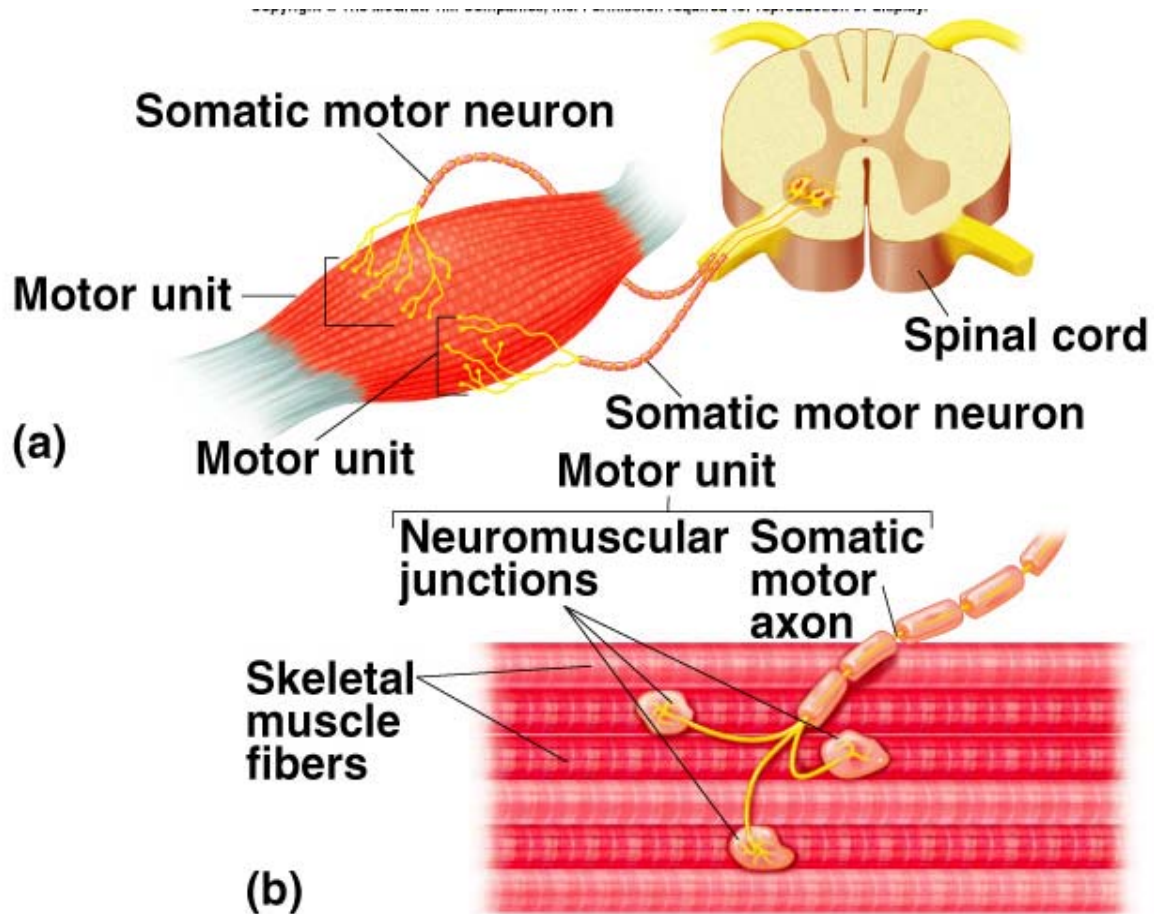# Muscles and Muscle Tissue part2

Depolarization
- Initially, this is a local electrical event called end plate potential
- Later, it ignites an action potential that spreads in all directions across the sarcolemma

Action Potential: Electrical Conditions of a Polarized

Sarcolemma
- The outside (extracellular) face is positive, while the inside face is negative
- This difference in charge is the resting membrane potential
- The predominant extracellular ion is Na^+
- The predominant intracellular ion is K^+
- The sarcolemma is relatively impermeable to both ions

The Muscle Fiber

Skeletal muscle is made up of thousands of cylindrical muscle **fibers** often running all the way from origin to insertion. The fibers are bound together by connective tissue through which run blood vessels and nerves.

Each muscle fibers contains:

- an array of **myofibrils** that are stacked lengthwise and run the entire length of the fiber.

- **mitochondria**

- an extensive **smooth endoplasmic reticulum (SER)**

- **many nuclei**.

The multiple nuclei arise from the fact that each muscle fiber develops from the fusion of many cells (called **myoblasts**).

The number of fibers is probably fixed early in life. This is regulated by **myostatin**, a cytokine that is synthesized in muscle cells (and circulates as a hormone later in life). Myostatin **suppresses** skeletal muscle development. Cattle and mice with inactivating mutations in their myostatin genes develop much larger muscles. Some athletes and other remarkably strong people have been found to carry one mutant myostatin gene. These discoveries have already led to the growth of an illicit market in drugs supposedly able to suppress myostatin.

In adults, increased strength and muscle mass comes about through an increase in the thickness of the individual fibers and increase in the amount of connective tissue. In the mouse, at least, fibers increase in size by attracting more myoblasts to fuse with them. The fibers attract more myoblasts by releasing the cytokine interleukin 4 (IL-4). Anything that lowers the level of myostatin also leads to an increase in fiber size.

Because a muscle fiber is not a single cell, its parts are often given special names such as

- **sarcolemma** for plasma membrane

- **sarcoplasmic reticulum** for endoplasmic reticulum

- **sarcosome** for mitochondrion

- **sarcoplasm** for cytoplasm

although this tends to obscure the essential similarity in structure and function of these structures and those found in other cells.

The

- nuclei and mitochondria are located just beneath the plasma membrane

- the endoplasmic reticulum extends between the myofibrils.

Seen from the side under the microscope, skeletal muscle fibers show a pattern of cross banding, which gives rise to the other name: **striated muscle**.

The striated appearance of the muscle fiber is created by a pattern of alternating

- dark **A bands** and

- light **I bands**.

- The A bands are bisected by the **H zone**

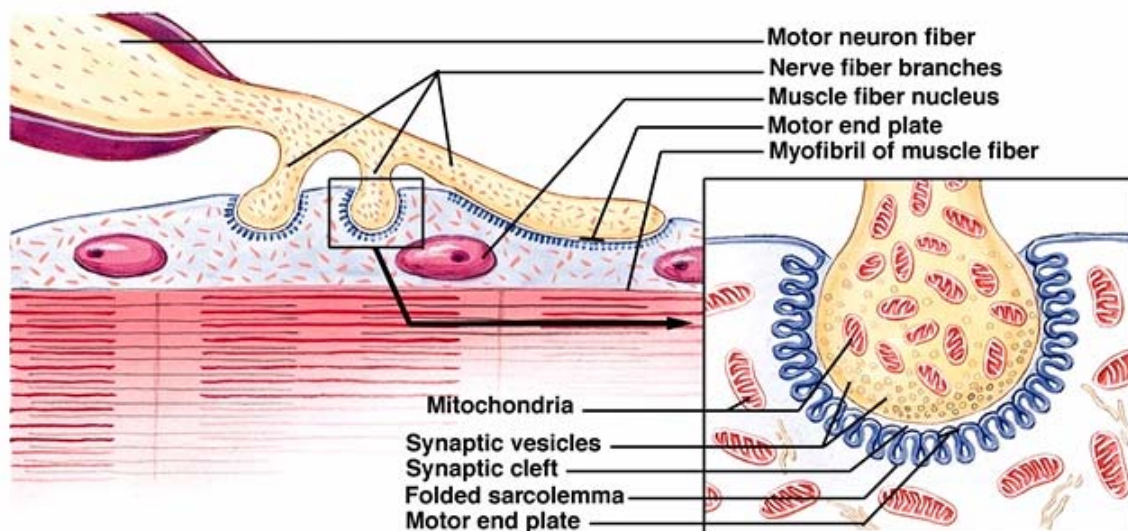- The I bands are bisected by the **Z line**.
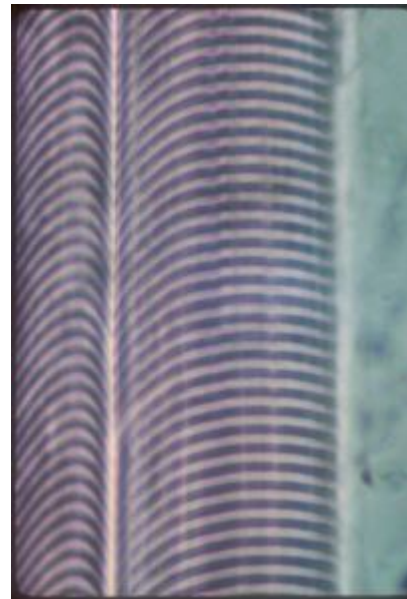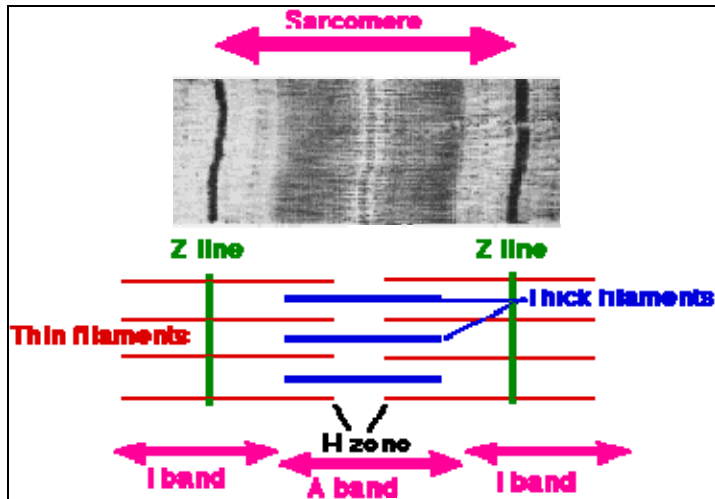
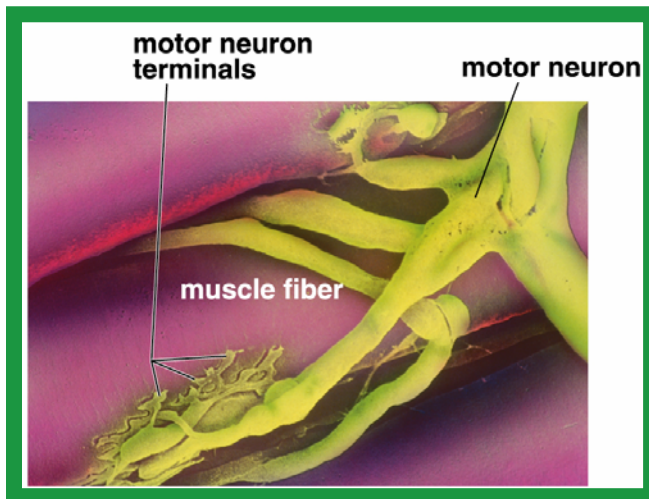Each myofibril is made up of arrays of parallel **filaments**.

- The **thick filaments** have a diameter of about 15 nm. They are composed of the protein **myosin**.

- The **thin filaments** have a diameter of about 5 nm. They are composed chiefly of the protein **actin** along with smaller amounts of two other proteins:

  - **troponin** and

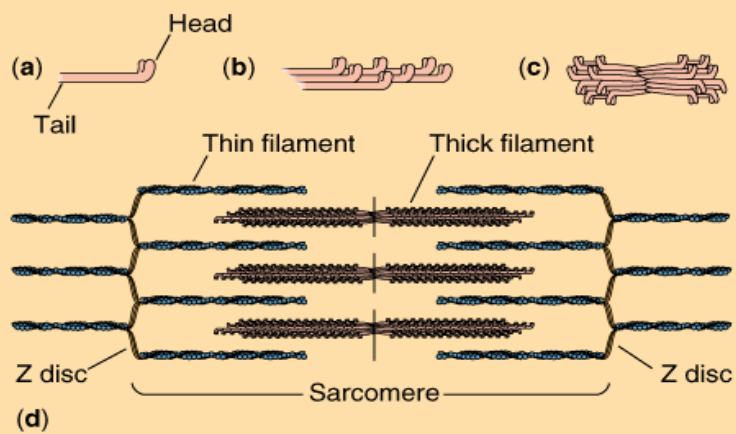 - **tropomyosin**.

The anatomy of a sarcomere

- The **thick filaments** produce the dark **A band**.

- The **thin filaments** extend in each direction from the Z line. Where they do not overlap the thick filaments, they create the light **I band**.

- The **H zone** is that portion of the A band where the thick and thin filaments do not overlap.

The entire array of thick and thin filaments between the Z lines is called a **sarcomere**. Shortening of the sarcomeres in a myofibril produces the shortening of the myofibril and, in turn, of the muscle fiber of which it is a part. [This electron micrograph of a single sarcomere was kindly provided by Dr. H. E. Huxley.]

3

motor neuron terminals

motor neuron

muscle fiber

► **Molecular Organization of Thick Filaments**

Head

(a)

Tail

(b)

(c)

Thin filament

Thick filament

Z disc

Z disc

Sarcomere

(d)

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Labels (left illustration): Skeletal muscle; Peripheral nerve (motor and sensory nerve fibers); Muscle spindle; Tendon; Bone; Waldrop

Labels (right illustration): Extrafusal fibers; Intrafusal fibers: Nuclear chain fibers; Nuclear bag fiber; Connective tissue sheath; Afferent nerve fibers (sensory): Primary fiber; Annulospiral endings; Secondary fiber; Flower-spray endings; Efferent nerve fibers (motor): Gamma fiber; Alpha fiber; Motor end plates

Type I vs. Type II Fibers

Two different types of muscle fiber can be found in most skeletal muscles. The Type I and Type II fibers differ in their structure and biochemistry.

Type I Fibers

- loaded with mitochondria and

- depend on cellular respiration for ATP production

- resistant to fatigue

- rich in myoglobin and hence red in color

- activated by small-diameter, thus slow-conducting, motor neurons

- also known as "slow-twitch" fibers

- dominant in muscles that depend on tonus, e.g., those responsible for posture
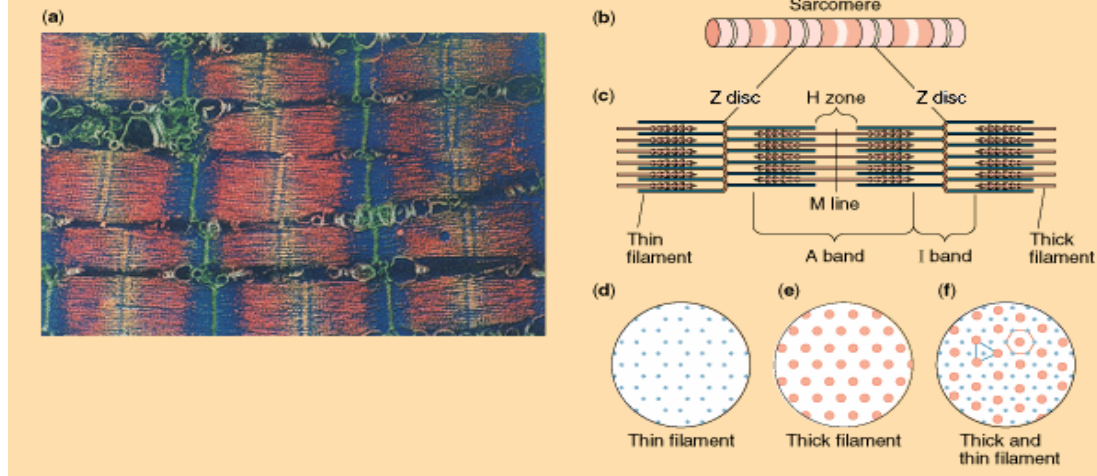
Type II Fibers

- few mitochondria

- rich in glycogen and

- depend on glycolysis for ATP production

- fatigue easily

- low in myoglobin hence whitish in color

- activated by large-diameter, thus fast-conducting, motor neurons

- also known as "fast-twitch" fibers

- dominant in muscles used for rapid movement

Most skeletal muscles contain some mixture of Type I and Type II fibers, but a single motor unit always contains one type or the other, never both.

The ratio of Type I and Type II fibers can be changed by endurance training (producing more Type I fibers).

▶ **Organization of a Muscle Fiber**

6

► Arrangements of Myofilaments in a Sarcomere

(a)

(b) Sarcomere

(c) Z disc   H zone   Z disc
    M line
    Thin filament   A band   I band   Thick filament

(d) Thin filament   (e) Thick filament   (f) Thick and thin filament

Action Potential: Depolarization and Generation of the Action Potential
- An axonal terminal of a motor neuron releases ACh and causes a patch of the sarcolemma to become permeable to Na^+ (sodium channels open)
- Na^+ enters the cell, and the resting potential is decreased (depolarization occurs)
- If the stimulus is strong enough, an action potential is initiated
- Polarity reversal of the initial patch of sarcolemma changes the permeability of the adjacent patch
- Voltage-regulated Na^+ channels now open in the adjacent patch causing it to depolarize
- Thus, the action potential travels rapidly along the sarcolemma
- Once initiated, the action potential is unstoppable, and ultimately results in the contraction of a muscle
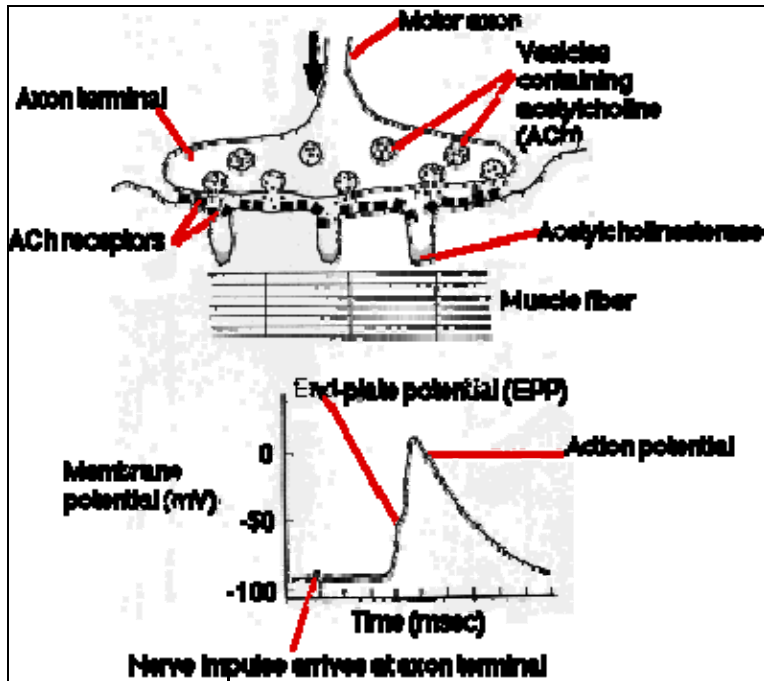
The Neuromuscular Junction

Nerve impulses (action potentials) traveling down the motor neurons of the sensory-somatic branch of the nervous system cause the skeletal muscle fibers at which they terminate to contract. The junction between the terminal of a motor neuron and a muscle fiber is called the neuromuscular junction. It is simply one kind of synapse. (The neuromuscular junction is also called the myoneural junction.)

The terminals of motor axons contain thousands of vesicles filled with **acetylcholine** (**ACh**).

When an action potential reaches the axon terminal, hundreds of these vesicles discharge their ACh onto a specialized area of postsynaptic membrane on the fiber. This area contains a cluster of transmembrane channels that are opened by ACh and let sodium ions (Na$^+$) diffuse in.

The interior of a resting muscle fiber has a **resting potential** of about −95 mV. The influx of sodium ions reduces the charge, creating an **end plate potential**. If the end plate potential reaches the **threshold** voltage (approximately −50 mV), sodium ions flow in with a rush and an **action potential** is created in the fiber. The action potential sweeps down the length of the fiber just as it does in an axon.

Golgi Tendon Organ

Golgi tendon organ

Helps prevent excessive muscle contraction or excessive passive muscle stretching.

A reflex.

Action potentials: A   B

EPP

Impulse arrives
at axon terminal

Stimulus to nerve
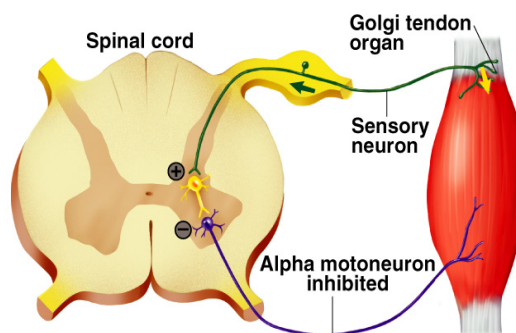
- The muscle fiber is stimulated by a motor neuron (Left).

- Arrival of a nerve impulse at the axon terminal of the motor neuron

  - causes acetylcholine to be released into the neuromuscular junction which

  - creates an **end plate potential** (**EPP**) in the membrane beneath it (**A**)

  - but not farther away (**B**).

- When the EPP reaches the threshold of the fiber (about -50 mv), an **action potential** is generated that sweeps along the fiber (**B**)

Action Potential: Repolarization
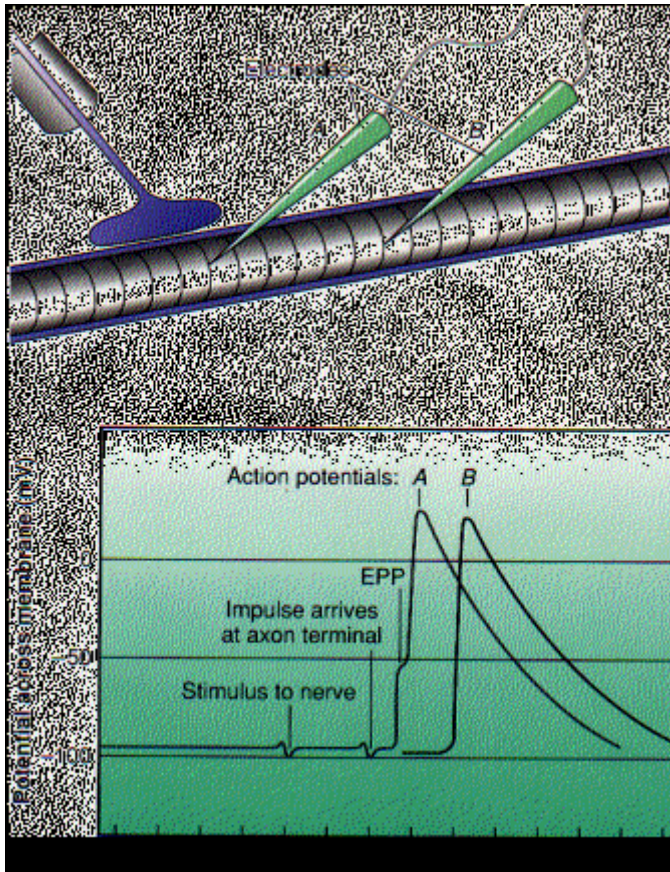- Immediately after the depolarization wave passes, the sarcolemma permeability changes
- Na^+ channels close and K^+ channels open
- K^+ diffuses from the cell, restoring the electrical polarity of the sarcolemma
- Repolarization occurs in the same direction as depolarization, and must occur before the muscle can be stimulated again (refractory period)
- The ionic concentration of the resting state is restored by the Na^+-K^+ pump

No visible change occurs in the muscle fiber during (and immediately following) the action potential. This period, called the **latent period**, lasts from 3–10 msec.

Before the latent period is over,
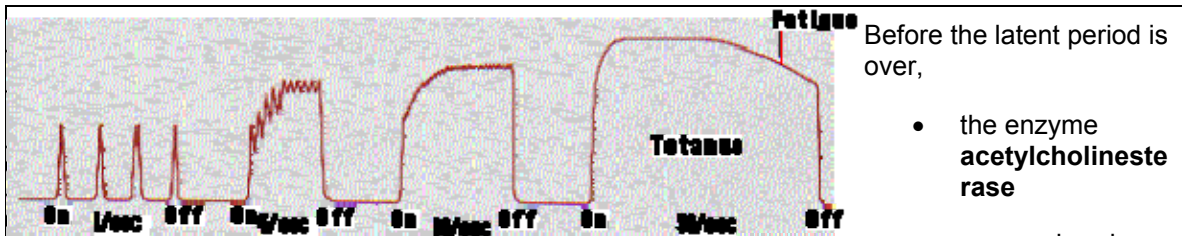
- the enzyme **acetylcholinesterase**
  - breaks down the ACh in the neuromuscular junction (at a speed of 25,000 molecules per second)
  - the sodium channels close, and
  - the field is cleared for the arrival of another nerve impulse.

- the resting potential of the fiber is restored by an outflow of **potassium ions**

The brief (1–2 msec) period needed to restore the resting potential is called the **refractory period**.

Tetanus

The process of contracting takes some 50 msec; relaxation of the fiber takes another 50–100 msec. Because the refractory period is so much shorter than the time needed for contraction and relaxation, the fiber can be maintained in the contracted state so long as it is stimulated frequently enough (e.g., 50 stimuli per second). Such sustained contraction is called **tetanus**.

In the figure,

- When shocks are given at 1/sec, the muscle responds with a single twitch.

- At 5/sec and 10/sec, the individual twitches begin to fuse together, a phenomenon called **clonus**.

- At 50 shocks per second, the muscle goes into the smooth, sustained contraction of tetanus.

Clonus and tetanus are possible because the refractory period is much briefer than the time needed to complete a cycle of contraction and relaxation. Note that the amount of contraction is greater in clonus and tetanus than in a single twitch.

As we normally use our muscles, the individual fibers go into tetanus for brief periods rather than simply undergoing single twitches.

The Sliding-Filament Model
Each molecule of myosin in the **thick filaments** contains a globular subunit called the **myosin head**. The myosin heads have binding sites for

- the **actin** molecules in the **thin filaments** and

- **ATP**

Activation of the muscle fiber causes the myosin heads to bind to actin. An allosteric change occurs which draws the thin filament a short distance (~10 nm) past the thick filament. Then the linkages break (for which ATP is needed) and reform farther along the thin filament to repeat the process. As a result, the filaments are pulled past each other in a ratchetlike action. There is no shortening, thickening, or folding of the individual filaments.
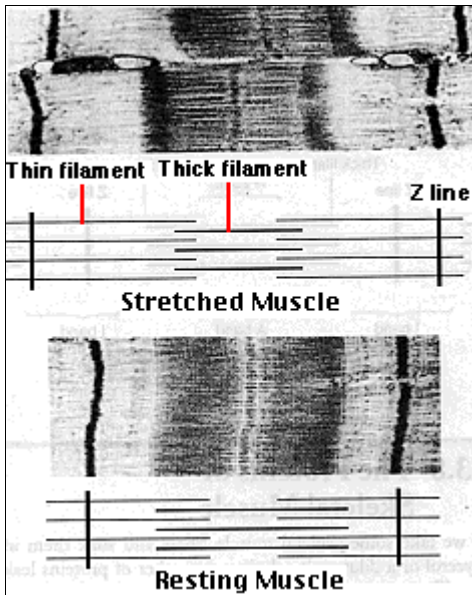
Electron microscopy supports this model.

As a muscle contracts,

- the Z lines come closer together

- the width of the I bands decreases

- the width of the H zones decreases, but

- there is no change in the width of the A band.

Conversely, as a muscle is stretched,

- the width of the I bands and H zones increases,

- but there is still no change in the width of the A band.

Excitation-Contraction Coupling
- Once generated, the action potential:
  - Is propagated along the sarcolemma
  - Travels down the T tubules
  - Triggers Ca^{2+} release from terminal cisternae
- Ca^{2+} binds to troponin and causes:
  - The blocking action of tropomyosin to cease
  - Actin active binding sites to be exposed
- Myosin cross bridges alternately attach and detach
- Thin filaments move toward the center of the sarcomere
- Hydrolysis of ATP powers this cycling process
- Ca^{2+} is removed into the SR, tropomyosin blockage is restored, and the muscle fiber relaxes

```
A band
Z disc          H zone          Z disc
```

Titin filament Thin filament M line Thick filament

Sarcomere
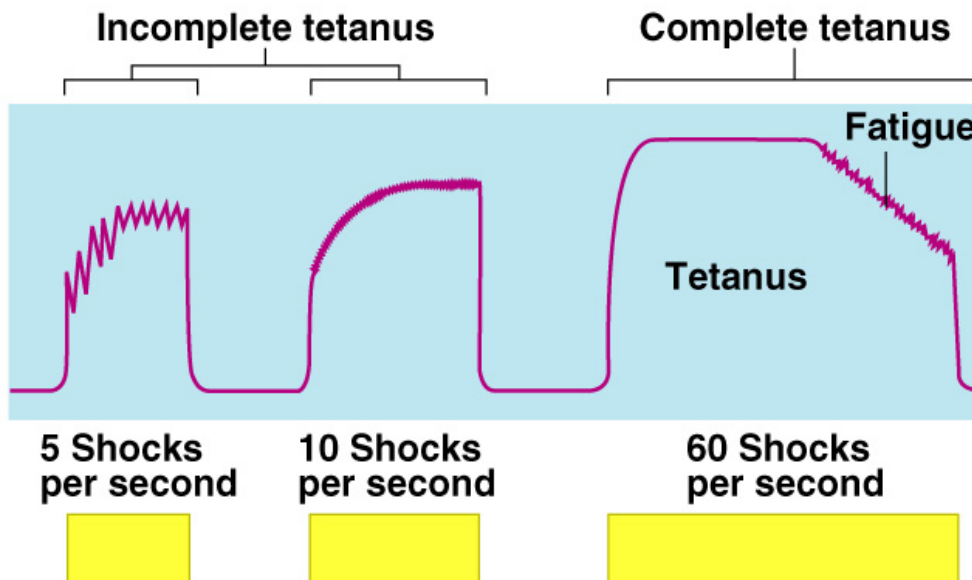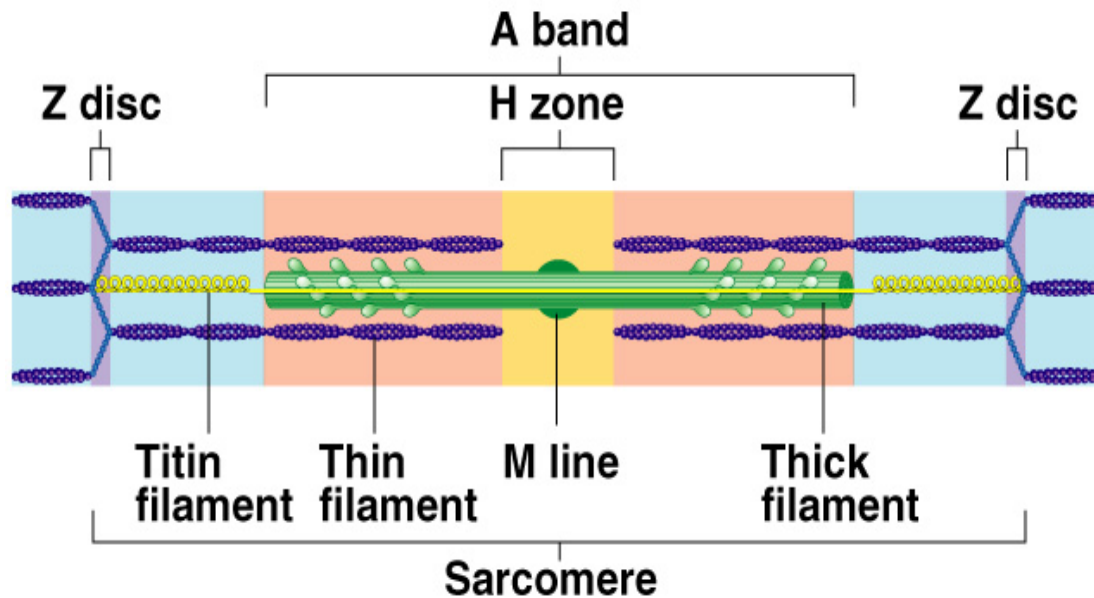
Treppe:
Second stimulus elicits a stronger response
Perhaps due to increase in intracellular Ca2+.

Contractions

Isotonic contractions:
  Force of contraction remains constant throughout the
    shortening process.

Isometric contractions:
  Length of muscle fibers remain constant.

Eccentric contractions:
  Force exerted on a muscle to stretch is greater than
    the force of muscle contraction.
    Running downhill

MYOFIBRIL AND SARCOMERE

sarcomere

thin filament

Z line

Z line

thick filament

CONTRACTED MUSCLE

RELAXED MUSCLE
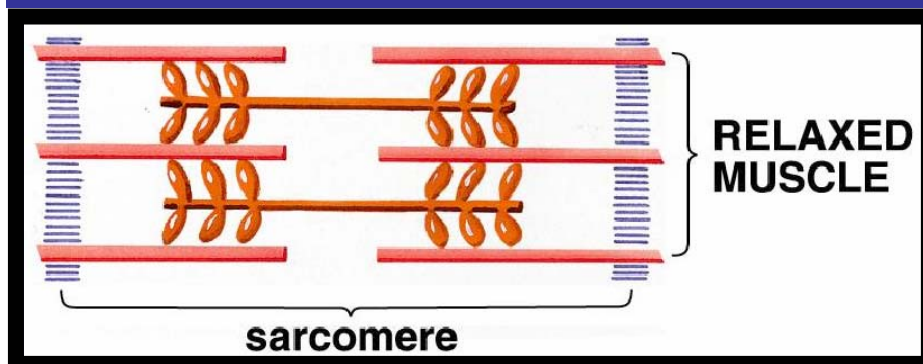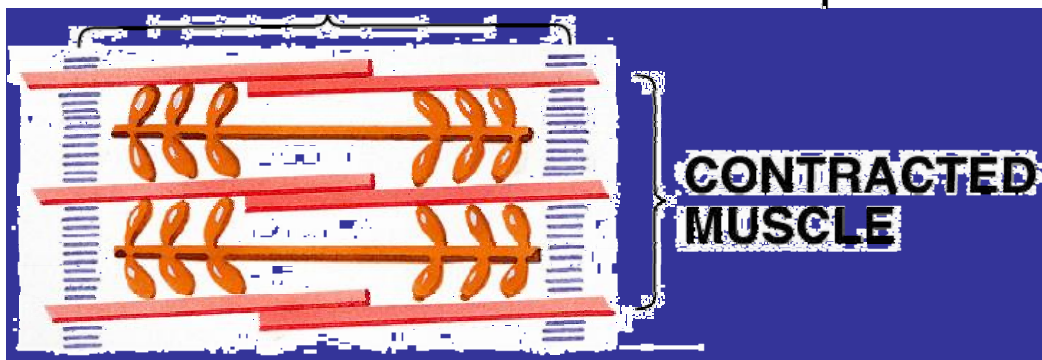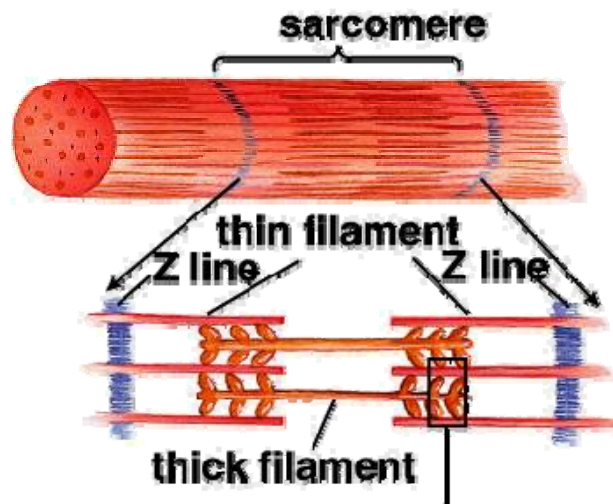
sarcomere

The Sliding Filament Model of Muscle Contraction

Myosin

Actin
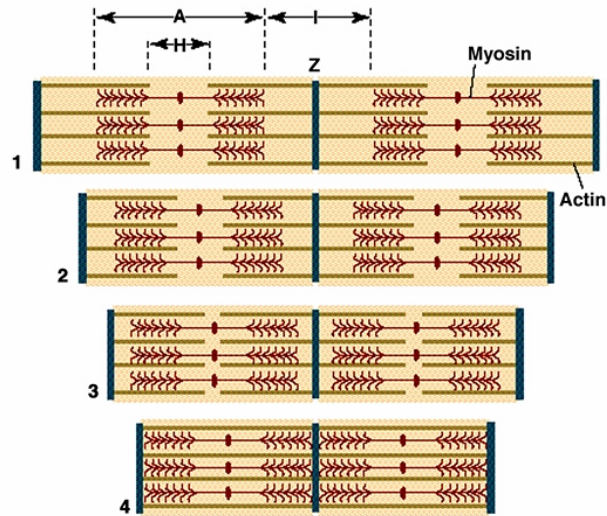
Changes in a Sarcomere During Contraction

Sarcomere

I band   A band

H zone

(a) Rest

(b) Contraction

Z disc
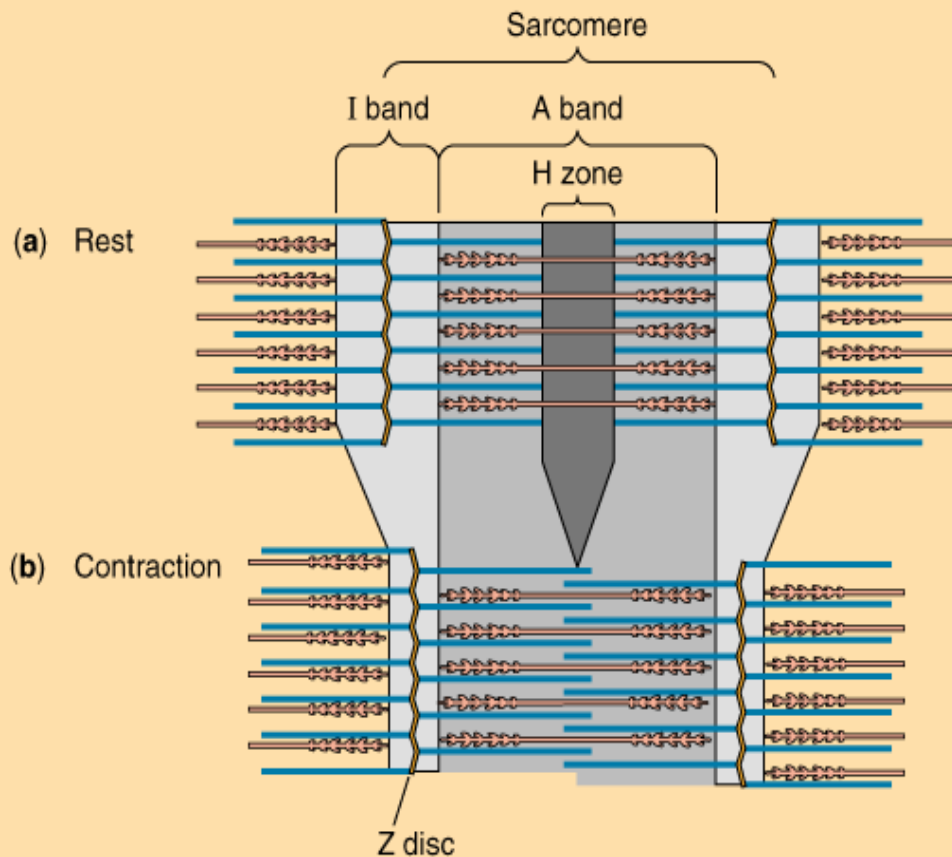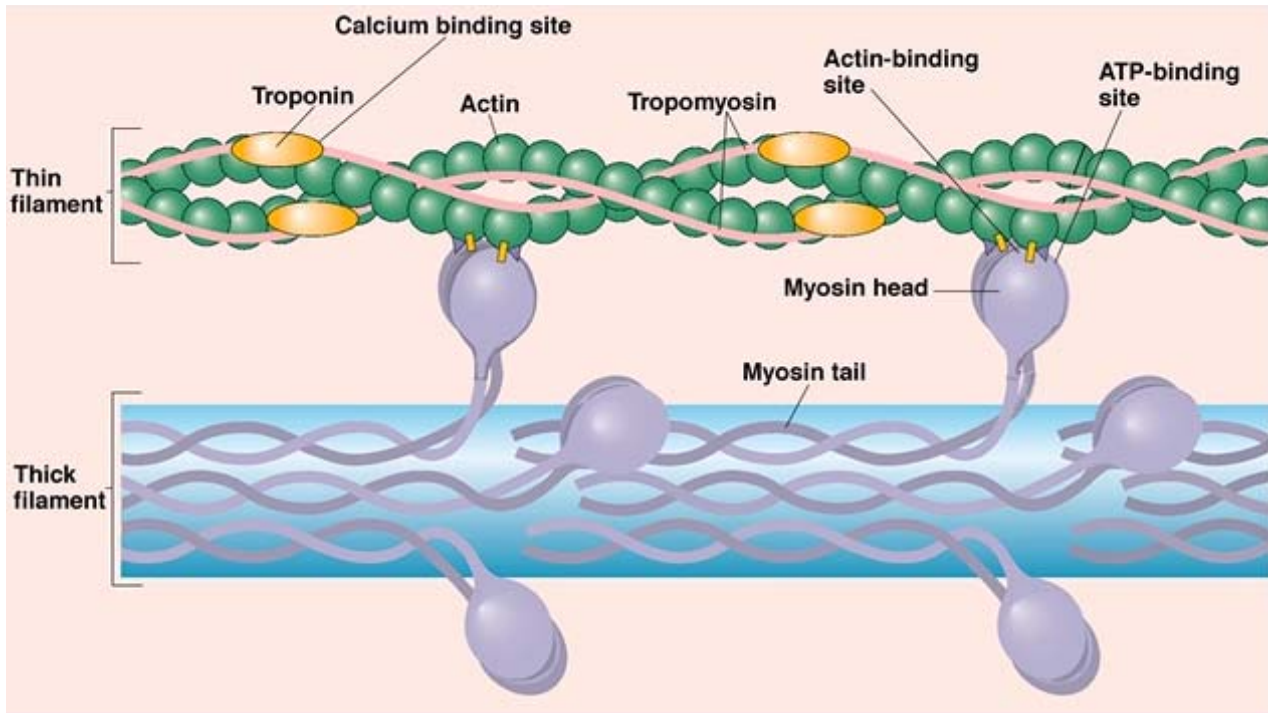
Excitation-Contraction (EC) Coupling
§   Action potential generated and propagated along sarcomere to T-tubules
§   Action potential triggers Ca2+ release
§   Ca++ bind to troponin; blocking action of tropomyosin released
§   contraction via crossbridge formation; ATP hyrdolysis
§   Removal of Ca+2 by active transport
§   tropomyosin blockage restored; contraction ends

(a)

(b)
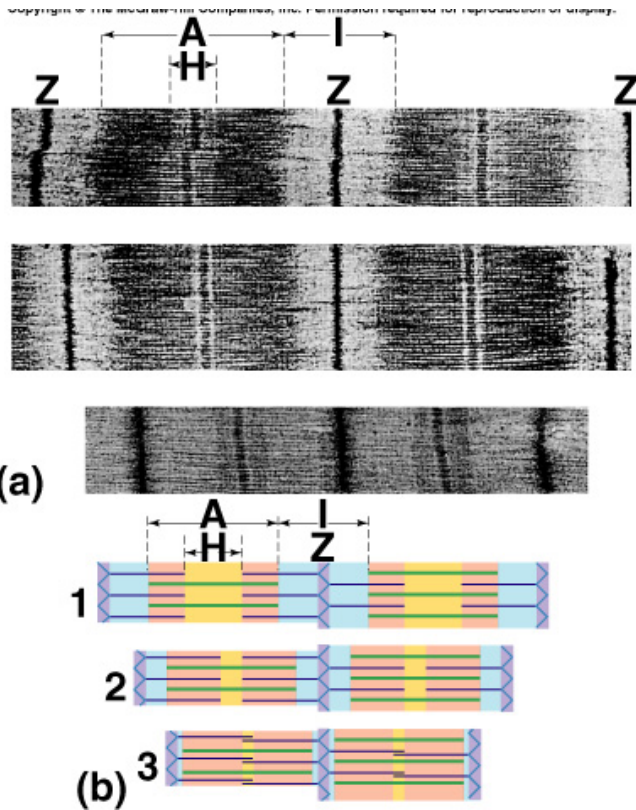
Role of Ionic Calcium (Ca^{2+}) in the Contraction Mechanism
- At low intracellular Ca^{2+} concentration:
    - Tropomyosin blocks the binding sites on actin
    - Myosin cross bridges cannot attach to binding sites on actin
    - The relaxed state of the muscle is enforced

Role of Ionic Calcium (Ca^{2+}) in the Contraction Mechanism
- At higher intracellular Ca^{2+} concentrations:
    - Additional calcium binds to troponin (inactive troponin binds two Ca^{2+})
    - Calcium-activated troponin binds an additional two Ca^{2+} at a separate regulatory site

Role of Ionic Calcium (Ca^{2+}) in the Contraction Mechanism
- Calcium-activated troponin undergoes a conformational change
- This change moves tropomyosin away from actin's binding sites

Role of Ionic Calcium (Ca^{2+}) in the Contraction Mechanism
- Myosin head can now bind and cycle
- This permits contraction (sliding of the thin filaments by the myosin cross bridges) to begin

(1) Resting fiber; cross bridge is not attached to actin

(6) ATP is hydrolyzed, causing cross bridge to return to its original orientation

Thin filament

ADP
P_i

Myosin head

Cross bridge

Thick filament

(2) Cross bridge binds to actin

ATP

(5) A new ATP binds to myosin head, allowing it to release from actin

(3) P_i is released, causing conformational change in myosin

(4) Power stroke causes filaments to slide; ADP is released

Ca2+ influx releases troponin/tropomyosin block -> muscle contracts!
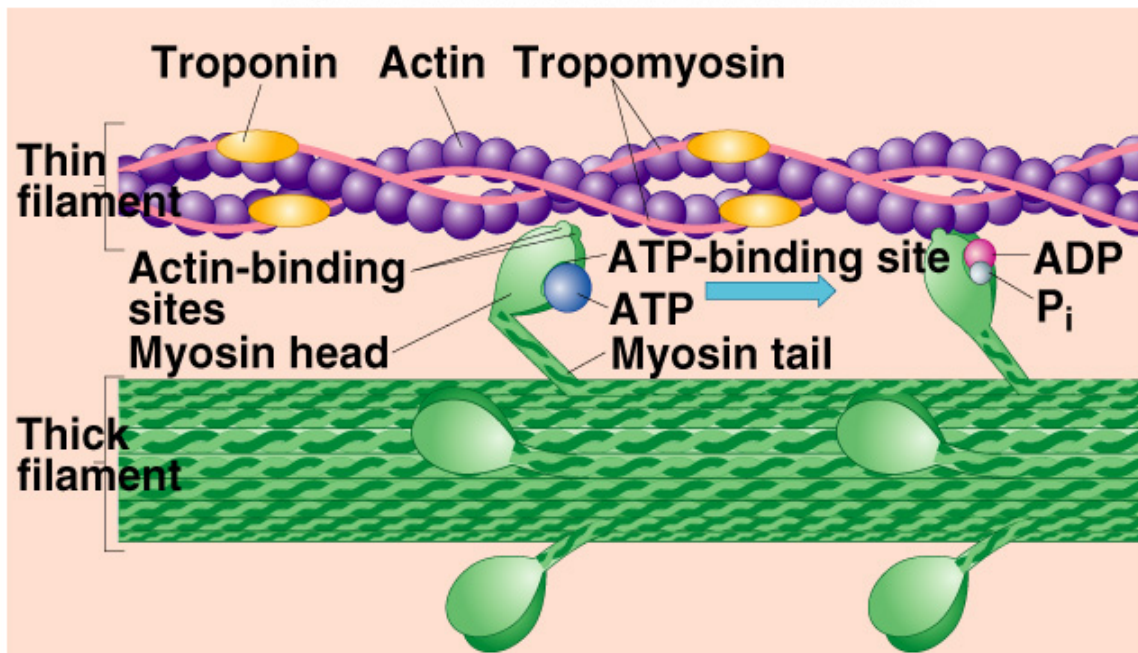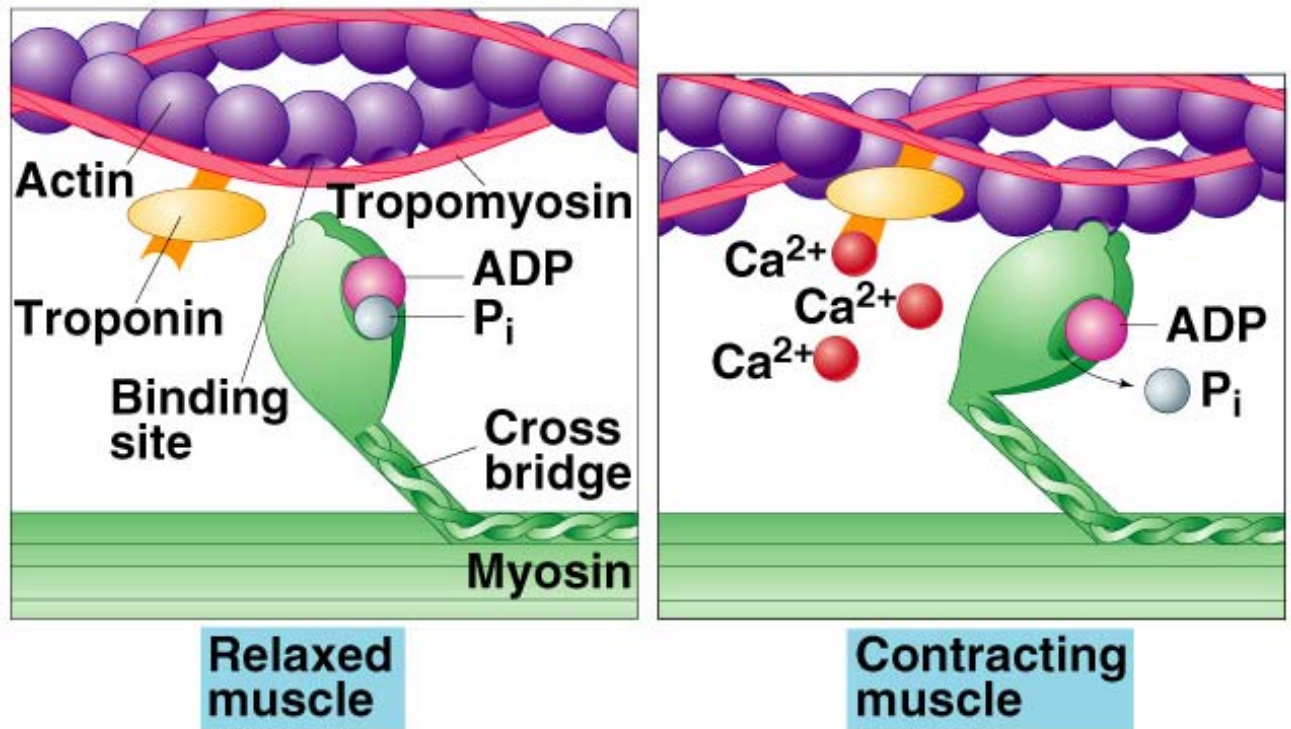
Troponin   Actin   Tropomyosin

Thin filament

Actin-binding sites
Myosin head

ATP-binding site
ATP
Myosin tail

ADP
P_i

Thick filament

Actin

Troponin

Binding
site

Tropomyosin

ADP
P_i

Cross
bridge

Myosin

**Relaxed
muscle**

Ca^{2+}
Ca^{2+}
Ca^{2+}

ADP

P_i

**Contracting
muscle**

Axon
terminal

Sarcolemma

Ca^{2+}

①

②

③

Transverse
tubule

④

Sarcoplasmic
reticulum

Y① Nicotinic acetylcholine
    receptor

■② Skeletal muscle voltage-
    gated sodium channel

■③ Transverse tubule voltage-
    gated calcium channel

Y④ Sarcoplasmic reticulum
    calcium release channel
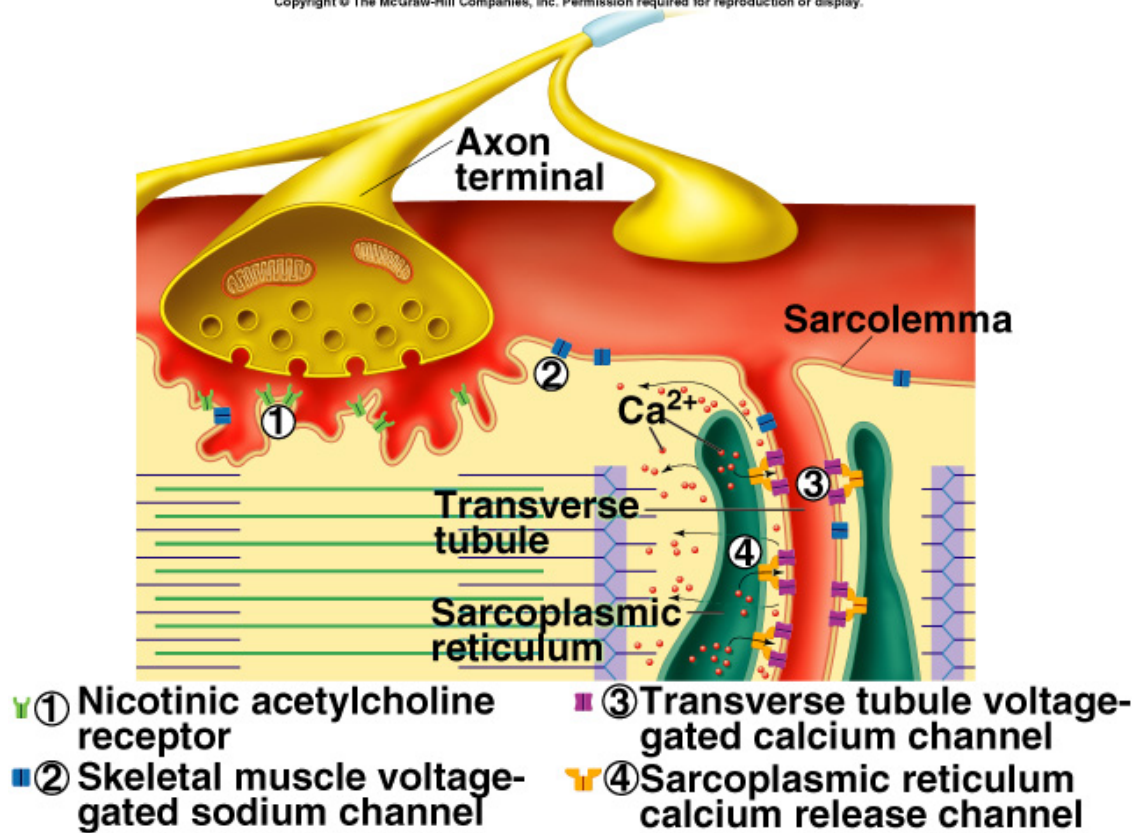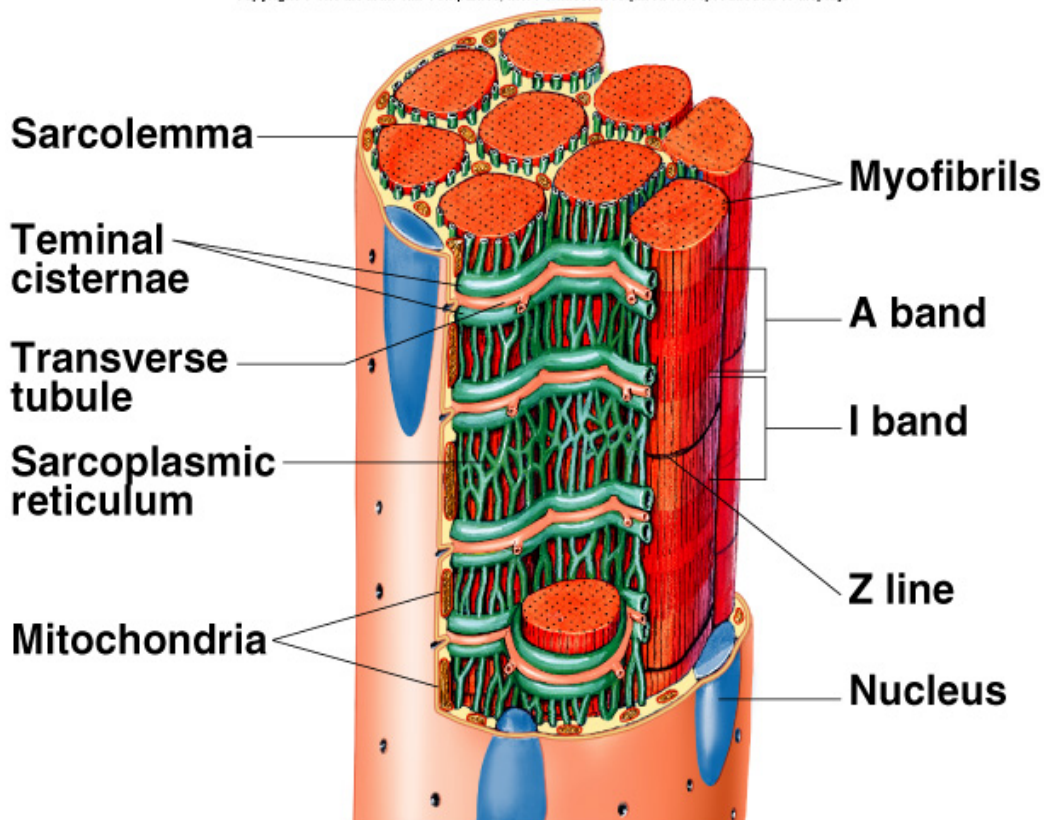
Sequential Events of Contraction
- Cross bridge formation – myosin cross bridge attaches to actin filament
- Working (power) stroke – myosin head pivots and pulls actin filament toward M line
- Cross bridge detachment – ATP attaches to myosin head and the cross bridge detaches
- "Cocking" of the myosin head – energy from hydrolysis of ATP cocks the myosin head into the high-energy state

Muscle Relaxation

Ca^{2+} pumped back into SR through **Ca^{2+}-ATPase** pumps (always on).

End of neuronal stimulation:

ACh-esterase degrades ACh.

Ca^{2+} channels close.

Choline recycled to make more ACh.

Coupling Excitation to Contraction

Calcium ions (Ca^{2+}) link action potentials in a muscle fiber to contraction.

- In resting muscle fibers, Ca^{2+} is stored in the endoplasmic (sarcoplasmic) reticulum.

- Spaced along the plasma membrane (**sarcolemma**) of the muscle fiber are inpocketings of the membrane that form **tubules** of the **"T system"**. These tubules plunge repeatedly into the interior of the fiber.

- The tubules of the T system terminate near the calcium-filled sacs of the **sarcoplasmic reticulum**.

- Each action potential created at the neuromuscular junction sweeps quickly along the sarcolemma and is carried into the T system.

The T system and sarcoplasmic reticulum in resting muscle

An action potential reverses the polarity of the tubules releasing calcium ions (dots) from the sarcoplasmic reticulum. Their binding to troponin on the thin filaments "turns on" in interaction of actin and myosin, and the sarcomere shortens.

Restoration of normal polarity is followed by return of calcium to the sarcoplasmic reticulum and relaxation of the sarcomere.

- The arrival of the action potential at the ends of the T system triggers the release of Ca^{2+}.

- The Ca^{2+} diffuses among the thick and thin filaments where it

- binds to **troponin** on the thin filaments.

- This turns on the interaction between actin and myosin and the sarcomere contracts.

- Because of the speed of the action potential (milliseconds), the action potential arrives virtually simultaneously at the ends of all the tubules of the T system, ensuring that all sarcomeres contract in unison.

- When the process is over, the calcium is pumped back into the sarcoplasmic reticulum using a **Ca^{2+} ATPase**

Contraction of Skeletal Muscle Fibers
- Contraction – refers to the activation of myosin's cross bridges (force-generating sites)
- Shortening occurs when the tension generated by the cross bridge exceeds forces opposing

shortening
- Contraction ends when cross bridges become inactive, the tension generated declines, and relaxation is induced

Contraction of Skeletal Muscle (Organ Level)
- Contraction of muscle fibers (cells) and muscles (organs) is similar
- The two types of muscle contractions are:
    - Isometric contraction – increasing muscle tension (muscle does not shorten during contraction)
    - Isotonic contraction – decreasing muscle length (muscle shortens during contraction)

Motor Unit: The Nerve-Muscle Functional Unit
- A motor unit is a motor neuron and all the muscle fibers it supplies
- The number of muscle fibers per motor unit can vary from four to several hundred
- Muscles that control fine movements (fingers, eyes) have small motor units
- Large weight-bearing muscles (thighs, hips) have large motor units
- Muscle fibers from a motor unit are spread throughout the muscle; therefore, contraction of a single motor unit causes weak contraction of the entire muscle

---

- Axon of motor neuron produces AP in sarcolemma of myofiber.
- APs travel down sarcolemma and T tubules.
- SR terminal cisternae releases Ca2+
- sarcomeres contract!

Isotonic versus Isometric Contractions

If a stimulated muscle is held so that it cannot shorten, it simply exerts tension. This is called an **isometric** ("same length") contraction. If the muscle is allowed to shorten, the contraction is called **isotonic** ("same tension").
Motor Units

All motor neurons leading to skeletal muscles have branching axons, each of which terminates in a neuromuscular junction with a single muscle fiber. Nerve impulses passing down a single motor neuron will thus trigger contraction in all the muscle fibers at which the branches of that neuron terminate. This minimum unit of contraction is called the **motor unit**.

The size of the motor unit is small in muscles over which we have precise control. Examples:

- a single motor neuron triggers fewer than 10 fibers in the muscles controlling eye movements

- the motor units of the muscles controlling the larynx are as small as 2–3 fibers per motor neuron

- In contrast, a single motor unit for a muscle like the gastrocnemius (calf) muscle may include 1000–2000 fibers (scattered uniformly through the muscle).

Although the response of a motor unit is all-or-none, the strength of the response of the entire muscle is determined by the **number of motor units** activated.

Even at rest, most of our skeletal muscles are in a state of partial contraction called **tonus**. Tonus is maintained by the activation of a few motor units at all times even in resting muscle. As one set of motor units relaxes, another set takes over.

Fueling Muscle Contraction

ATP is the immediate source of energy for muscle contraction. Although a muscle fiber contains only enough ATP to power a few twitches, its ATP "pool" is replenished as needed. There are three sources of high-energy phosphate to keep the ATP pool filled.

- **creatine phosphate**

- **glycogen**

- **cellular respiration** in the mitochondria of the fibers.

Creatine phosphate
The phosphate group in creatine phosphate is attached by a "high-energy" bond like that in ATP.

Creatine phosphate derives its high-energy phosphate from ATP and can donate it back to ADP to form ATP.

Creatine phosphate + ADP ↔ creatine + ATP
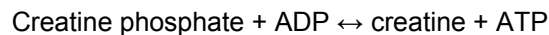
The pool of creatine phosphate in the fiber is about 10 times larger than that of ATP and thus serves as a modest reservoir of ATP.

Glycogen

Skeletal muscle fibers contain about 1% **glycogen**. The muscle fiber can degrade this glycogen by glycogenolysis producing glucose-1-phosphate. This enters the glycolytic pathway to yield two molecules of ATP for each pair of lactic acid molecules produced. Not much, but enough to keep the muscle functioning if it fails to receive sufficient oxygen to meet its ATP needs by respiration.

However, this source is limited and eventually the muscle must depend on cellular respiration.

Cellular respiration

Cellular respiration not only is required to meet the ATP needs of a muscle engaged in prolonged activity (thus causing more rapid and deeper breathing), but is also required afterwards to enable the body to resynthesize glycogen from the lactic acid produced earlier (deep breathing continues for a time after exercise is stopped). The body must repay its **oxygen debt**.

Type I vs. Type II Fibers

Two different types of muscle fiber can be found in most skeletal muscles. The Type I and Type II fibers differ in their structure and biochemistry.

Type I Fibers

- loaded with mitochondria and

- depend on cellular respiration for ATP production

- resistant to fatigue

- rich in myoglobin and hence red in color

- activated by small-diameter, thus slow-conducting, motor neurons

- also known as "slow-twitch" fibers

- dominant in muscles that depend on tonus, e.g., those responsible for posture

Type II Fibers

- few mitochondria

- rich in glycogen and

- depend on glycolysis for ATP production

- fatigue easily

- low in myoglobin hence whitish in color

- activated by large-diameter, thus fast-conducting, motor neurons

- also known as "fast-twitch" fibers

- dominant in muscles used for rapid movement

Most skeletal muscles contain some mixture of Type I and Type II fibers, but a single motor unit always contains one type or the other, never both.

The ratio of Type I and Type II fibers can be changed by endurance training (producing more Type I fibers).

Muscle Twitch
- A muscle twitch is the response of a muscle to a single, brief threshold stimulus
- There are three phases to a muscle twitch
  - Latent period
  - Period of contraction
  - Period of relaxation

Phases of a Muscle Twitch
- Latent period – first few msec after stimulus; EC coupling taking place
- Period of contraction – cross bridges from; muscle shortens
- Period of relaxation – Ca^{2+} reabsorbed; muscle tension goes to zero

Muscle Twitch

Latent Period – the first few ms after stimulation when excitation-contraction is occurring

Period of Contraction – cross bridges are active and the muscle shortens if the tension is great enough to overcome the load

Period of Relaxation – Ca^{2+} is pumped back into SR and muscle tension decreases to baseline level
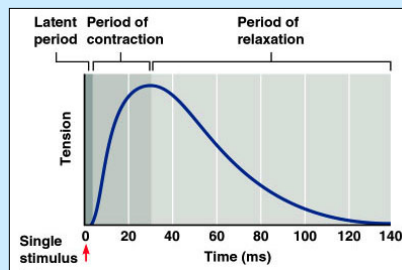
Muscle Twitch

Twitch contraction of some muscles (extraocular) are rapid and brief, others (gastrocnemius, soleus) are slower and longer
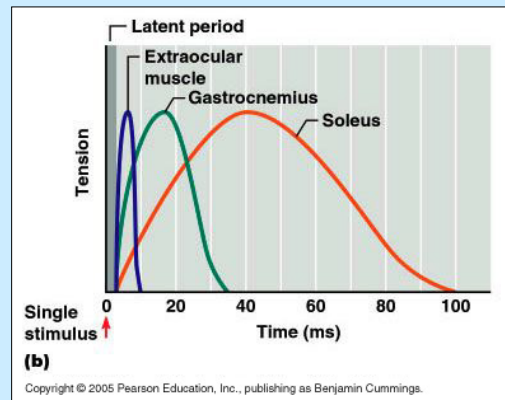
Muscle Twitch Comparisons

Graded Muscle Responses
- Graded muscle responses are:
  - Variations in the degree of muscle contraction
  - Required for proper control of skeletal movement
- Responses are graded by:
  - Changing the frequency of stimulation
  - Changing the strength of the stimulus

Graded Muscle Responses

Graded muscle responses are:

Variations in the degree or strength of muscle contraction in response to demand

Required for proper control of skeletal movement

Muscle contraction can be graded (varied) in two ways:

By changing the Frequency of the stimulus

By changing the Strength of the stimulus

Muscle Response to Stimulation Frequency

- A single stimulus results in a single contractile response – a muscle twitch (contracts and relaxes)

- More frequent stimuli increases contractile force – wave summation - muscle is already partially contracted when next stimulus arrives and contractions are summed (refractory period applies)
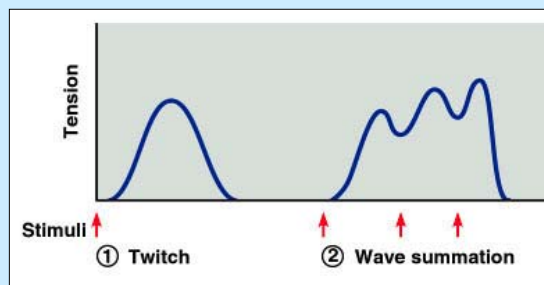
Muscle Response to Stimulation Frequency

- More rapidly delivered stimuli result in incomplete tetanus – sustained but quivering contraction

- If stimuli are given quickly enough, complete tetanus results – smooth, sustained contraction with no relaxation period
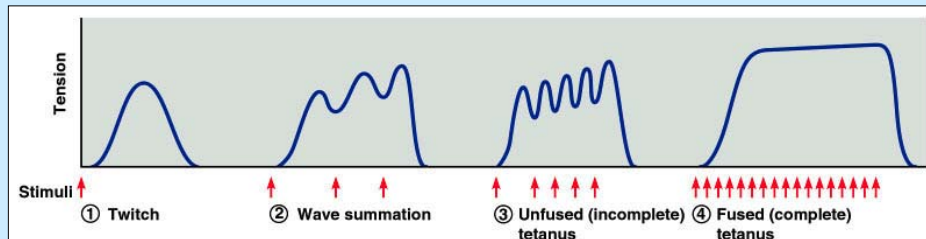
Muscle Response to Stronger Stimuli

- Threshold stimulus – the stimulus strength at which the first observable muscle contraction occurs

- Beyond threshold, muscle contracts more vigorously as stimulus strength is increased

- Force of contraction is precisely controlled by multiple motor unit summation

- This phenomenon, called recruitment, brings more and more muscle fibers into play

Stimulus Intensity and Muscle Tension

Below threshold – no muscle response

Above threshold – increases in voltage excite (recruit) more (and larger) motor units until maximal stimulus is reached

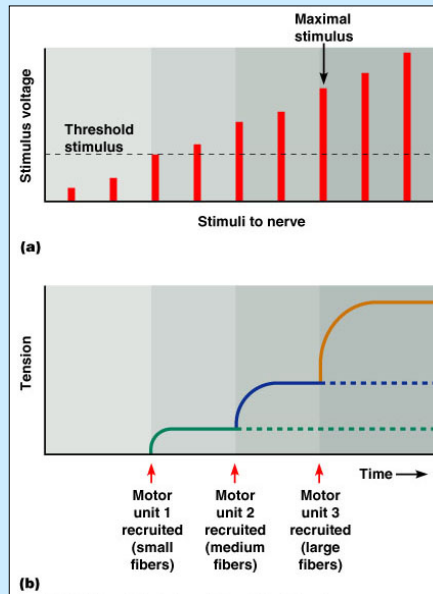**Muscle Response to Varying Stimuli**
- A single stimulus results in a single contractile response – a muscle twitch
- Frequently delivered stimuli (muscle does not have time to completely relax) increases contractile force – wave summation
- More rapidly delivered stimuli result in incomplete tetanus
- If stimuli are given quickly enough, complete tetanus results

Muscle Response: Stimulation Strength
- Threshold stimulus – the stimulus strength at which the first observable muscle contraction occurs
- Beyond threshold, muscle contracts more vigorously as stimulus strength is increased
- Force of contraction is precisely controlled by multiple motor unit summation
- This phenomenon, called recruitment, brings more and more muscle fibers into play

Stimulus Intensity and Muscle Tension

Size Principle

Treppe: The Staircase Effect
- Staircase – increased contraction in response to multiple stimuli of the same strength
- Contractions increase because:
  - There is increasing availability of Ca^{2+} in the sarcoplasm
  - Muscle enzyme systems become more efficient because heat is increased as muscle contracts

Muscle Tone
- Muscle tone:
  - Is the constant, slightly contracted state of all muscles, which does not produce active movements
  - Keeps the muscles firm, healthy, and ready to respond to stimulus

- Spinal reflexes account for muscle tone by:
    - Activating one motor unit and then another
    - Responding to activation of stretch receptors in muscles and tendons

Isotonic Contractions
- In isotonic contractions, the muscle changes in length (decreasing the angle of the joint) and moves the load
- The two types of isotonic contractions are concentric and eccentric
    - Concentric contractions – the muscle shortens and does work
    - Eccentric contractions – the muscle contracts as it lengthens

Isometric Contractions
- Tension increases to the muscle's capacity, but the muscle neither shortens nor lengthens
- Occurs if the load is greater than the tension the muscle is able to develop

Isotonic and Isometric Contractions

(a) Muscle contracts and shortens

Movement

(b) Muscle contracts but does not shorten

No movement
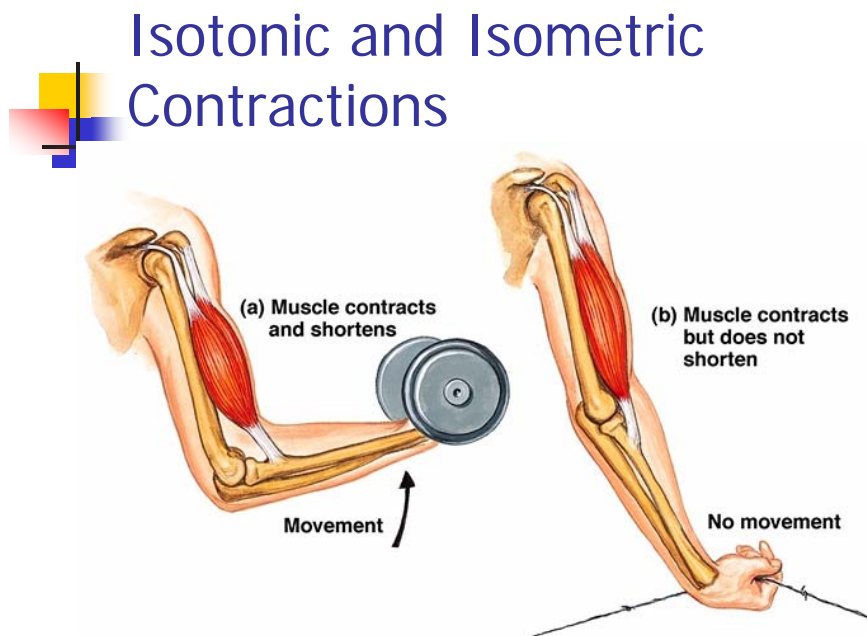
Muscle Metabolism: Energy for Contraction
- ATP is the only source used directly for contractile activity
- As soon as available stores of ATP are hydrolyzed (4-6 seconds), they are regenerated by:
    - The interaction of ADP with creatine phosphate (CP)
    - Anaerobic glycolysis
    - Aerobic respiration

Isometric Contractions

No change in overall muscle length

(b) Isometric contraction
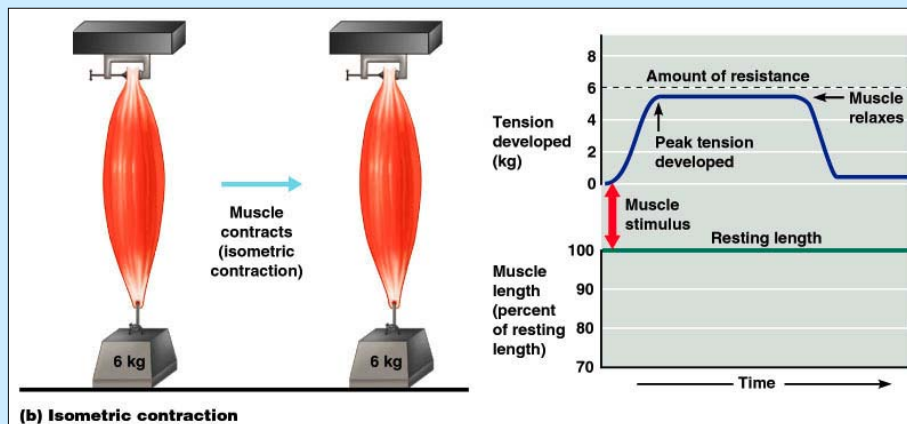
In isometric contractions, increasing muscle tension (force) is measured

Isotonic Contraction

This illustrates a concentric isotonic contraction

(a) Isotonic (concentric) contraction
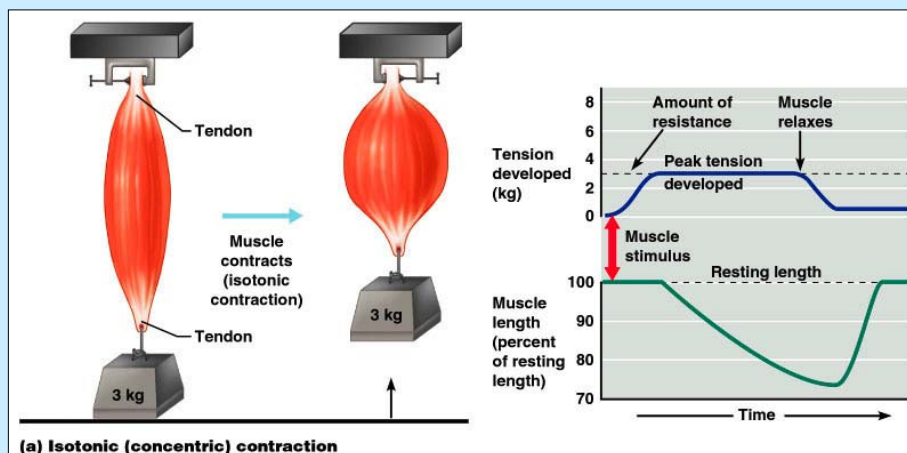
In isotonic contractions, the amount of shortening (distance in mm) is measured

Muscle Metabolism: Anaerobic Glycolysis
- When muscle contractile activity reaches 70% of maximum:
  - Bulging muscles compress blood vessels
  - Oxygen delivery is impaired
  - Pyruvic acid is converted into lactic acid
- The lactic acid:
  - Diffuses into the bloodstream
  - Is picked up and used as fuel by the liver, kidneys, and heart
  - Is converted back into pyruvic acid by the liver

Figure 3: The energy pathways

Glucose (sugar)   Triglyceride (fat)

Anaerobic
glycolysis   glycerol   fatty acids

2 ATP + lactate
from anaerobic glycolysis

Aerobic glycolysis

Krebs cycle   Beta oxidation of fats

36 ATP from aerobic glycolysis   460 ATP from fats feeding into the Krebs cycle

Starch
↓   (Phosphorylase)
Glucose-1-phosphate
↓   (Phosphoglucomutase)
Glucose ──(Hexokinase)──→ Glucose-6-phosphate
        ATP   ↓   (Phosphohexoisomerase)
Fructose-6-phosphate
↓   (Phosphohexokinase)+ ATP
Fructose-1,6-diphosphate
↓   (Aldolase)
Glyceraldehyde-3-phosphate ↔ Dihydroxyacetone phosphate
↓   (Triosephosphate dehydrogenase)+ 2DPN
2 1,3-Diphosphoglyceric acid
↓   (Phosphoglycerate kinase)
2 3-Phosphoglyceric acid+ 2 ATP
↓   (Phosphoglyceromutase)
2 2-Phosphoglyceric acid
↓   (Enolase)
2 Phosphoenolpyruvic acid
↓   (Pyruvate kinase)
2 Pyruvic acid+ 2 ATP

2 DPNH$_2$ (Lactate dehydrogenase)   (Pyruvate decarboxylase)

2 Lactic acid   2 Acetaldehyde + 2 CO_2

2 DPNH$_2$ | (Alcohol dehydrogenase)

2 Ethanol

Muscle Fatigue
▪ Muscle fatigue – the muscle is in a state of physiological inability to contract
▪ Muscle fatigue occurs when:
  ▪ ATP production fails to keep pace with ATP use

- There is a relative deficit of ATP, causing contractures
- Lactic acid accumulates in the muscle
- Ionic imbalances are present
- Intense exercise produces rapid muscle fatigue (with rapid recovery)
- Na^+-K^+ pumps cannot restore ionic balances quickly enough
- Low-intensity exercise produces slow-developing fatigue
- SR is damaged and Ca^{2+} regulation is disrupted

Muscle Metabolism: Energy

ATP is the only energy source that is used directly for contractile activity

As soon as available ATP is hydrolyzed (4-6 seconds), it is regenerated by three pathways:

Interaction of ADP with Creatine Phosphate (CP)

From stored glycogen via Anaerobic Glycolysis

From Aerobic Respiration

CP-ADP Reaction

Creatine phosphate + ADP → creatine + ATP

(a) Direct phosphorylation
(coupled reaction of creatine
phosphate [CP] and ADP)

Energy source: CP

Oxygen use: None
Products: 1 ATP per CP, creatine
Duration of energy provision: 15 sec.
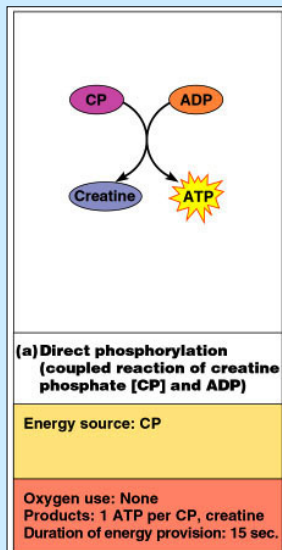
Transfer of energy as a phosphate group is moved from CP to ADP – the reaction is catalyzed by the enzyme <u>creatine kinase</u>

Stored ATP and CP provide energy for maximum muscle power for 10-15 seconds

Oxygen Debt
- Vigorous exercise causes dramatic changes in muscle chemistry
- For a muscle to return to a resting state:
  - Oxygen reserves must be replenished
  - Lactic acid must be converted to pyruvic acid
  - Glycogen stores must be replaced
  - ATP and CP reserves must be resynthesized

- Oxygen debt – the extra amount of O2 needed for the above restorative processes
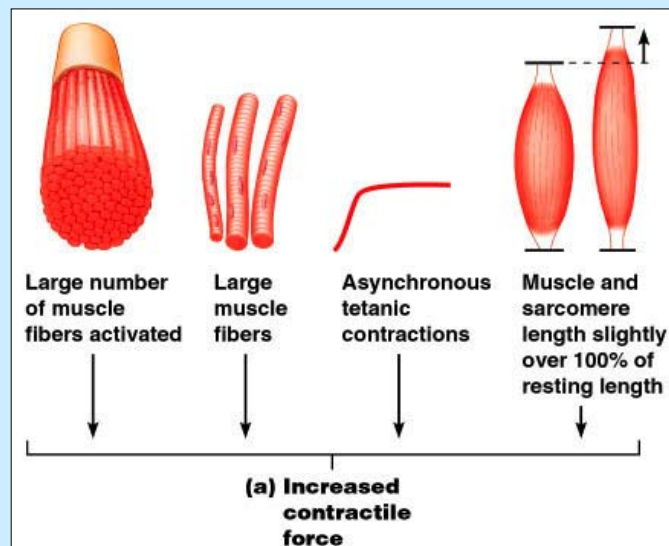
Heat Production During Muscle Activity
- Only 40% of the energy released in muscle activity is useful as work
- The remaining 60% is given off as heat
- Dangerous heat levels are prevented by radiation of heat from the skin and sweating

Force of Muscle Contraction
- The force of contraction is affected by:
    - The number of muscle fibers contracting – the more motor fibers in a muscle, the stronger the contraction
    - The relative size of the muscle – the bulkier the muscle, the greater its strength
    - Degree of muscle stretch – muscles contract strongest when muscle fibers are 80-120% of their normal resting length

Force of Muscle Contraction

Large number of muscle fibers activated | Large muscle fibers | Asynchronous tetanic contractions | Muscle and sarcomere length slightly over 100% of resting length

(a) Increased contractile force

Stimulus Frequency and Tension

Twitch
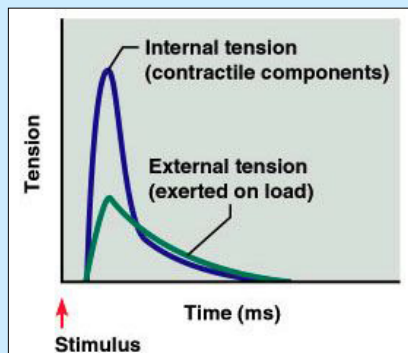
Tetanic Contraction

Muscle Fiber Type: Functional Characteristics
- Speed of contraction – determined by speed in which ATPases split ATP
    - The two types of fibers are slow and fast
- ATP-forming pathways
    - Oxidative fibers – use aerobic pathways
    - Glycolytic fibers – use anaerobic glycolysis
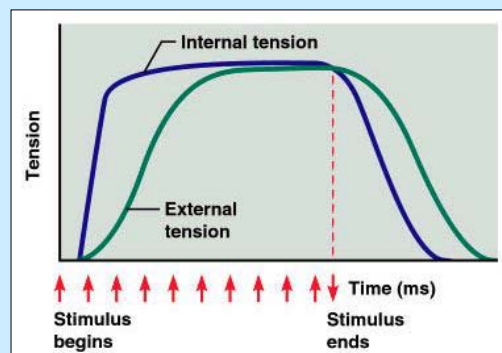- These two criteria define three categories – slow oxidative fibers, fast oxidative fibers, and fast glycolytic fibers

Muscle Fiber Type: Speed of Contraction
- Slow oxidative fibers contract slowly, have slow acting myosin ATPases, and are fatigue resistant
- Fast oxidative fibers contract quickly, have fast myosin ATPases, and have moderate resistance to fatigue
- Fast glycolytic fibers contract quickly, have fast myosin ATPases, and are easily fatigued

Load and Contraction

Effects of Aerobic Exercise
- Aerobic exercise results in an increase of:
    - Muscle capillaries
    - Number of mitochondria
    - Myoglobin synthesis

Effects of Resistance Exercise
- Resistance exercise (typically anaerobic) results in:
    - Muscle hypertrophy
    - Increased mitochondria, myofilaments, and glycogen stores

The Overload Principle
- Forcing a muscle to work promotes increased muscular strength
- Muscles adapt to increased demands
- Muscles must be overloaded to produce further gains

Smooth Muscle
- Composed of spindle-shaped fibers with a diameter of 2-10 μm and lengths of several hundred μm
- Lack the coarse connective tissue sheaths of skeletal muscle, but have fine endomysium
- Organized into two layers (longitudinal and circular) of closely apposed fibers
- Found in walls of hollow organs (except the heart)
- Have essentially the same contractile mechanisms as skeletal muscle

Cell-to-cell contacts

In smooth muscle there are four general types of cell-to-cell contacts

☞ Simple apposition
☞ Intermediate contacts
☞ Desmosomes
☞ Gap junctions

The contact is successively more intimate and complex

The first three types serve as mechanical junctions to transmit mechanical forces between cells

Gap junctions provide cytoplasmic continuity between cells and thus allow chemical and electrical signals to pass between adjacent cells.

Smooth Muscle

Smooth muscle is made of single, spindle-shaped cells. It gets its name because no striations are visible in them. Nonetheless, each smooth muscle cell contains **thick** (myosin) and **thin** (actin) filaments that slide against each other to produce contraction of the cell. The thick and thin filaments are anchored near the plasma membrane (with the help of intermediate filaments)).

Smooth muscle (like cardiac muscle) does not depend on motor neurons to be stimulated. However, motor neurons (of the autonomic system) reach smooth muscle and can stimulate it — or relax it — depending on the neurotransmitter they release (e.g. noradrenaline or nitric oxide, NO)).

Smooth muscle can also be made to contract

- by other substances released in the vicinity (paracrine stimulation)

  o Example: release of **histamine** causes contraction of the smooth muscle lining our air passages (triggering an attack of **asthma**)

- by hormones circulating in the blood

  o Example: oxytocin reaching the uterus stimulates it to contract to begin childbirth.

The contraction of smooth muscle tends to be slower than that of striated muscle. It also is often sustained for long periods. This, too, is called **tonus** but the mechanism is not like that in skeletal muscle

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Peristalsis
- When the longitudinal layer contracts, the organ dilates and contracts
- When the circular layer contracts, the organ elongates
- Peristalsis – alternating contractions and relaxations of smooth muscles that mix and squeeze substances through the lumen of hollow organs

Innervation of Smooth Muscle
- Smooth muscle lacks neuromuscular junctions
- Innervating nerves have bulbous swellings called varicosities
- Varicosities release neurotransmitters into wide synaptic clefts called diffuse junctions

Microscopic Anatomy of Smooth Muscle
- SR is less developed than in skeletal muscle and lacks a specific pattern
- T tubules are absent
- Plasma membranes have pouchlike infoldings called caveoli
- Ca2+ is sequestered in the extracellular space near the caveoli, allowing rapid influx when channels are opened
- There are no visible striations and no sarcomeres
- Thin and thick filaments are present

Proportion and Organization of Myofilaments in Smooth Muscle
- Ratio of thick to thin filaments is much lower than in skeletal muscle
- Thick filaments have heads along their entire length
- There is no troponin complex
- Thick and thin filaments are arranged diagonally, causing smooth muscle to contract in a corkscrew manner
- Noncontractile intermediate filament bundles attach to dense bodies (analogous to Z discs) at regular intervals

Contraction of Smooth Muscle
- Whole sheets of smooth muscle exhibit slow, synchronized contraction
- They contract in unison, reflecting their electrical coupling with gap junctions
- Action potentials are transmitted from cell to cell
- Some smooth muscle cells:
    - Act as pacemakers and set the contractile pace for whole sheets of muscle
    - Are self-excitatory and depolarize without external stimuli

Contraction Mechanism
- Actin and myosin interact according to the sliding filament mechanism
- The final trigger for contractions is a rise in intracellular Ca^{2+}
- Ca^{2+} is released from the SR and from the extracellular space
- Ca^{2+} interacts with calmodulin and myosin light chain kinase to activate myosin

Role of Calcium Ion
- Ca^{2+} binds to calmodulin and activates it
- Activated calmodulin activates the kinase enzyme
- Activated kinase transfers phosphate from ATP to myosin cross bridges
- Phosphorylated cross bridges interact with actin to produce shortening
- Smooth muscle relaxes when intracellular Ca^{2+} levels drop

Special Features of Smooth Muscle Contraction
- Unique characteristics of smooth muscle include:
    - Smooth muscle tone
    - Slow, prolonged contractile activity
    - Low energy requirements

- Response to stretch

Response to Stretch
- Smooth muscle exhibits a phenomenon called stress-relaxation response in which:
  - Smooth muscle responds to stretch only briefly, and then adapts to its new length
  - The new length, however, retains its ability to contract
  - This enables organs such as the stomach and bladder to temporarily store contents

Hyperplasia
- Certain smooth muscles can divide and increase their numbers by undergoing hyperplasia
- This is shown by estrogen's effect on the uterus
  - At puberty, estrogen stimulates the synthesis of more smooth muscle, causing the uterus to grow to adult size
  - During pregnancy, estrogen stimulates uterine growth to accommodate the increasing size of the growing fetus

Types of Smooth Muscle: Single Unit
- The cells of single-unit smooth muscle, commonly called visceral muscle:
  - Contract rhythmically as a unit
  - Are electrically coupled to one another via gap junctions
  - Often exhibit spontaneous action potentials
  - Are arranged in opposing sheets and exhibit stress-relaxation response

Types of Smooth Muscle: Multiunit
- Multiunit smooth muscles are found:
  - In large airways to the lungs
  - In large arteries
  - In arrector pili muscles
  - Attached to hair follicles
  - In the internal eye muscles
- Their characteristics include:
  - Rare gap junctions
  - Infrequent spontaneous depolarizations
  - Structurally independent muscle fibers
  - A rich nerve supply, which, with a number of muscle fibers, forms motor units
  - Graded contractions in response to neural stimuli

Cardiac Muscle

Cardiac or heart muscle resembles skeletal muscle in some ways: it is striated and each cell contains sarcomeres with sliding filaments of actin and myosin.

Sarcomere · Z line · Adherens junction · Red blood cell · Gap junction · Mitochondrion · Capillary wall
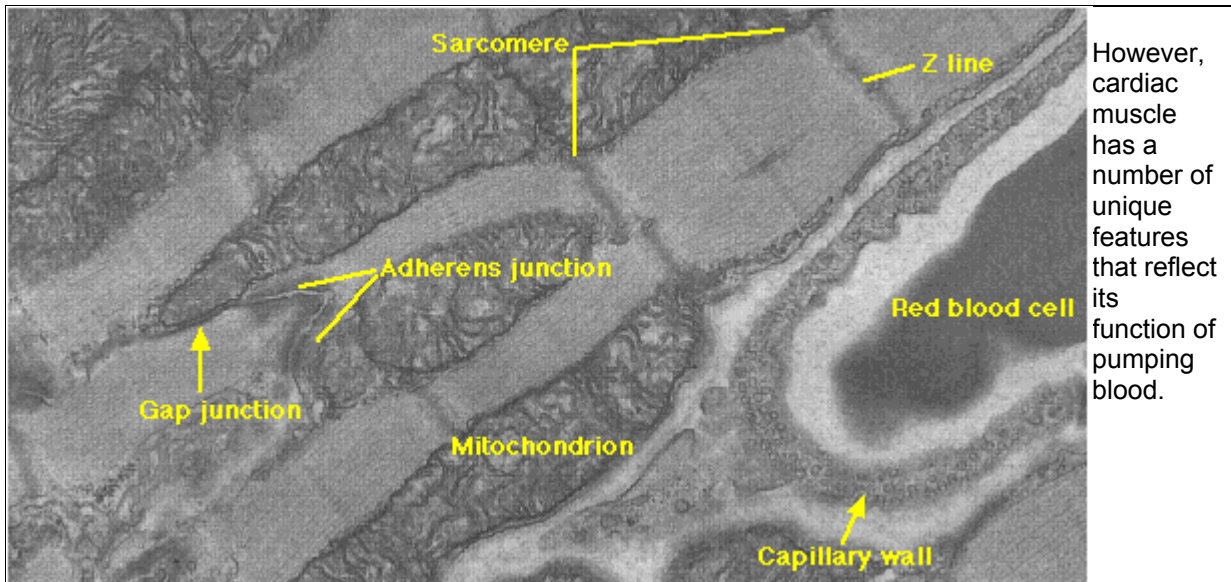
However, cardiac muscle has a number of unique features that reflect its function of pumping blood.

- The myofibrils of each cell (and cardiac muscle is made of single cells — each with a single nucleus) are branched.

- The branches interlock with those of adjacent fibers by adherens junctions. These strong junctions enable the heart to contract forcefully without ripping the fibers apart.

This electron micrograph (reproduced with permission from Keith R. Porter and Mary A. Bonneville, *An Introduction to the Fine Structure of Cells and Tissues*, 4th ed., Lea & Febiger, Philadelphia, 1973) shows an adherens junction and several of the other features listed here.

- The action potential that triggers the heartbeat is generated within the heart itself. Motor nerves (of the autonomic nervous system) do run to the heart, but their effect is simply to modulate — increase or decrease — the intrinsic rate and the strength of the heartbeat. Even if the nerves are destroyed (as they are in a transplanted heart), the heart continues to beat.

- The action potential that drives contraction of the heart passes from fiber to fiber through gap junctions.

  - Significance: All the fibers contract in a synchronous wave that sweeps from the atria down through the ventricles and pumps blood out of the heart. Anything that interferes with this synchronous wave (such as damage to part of the heart muscle from a heart attack) may cause the fibers of the heart to beat at random — called **fibrillation**. Fibrillation is the ultimate cause of most deaths and its reversal is the function of defibrillators that are part of the equipment in ambulances, hospital emergency rooms, and — recently — even on U.S. air lines.

- The **refractory period** in heart muscle is **longer** than the period it takes for the muscle to contract (systole) and relax (diastole). Thus **tetanus** is not possible (a good thing, too!).

- Cardiac muscle has a much richer supply of mitochondria than skeletal muscle. This reflects its greater dependence on cellular respiration for ATP.

- Cardiac muscle has little glycogen and gets little benefit from glycolysis when the supply of oxygen is limited.

  - Thus anything that interrupts the flow of oxygenated blood to the heart leads quickly to damage — even death — of the affected part. This is what happens in heart

attacks.

Muscular Dystrophy
- Muscular dystrophy – group of inherited muscle-destroying diseases where muscles enlarge due to fat and connective tissue deposits, but muscle fibers atrophy
- Duchenne muscular dystrophy (DMD)
    - Inherited, sex-linked disease carried by females and expressed in males (1/3500)
    - Diagnosed between the ages of 2-10
    - Victims become clumsy and fall frequently as their muscles fail
    - Progresses from the extremities upward, and victims die of respiratory failure in their 20s
    - Caused by a lack of the cytoplasmic protein dystrophin
    - There is no cure, but myoblast transfer therapy shows promise

Developmental Aspects
- Muscle tissue develops from embryonic mesoderm called myoblasts
- Multinucleated skeletal muscles form by fusion of myoblasts
- The growth factor *agrin* stimulates the clustering of ACh receptors at newly forming motor end plates
- As muscles are brought under the control of the somatic nervous system, the numbers of fast and slow fibers are also determined
- Cardiac and smooth muscle myoblasts do not fuse but develop gap junctions at an early embryonic stage

Developmental Aspects: Regeneration
- Cardiac and skeletal muscle become amitotic, but can lengthen and thicken
- Myoblastlike satellite cells show very limited regenerative ability
- Cardiac cells lack satellite cells
- Smooth muscle has good regenerative ability

Developmental Aspects: After Birth
- Muscular development reflects neuromuscular coordination
- Development occurs head-to-toe, and proximal-to-distal
- Peak natural neural control of muscles is achieved by midadolescence
- Athletics and training can improve neuromuscular control

Developmental Aspects: Male and Female
- There is a biological basis for greater strength in men than in women
- Women's skeletal muscle makes up 36% of their body mass
- Men's skeletal muscle makes up 42% of their body mass
- These differences are due primarily to the male sex hormone testosterone
- With more muscle mass, men are generally stronger than women
- Body strength per unit muscle mass, however, is the same in both sexes

Developmental Aspects: Age Related
- With age, connective tissue increases and muscle fibers decrease
- Muscles become stringier and more sinewy
- By age 80, 50% of muscle mass is lost (sarcopenia)
- Regular exercise reverses sarcopenia
- Aging of the cardiovascular system affects every organ in the body

Atherosclerosis may block distal arteries, leading to intermittent claudication and causing severe pain in leg

The Muscular Dystrophies (MD)

Together myosin, actin, tropomyosin, and troponin make up over three-quarters of the protein in muscle fibers. Some two dozen other proteins make up the rest. These serve such functions as attaching and organizing the filaments in the sarcomere and connecting the sarcomeres to the plasma membrane and the extracellular matrix. Mutations in the genes encoding these proteins may produce defective proteins and resulting defects in the muscles.

Among the most common of the muscular dystrophies are those caused by mutations in the gene for **dystrophin**.

The gene for dystrophin is huge, containing 79 exons spread out over 2.3 million base pairs of DNA. Thus this single gene represents about 0.1% of the entire human genome (3×10^9 bp) and is almost half the size of the entire genome of E. coli!

- **Duchenne muscular dystrophy** (**DMD**)

  Perhaps its great size makes this gene so susceptible to partial deletions. If these cause a change in the reading frame, no dystrophin is synthesized and DMD, a very severe form of the disease, results.

- **Becker muscular dystrophy** (**BMD**).

  If the deletion simply removes certain exons, a shortened protein results that produces BMD, a milder form of the disease.

The gene for dystrophin is on the X chromosome, so these two diseases strike males in a typical X-linked pattern of inheritance.

Myasthenia Gravis

Myasthenia gravis is an autoimmune disorder affecting the neuromuscular junction. Patients have smaller end plate potentials (EPPs) than normal. With repeated stimulation, the EPPs become too small to trigger further action potentials and the fiber ceases to contract. Administration of an inhibitor of acetylcholinesterase temporarily can restore contractility by allowing more ACh to remain at the site.

Patients with myasthenia gravis have only 20% or so of the number of ACh receptors found in normal neuromuscular junctions. This loss appears to be caused by antibodies directed against the receptors. Some evidence:

- A disease resembling myasthenia gravis can be induced in experimental animals by immunizing them with purified ACh receptors.

- Anti-ACh receptor antibodies are found in the serum of human patients.

- Experimental animals injected with serum from human patients develop the signs of myasthenia gravis.

- Newborns of mothers with myasthenia gravis often show mild signs of the disease for a short time after their birth. This is the result of the transfer of the mother's antibodies across the placenta during gestation.

The reason some people develop autoimmune antibodies against the ACh receptor is unknown.

The Cardiac Myopathies

Cardiac muscle, like skeletal muscle, contains many proteins in addition to actin and myosin. Mutations in the genes for these may cause the wall of the heart to become weakened and, in due course, enlarged. Among the genes that have been implicated in these diseases are those encoding:

- actin

- two types of myosin

- troponin

- tropomyosin

- myosin-binding protein C (which links myosin to titin)

The severity of the disease varies with the particular mutation causing it (over 100 have been identified so far) . Some mutations are sufficiently dangerous that they can lead to sudden catastrophic heart failure in seemingly healthy and active young adults.