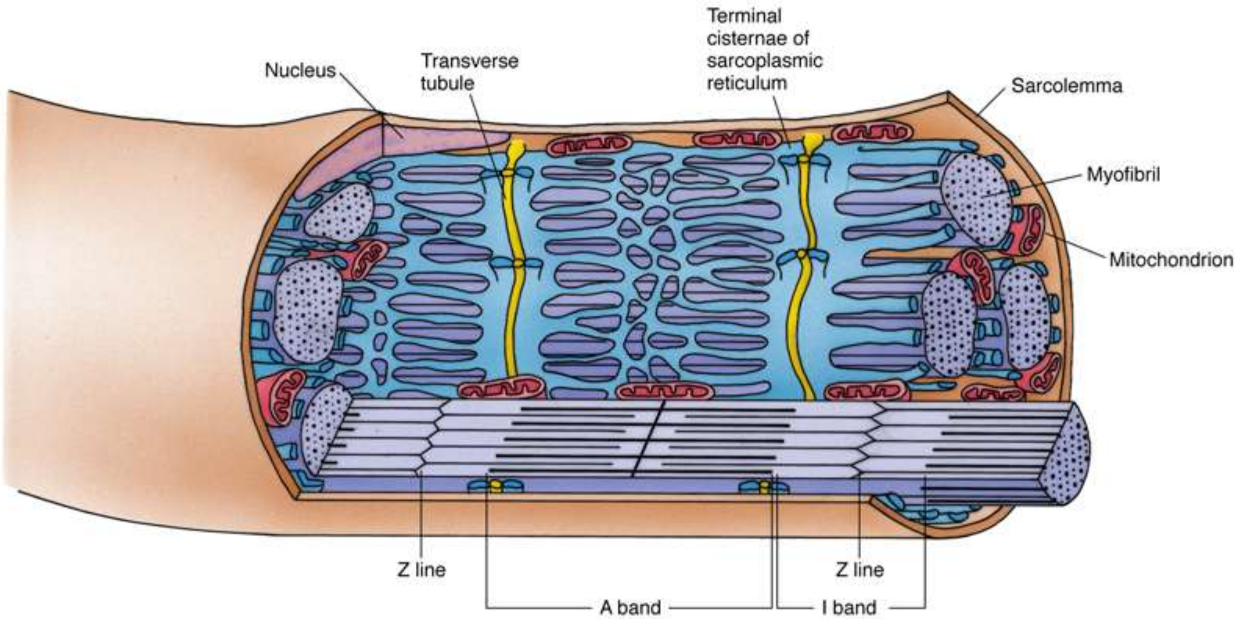
# Thin filaments are made of actin alfa, troponin and tropomyosin.

300-400 G-actins form
the F-actina.




# Electron Microscopy of Skeletal Muscle

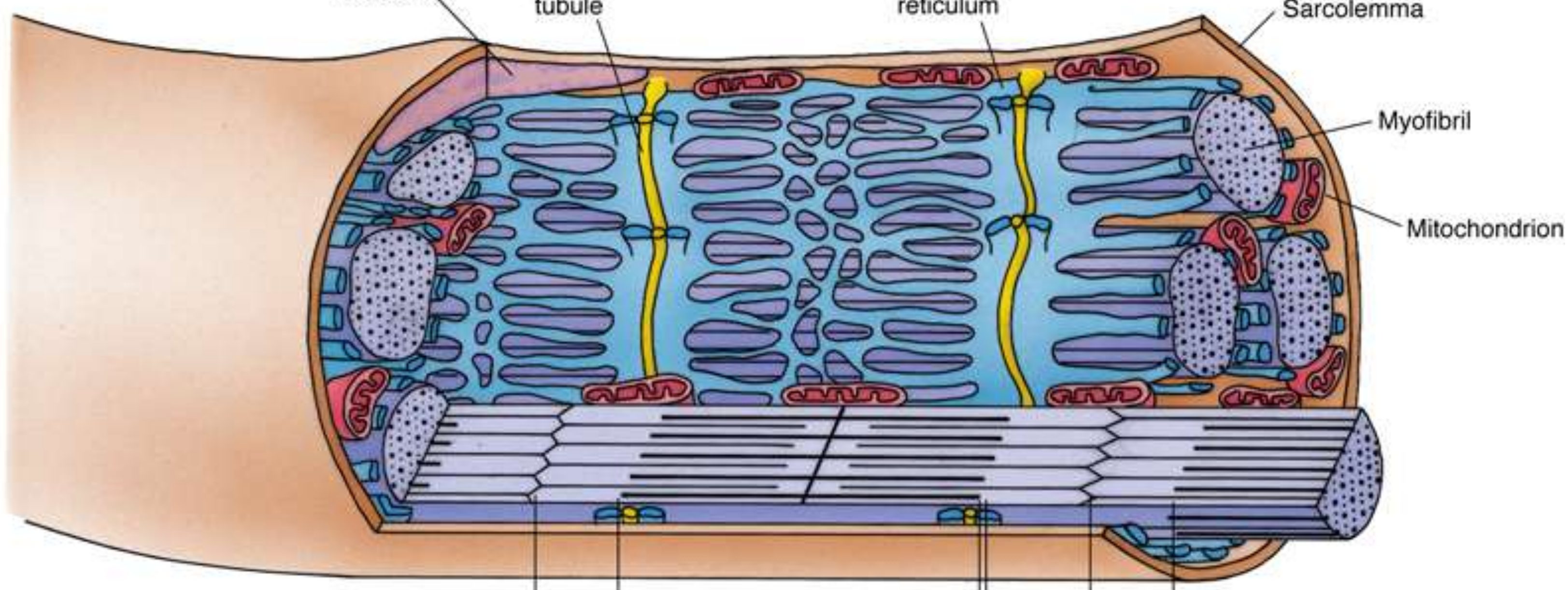



Organization of triads and sarcomeres of skeletal muscle. Note that in skeletal muscle the triad is always located at the junction of the A and I bands, permitting the quick release of calcium ions from the terminal cisternae of the sarcoplasmic reticulum just in the region where the interaction of the thick and thin filaments can produce efficient sarcomere shortening. Observe the presence of mitochondria around the periphery of the myofibrils.

A distinguishing feature of the sarcolemma is that it is continued within the skeletal muscle fiber as numerous **T tubules,** long, tubular invaginations that intertwine among the myofibrils.

T tubules pass transversely across the fiber and each sarcomere possesses two sets of T tubules, one at each interface of the A and I bands. Thus, T tubules extend deep into the interior of the fiber and facilitate the conduction of waves of depolarization along the sarcolemma.

# Electron Microscopy of Skeletal Muscle




Associated with this system of T tubules is the **sarcoplasmic reticulum,** which is maintained in close register with the A and I bands as well as with the T tubules. The sarcoplasmic reticulum, which stores intracellular calcium, forms a meshwork around each myofibril and displays dilated **terminal cisternae** at each A-I junction.

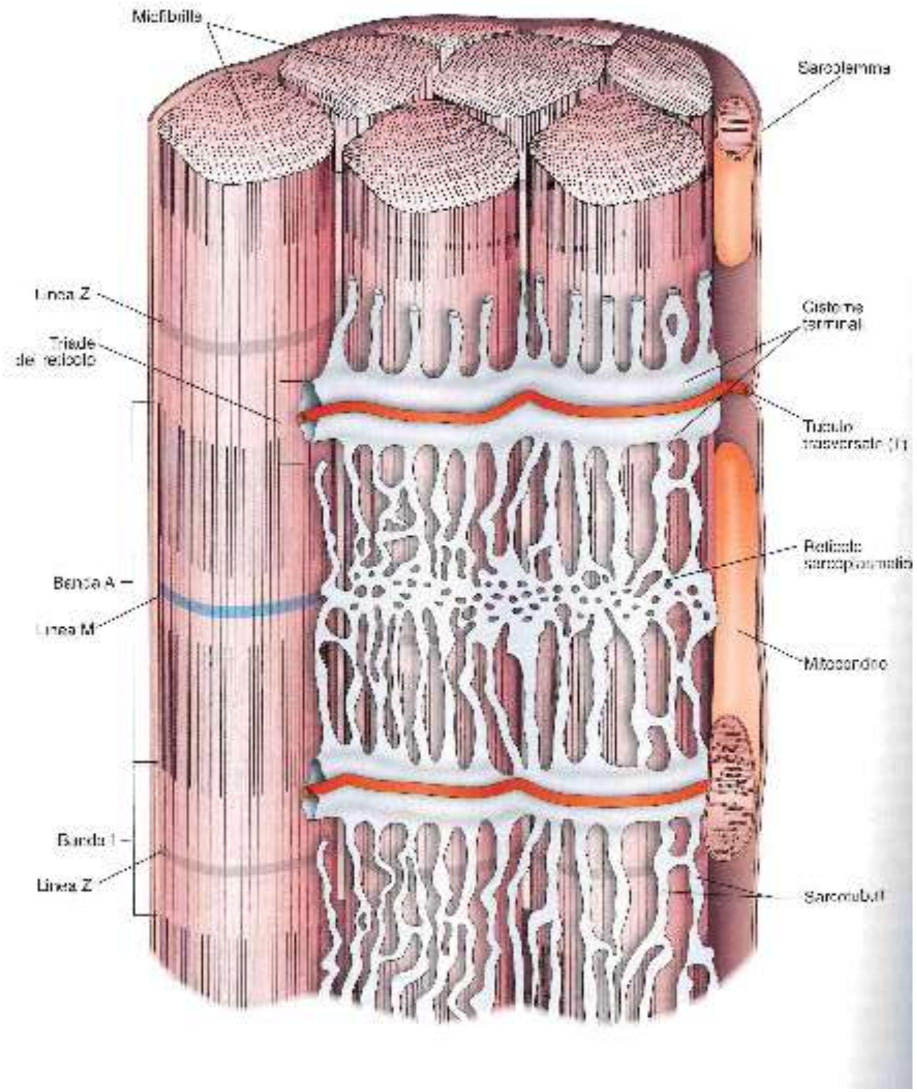
Thus, two of these cisternae are always in close apposition to a T tubule, forming a **triad** in which a T tubule is flanked by **two terminal cisternae**. This arrangement permits a wave of depolarization to spread, almost instantaneously, from the surface of the sarcolemma throughout the cell, reaching the terminal cisternae, which have **voltage-gated** calcium release channels **(junctional feet)** in their membrane.

Myofibrils are held in register with one another by the intermediate filaments **desmin** and **vimentin**.

# Muscle Contraction

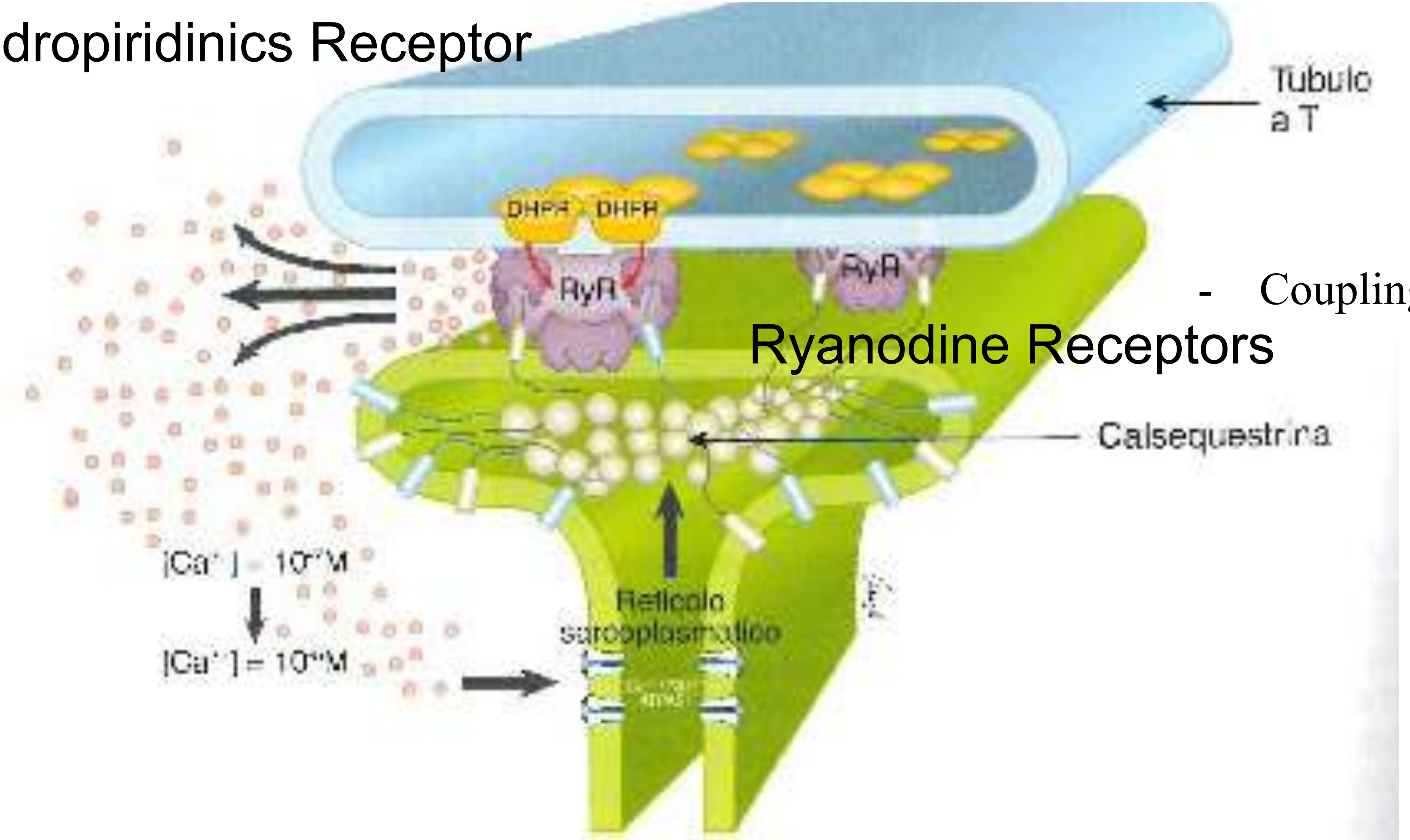
Triad:
- Coupling
- Excitation
- Contraction

Sarcoplasmic reticulum anastomoses in a fenestrated network (central fenestrated cisterna). It flows into peripheral terminal cisterna arranged around the invagination of the sarcoplasm (T tubule).
In register at the axis of the myofibrils, at the interface of the A / I bands of each sarcomere.



# T tubules, calcium ions and muscle contraction

Diidropiridinics Receptor

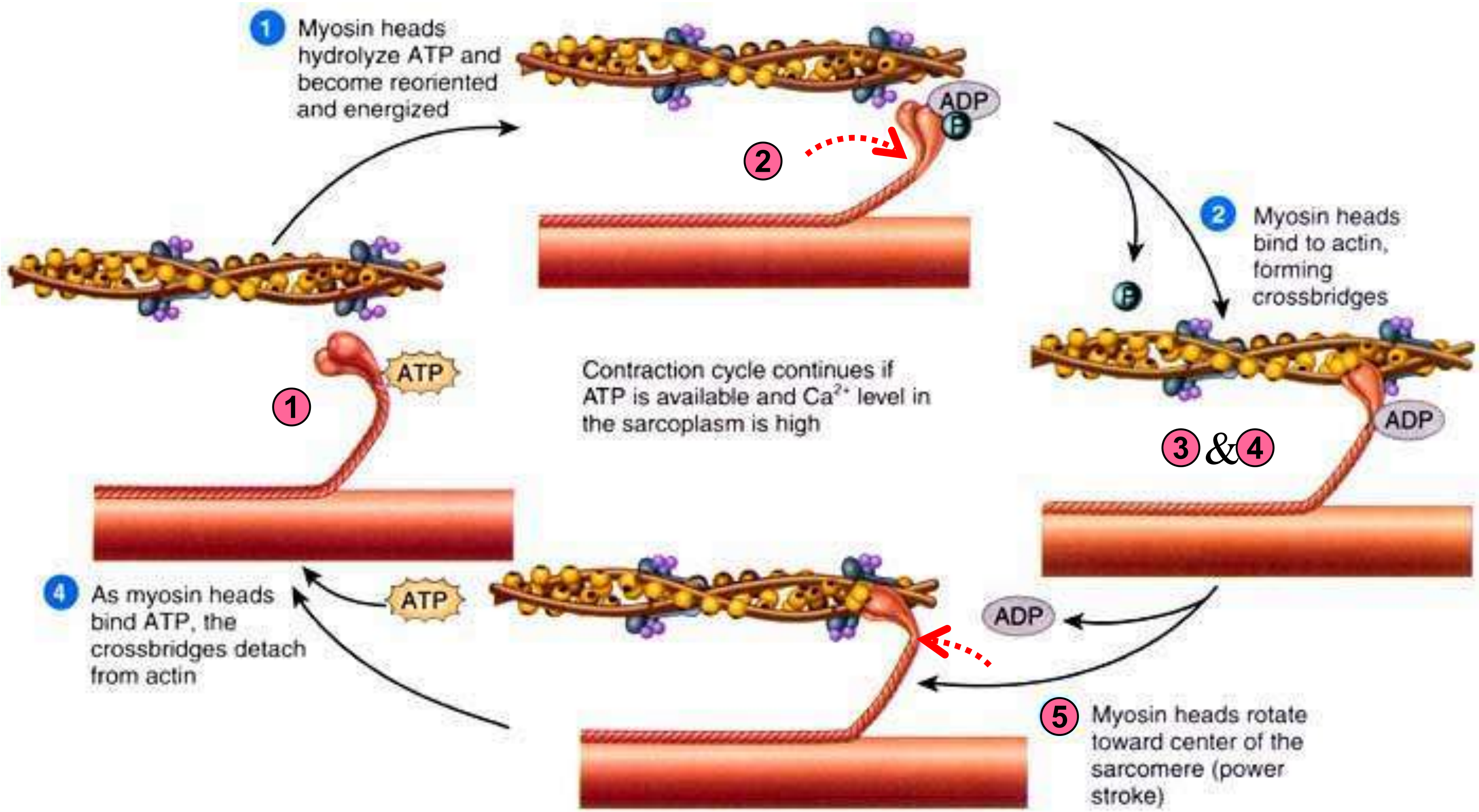



- Coupling

Ryanodine Receptors

Ryanodine **receptor (on the RER)**, tetramers forming canals for the release of the Ca2+

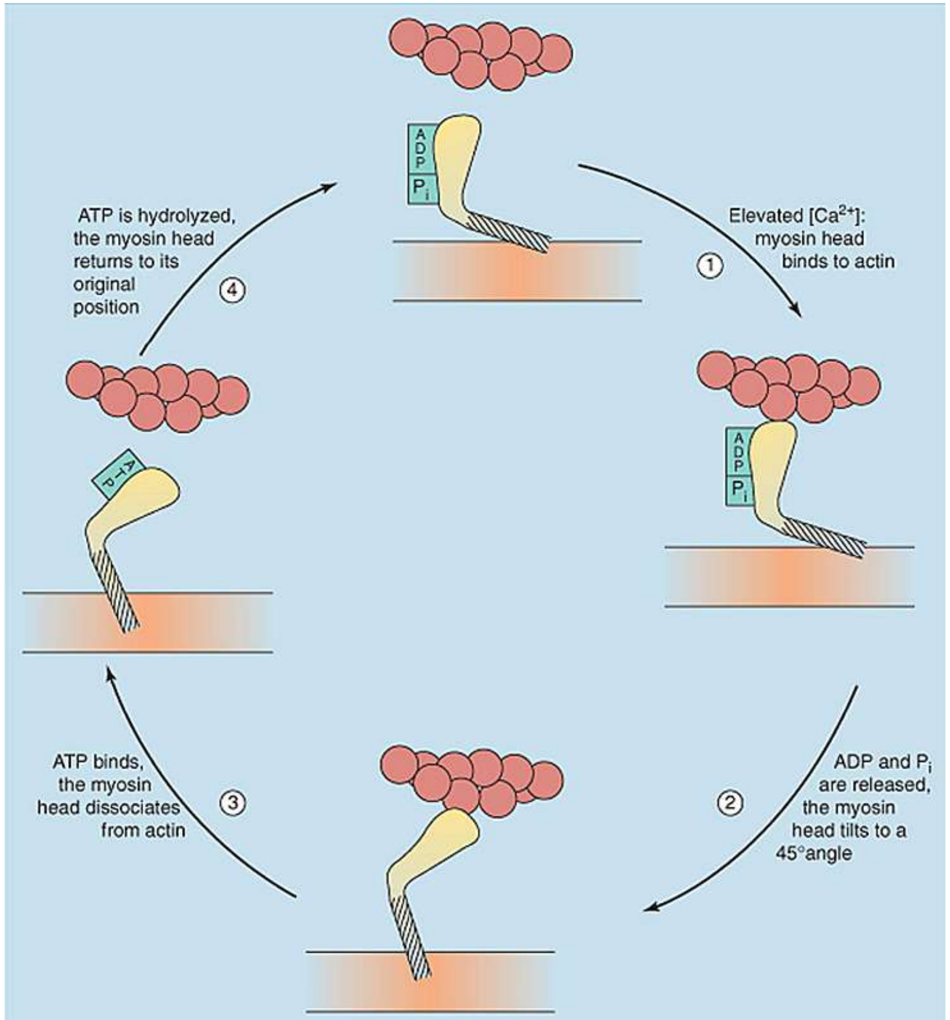
# Contraction is Ca+ dependent




1. In resting state, free ATP is bound to myosin
2. ATP hydrolysis induces conformational change of myosin head (ADP+$P_i$ remain bound to myosin).
3. Stimulation by nerves cause release of calcium (green) into cytoplasm; calcium binds troponin (purple) and reveals **myosin binding site (black)** on actin (yellow)
4. Myosin binds weakly to actin, causing release of $P_i$
5. Release of $P_i$ from myosin induces strong binding to actin, power stroke, and release of ADP

**Cycle continues if ATP is available and cytoplasmic Ca+ level is high**

# Skeletal Muscle Contraction




The mechanism of muscle contraction. In this model, the conformational change of the myosin molecule ("power stroke") is induced by the binding of the myosin head to the thin filament and the subsequent release of ADP and inorganic phosphate ($P_i$). ATP is needed to detach the myosin head from the thin filament. *(From Meisenberg, G, Simmons WH: Principles of Medical Biochemistry, 2e. Philadelphia, Elsevier/Mosby, 2006, p 226.)*

During muscle contraction, the thin filaments slide past the thick filaments in the following sequence of events:

•An impulse, generated along the sarcolemma, is transmitted via the T tubules, where it is conveyed to the terminal cisternae. Calcium ions leave the terminal cisternae and bind to the TnC subunit of troponin, altering its conformation.

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

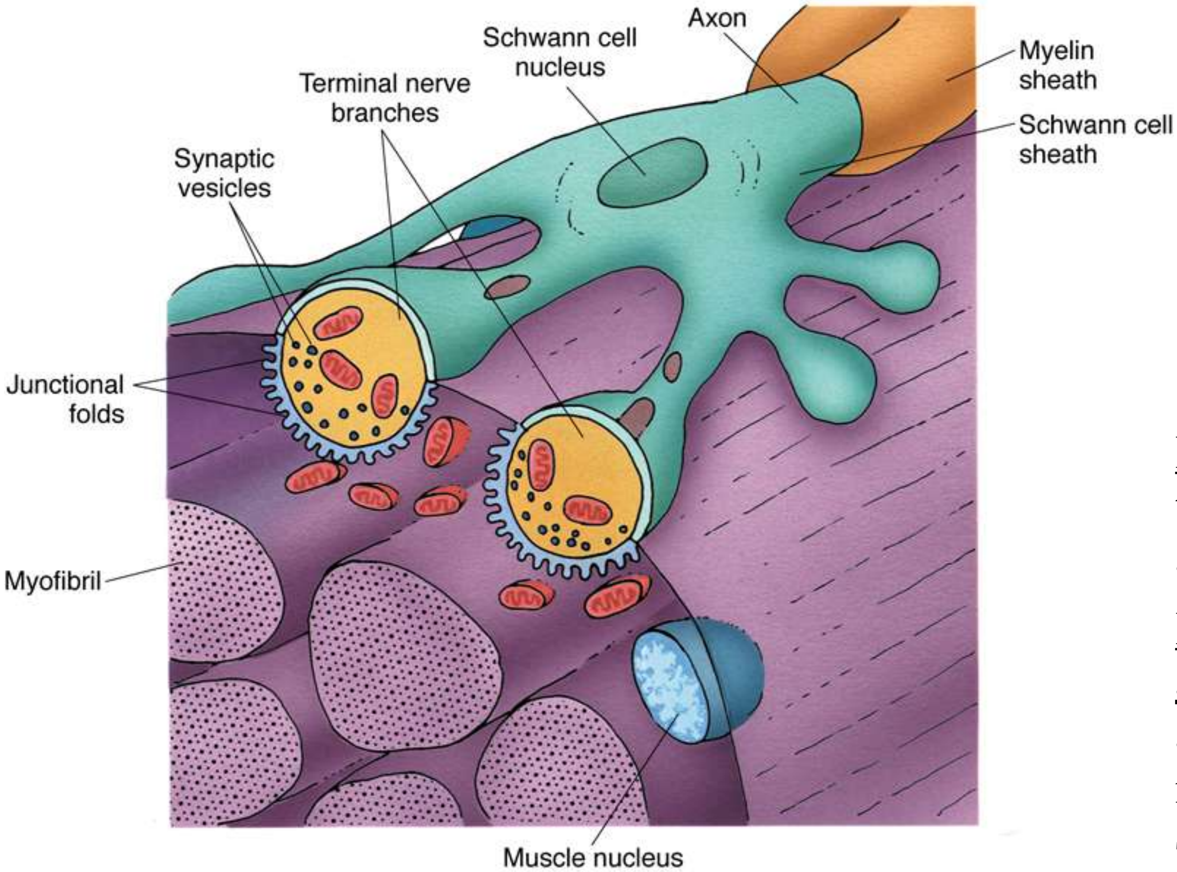
•ATP present on the $S_1$ subfragment of myosin is hydrolyzed, but both adenosine diphosphate (ADP) and inorganic phosphate ($P_i$) remain attached to the $S_1$ subfragment, and the complex binds to the active site on actin.

•Inorganic phosphate is released, resulting not only in a greater bond strength between the actin and myosin, ADP is also released, and the thin filament is dragged toward the center of the sarcomere ("power **stroke**").

•A new ATP molecule binds to the $S_1$ 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 motion.

# Neuromuscular Junction-motor end plate




Neuromuscular junction. Note that the myelin sheath stops as the axon arborizes over the skeletal muscle fiber, but the Schwann cell sheath continues to insulate the nerve fiber. The terminal nerve branches expand to form axon terminals that overlie the motor endplates of individual muscle fibers.

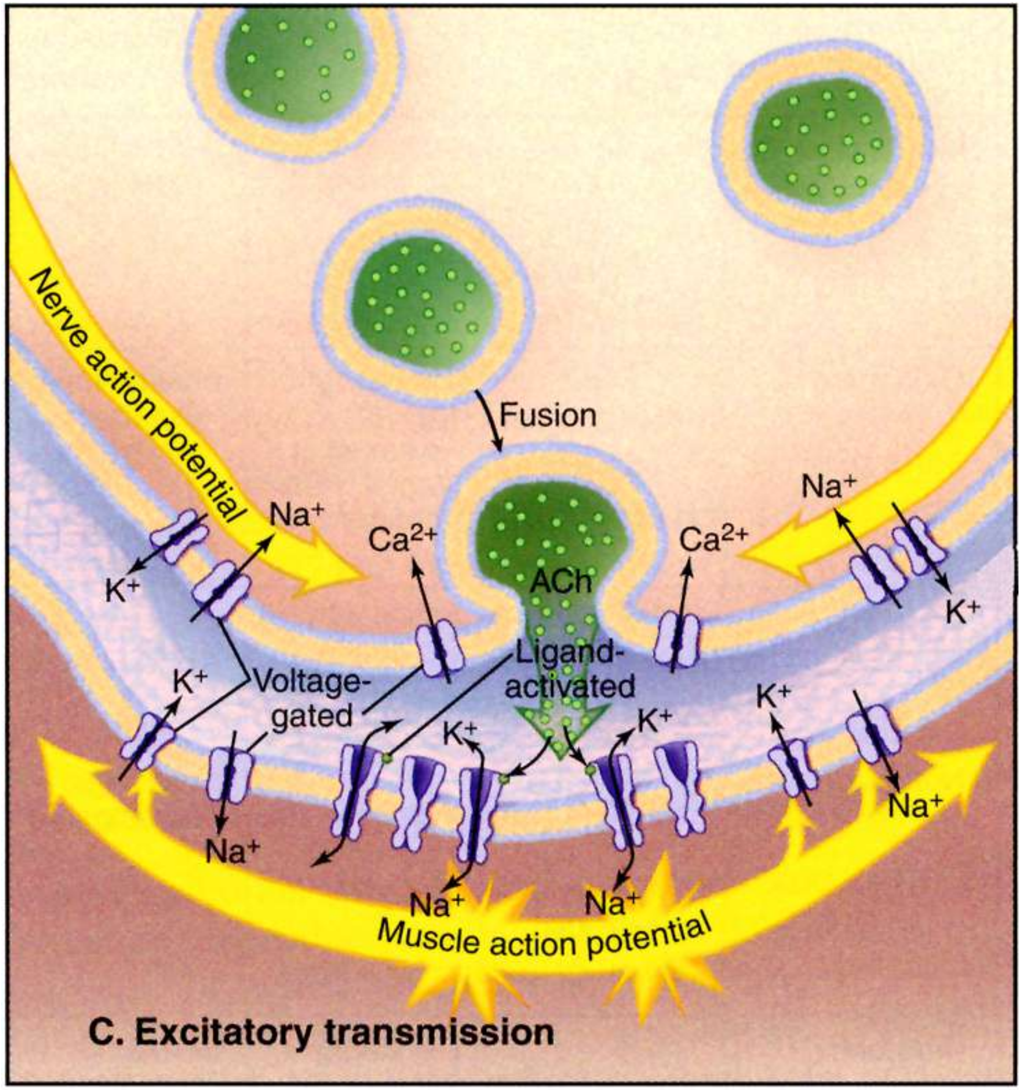
## The function of the neuromuscular junction is to transmit a stimulus from the nerve fiber to the muscle fiber

Motor nerve fibers are **myelinated** and pass in the connective tissue of the muscle. The axon arborizes, eventually losing its myelin sheath.

Each of these muscle-nerve junctions, known as a **neuromuscular junction,** is composed of an axon terminal, a synaptic cleft, and the muscle cell membrane.

The axon terminal, covered by Schwann cells, houses mitochondria, smooth endoplasmic reticulum, and as many as 300,000 **synaptic vesicles** (each 40 to 50 nm in diameter) containing the neurotransmitter **acetylcholine.**

# Neuromuscular Junction (cont.)

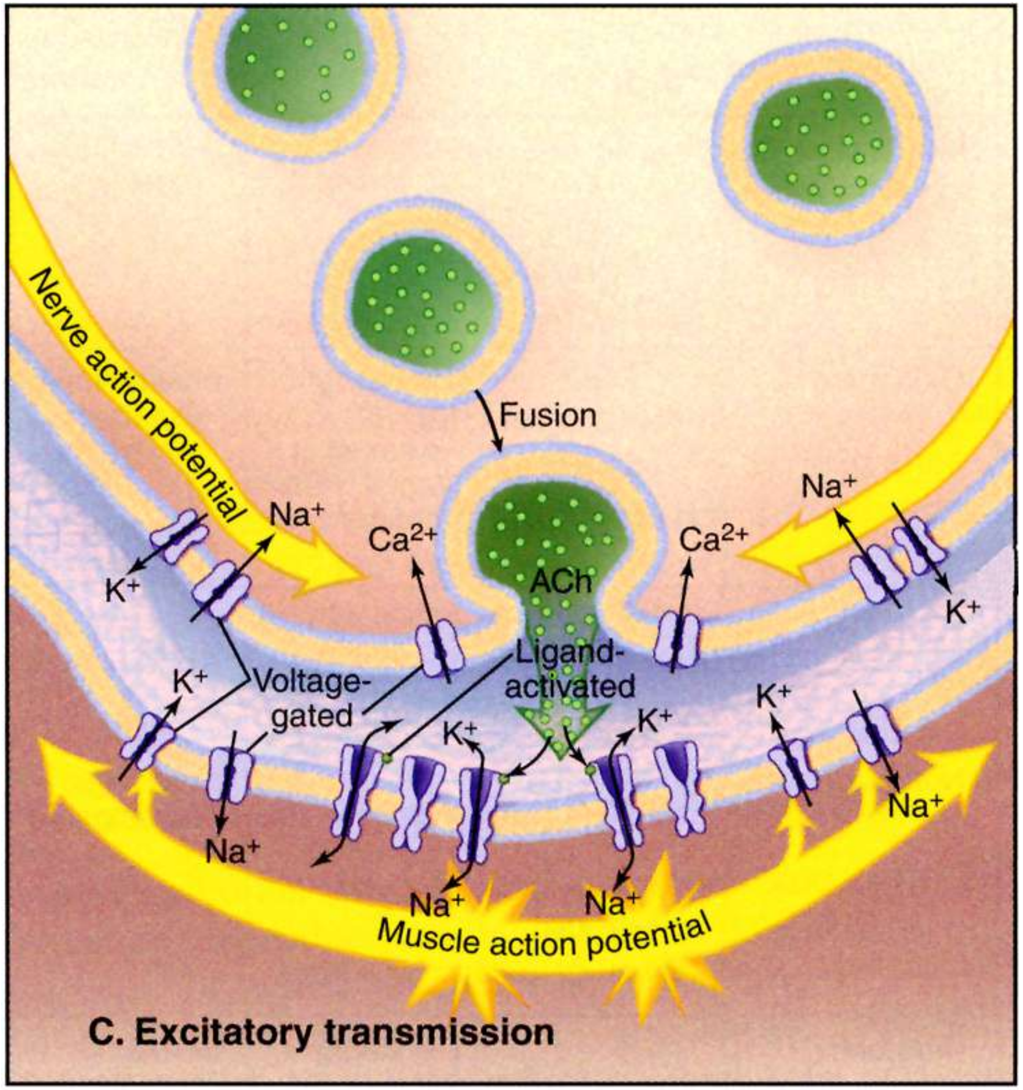



Neuromuscular junction. *C*, Excitatory synaptic transmission. The nerve action potential opens voltage-gated calcium channels. Entry of $Ca^{2+}$ triggers fusion of a synaptic vesicle containing acetylcholine (ACh) with the plasma membrane. Acetylcholine binds and opens postsynaptic channels on the muscle cell which trigger an action potential. *(From Pollard TD, Earnshaw WC: Cell Biology. Philadelphia, Elsevier/Saunders, 2004, p 156.)*

**Stimulus transmission** across a synaptic cleft involves the following sequence of events:

1. **A stimulus depolarizes** the membrane of the axon terminal, opens voltage-gated calcium channels**.**
**2.** Calcium causes the **fusion of synaptic vesicles** with subsequent release of **acetylcholine** in the synaptic cleft.
**3.** Acetylcholine then diffuses across the synaptic cleft and binds to **acetylcholine receptors** in the muscle cell membrane. These receptors, are ligand-gated ion channels, which open in response to the binding of acetylcholine. The resulting ion influx leads to **depolarization** of the sarcolemma and generation of an **action potential**.

# Neuromuscular Junction (cont.)

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**4.** The impulse generated spreads quickly throughout the muscle fiber via the system of T tubules, initiating muscle contraction.

**5.** To prevent a single stimulus from eliciting multiple responses, **acetylcholinesterase** degrades acetylcholine into acetate and choline, thus permitting the re-establishment of the **resting potential**. Choline is transported back into the axon terminal by a sodium-choline symport. Within the axon terminal the acetylcholine, synthesized from activated acetate (produced in mitochondria) and the recycled choline, a reaction catalyzed by **choline acetyl transferase,** into newly formed synaptic vesicles.

## *How does a nerve impulse reach and deliver contractile signals to myofibrils located in the interior of the muscle cell?*

- An excitation-contraction signal is generated when **acetylcholine**, a chemical transmitter, is released from a nerve terminal in response to an **action potential**. Acetylcholine diffuses into the **neuromuscular junction**, between the muscle and a nerve terminal. The action potential spreads from the sarcolemma to the T tubules, which transport the excitation signal to the interior of the muscle cell.

***T tubules*** *form rings around every sarcomere of every myofibril* ***at the A-I junction****.*

The channels of the sarcoplasmic reticulum, in contact with T tubules, contain calcium ions. Calcium ions are released inside the cytosol to activate muscle contraction when the action potential reaches the T tubule. This excitation-contraction sequence occurs in about 15 milliseconds.

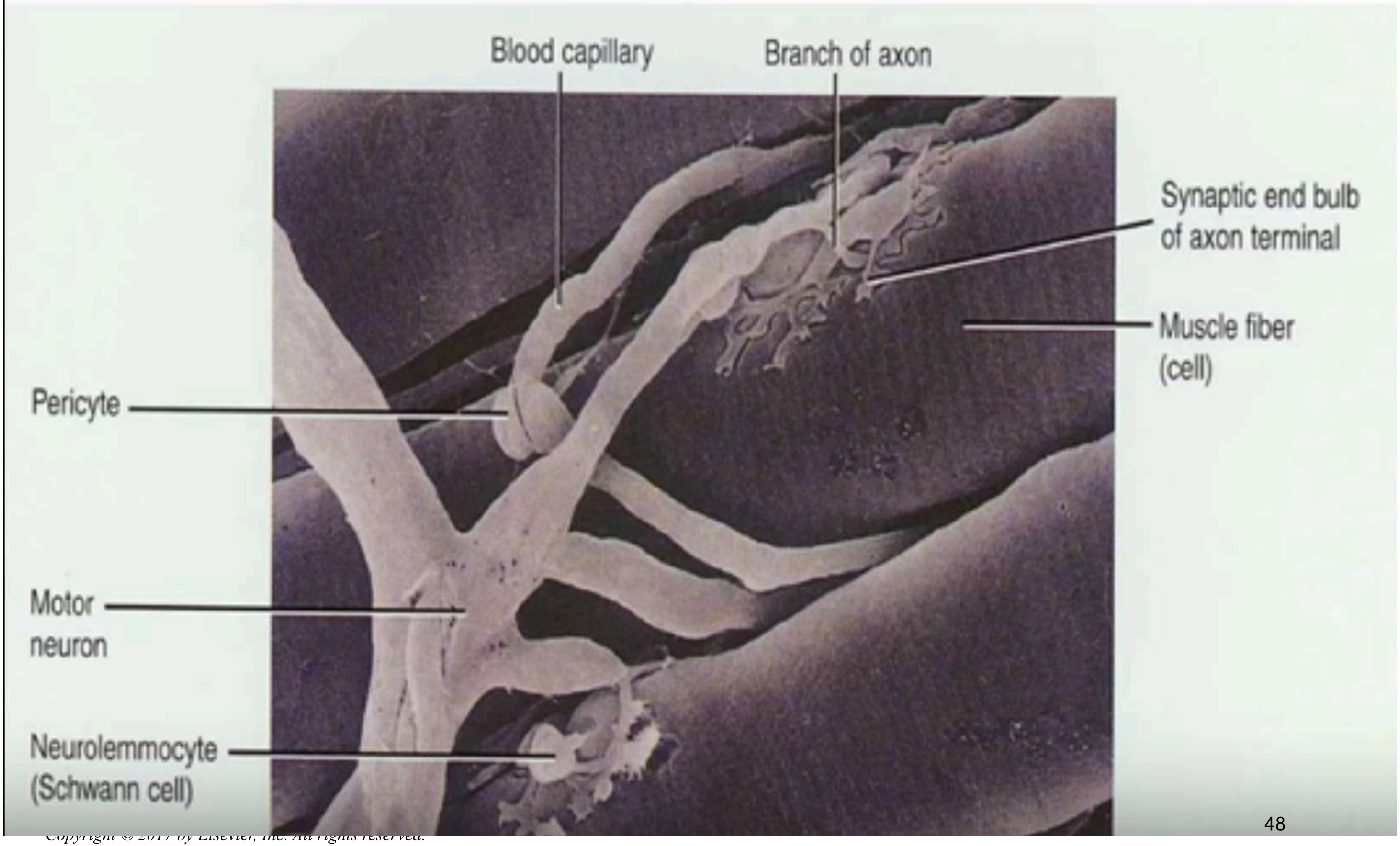
In the absence of $Ca^{2+}$, muscle is relaxed and the troponin-tropomyosin complex blocks the myosin binding site on the actin filament.

When a depolarization signal arrives, $Ca^{2+}$ exits the terminal cisternae of the sarcoplasmic reticulum. Depolarization activates **Dihydropyridine receptors, sensitive $Ca^{2+}$** channel on the T tubule membrane, which in turn activates a **ryanodine-sensitive $Ca^{2+}$ channel**, on the sarcoplasmic membrane.

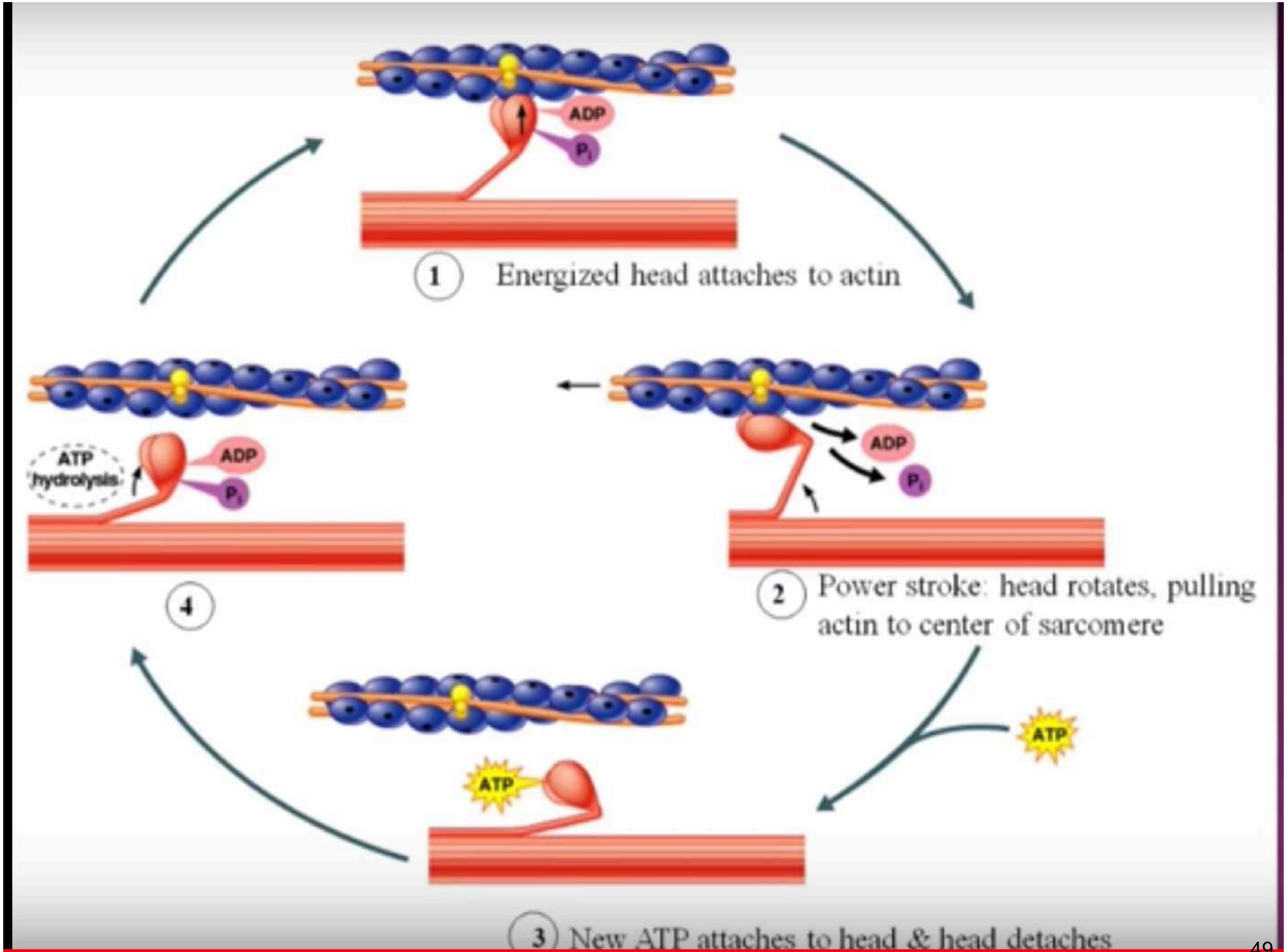
In the cytosol, $Ca^{2+}$ binds to troponin C and causes a change in configuration of the troponin-tropomyosin complex. As a result, the myosin-binding site on the actin filament is exposed. Myosin heads bind to the actin filament and hydrolysis of ATP occurs.

The energy of hydrolysis of ATP produces a change in the position of the myosin head and the thin filaments are pulled past the thick filaments. Contraction results in the complete overlap of the A and I bands. The contraction continues until $Ca^{2+}$ is removed

# Neuromuscolar Junction-motor end-plate



# Sarcomere Contraction



# Skeletal Muscle Contraction - review

**First:**

- Motor neuron releases ACh (Ca2+dependent)
- Electrical impulse is generated in the muscle
- Electrical impulse travel across sarcolemma and down T-tubules
- Terminal Cisternae release (----) into sarcoplasm

# Skeletal Muscle Contraction - review

**Second:**

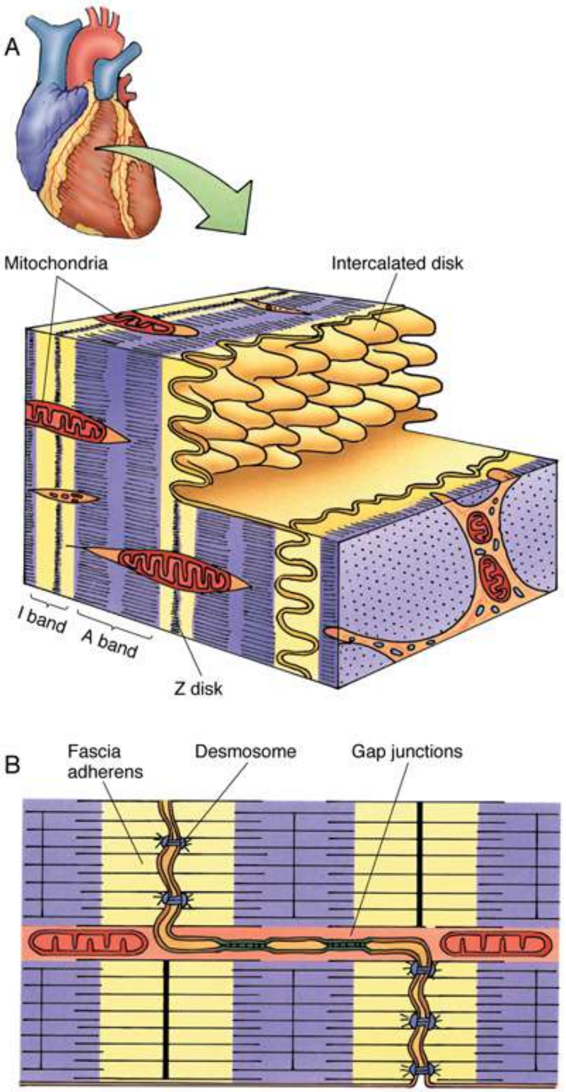
- Calcium binds to (______)
- Troponin changes shape and pushes Tropomyosin off actin binding sites
- Energized (___) myosin heads bind actin filaments
- Myosin heads give “power stroke”using 1 ATP
- New ATP molecule attaches to myosin head and head detaches
- Terminal Cisternae release Ca2+ into sarcoplasm

# Rigor Mortis

- A state of muscular rigidity that begins 3-4 hours after death and lasts about 24-36 hrs
- After death, $Ca2^{+}$ ions leak out of the sarcoplasmic reticulum and allow myosin heads to bind actin
- Since ATP synthesis has ceased, it cannot detach myosin from actin until proteolytic enzymes begin to digest the decomposing cells.

http://www.histologyguide.com/quizzes/04-muscle-tissue.html

# Cardiac Muscle




Cardiac muscle. **A,** Three-dimensional view of an intercalated disk. **B,** Two-dimensional view of the intercalated disk with a display of adhering and communicating junctions. The transverse portions of the intercalated disk act as a Z plate, and thin filaments are embedded in them.

**Cardiac muscle (heart muscle),** another form of striated muscle, is found only in the heart and in pulmonary veins where they join the heart.

The adult myocardium consists of an anastomosing network of branching cardiac muscle cells arranged in layers **(laminae).** Laminae are separated from one another by slender connective tissue sheets that convey blood vessels, nerves, and the conducting system of the heart.

# Cardiac Muscle

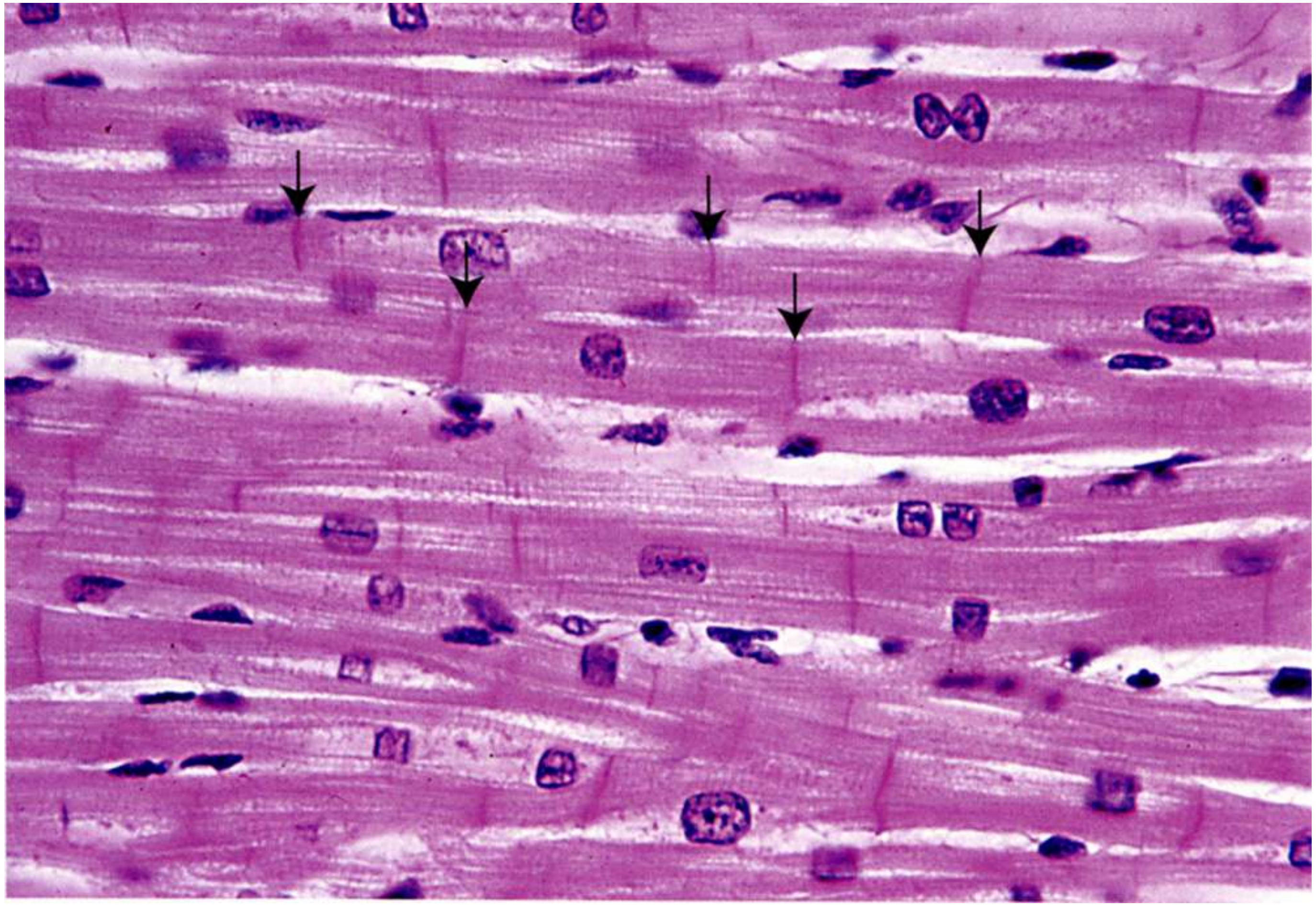
Tissue Features:

- Striated (same contractile machinery)
- Self-excitatory and electrically coupled
- Rate of contractions modulated by <u>autonomic nervous system</u>
  - innervation is <u>neuroendocrine</u> in nature (i.e. no "motor end plates")

Cell Features:

- 1 or 2 centrally placed nuclei
- Branched fibers with <u>intercalated disks</u>
- Numerous mitochondria (up to 40% of cell volume)
- Sarcoplasmic reticulum & T-tubules appear as <u>diads</u> at Z lines
  - Sarcoplasmic reticulum does not form terminal cisternae
  - T tubules are about 2x larger in diameter than in skeletal muscle
    - transport $Ca^{2+}$ into fibers

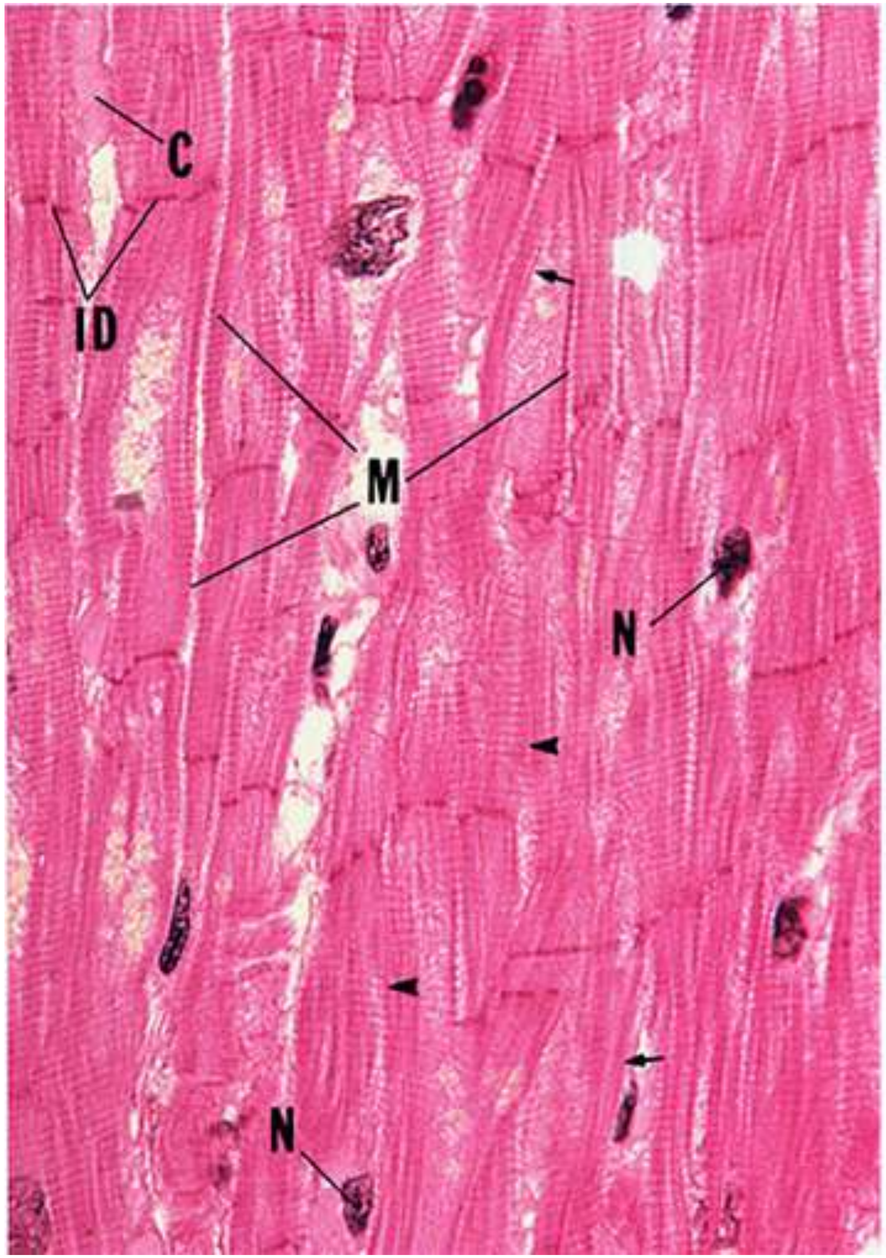
# Cardiac Muscle (longitudinal section)



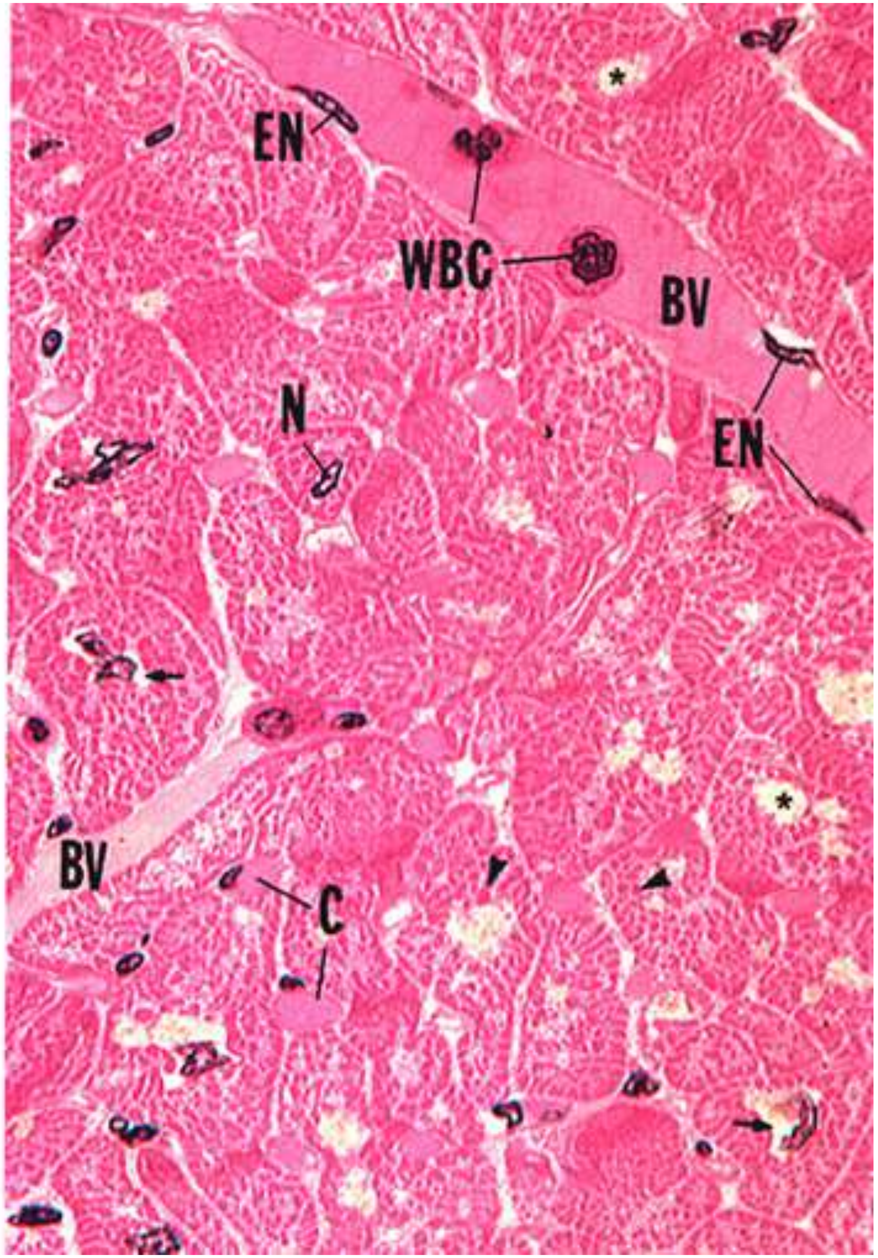
- Central nuclei, often with a biconical, clear area next to nucleus – this is where organelles and glycogen granules are concentrated (and atrial natriuretic factor in atrial cardiac muscle)
- Striated, branched fibers joined by **intercalated disks** (arrows) forms interwoven meshwork

https://virtualmicroscopy.patologia-sperimentale.unibo.it/_contenuti/index.php?viewPage=9&bttl=2&lingua=ITA&page=2&cell_id=318

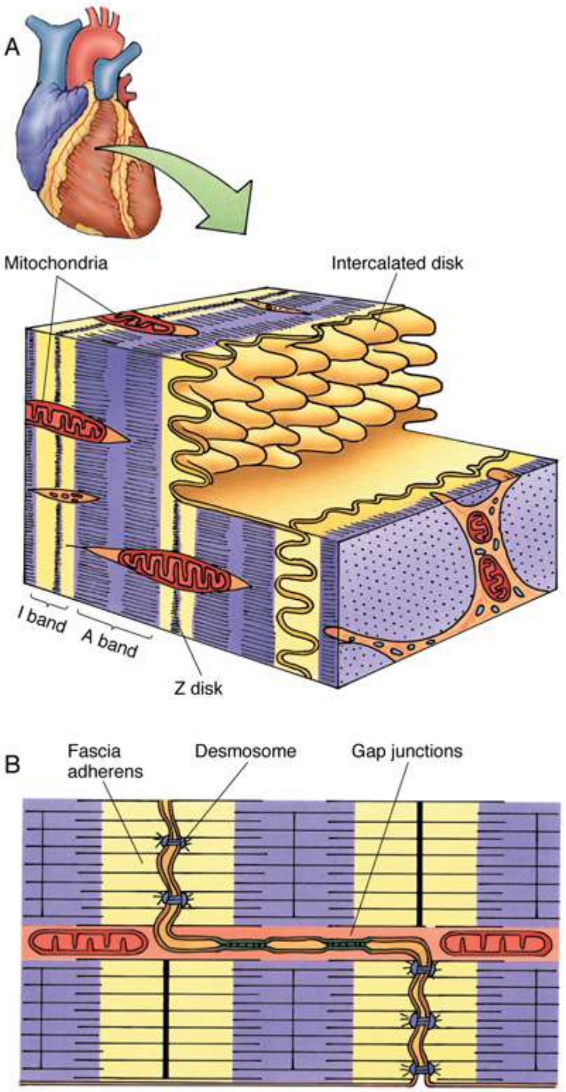
## Cardiac Muscle (longitudinal section)




## Cardiac Muscle (transverse section)



# Cardiac Muscle

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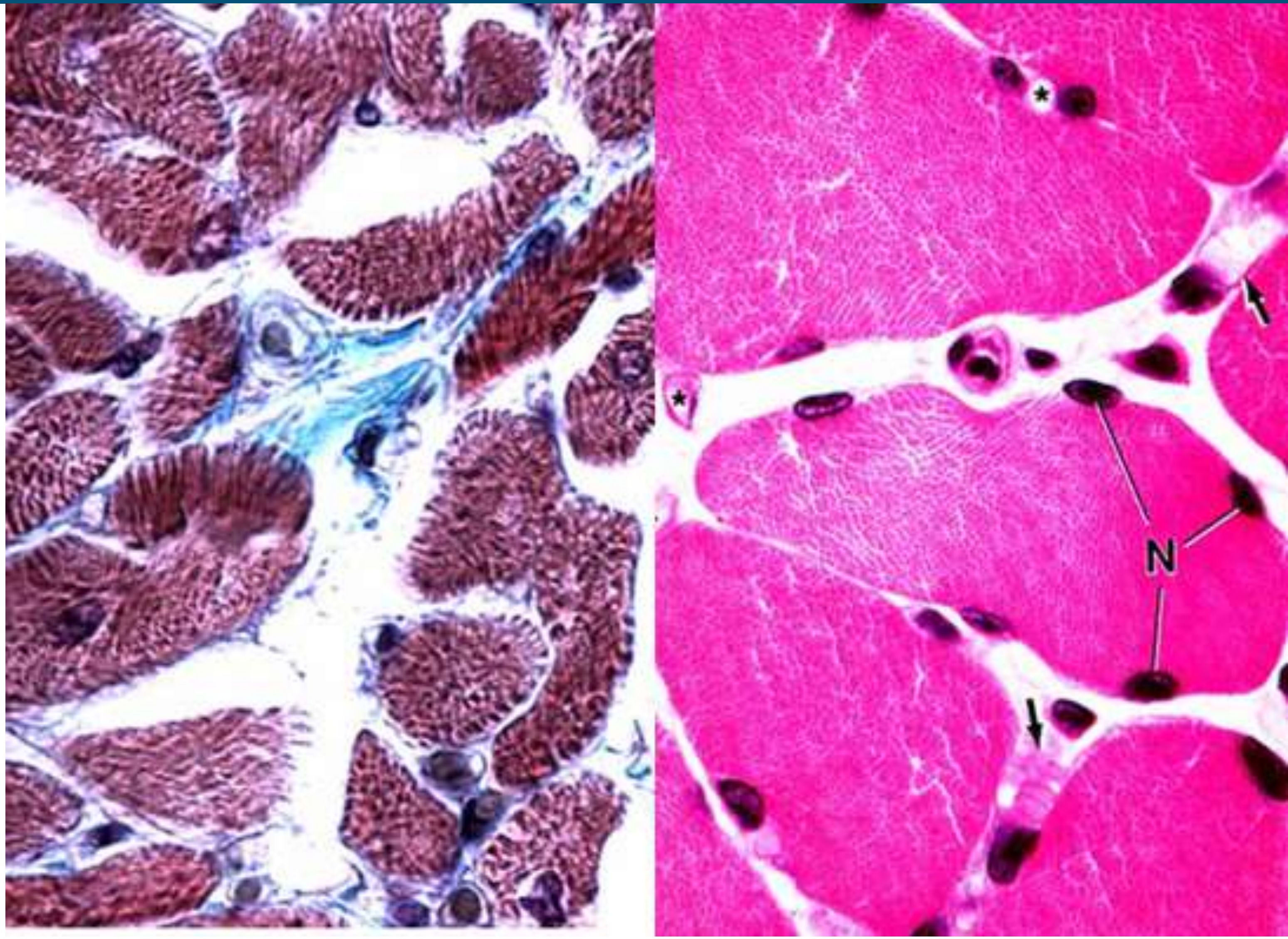
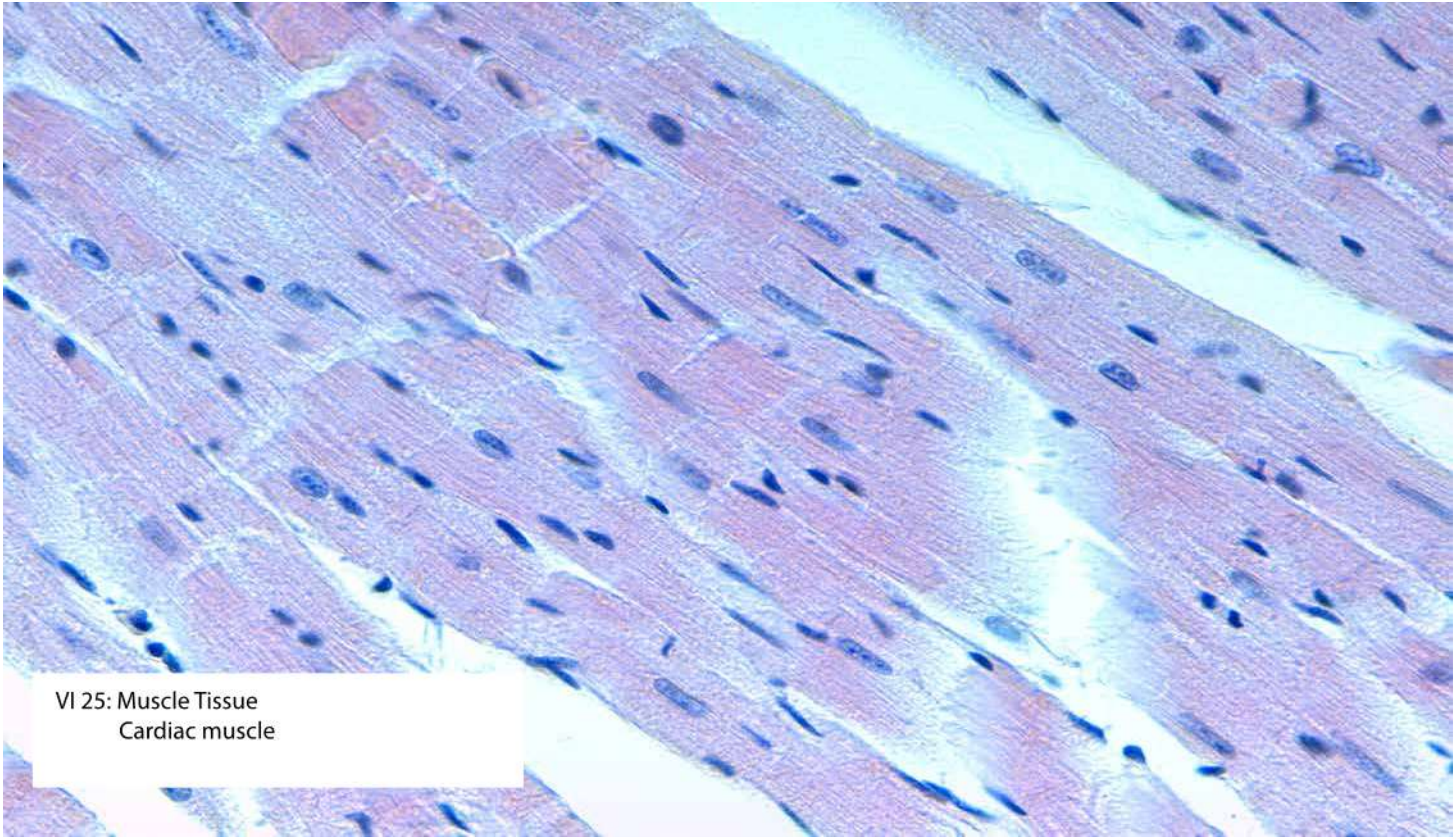
Capillaries, derived from these branches, invade the intercellular connective tissue, forming a rich, dense network of capillary beds surrounding every cardiac muscle cell.

Cardiac muscle differs from skeletal and smooth muscles in that it possesses an **inherent rhythmicity** as well as the ability to **contract spontaneously**.

# Transverse Section of Cardiac Muscle versus Skeletal Muscle



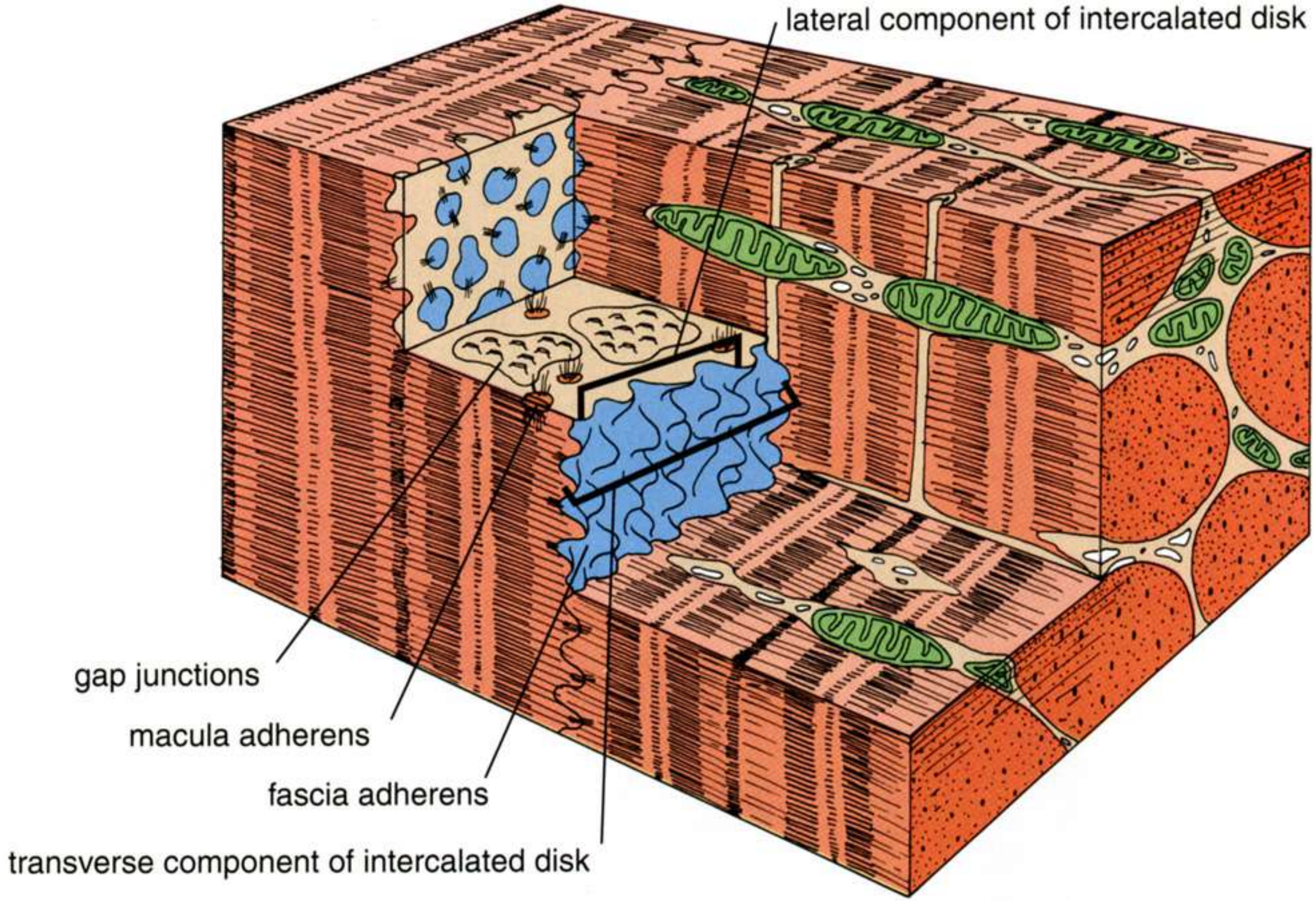

As with skeletal muscle, delicate, highly vascularized connective tissue (**<u>endomysium</u>**) surrounds each cardiac muscle cell.  Fibers are bundled into fascicles, so there is also **perimysium**. However, there really isn't an **epimysium**; instead, the connective tissue ensheathing the muscle of the heart is called the **<u>epicardium</u>**


VI 25: Muscle Tissue
Cardiac muscle


VI 24: Muscle Tissue
Cardiac muscle (cross section)

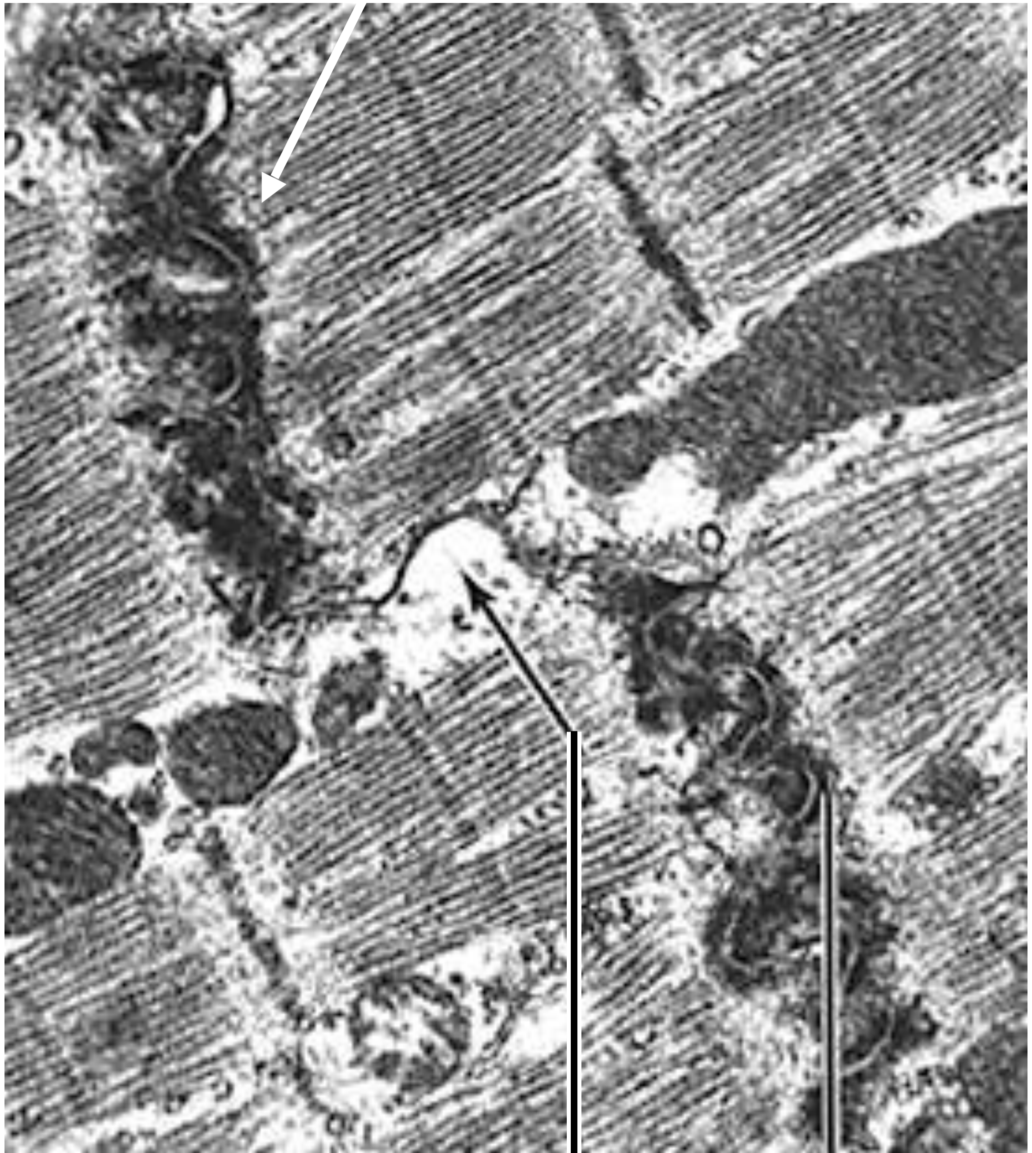
# Intercalated Discs -

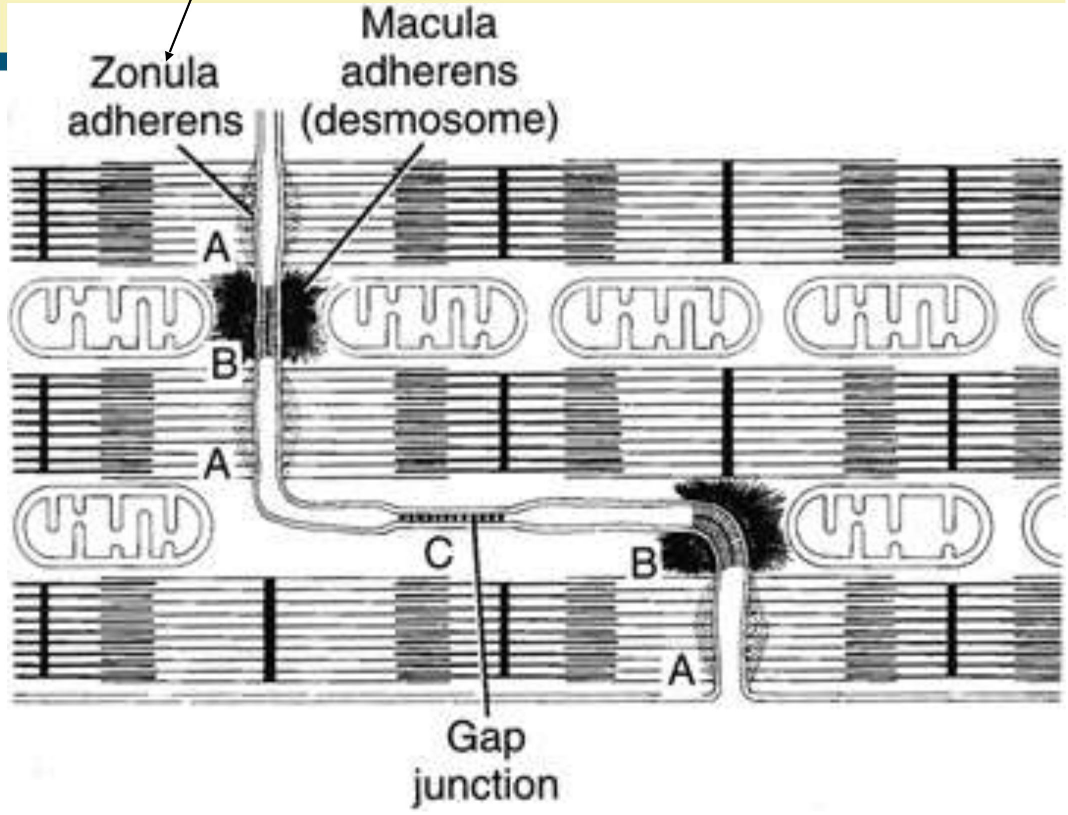
## Couple Heart Muscle Mechanically and Electrically



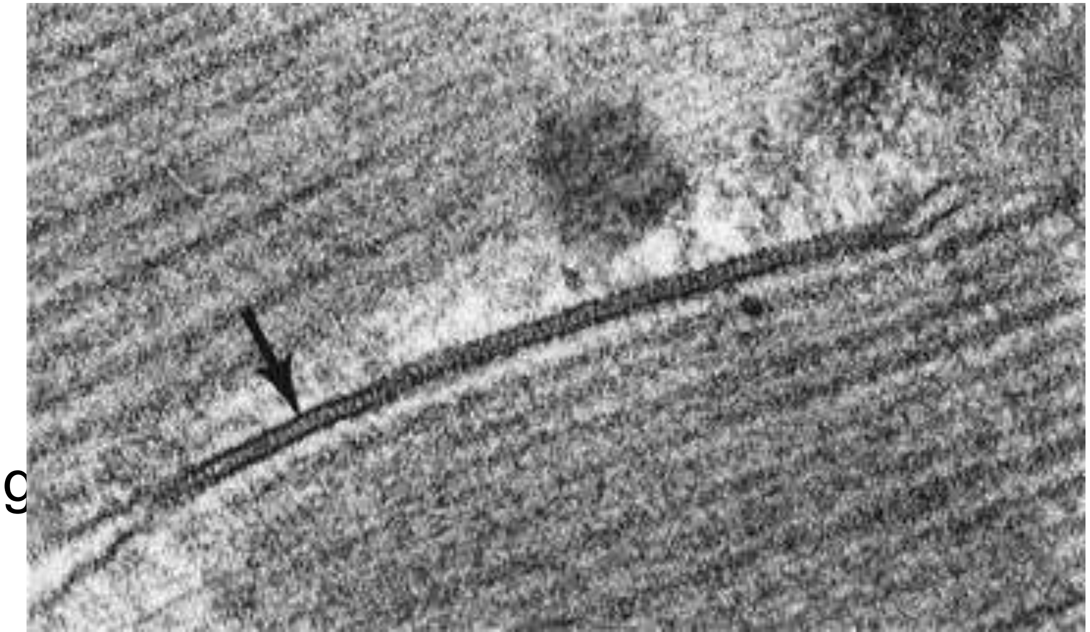
# Transverse portion: forms mechanical coupling

aka "Fascia adherens"

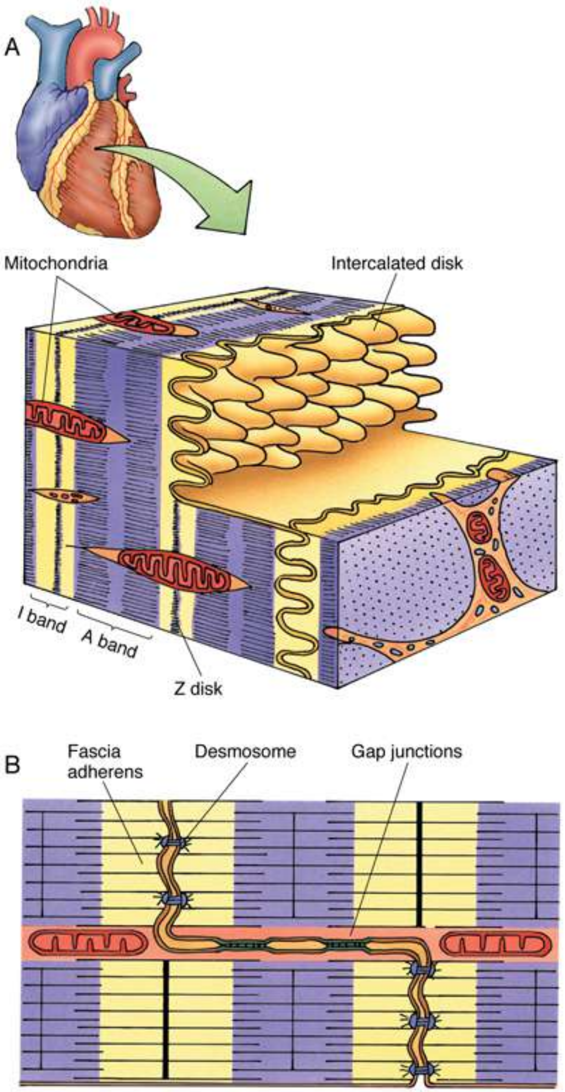





Lateral Portion: forms electrical coupling



# Cardiac Muscle

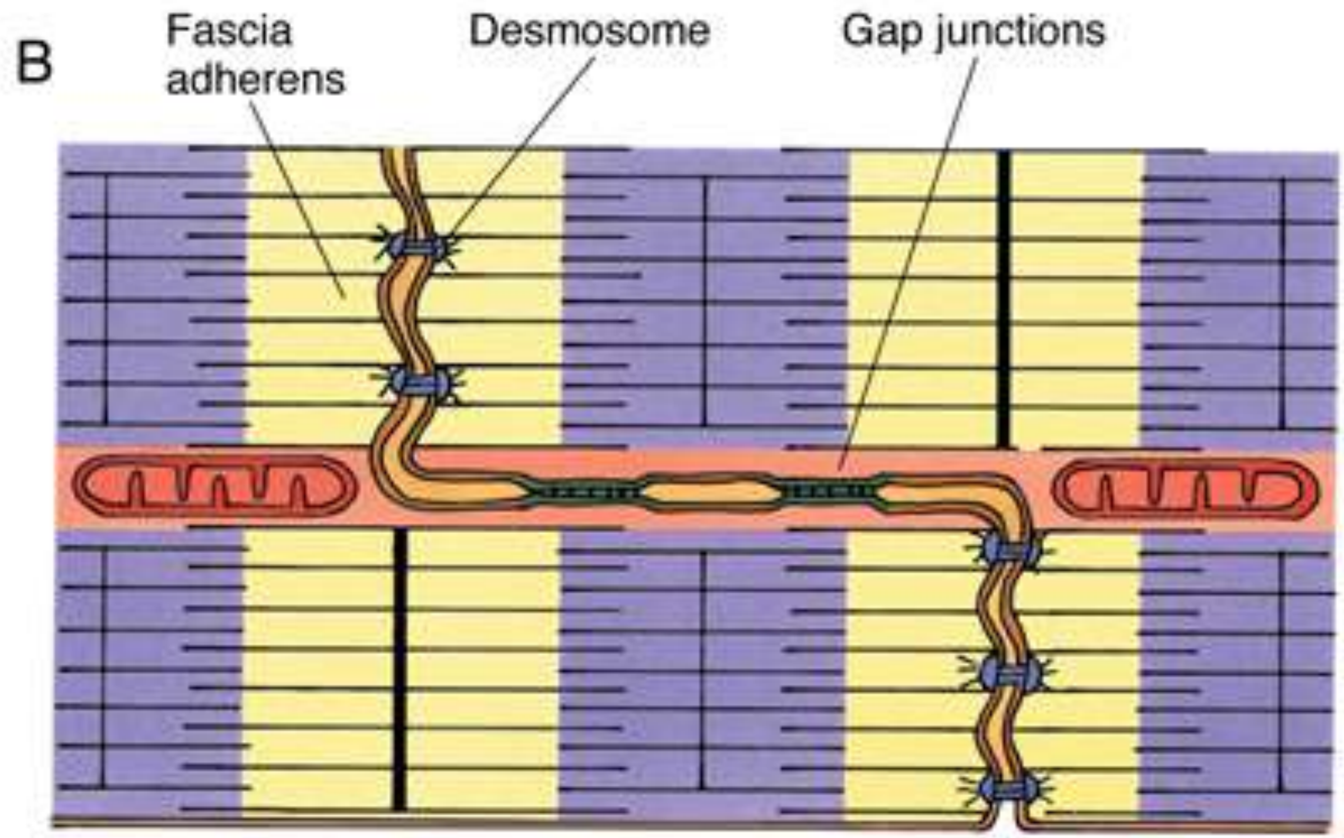



Cardiac muscle. **A,** Three-dimensional view of an intercalated disk. **B,** Two-dimensional view of the intercalated disk with a display of adhering and communicating junctions. The transverse portions of the intercalated disk act as a Z plate, and thin filaments are embedded in them.

Intercalated disks have **transverse portions,** where fasciae adherentes and desmosomes abound, as well as **lateral portions** rich in gap junctions. On the cytoplasmic aspect of the sarcolemma of intercalated disks, **thin myofilaments** attach to the **fasciae adherentes**, which are the analogous to Z discs.

Gap junctions, in the **lateral portions,** function in permitting rapid flow of information from one cell to the next, also form in regions where cells lying side by side come in close contact with each other.

# Cardiac Sarcomer

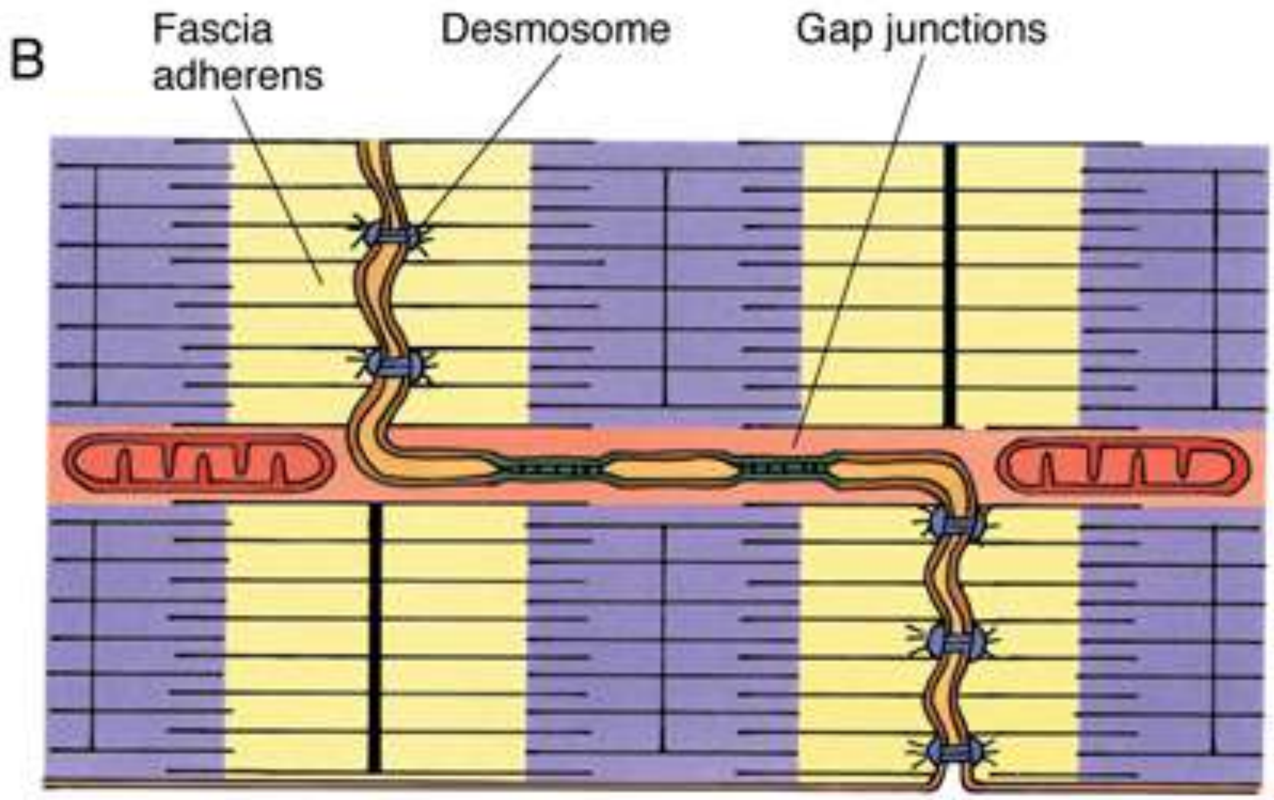



1- Nebulin extends up to 20% of the length of thin filaments

T- tubule as diad located on the Z-line

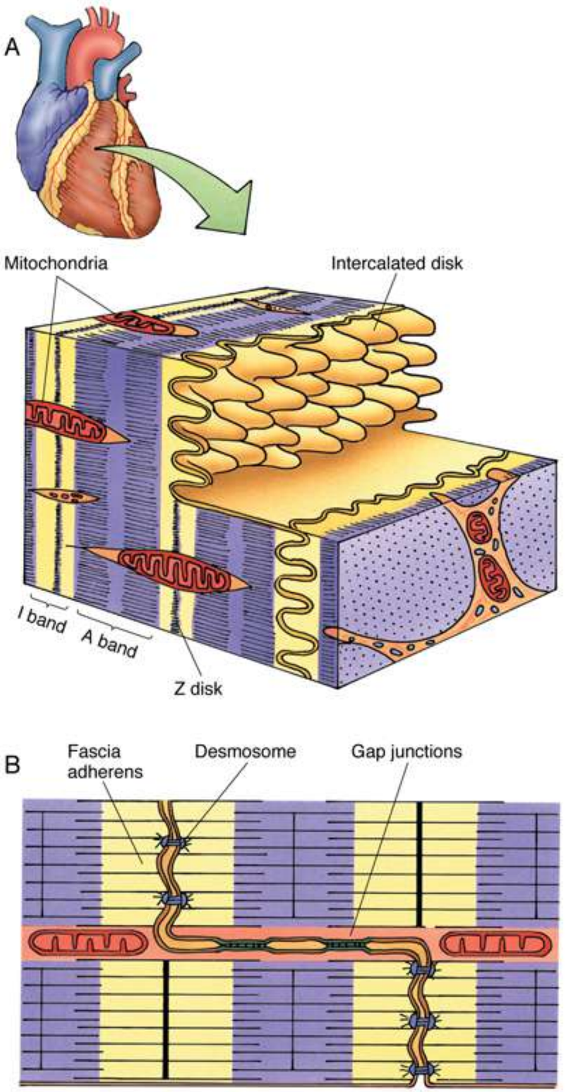
- No terminal cisternae
- Negatively charged external lamina storage of calcium

# Cardiac Sarcomer




Slow sodium channel- slow to open but they remain open for longer time - about several tenths of second
During this time the Na and Ca enter the cytoplasm to overcome the lack of a proper internal storage of Calcium

# Cardiac Muscle

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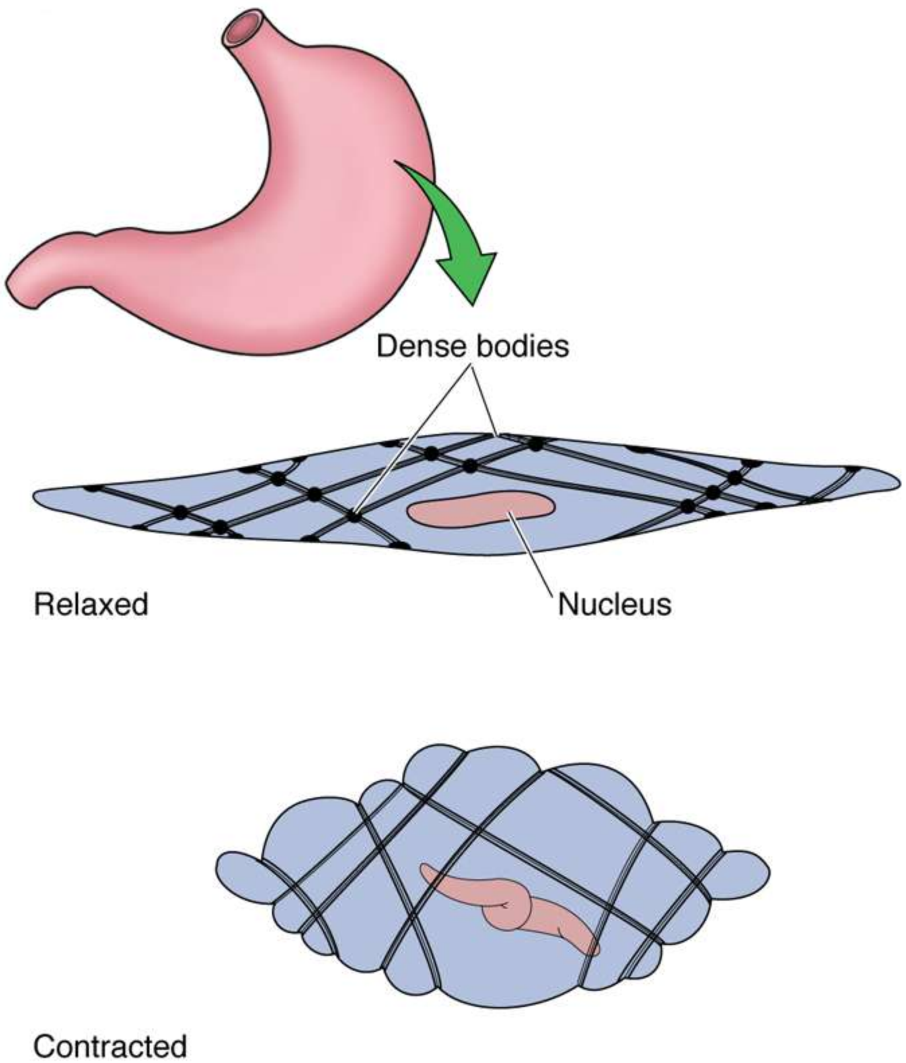
Because the sarcoplasmic reticulum is relatively sparse, it cannot store enough calcium to accomplish a forceful contraction; therefore, additional sources of calcium are available.

Because the T tubules open into the extracellular space and have a relatively large pore, extracellular calcium flows through the T tubules and enters the cardiac muscle cells at the time of depolarization. Moreover, the negatively charged **external lamina coating of the T tubule stores calcium** for instantaneous release.

# Cardiac Muscle

Lack of $Ca^{2+}$ in the extracellular compartment results in cessation of cardiac muscle contraction within 1 minute, whereas skeletal muscle fibers can continue to contract for several hours

# Smooth Muscle



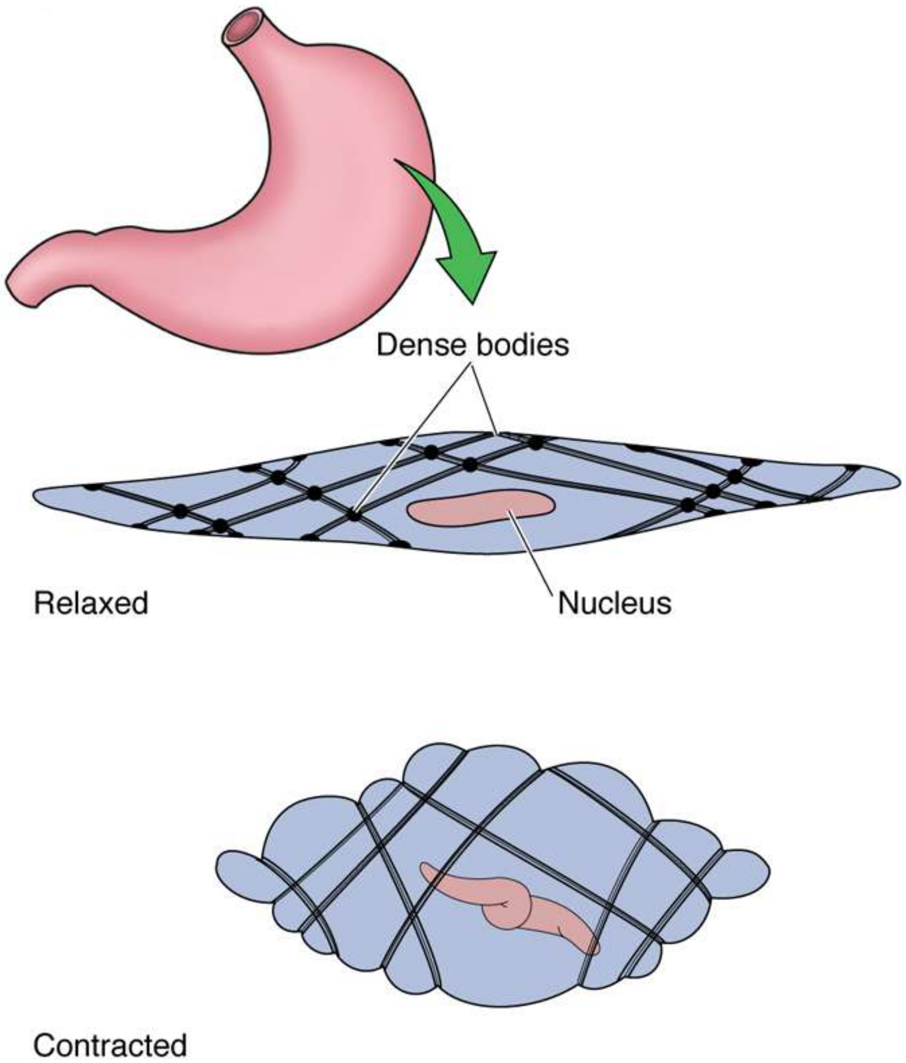

A relaxed smooth muscle cell and a contracted smooth muscle cell. Note that in a contracted smooth muscle cell the nucleus appears corkscrew-shaped.

The cells of the third type of muscle exhibit no striations; therefore, they are referred to as **smooth muscle.**

Additionally, smooth muscle cells do not possess a system of T tubules. Smooth muscle is not under voluntary control; it is regulated by the autonomic nervous system and local physiological conditions.

Hence, smooth muscle is also referred to as **involuntary muscle**.

# Smooth Muscle



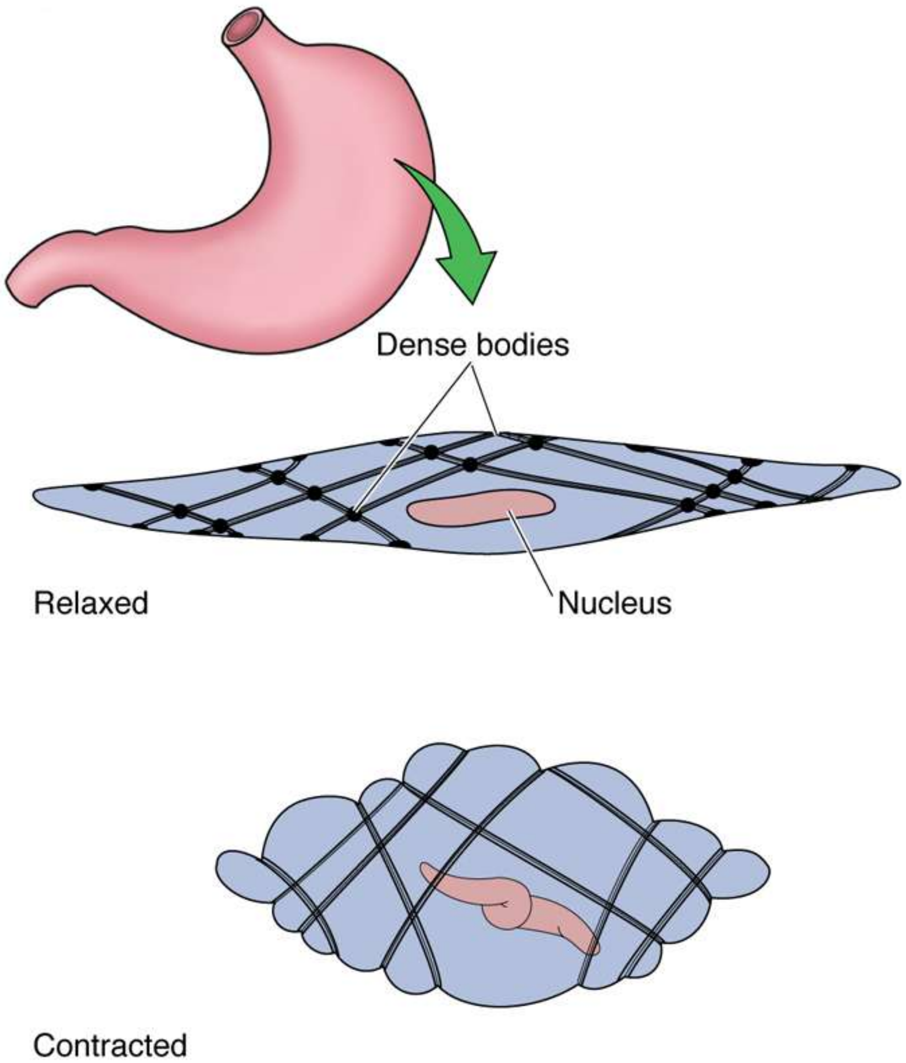

There are two types of smooth muscle:

1. Cells of **multiunit smooth muscle** can contract independently of one another, because each muscle cell has its own nerve supply.

2. Cell membranes of **unitary (single-unit, vascular) smooth muscle** form gap junctions with those of contiguous smooth muscle cells, and nerve fibers form synapses with only a few of the muscle fibers and cannot contract independently of one another.

A relaxed smooth muscle cell and a contracted smooth muscle cell. Note that in a contracted smooth muscle cell the nucleus appears **corkscrew-shaped.**

# Smooth Muscle



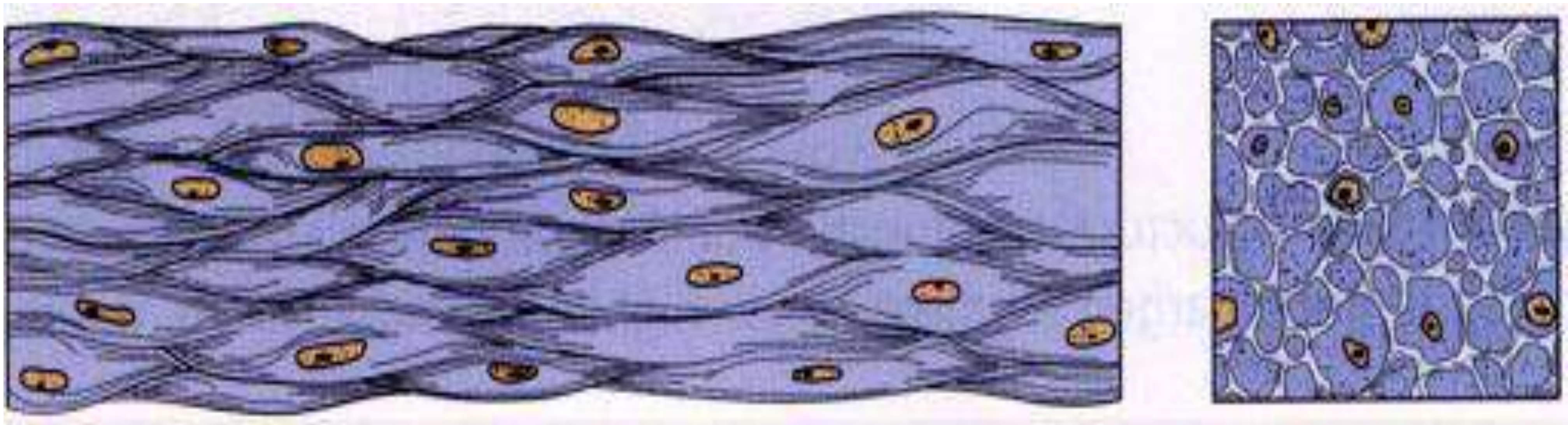

A relaxed smooth muscle cell and a contracted smooth muscle cell. Note that in a contracted smooth muscle cell the nucleus appears corkscrew-shaped.

Smooth muscle fibers are **fusiform,** elongated cells with **a central portion containing an oval nucleus housing** two or more nucleoli. During muscle shortening, the nucleus assumes a characteristic "corkscrew appearance."

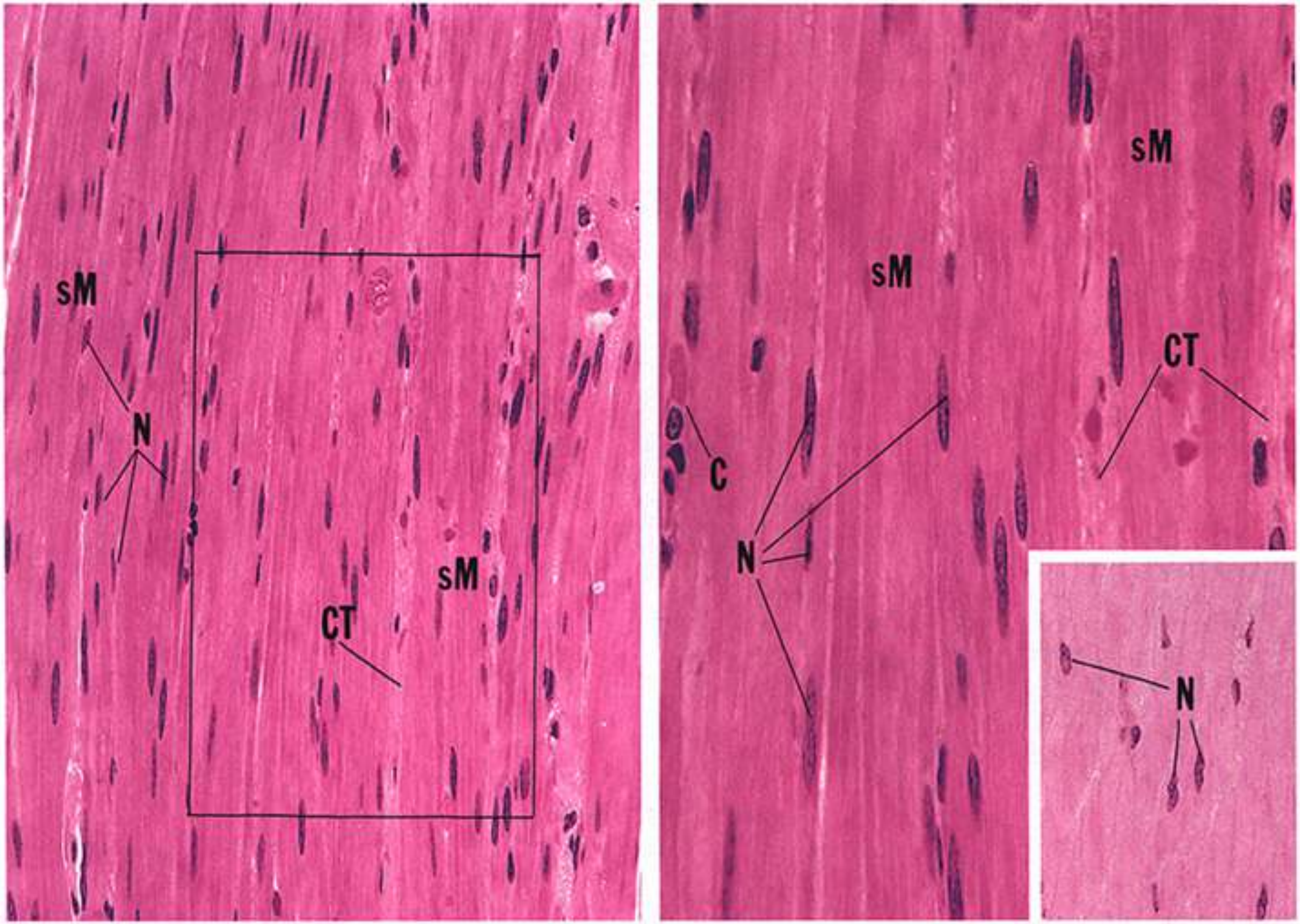
In addition to its contractile functions, some smooth muscle is capable of exogenous **protein synthesis.** Among the substances manufactured by smooth muscle cells for extracellular utilization are collagen, elastin, glycosaminoglycans, proteoglycans, and growth factors.

# Smooth Muscle

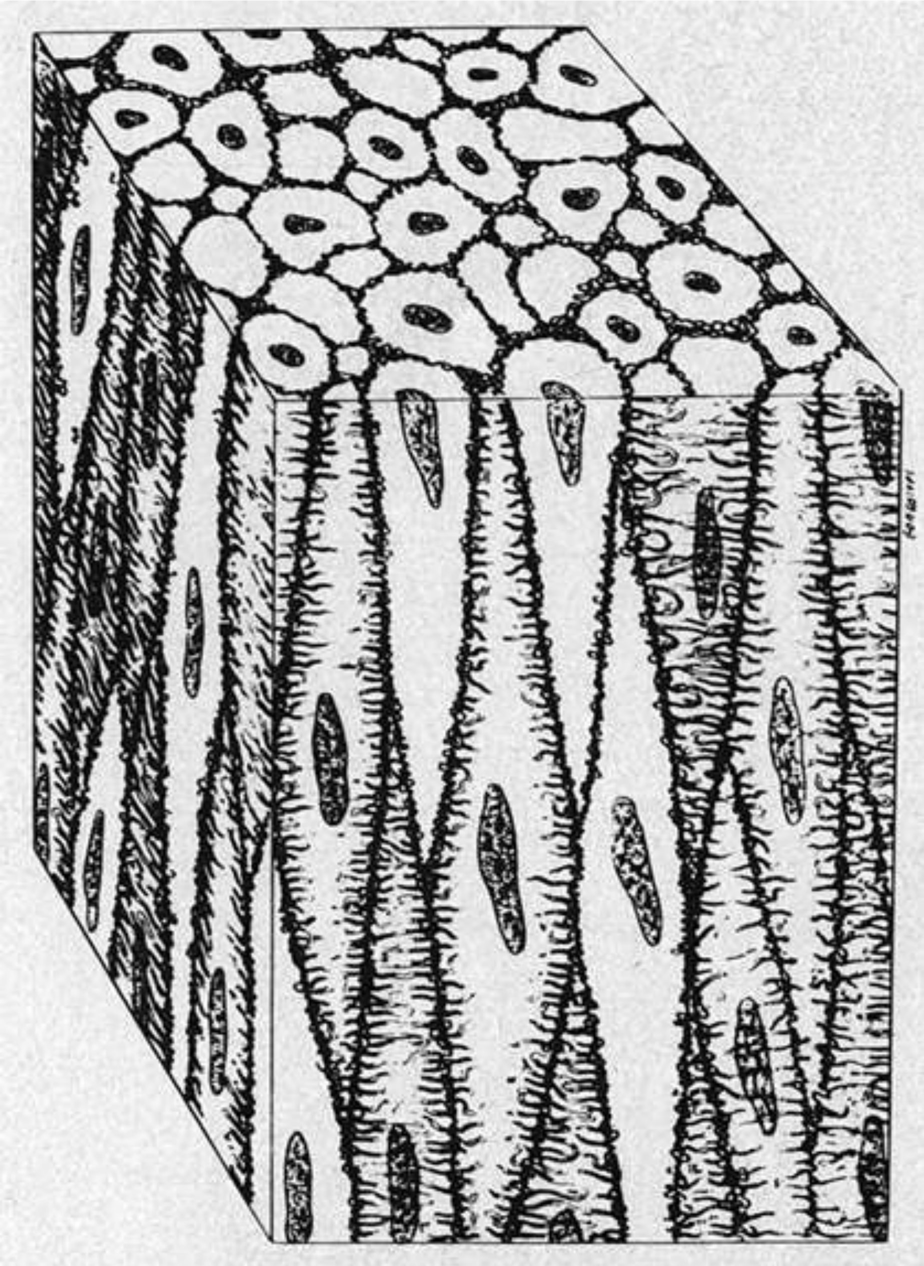
- Fusiform, non-striated cells
- Single, centrally-placed nucleus
- Contraction is non-voluntary
- Contraction is modulated in a neuroendocrine manner
- Found in blood vessels, GI and urogenital organ walls, dermis of skin

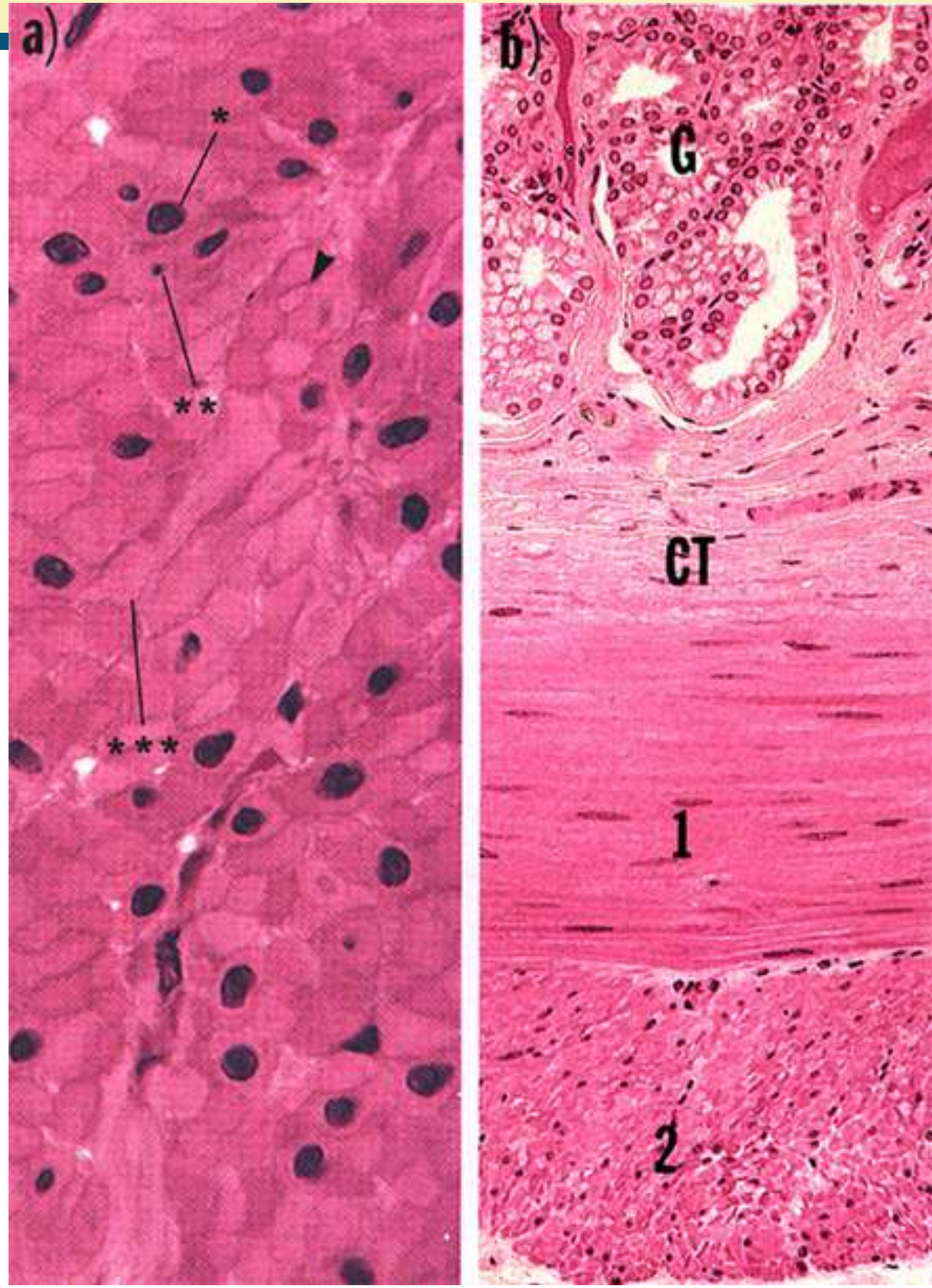


# Smooth Muscle (longitudinal section)



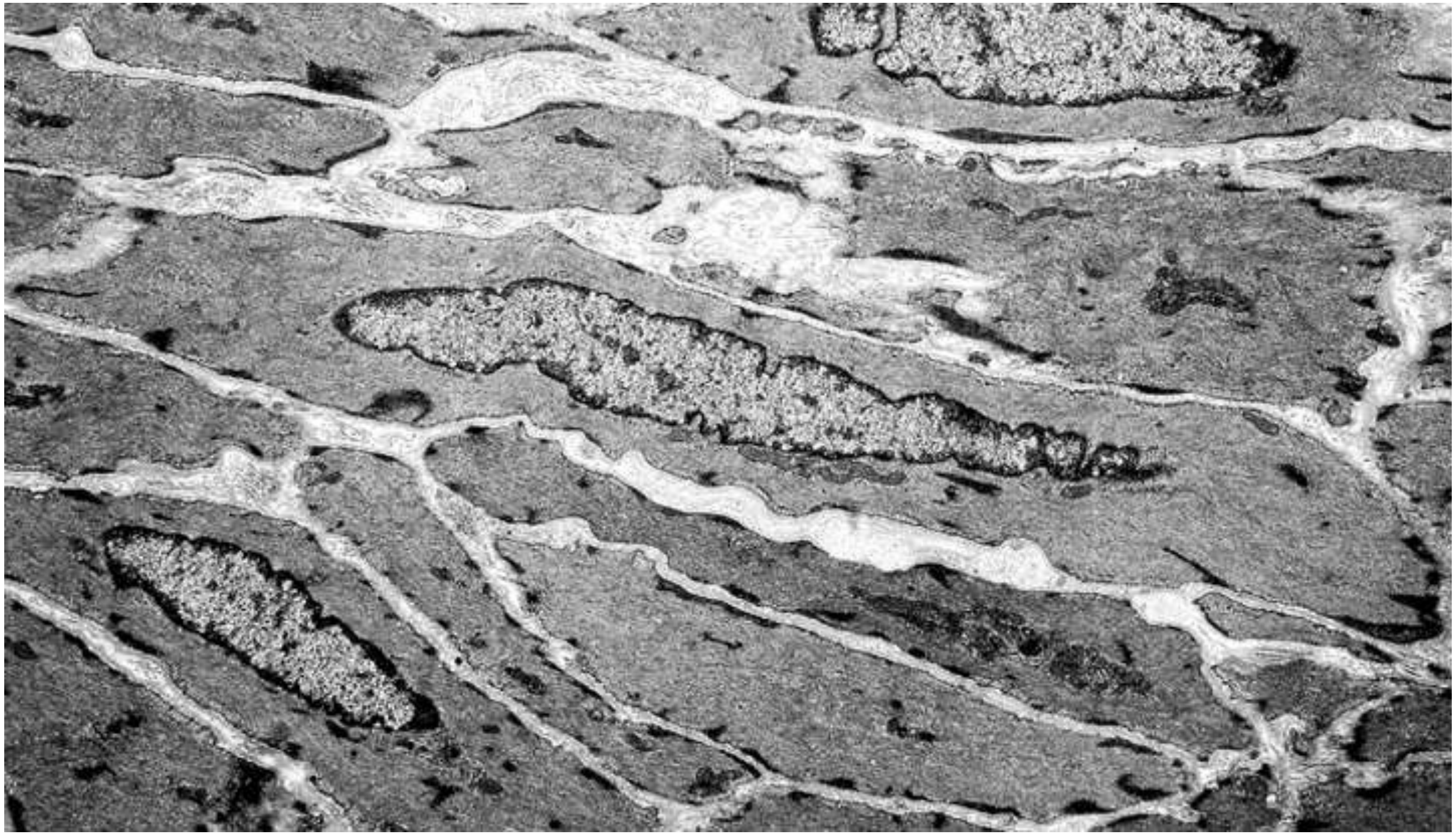
## Smooth Muscle Viewed in Transverse and Longitudinal Section





# Ultrastructure of Smooth Muscle:

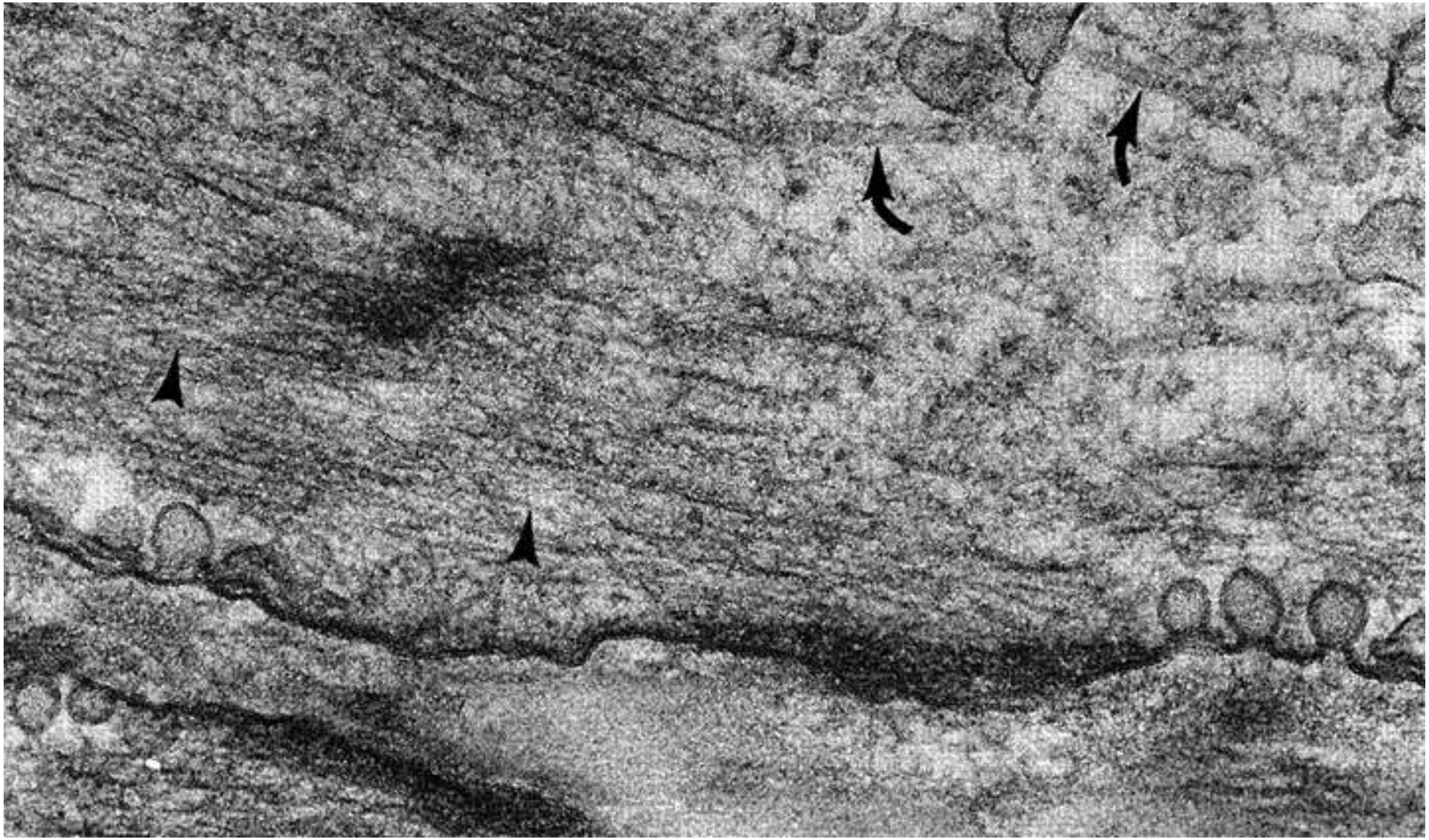
- actin and myosin filaments
- intermediate filaments of desmin (also vimentin in vascular smooth muscle)
- membrane associated and cytoplasmic dense bodies containing $\alpha$ actinin (similar to Z lines)
- relatively active nucleus (smooth muscle cells make collagen, elastin, and proteoglycans)



# More Ultrastructure of Smooth Muscle Cells:

- microtubules (curved arrows)
- actin filament (arrowheads)
- intermediate filaments

- dense bodies (desmin/vimentin plaques)
- caveoli (membrane invaginations & vesicular system contiguous with SER–**functionally analogous to sarcoplasmic reticulum**)



# Smooth Muscle

- Fibers are stimulated by neurotransmitters (ACh), hormones (norepinephrine ) or autorhythmic signals
- Action Potential is transmitted via gap junctions

Found in:

- Walls of arteries
- Walls of hollow organs
- Wall of airways to the lungs
- Muscle that attach the hair follicles
- Muscle that adjust focus of the lens

# Contraction of Smooth Muscle

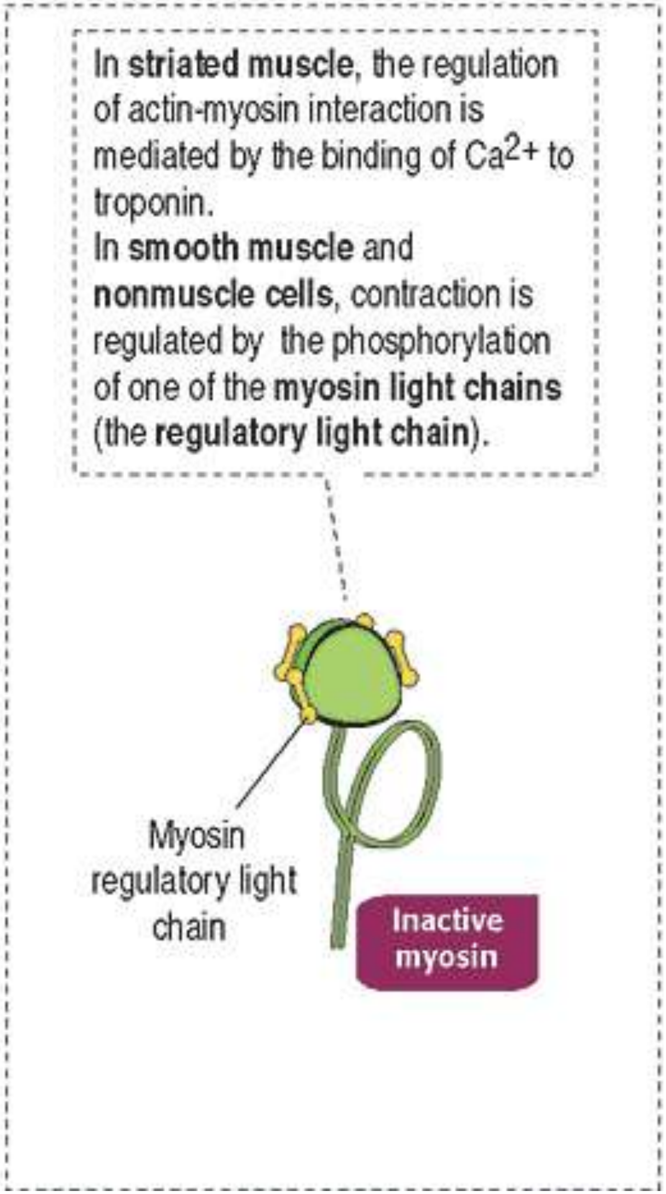
1-Thin filaments of actin insert into the **dense bodies (**not anymore the Z-disc**)**

2- Thick filaments of myosin II

3- And intermediate filaments of Vimentin and Desmin that insert into **the dense bodies** and twist or shorten the cell along its longitudinal axis.

Associate with the sarcolemma there are caveolae that act as T tubules, in regulating the cytosolic free $Ca^{2+}$.

# Contraction of Smooth Muscle




1- Regulation of contraction in smooth muscle also depends on $Ca^{2+}$ but the control mechanism differs from that of striated muscle because smooth muscle thin filaments have no troponin, but CALMODULINE (calcium binding protein)

Additionally, myosin molecules assume a different configuration, in that their actin binding site is masked by their light **meromyosin** moiety.

# Contraction of Smooth Muscle

Contraction of smooth muscle fibers is as follows:

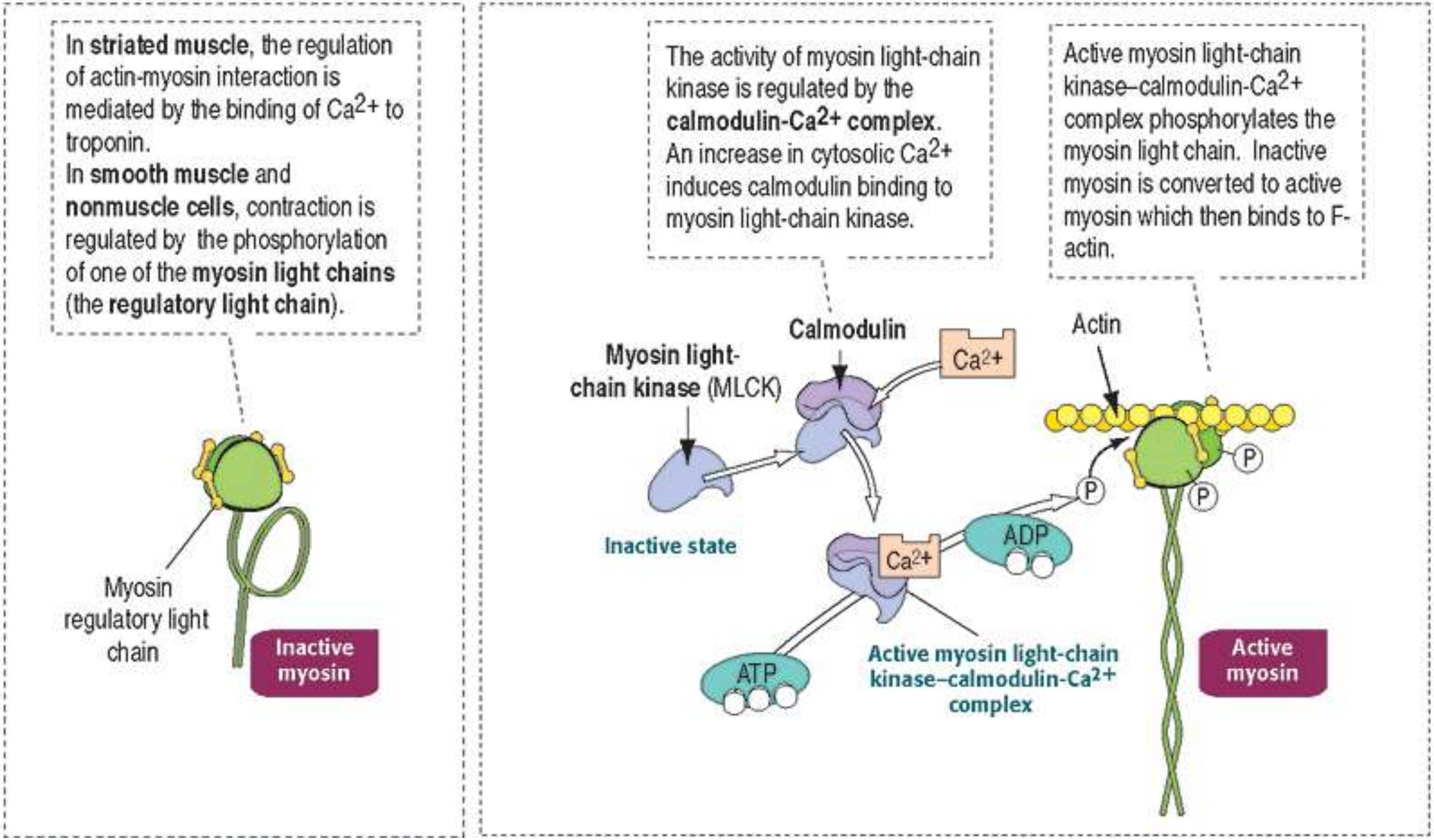
**1**. Calcium ions, released from caveolae, bind to **calmodulin** (a regulatory protein ubiquitous in living organisms), thereby altering its conformation. The $Ca^{2+}$-calmodulin complex then activates **myosin light chain kinase (MLCK).**

**2**. Myosin light chain kinase phosphorylates one of the myosin light chains, known as the **regulatory chain**, permitting the unfolding of the light **meromyosin moiety** to form the typical, "golf club"–shaped myosin molecule.

**3**. The phosphorylated light chain unmasks the myosin's actin binding site, permitting the interaction between actin and the $S_1$ subfragment of myosin that results in contraction.

Smooth muscle contraction not only is *prolonged* but also requires *less energy*.

# Contraction of Smooth Muscle




The regulation of smooth muscle contraction. *(From Kierszenbaum A: Histology and Cell Biology. Philadelphia, Elsevier/ Mosby, 2002, p 197.)*

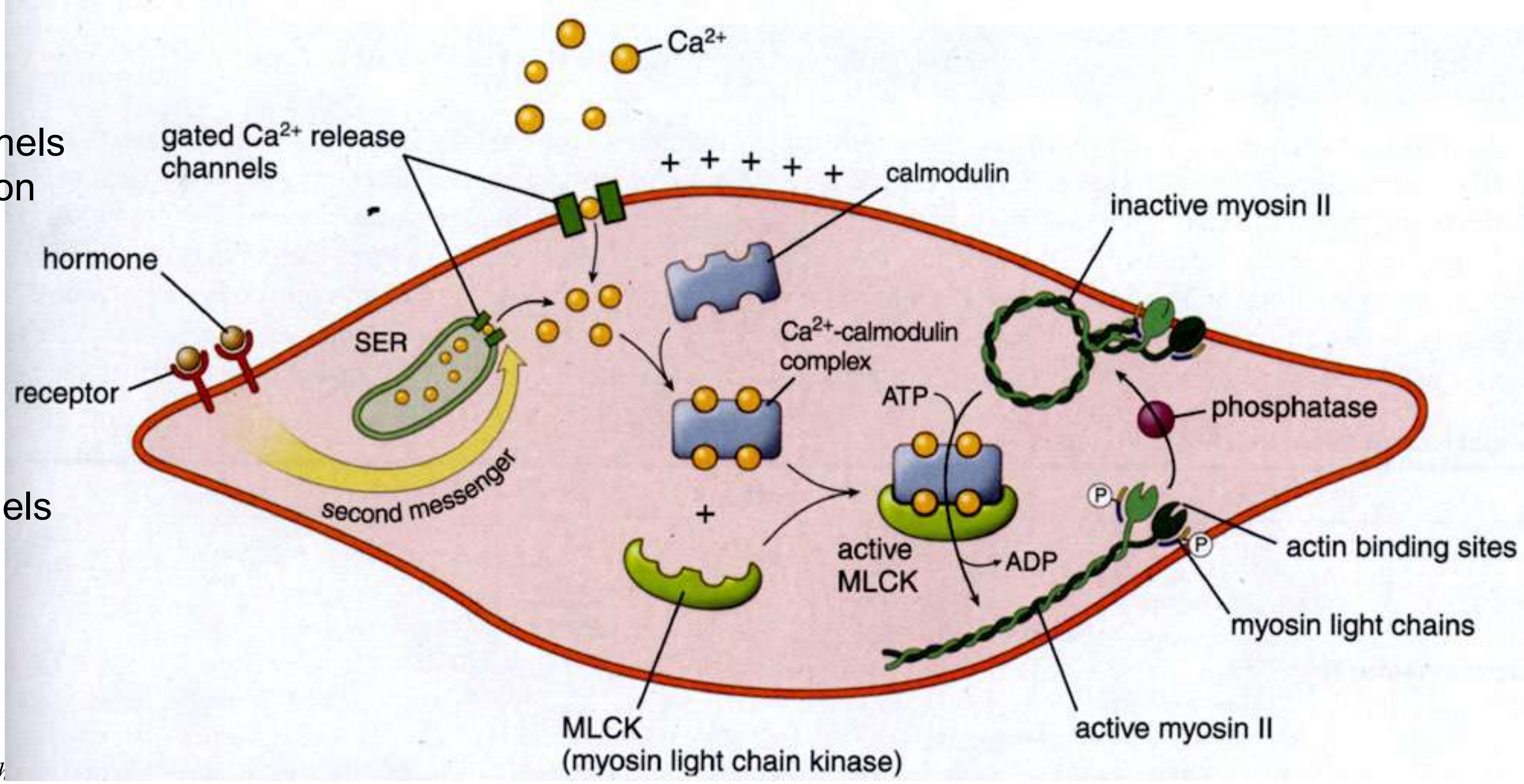
# Smooth Muscle Contraction:

also Ca+ dependent, but mechanism is different than striated muscle

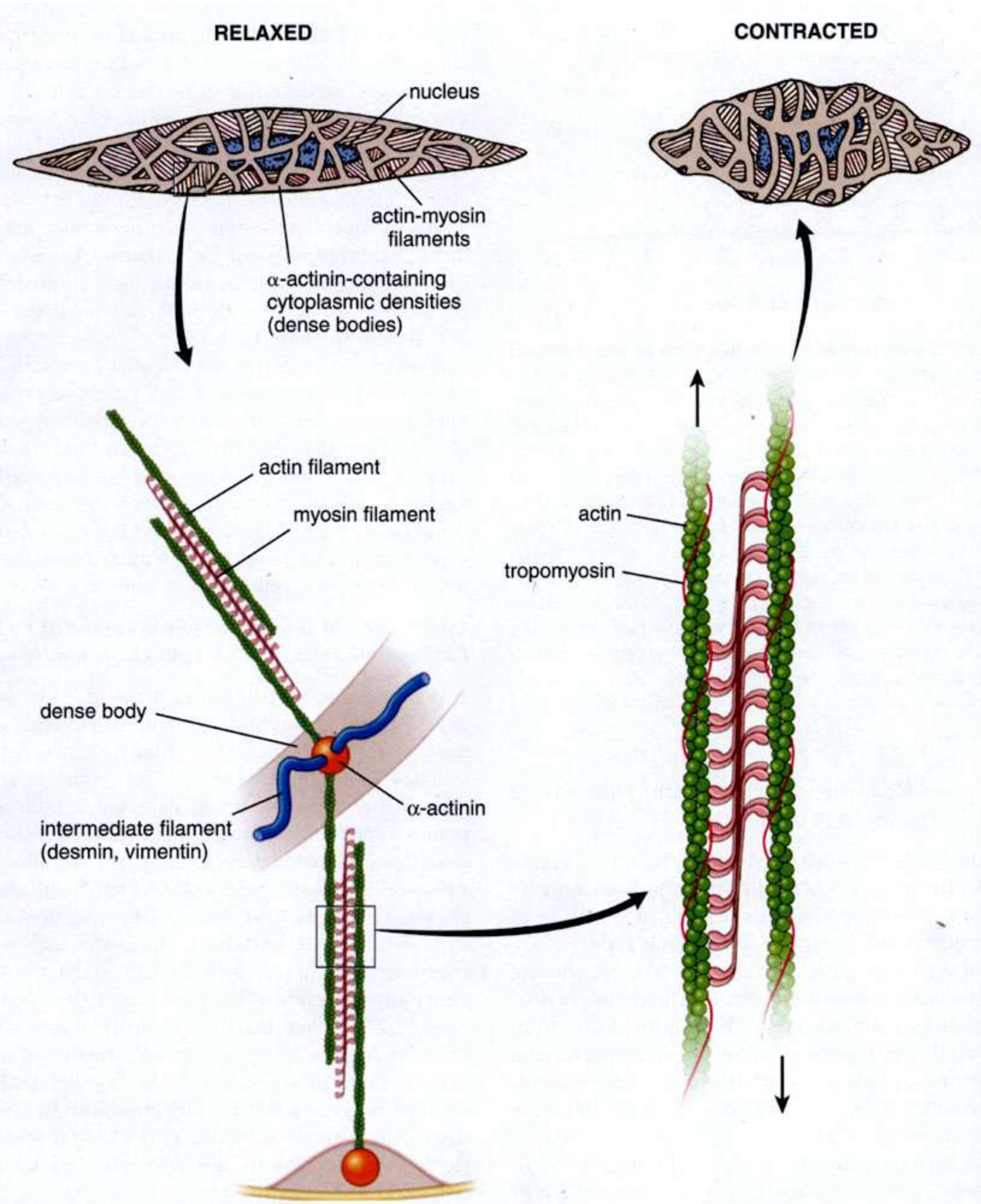
1. Ca2+ ions released from caveloae/SER and complex with calmodulin
2. Ca2+-calmodulin **activates myosin light chain kinase (MLKC)**
3. MLCK phosphorylates myosin light chain
4. Myosin unfolds & binds actin; ATP-dependent contraction cycle ensues.
5. Contraction continues as long as myosin is phosphorylated.
6. "Latch" state: myosin head attached to actin dephosphorylated causing decrease in ATPase activity –myosin head unable to detach from actin (similar to "rigor mortis" in skeletal muscle).
7. Smooth muscle cells often electrically coupled via gap junctions

Triggered by:

- Voltage-gated Ca+ channels activated by depolarization
  - Mechanical stimuli
  - Neural stimulation
- Ligand-gated Ca+ channels



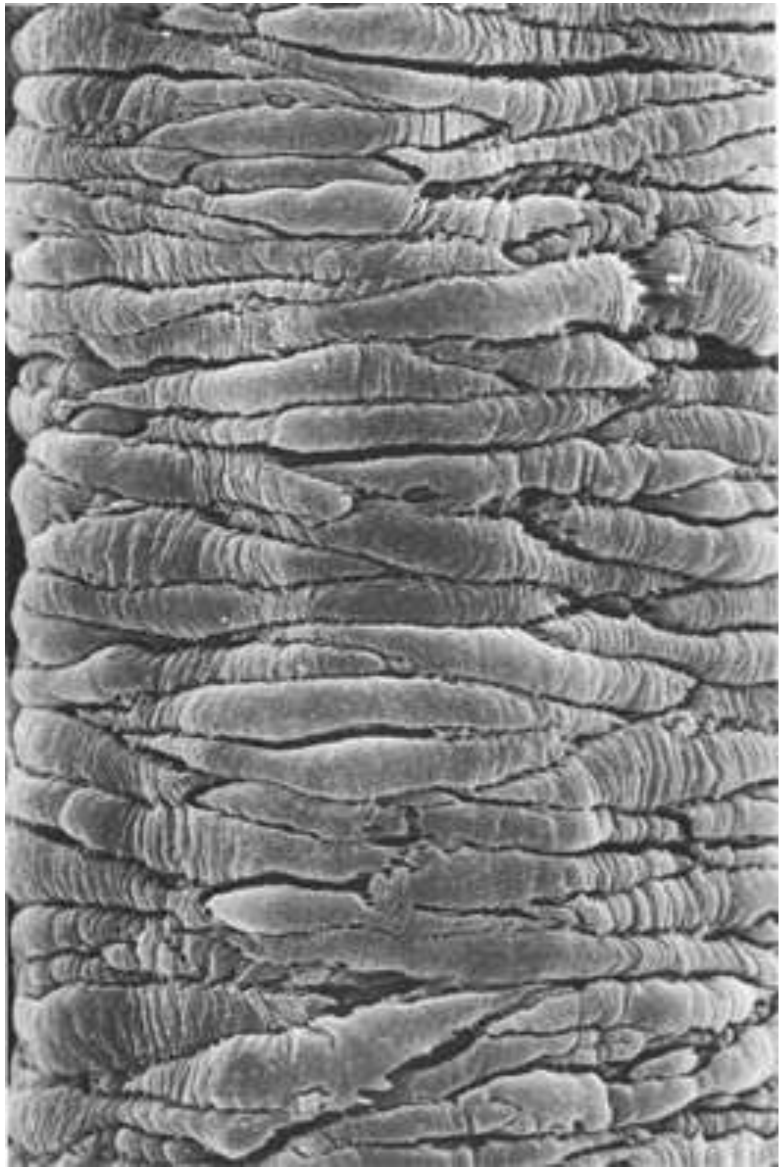
# Mechanics of Smooth Muscle Contraction



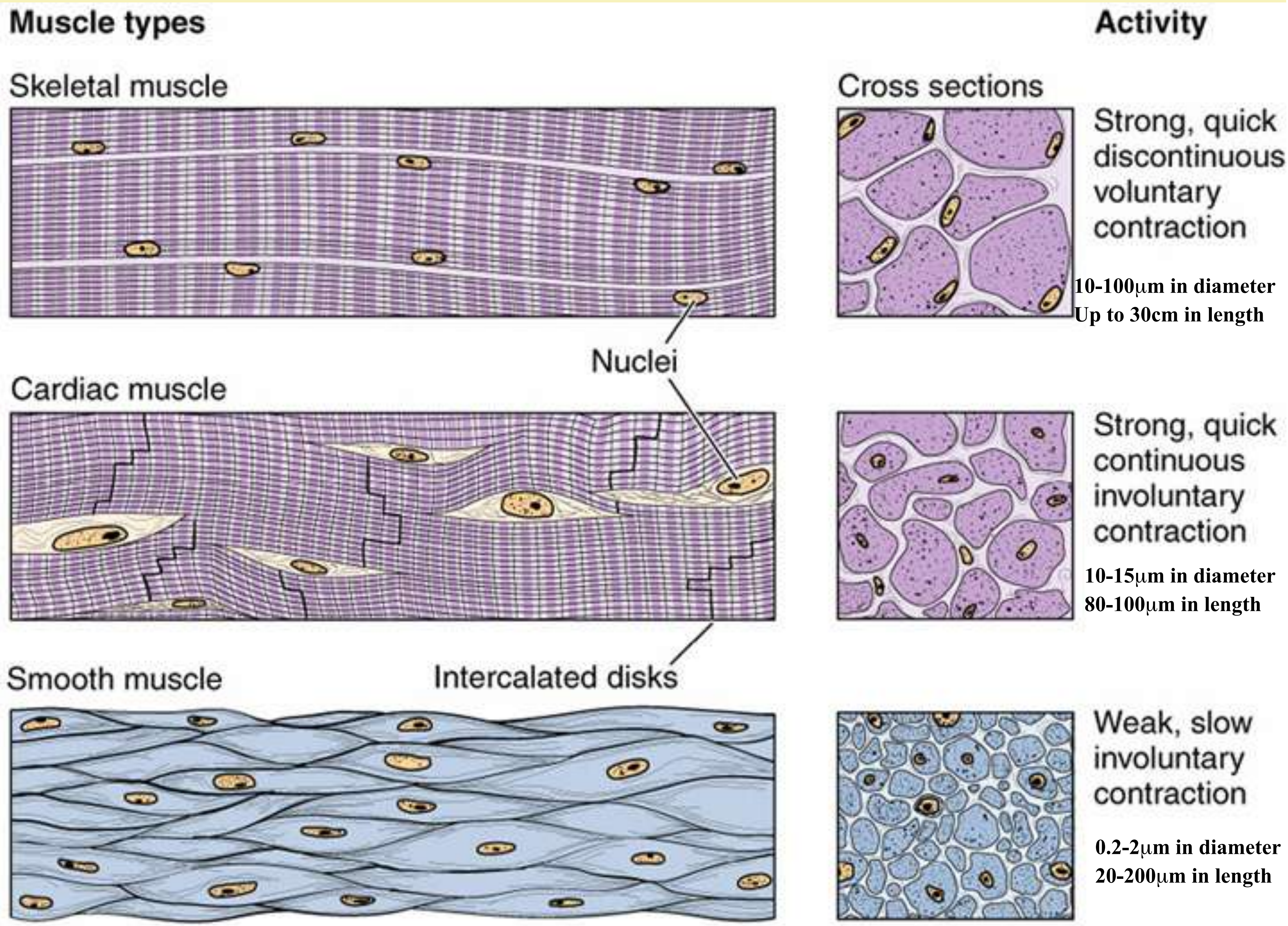

- Dense bodies are analogous to Z lines (plaques into which actin filaments insert)
- Myosin heads oriented in “side polar” arrangement
- Contraction pulls dense bodies together
- Contraction is **slow** and **sustained**

# Smooth Muscle (vascular)

Relaxed

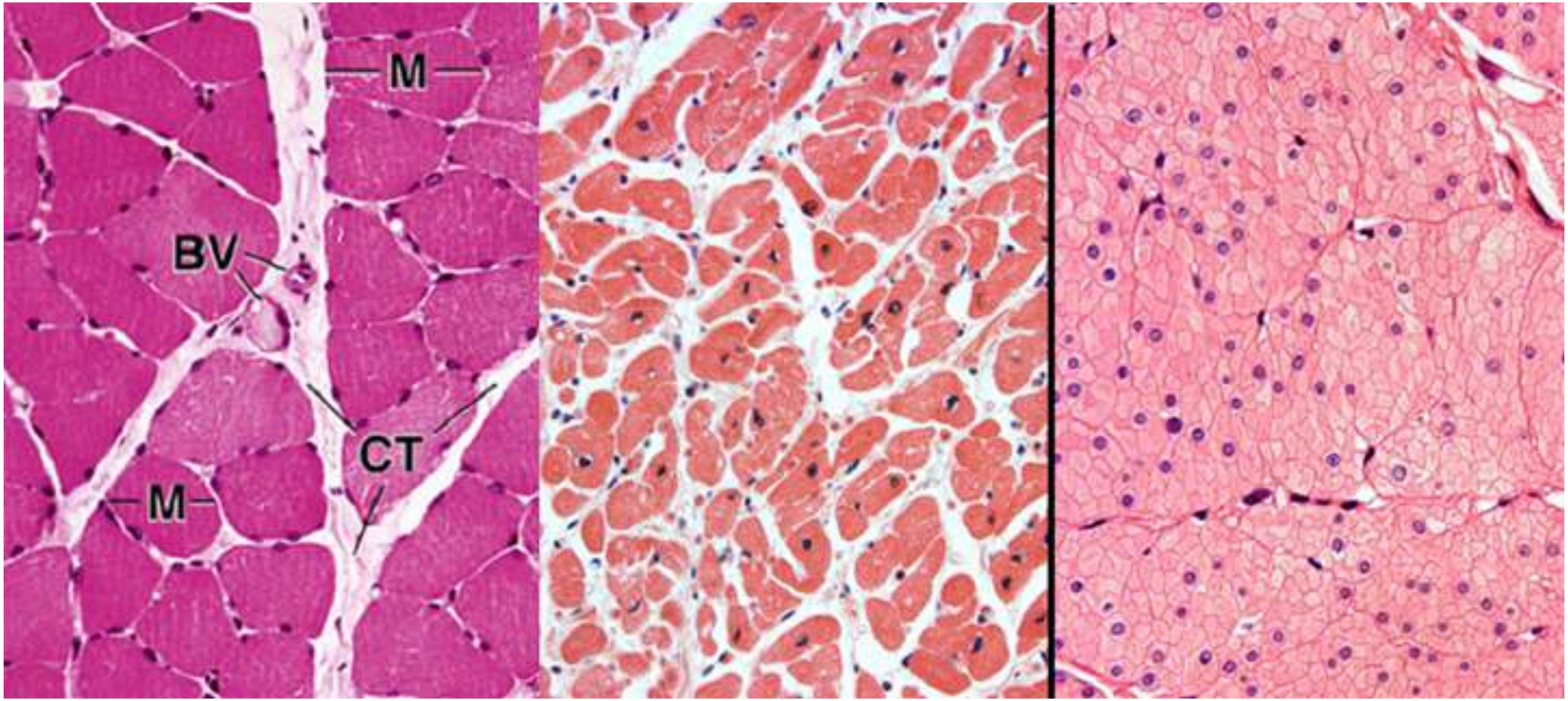


Contracted

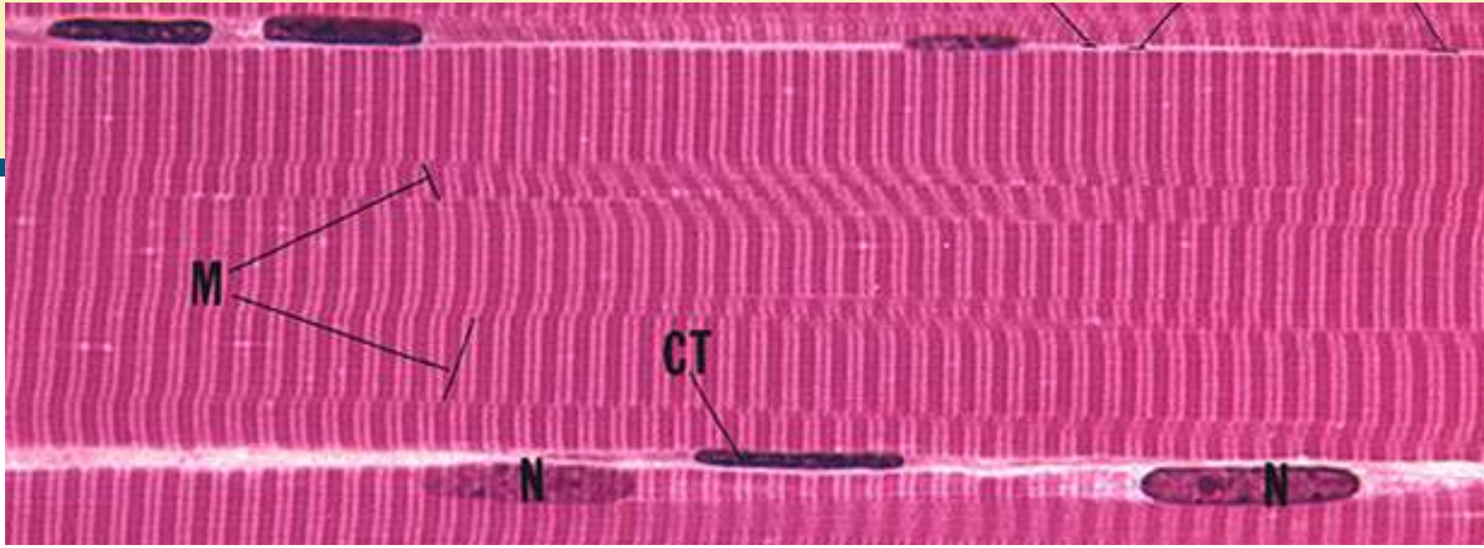


Muscle types
Activity
Skeletal muscle
Cross sections
Strong, quick discontinuous voluntary contraction
10-100μm in diameter
Up to 30cm in length
Nuclei
Cardiac muscle
Strong, quick continuous involuntary contraction
10-15μm in diameter
80-100μm in length
Smooth muscle
Intercalated disks
Weak, slow involuntary contraction
0.2-2μm in diameter
20-200μm in length

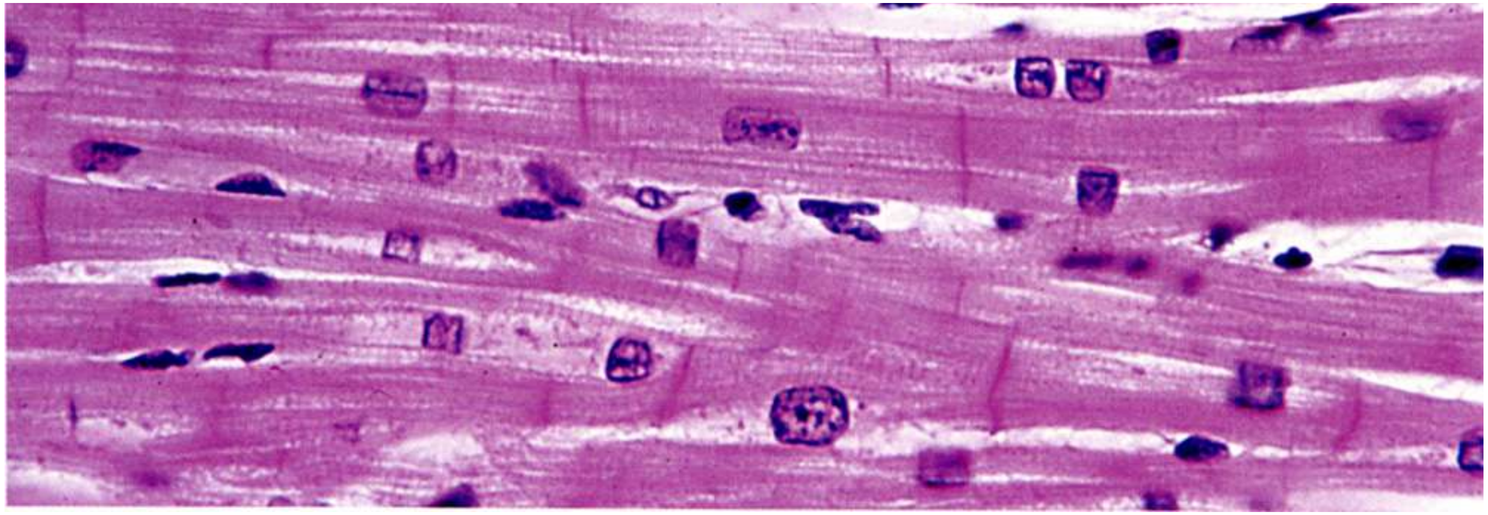
Skeletal Muscle Cardiac Muscle Smooth Muscle



Skeletal Muscle




Cardiac Muscle



Smooth Muscle