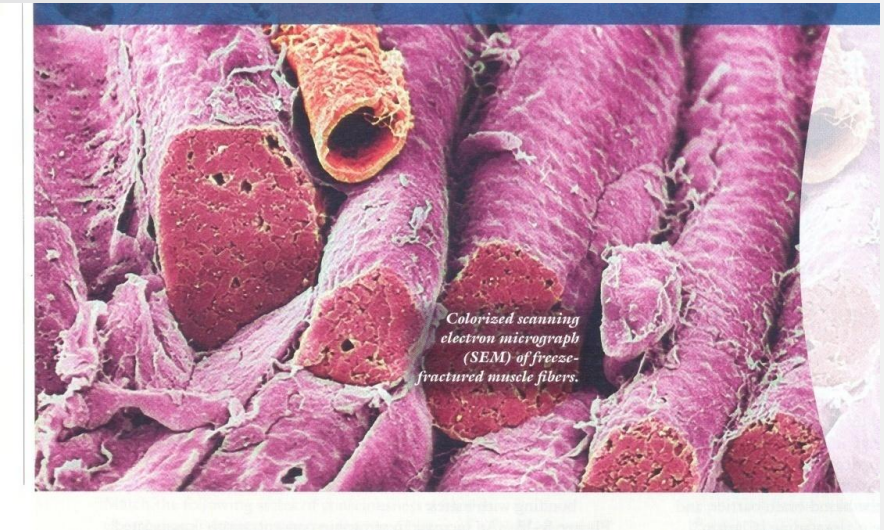
FISIOLOGI KLINIS OTOT



Dr. Juni Chudri, MARS, AIFO-K

Bagian Fisiologi

Fakultas Kedokteran

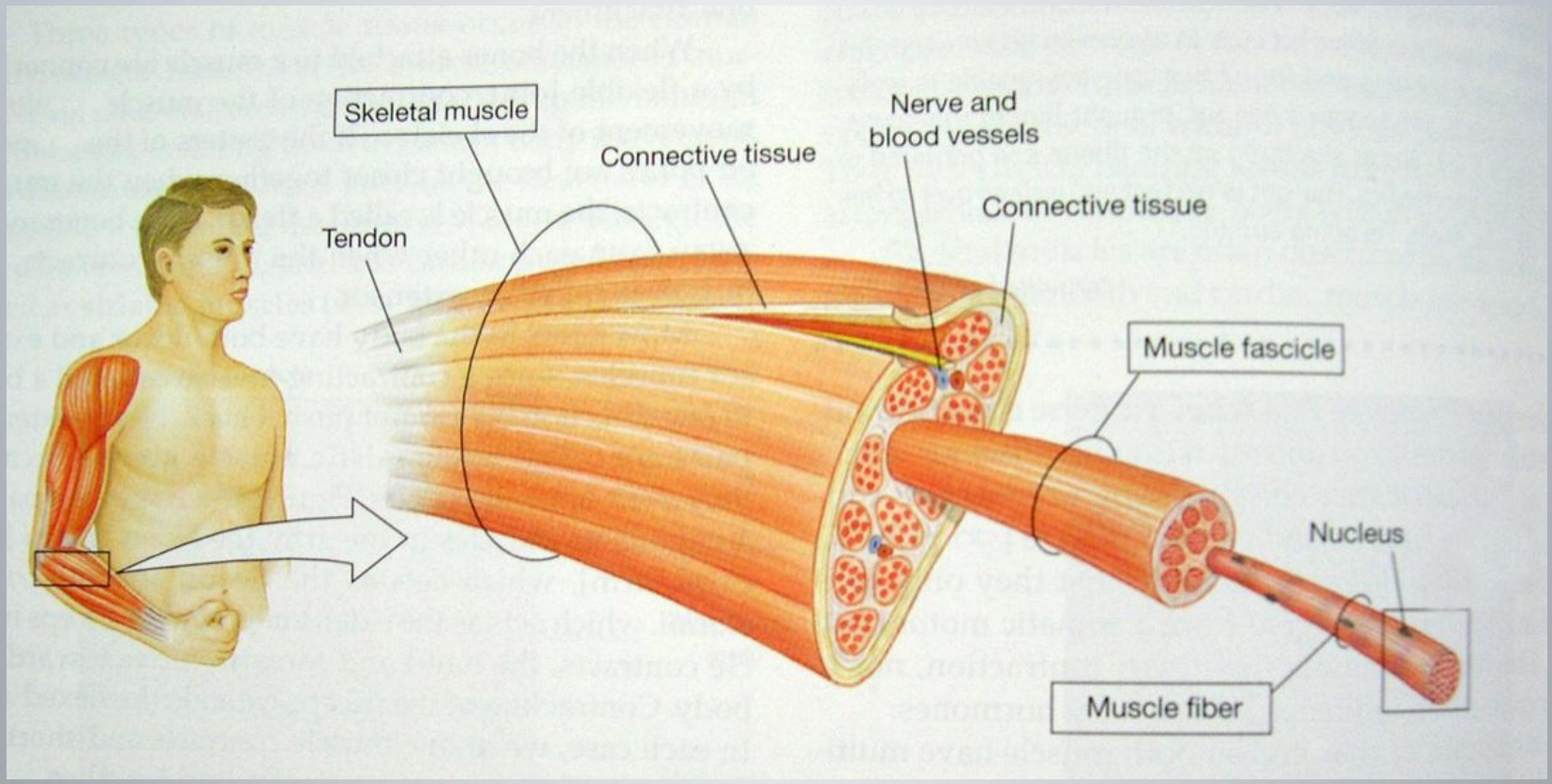
Universitas Trisakti

CAPAIAN PEMBELAJARAN MATA KULIAH (CPMK)

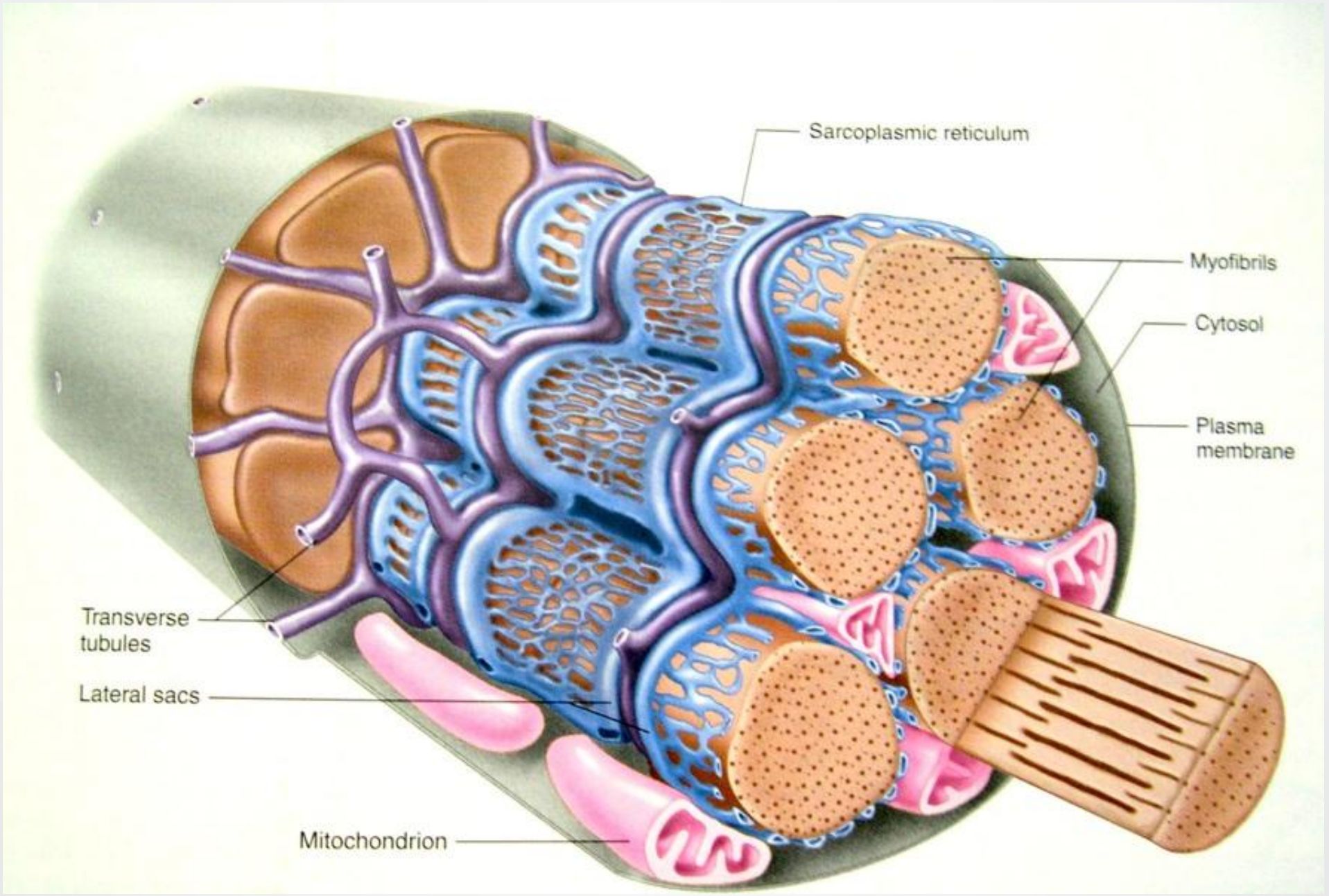
- Menjelaskan patogenesis dan patofisiologi terjadinya masalah kesehatan sistem muskuloskletal sesuai dengan teori ilmu Biomedik, ilmu Kedokteran Klinik dan Ilmu Kedokteran Komunitas (M3)

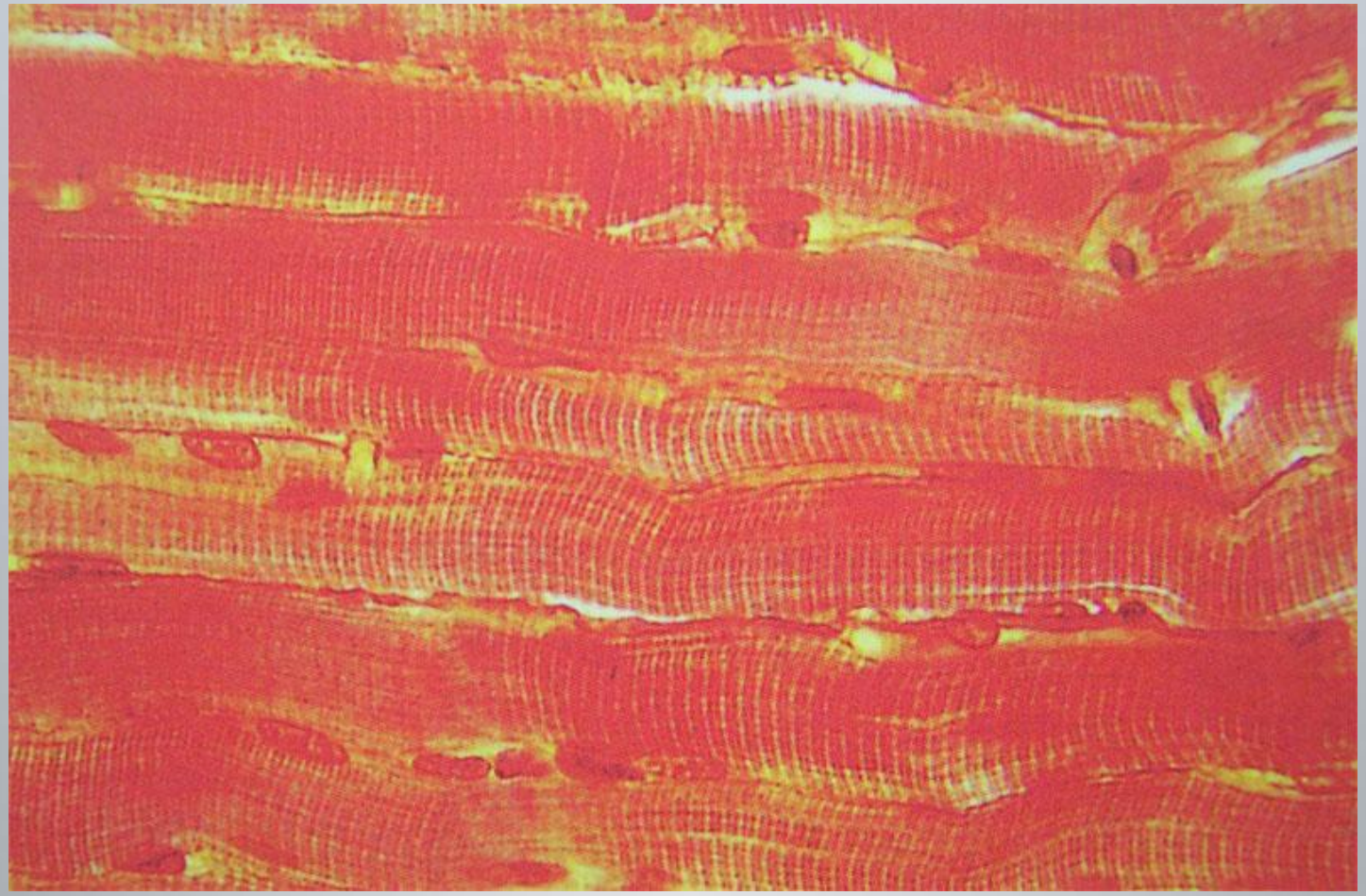
SUB-CAPAIAN PEMBELAJARAN MATA KULIAH (SUB CPMK)

- Menjelaskan mekanisme neuromuskular junction dan mengaitkan dengan kondisi patologis
- Menjelaskan fase dan jenis kontraksi otot

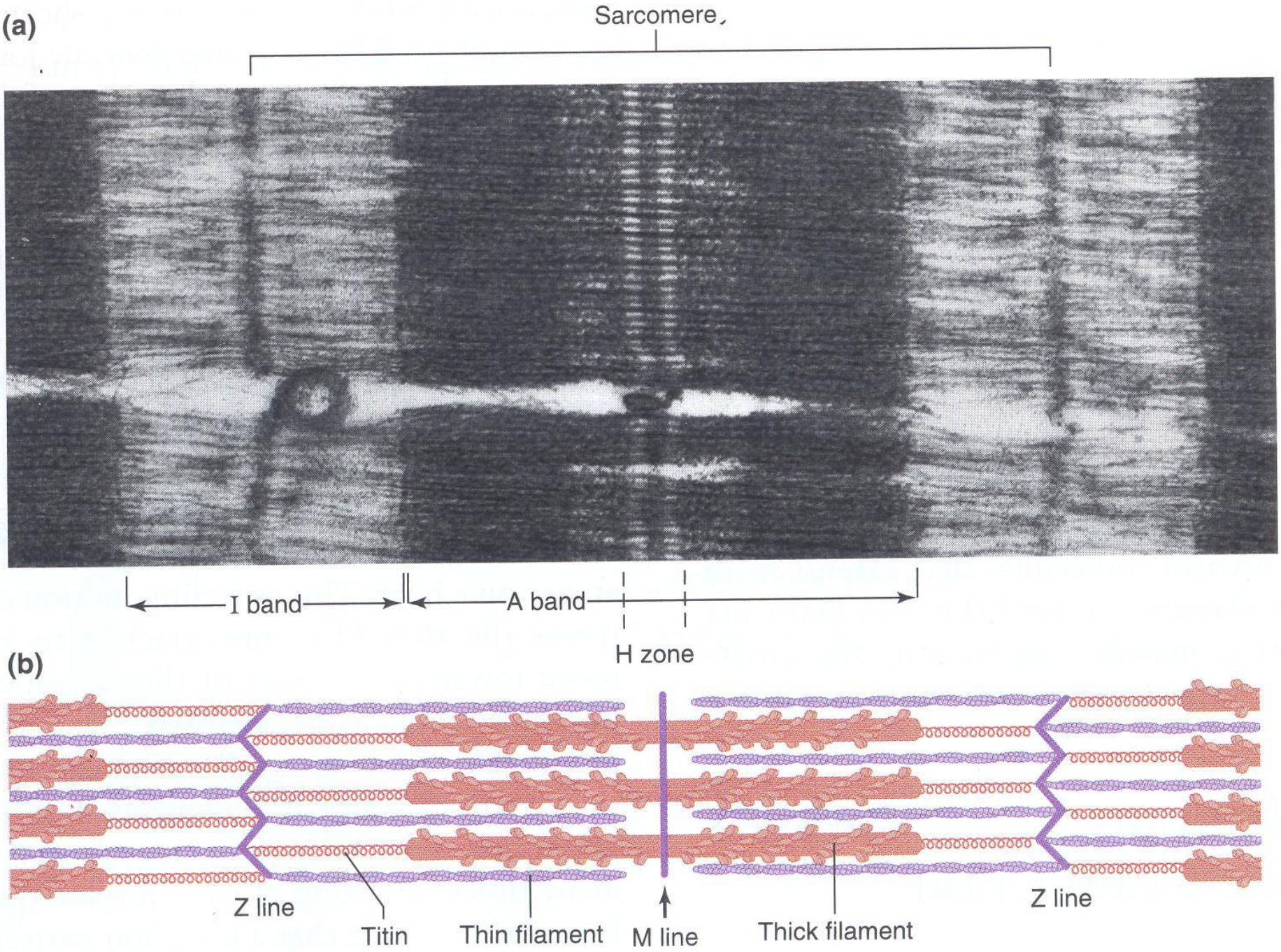

Skeletal muscle
Nerve and
blood vessels
Connective tissue
Connective tissue
Tendon
Muscle fascicle
Nucleus
Muscle fiber

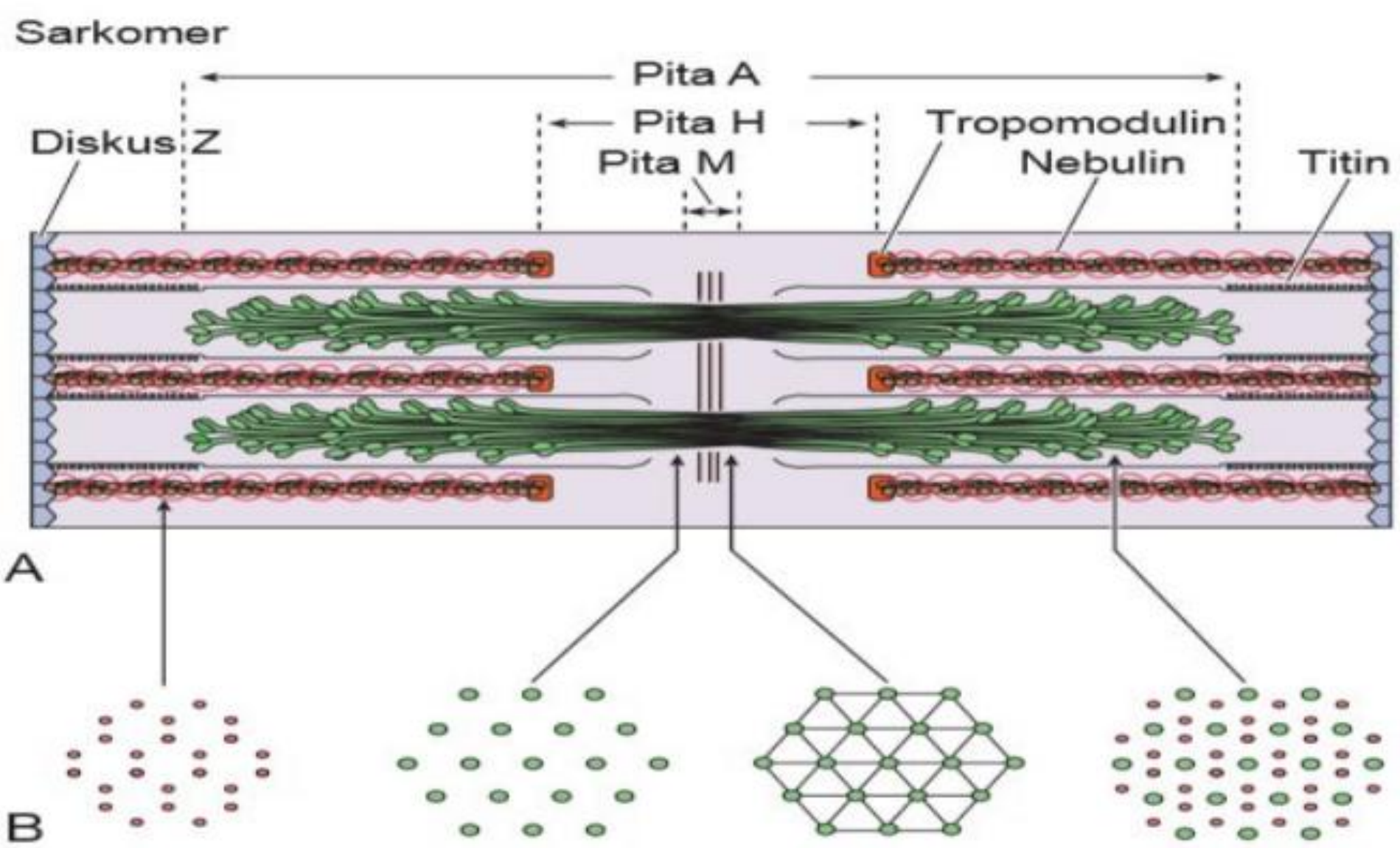
OTOT RANGKA


Sarcoplasmic reticulum
Myofibrils
Cytosol
Plasma membrane
Transverse tubules
Lateral sacs
Mitochondrion



Histologi Otot Rangka


(a)
Sarcomere
I band
A band
H zone
(b)
Z line
Titin
Thin filament
M line
Thick filament
Z line


Sarkomer
Pita A
Pita H
Pita M
Diskus Z
Tropomodulin
Nebulin
Titin
A
B

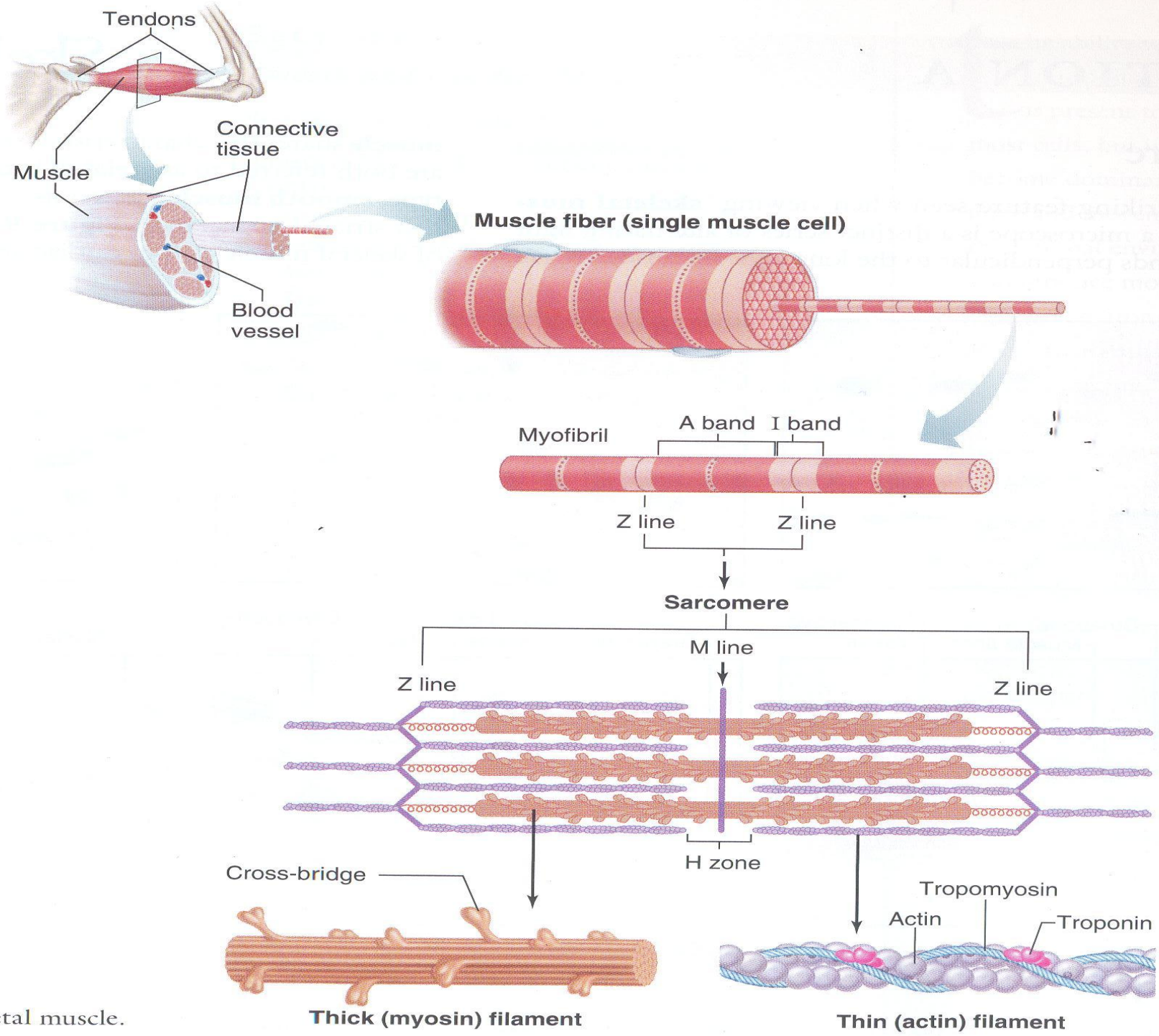
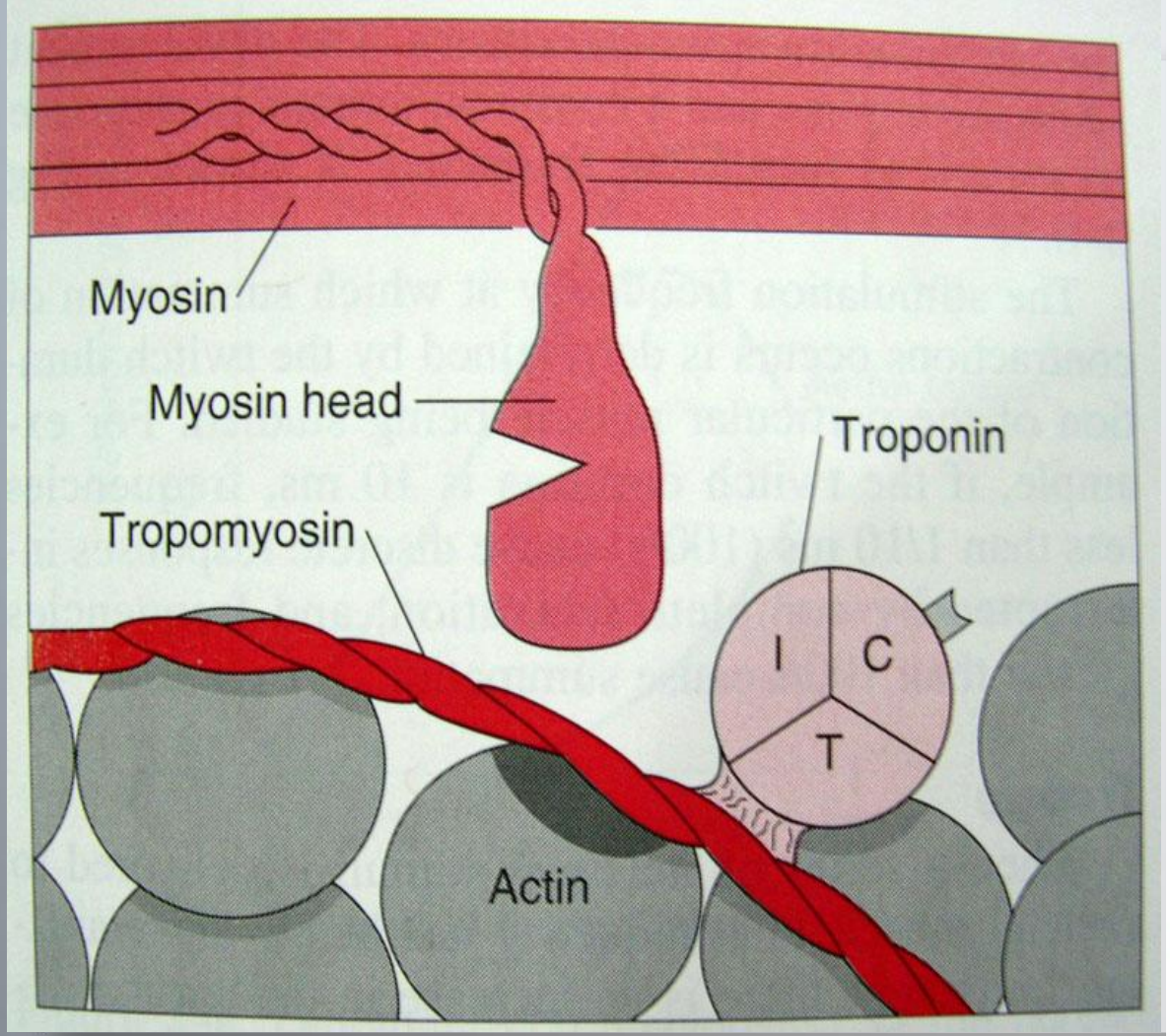
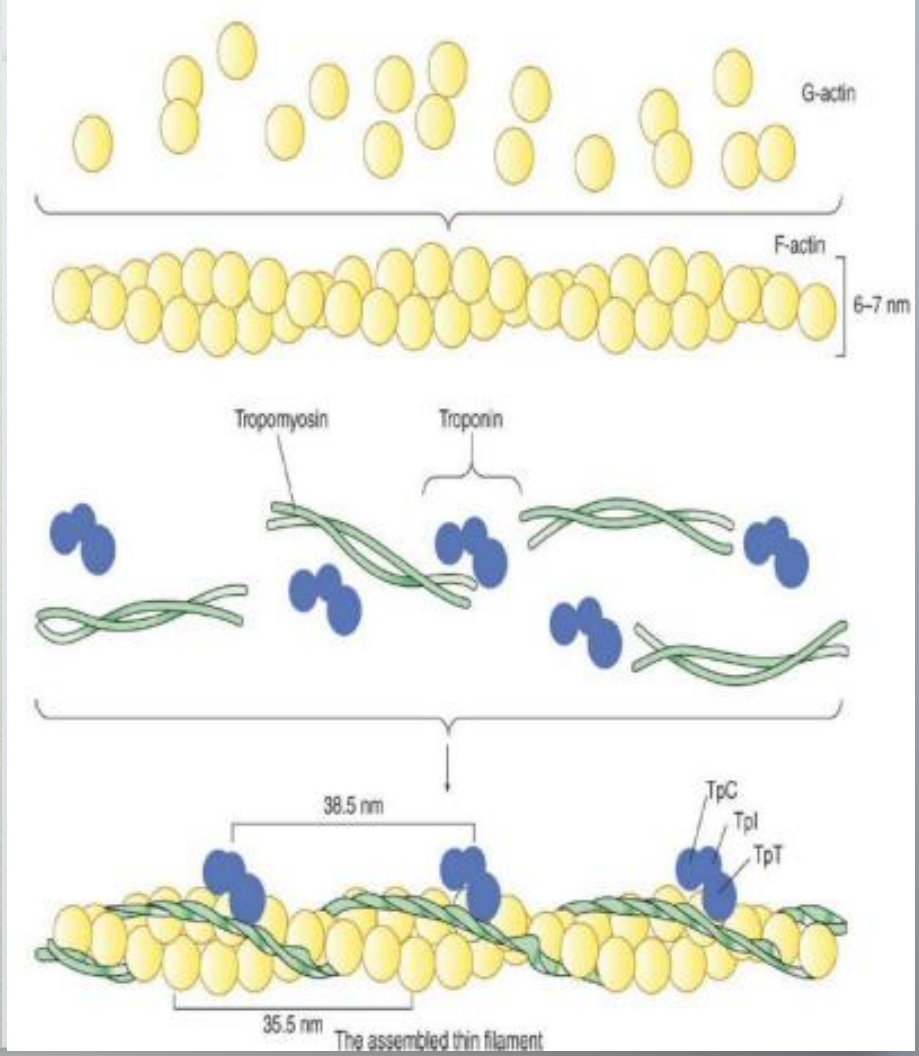


Figure 9–2
Structure of skeletal muscle.





Actin, Troponin, & Tropomyosin

KONTRAKSI OTOT

- Bagaimana penghantaran impuls melalui sinaps ?
- Penggunaan energi pada mekanisme kontraksi otot terjadi pada saat ?
- Dari mana saja sumber energi untuk kontraksi otot ?

KONTRAKSI OTOT

- Kontraksi otot terjadi karena adanya impuls listrik dari motorneuron yang disampaikan ke sel otot
- Proses kontraksi otot disebut ***excitation-contraction coupling***

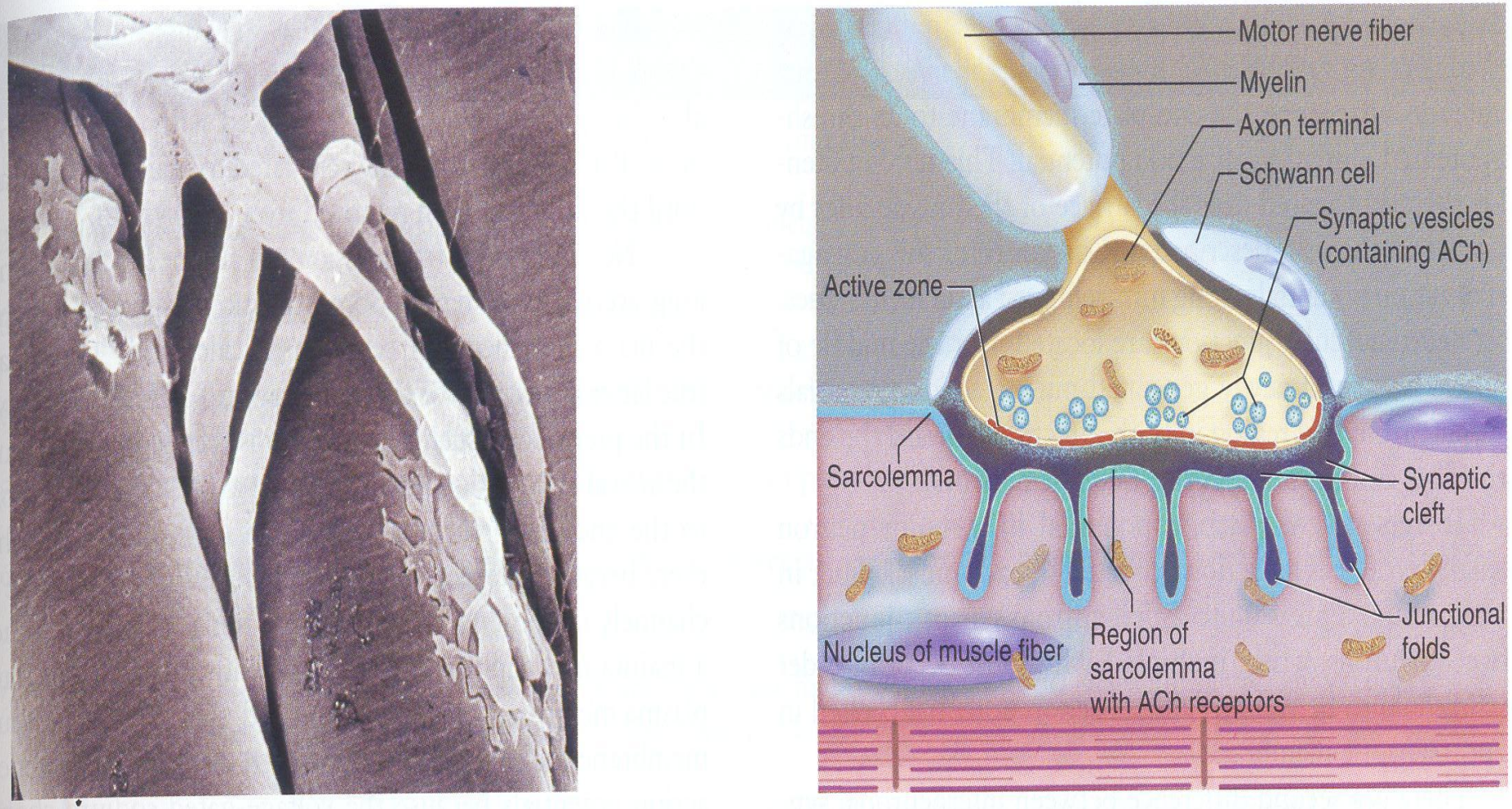


Figure 9–14

The neuromuscular junction. (a) Scanning electron micrograph showing branching of motor axons, with terminals embedded in grooves in the muscle fiber's surface. (b) Structure of a neuromuscular junction.

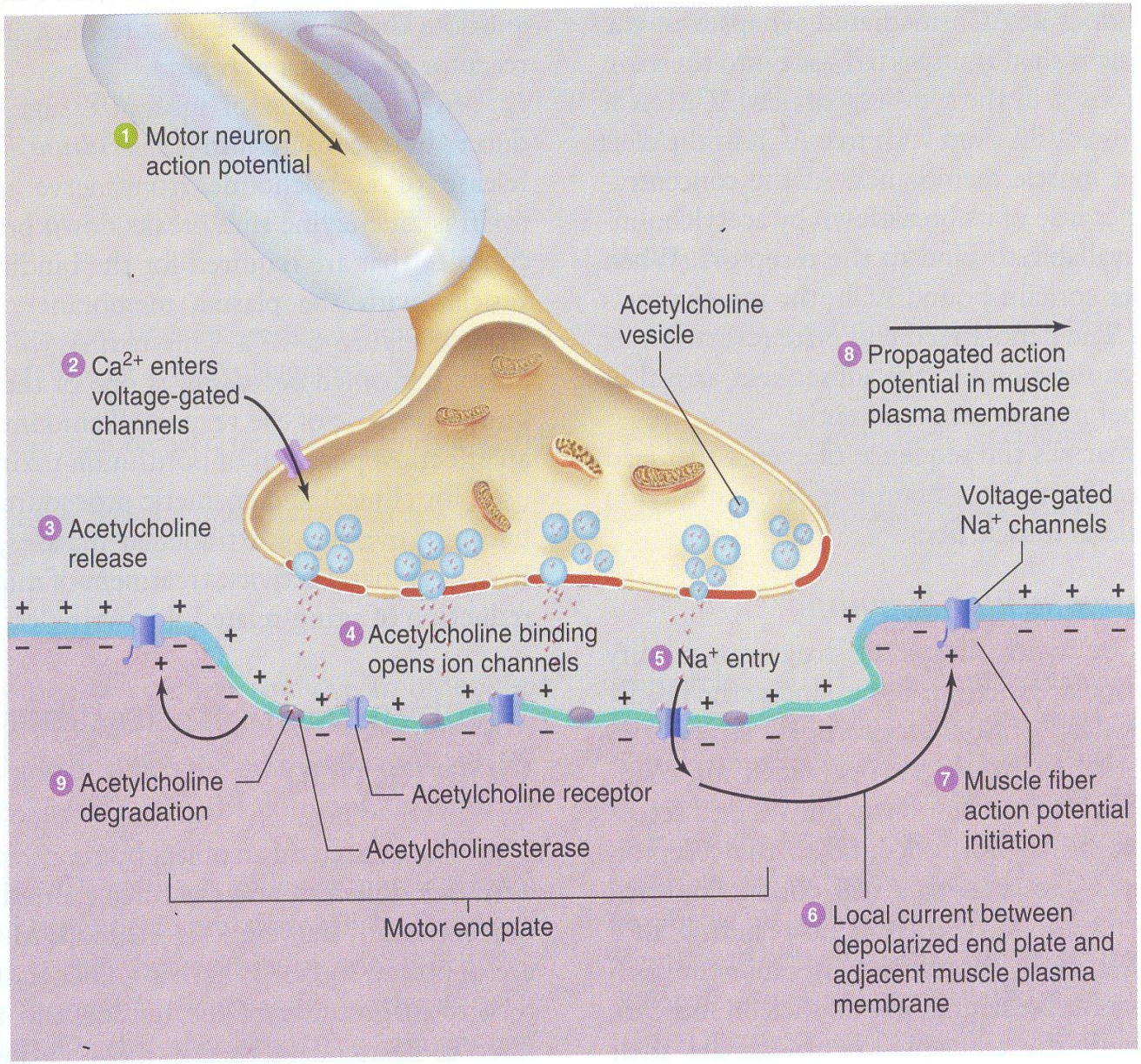
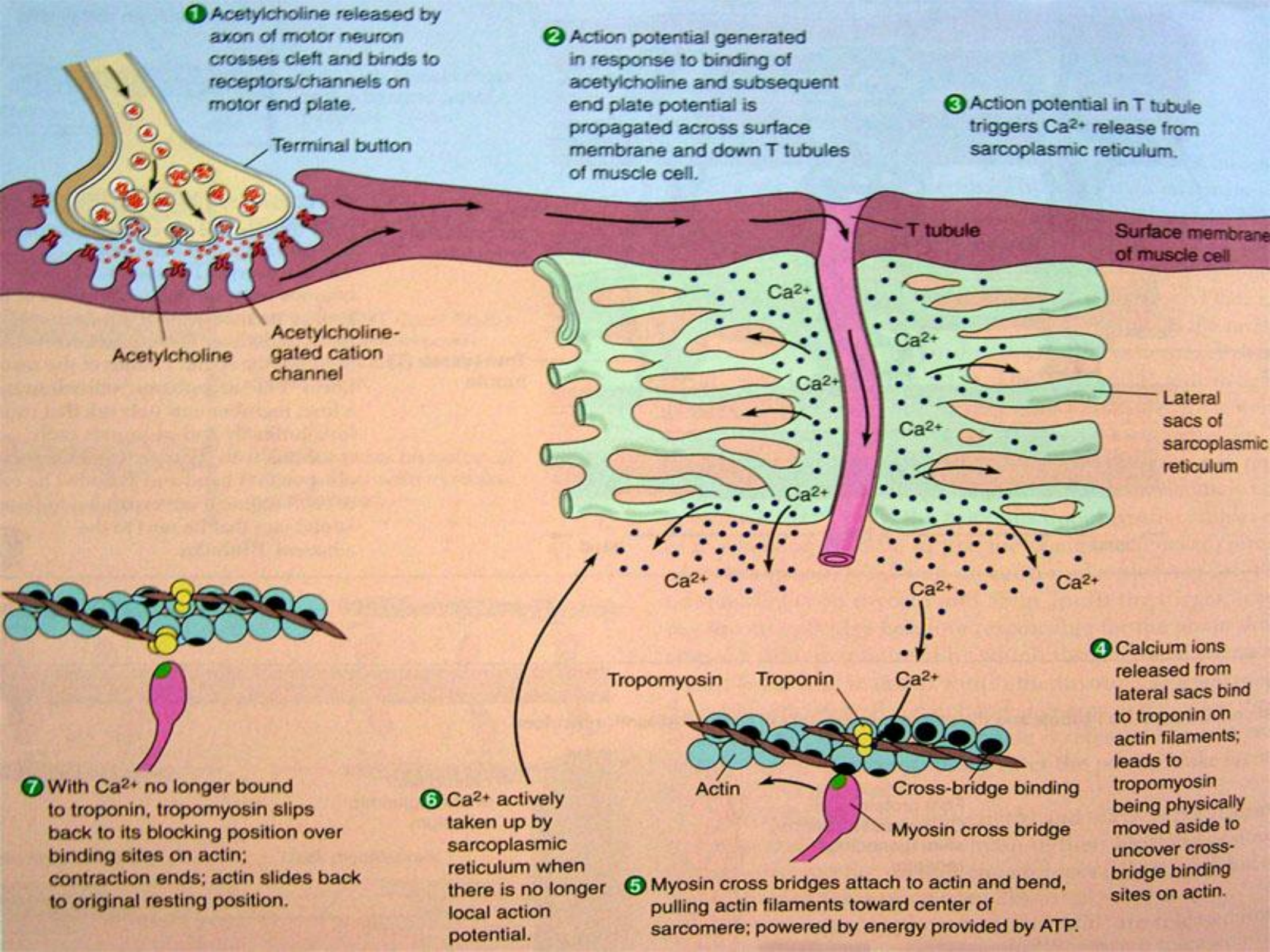
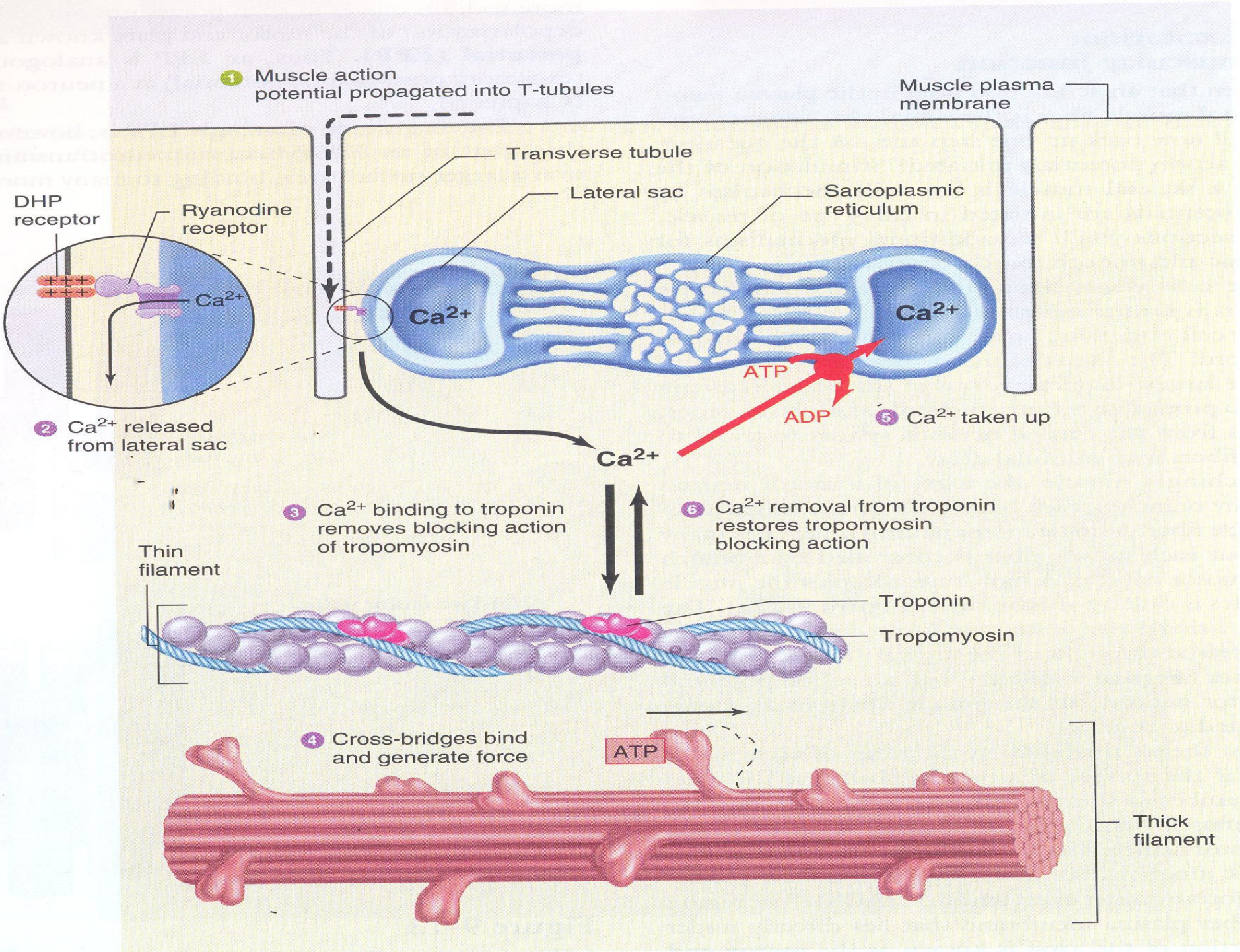


Figure 9–15

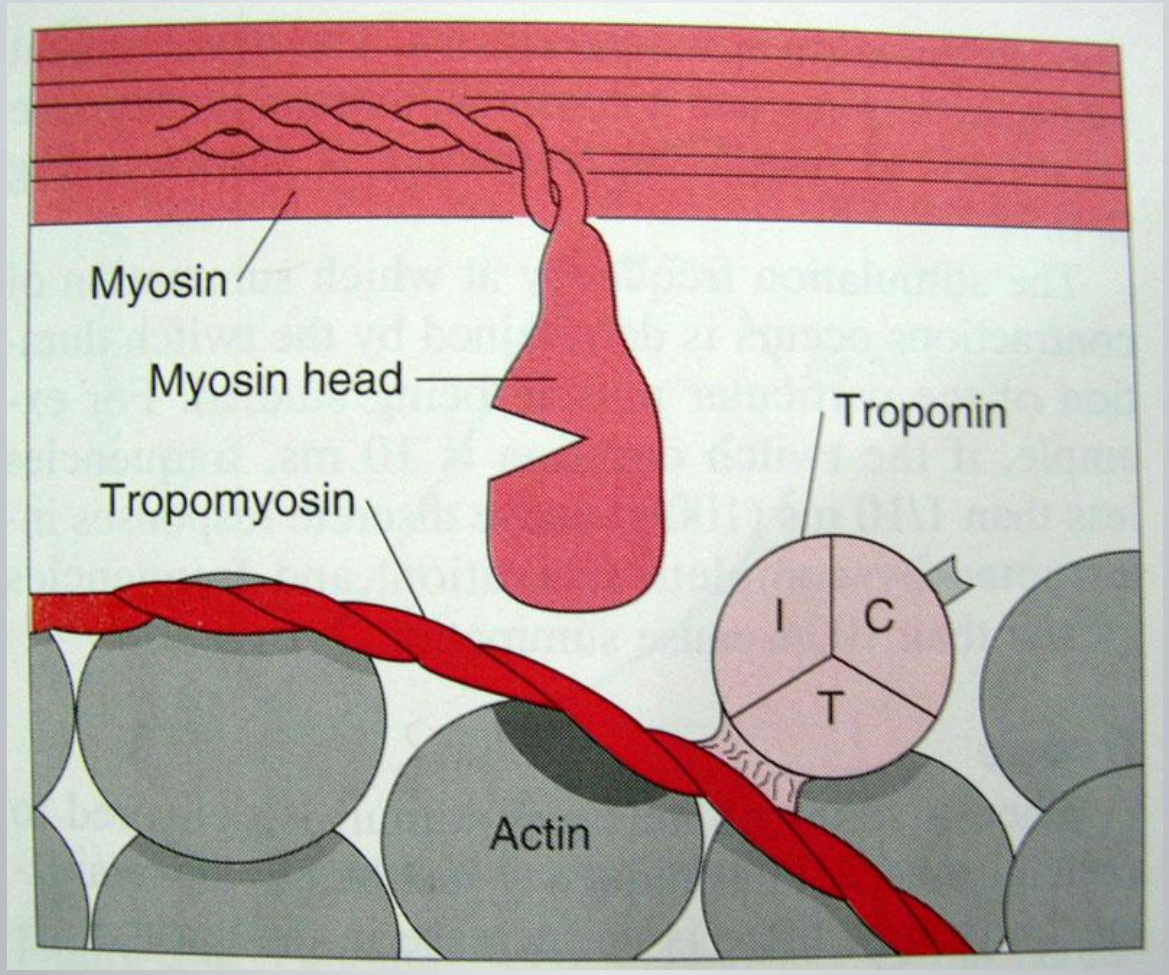
Events at the neuromuscular junction that lead to an action potential in the muscle fiber plasma membrane. Although potassium also exits the muscle cell when ACh receptors are open, sodium entry and depolarization dominates, as shown here.


1 Acetylcholine released by axon of motor neuron crosses cleft and binds to receptors/channels on motor end plate.
Terminal button
Acetylcholine
Acetylcholine-gated cation channel
2 Action potential generated in response to binding of acetylcholine and subsequent end plate potential is propagated across surface membrane and down T tubules of muscle cell.
3 Action potential in T tubule triggers Ca2+ release from sarcoplasmic reticulum.
T tubule
Surface membrane of muscle cell
Ca2+
Lateral sacs of sarcoplasmic reticulum
4 Calcium ions released from lateral sacs bind to troponin on actin filaments; leads to tropomyosin being physically moved aside to uncover cross-bridge binding sites on actin.
Tropomyosin
Troponin
Actin
Cross-bridge binding
Myosin cross bridge
5 Myosin cross bridges attach to actin and bend, pulling actin filaments toward center of sarcomere; powered by energy provided by ATP.
6 Ca2+ actively taken up by sarcoplasmic reticulum when there is no longer local action potential.
7 With Ca2+ no longer bound to troponin, tropomyosin slips back to its blocking position over binding sites on actin; contraction ends; actin slides back to original resting position.

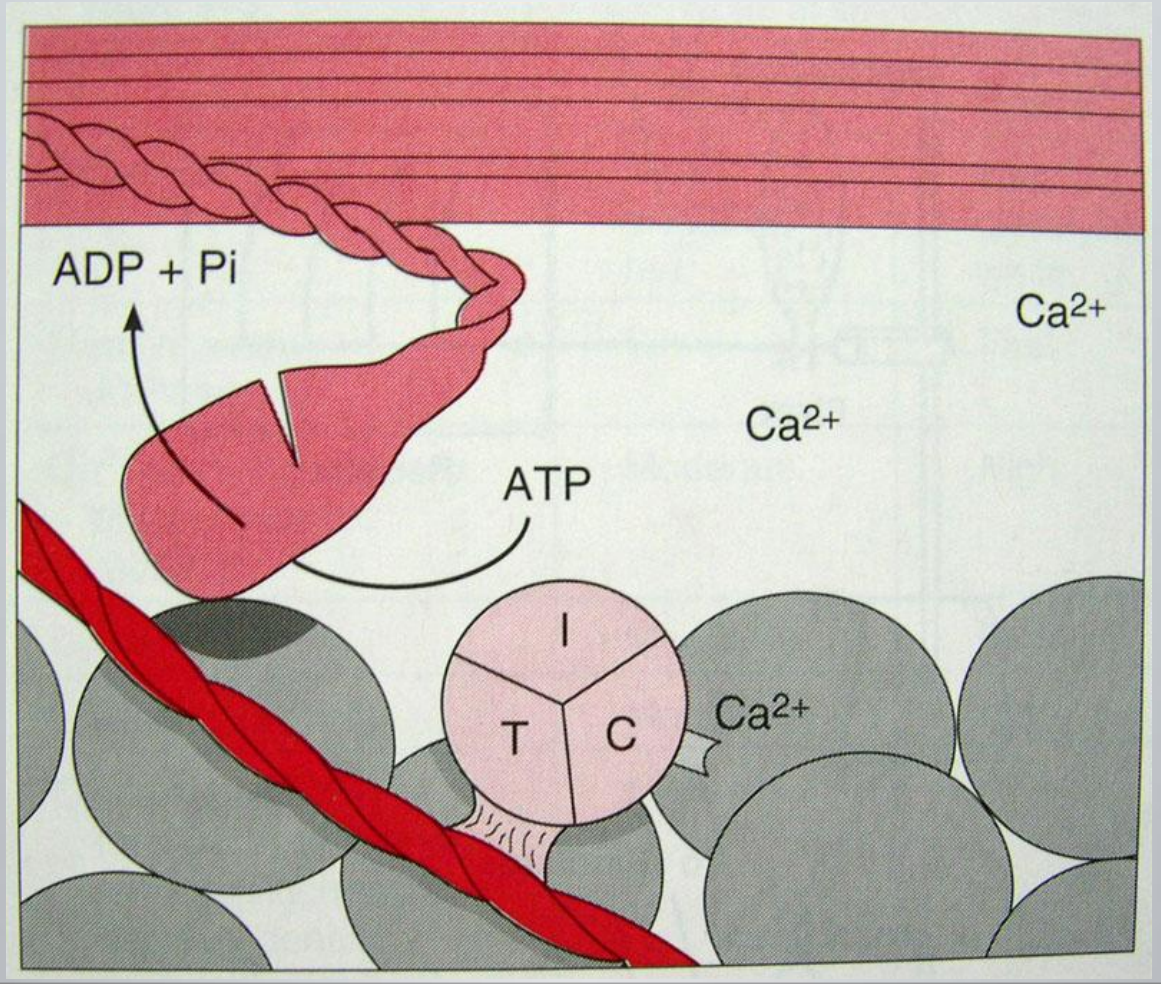


e 9–12

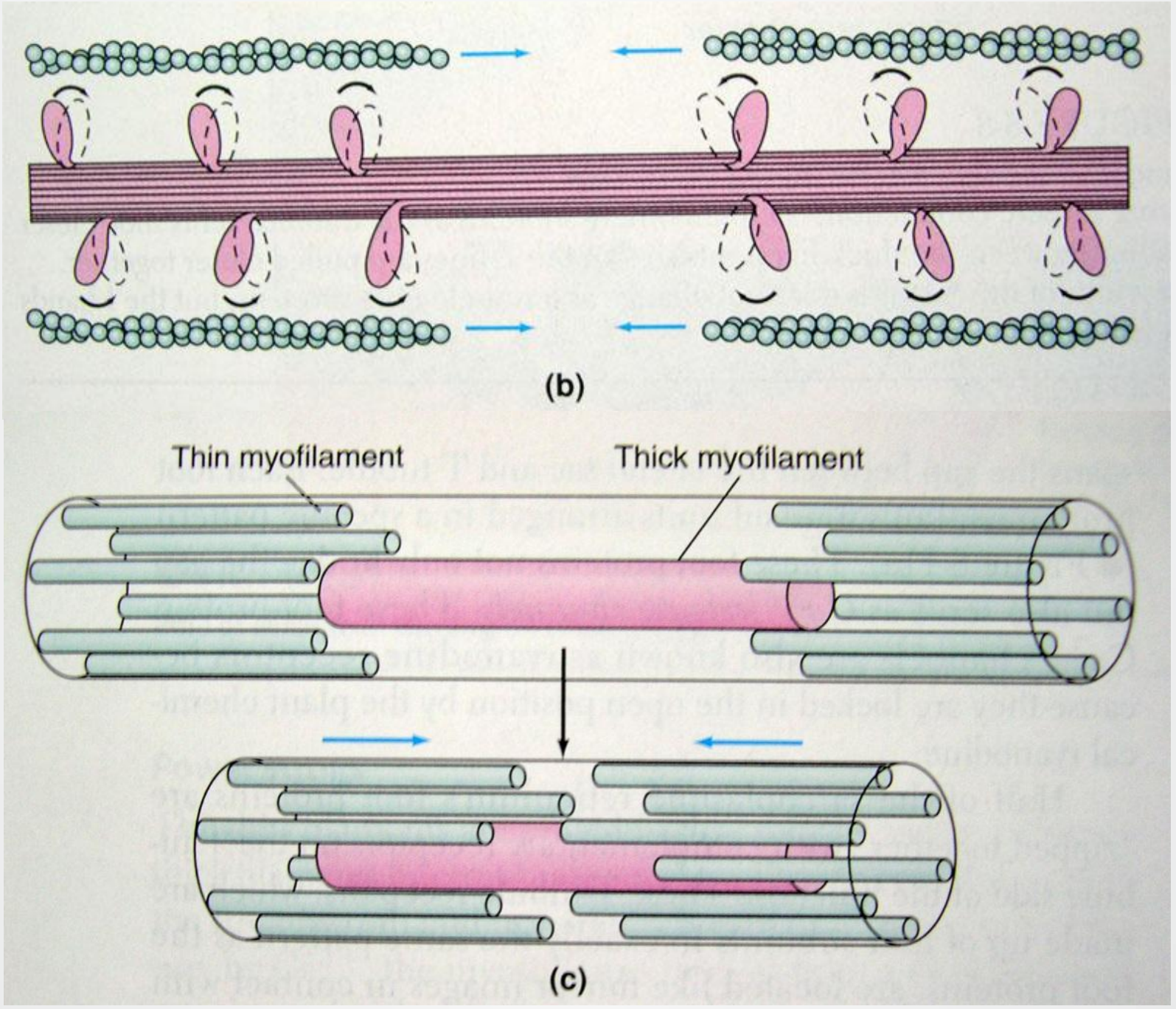
and uptake of calcium by the sarcoplasmic reticulum during contraction and relaxation of a skeletal muscle fiber.

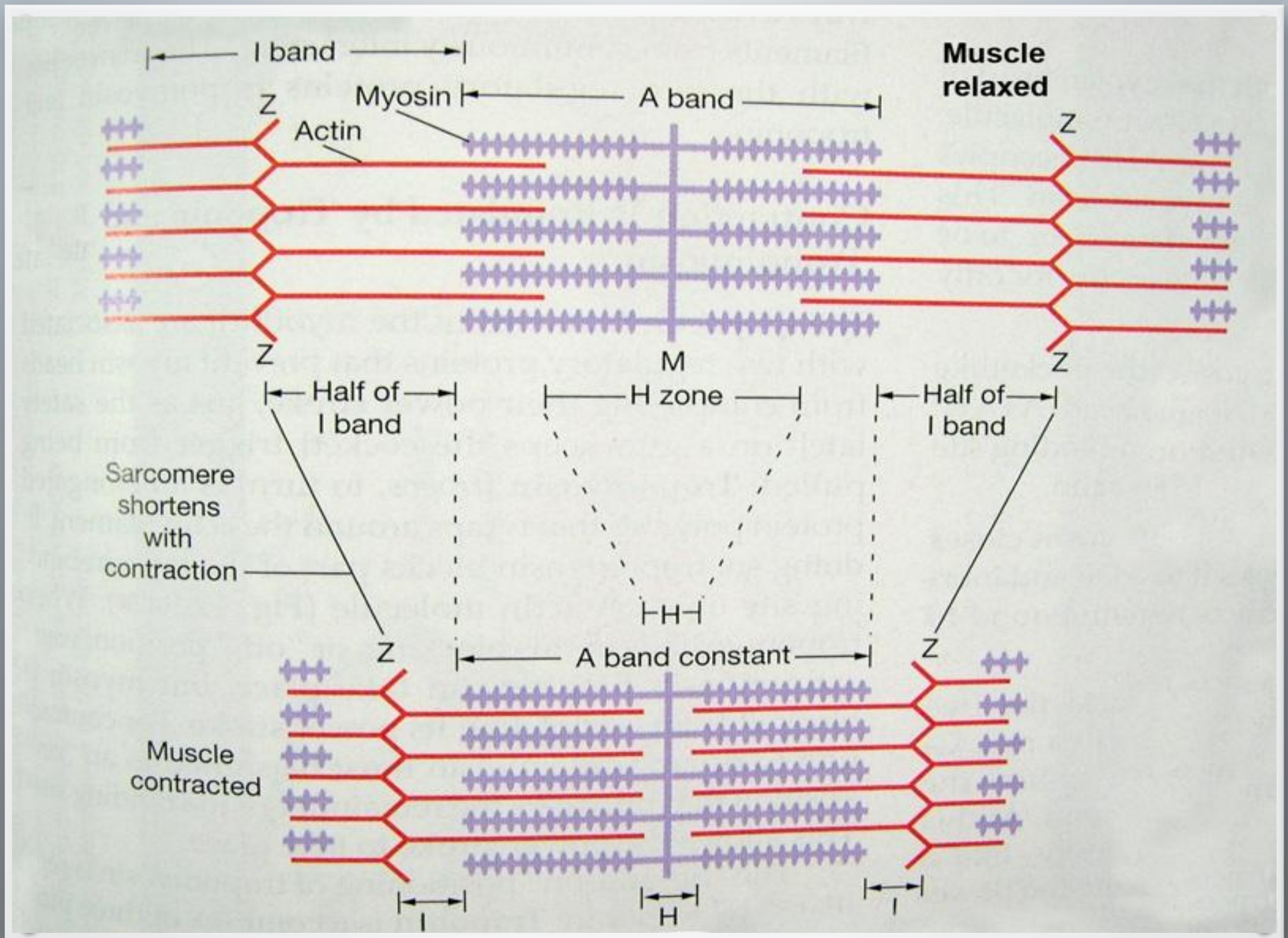


Actin, Troponin, & Tropomyosin



Actin, Troponin, & Tropomyosin


(b)
Thin myofilament
Thick myofilament
(c)


I band
Muscle relaxed
Myosin
A band
Actin
Z
Z
Z
M
Z
Half of I band
H zone
Half of I band
Sarcomere shortens with contraction
H
A band constant
Z
Z
Muscle contracted
I
H
I

Steps in relaxation

- Ca^{2+} pumped back into sarcoplasmic reticulum
- Release of Ca^{2+} from Troponin
- Cessation of interaction between actin and myosin

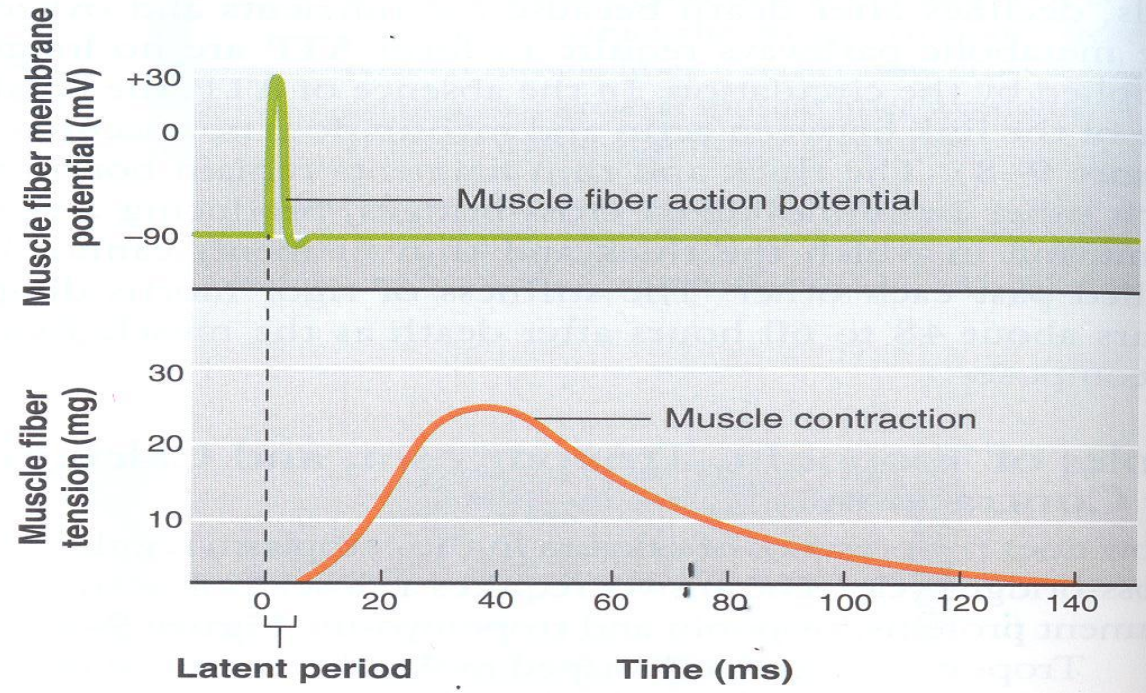
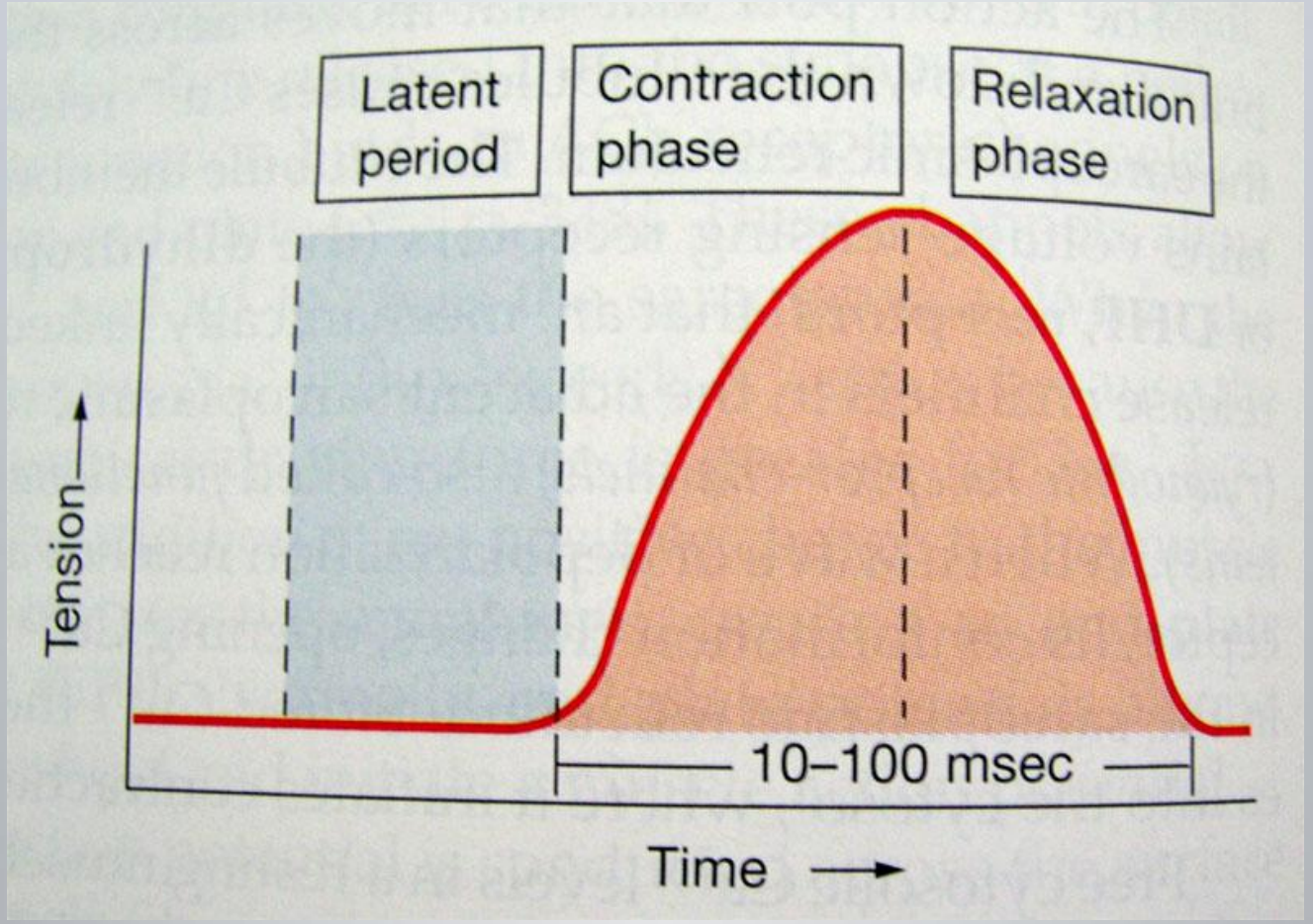


Figure 9–10

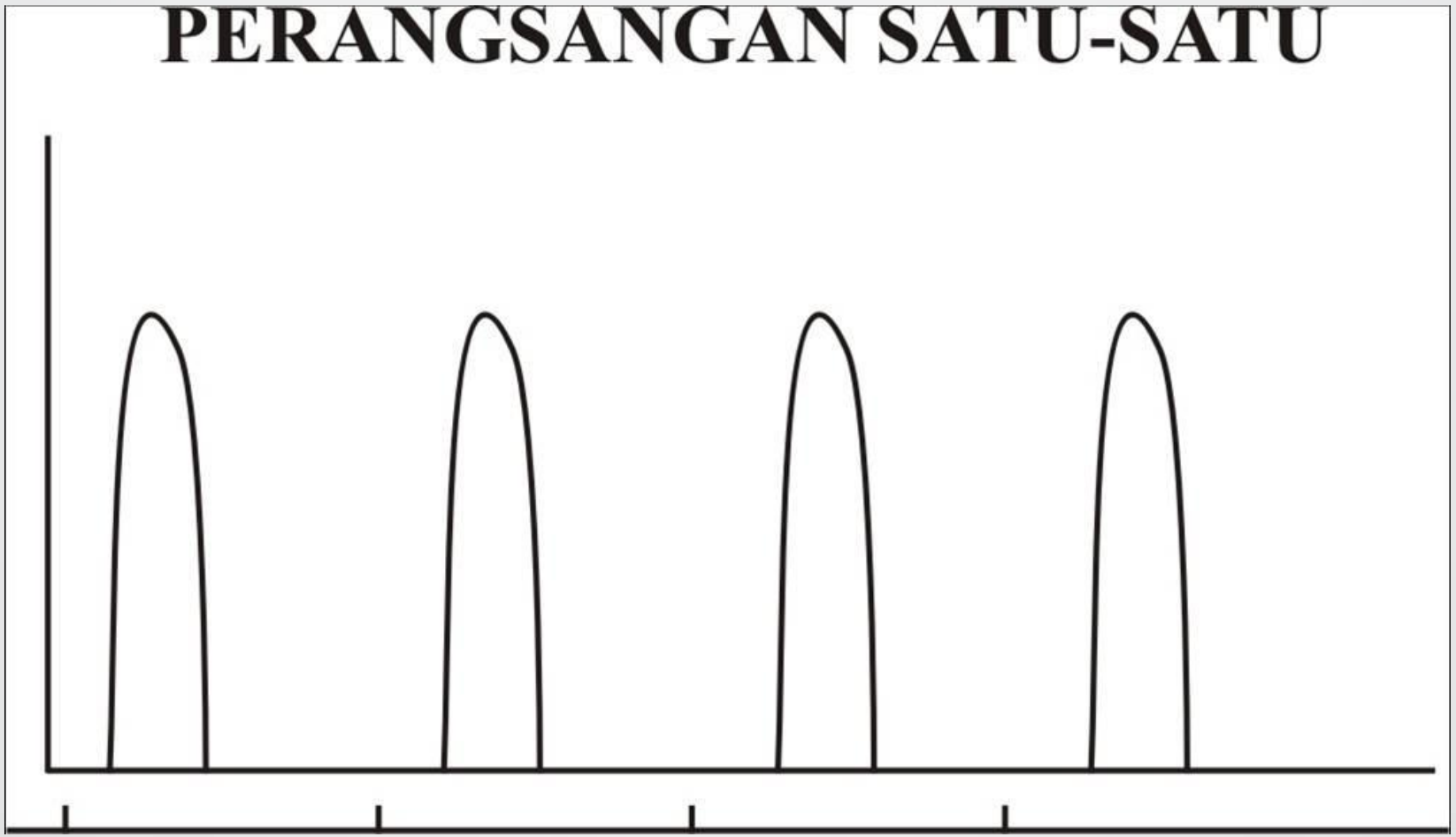
Time relationship between a skeletal muscle fiber action potential and the resulting contraction and relaxation of the muscle fiber.

Elektromyogram & Mekanomyogram

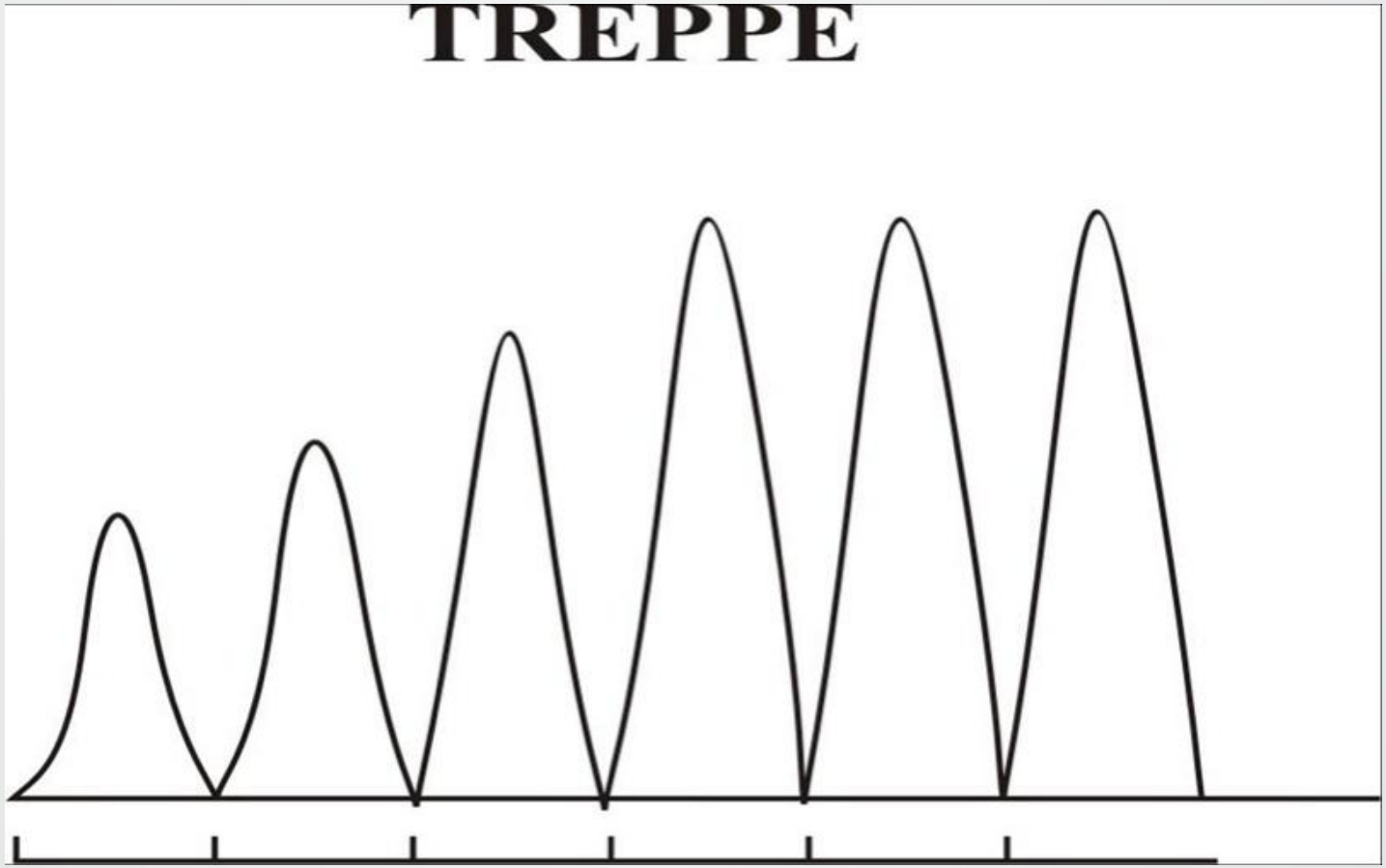


Fase Kontraksi Otot

Respon Terhadap Rangsang

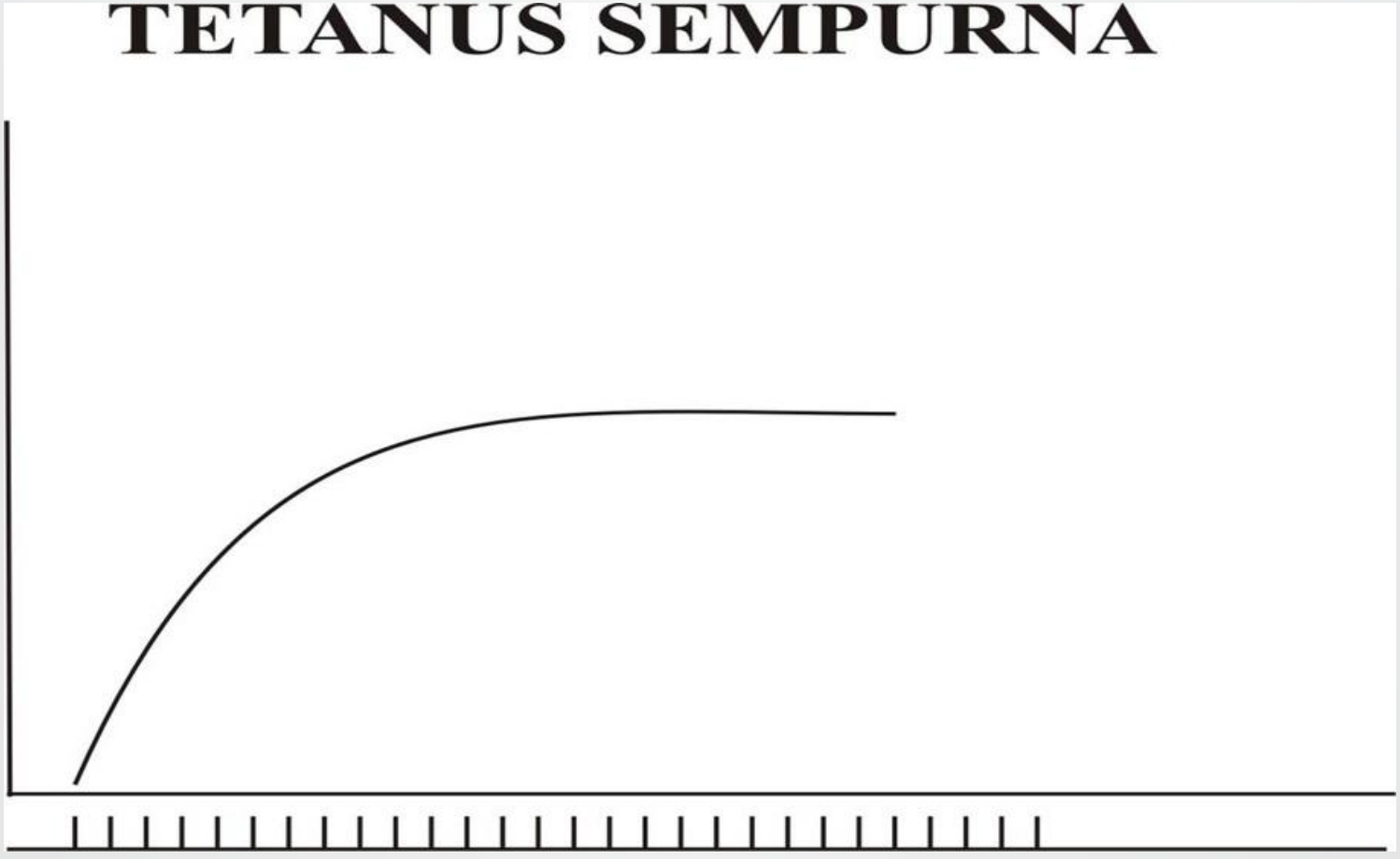


Respon Terhadap Rangsang



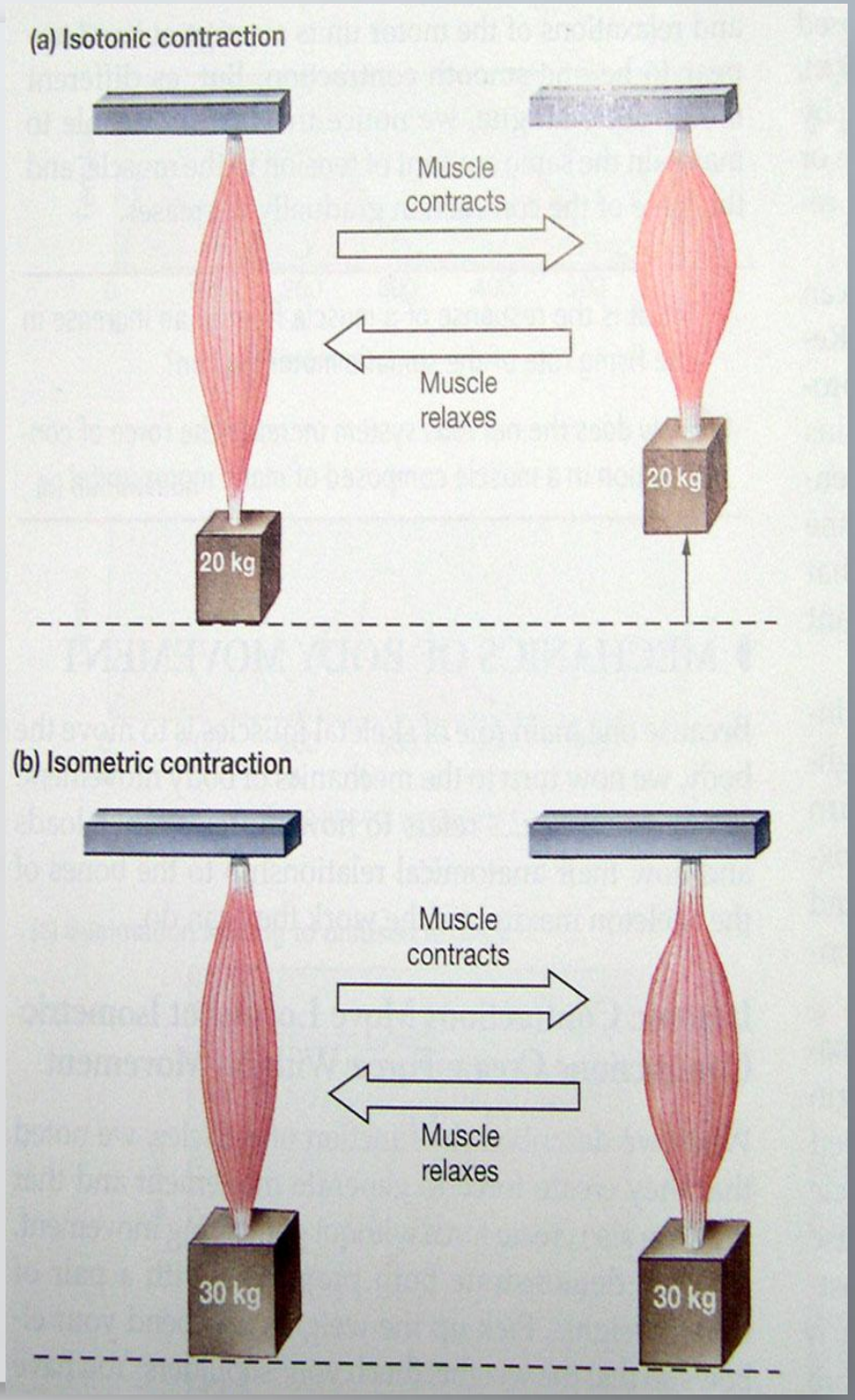
Respon Terhadap Rangsang

Respon Terhadap Rangsang



Jenis Kontraksi

- Kontraksi isotonik
  - ✓ kontraksi konsentrik
  - ✓ kontraksi eksentrik
- Kontraksi isometrik



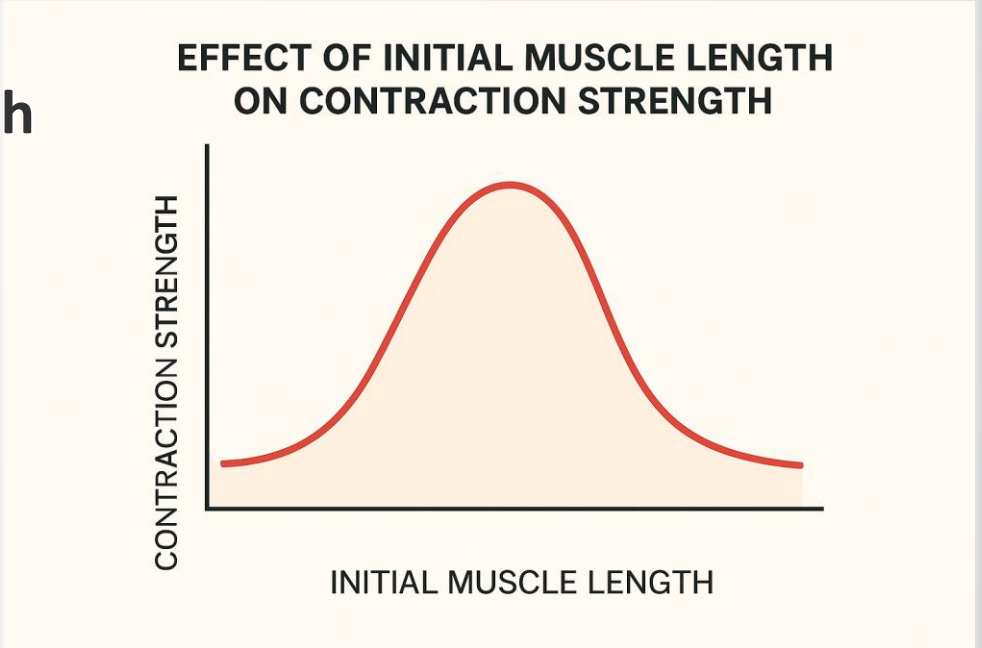
Kekuatan Kontraksi

★ **Panjang awal / initial length**

Panjang sarkomer optimal → jumlah cross-bridge maksimal.

Jika otot terlalu pendek → filamen-tebal dan tipis saling terlalu tumpang tindih → cross-bridge sulit bekerja.

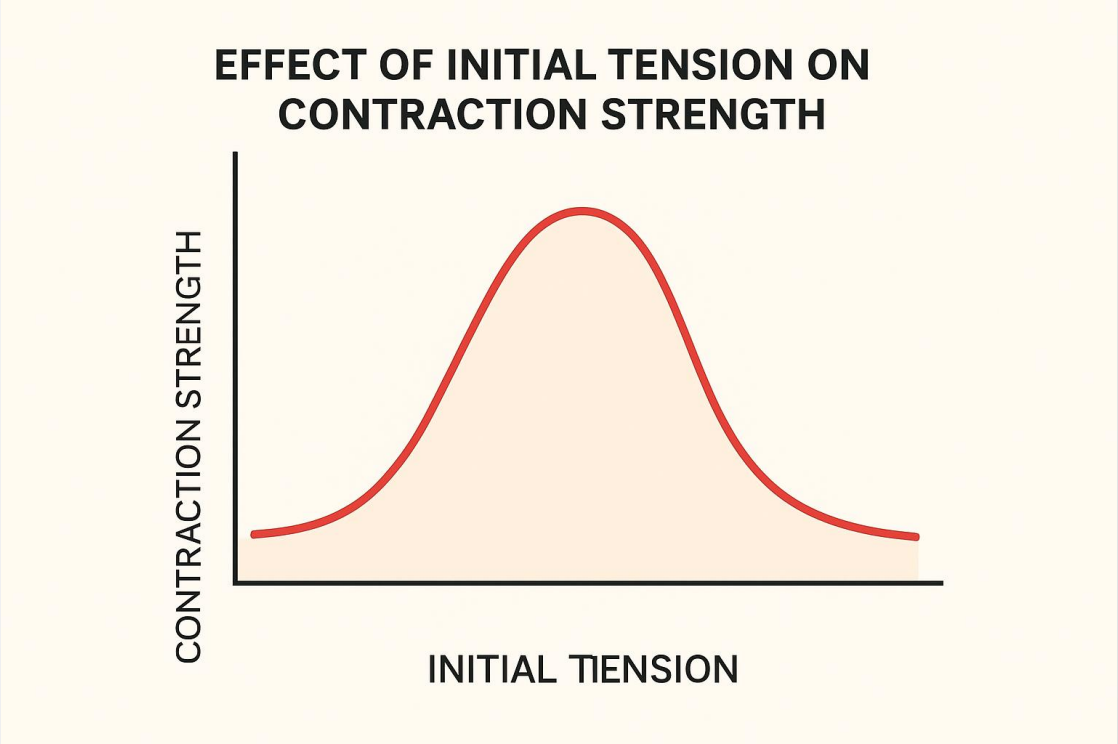
Jika terlalu panjang → sedikit overlap → sangat sedikit cross-bridge bisa terbentuk → kekuatan menurun



Kekuatan Kontraksi

- **Tegangan awal / initial tension (preload)**

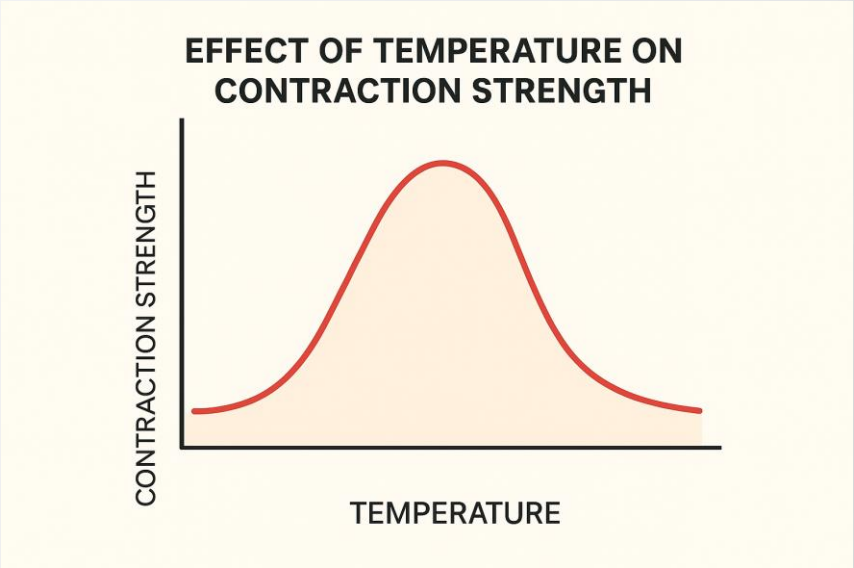
  Preload → sedikit peregangan pada otot → panjang sarkomer optimal → pembentukan cross-bridge → panjang awal



Kekuatan Kontraksi

★ **Suhu**

- ✓ Suhu → meningkatkan kecepatan reaksi kimia dan aktivitas enzim → myosin ATPase, pelepasan Ca^{2+} dan pengambilan kembali Ca^{2+} oleh retikulum sarkoplasma lebih cepat → siklus cross-bridge lebih sering → kontraksi lebih cepat dimulai dan selesai.
- ✓ Suhu ↑ → viskositas cairan dalam sel lebih "encer" → difusi ion dan molekul, termasuk Ca^{2+} >>
- ✓ Suhu ↓ → latensi kontraksi lebih lama → fase naik kontraksi lebih lambat → fase relaksasi lambat → kekuatan maksimal menurun.



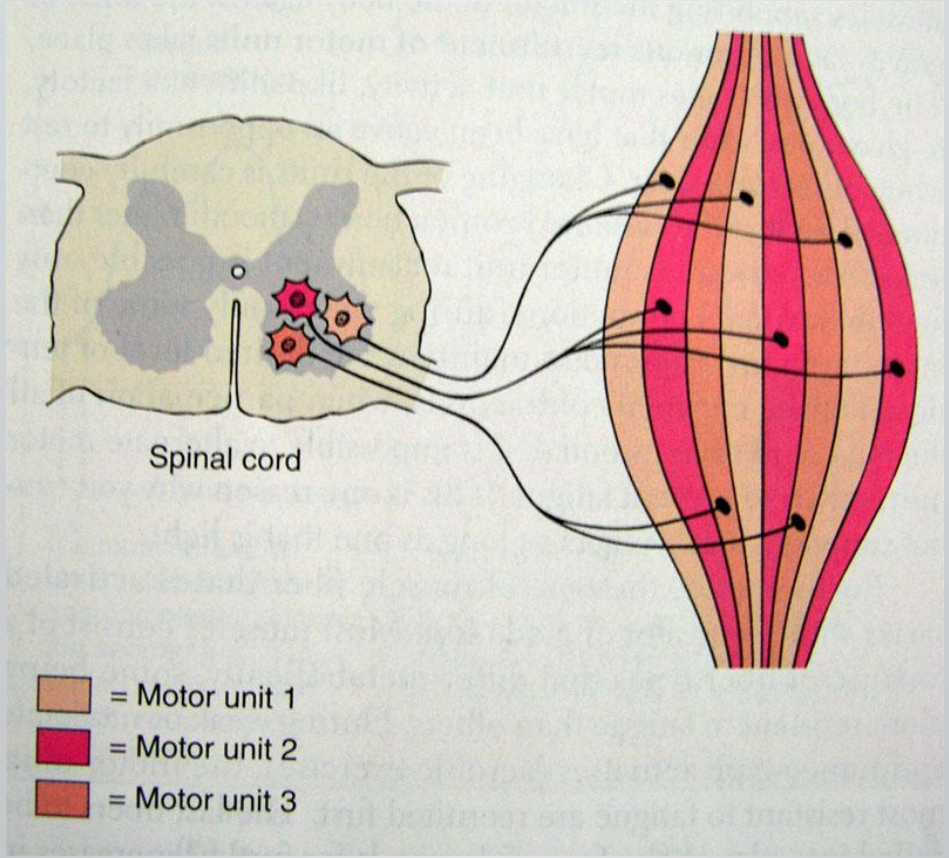
Kekuatan Kontraksi

★ **Kekuatan rangsang**

- ✓ Kekuatan rangsang → intensitas stimulus listrik → jumlah neuron motorik yang diaktifkan
- ✓ Pada tingkat rangsangan yang sangat rendah → hanya beberapa saraf motorik/unit motor yang tebal atau yang ambang rendah akan aktif→ jadi hanya sebagian kecil serabut otot yang berkontraksi → tegangan yang dihasilkan kecil.
- ✓ Ketika kekuatan rangsang ditingkatkan, lebih banyak neuron motorik teraktive (rekrutmen spasial meningkat) → lebih banyak serabut otot bekerja → tegangan total kontraksi bertambah.
- ✓ Kontraksi maksimal → semua unit motor potensial sudah terekrut → peningkatan rangsang tidak menambah kekuatan.

Pengaturan Kekuatan Kontraksi

- **Motor unit : kesatuan antara satu serat motorneuron dengan serat-serat otot yang dipersarafinya**
- **Motor unit berperan dalam mekanisme pengaturan kekuatan kontraksi otot melalui proses** *recruitment*



Motor Unit

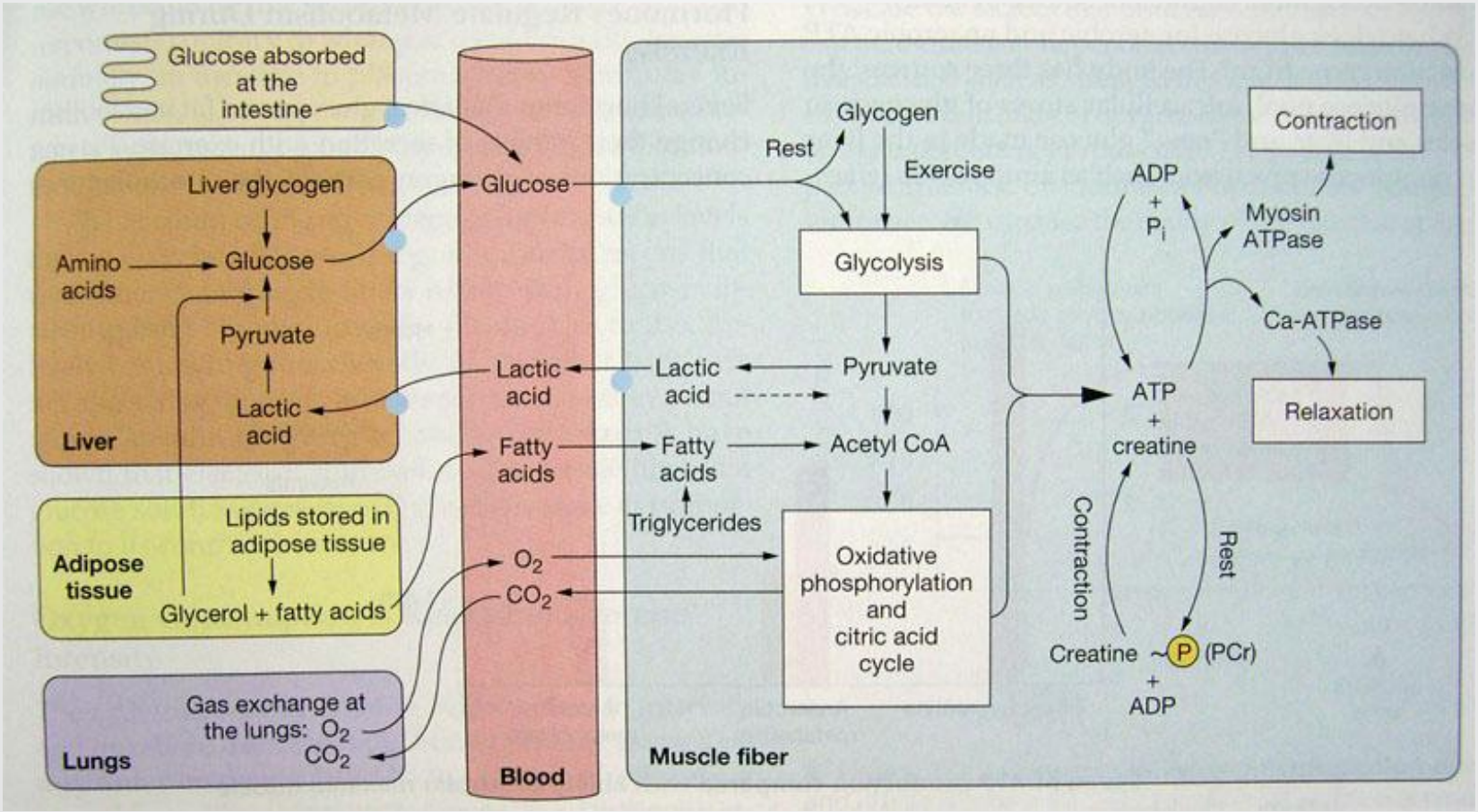
Energi pada kerja otot

- Energi diperlukan otot untuk :
  - Pergeseran aktin oleh cross-bridges myosin. (Kepala myosin mempunyai enzim ATPase)
  - Memompa ion Ca2+ dari sitosol ke dalam reticulum sarcoplasma
  - Memompa Na+ dan K+ melalui membran sel otot

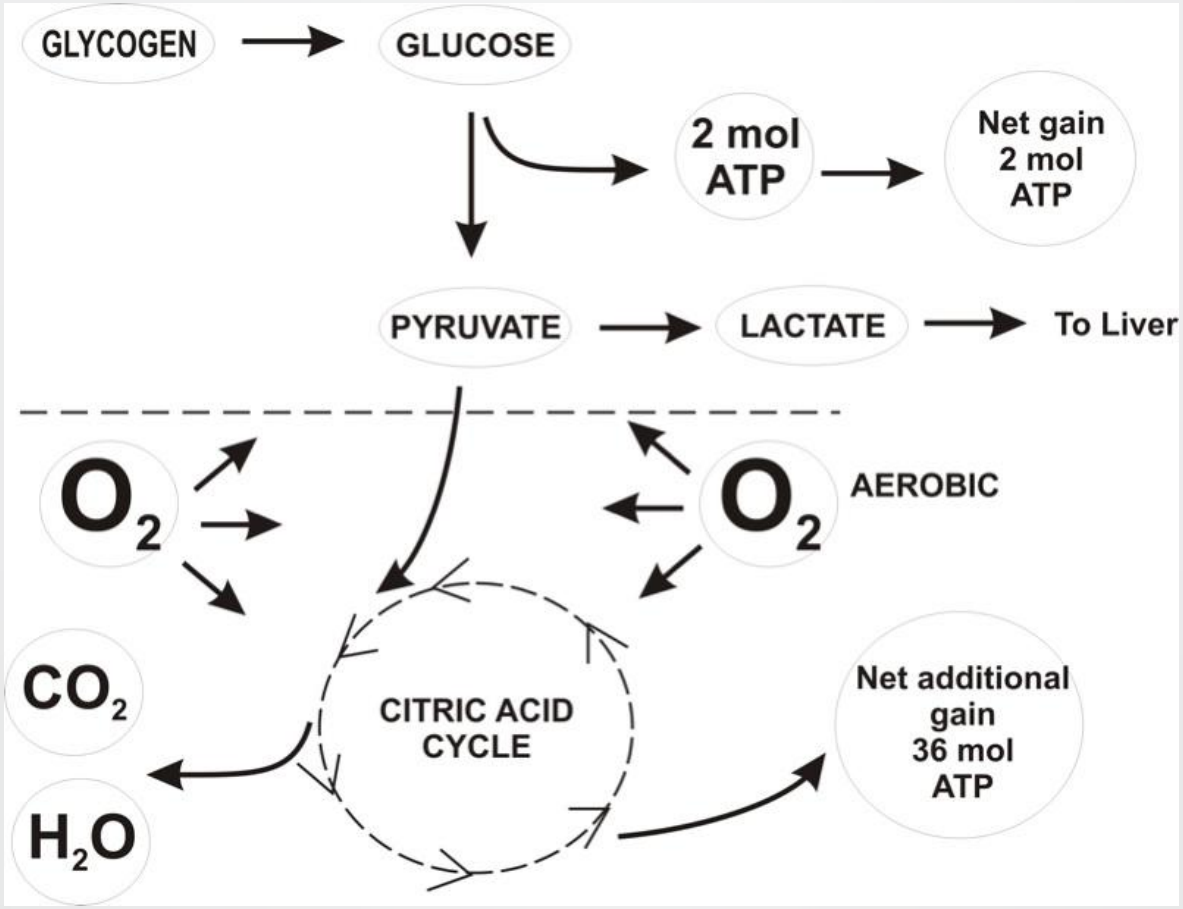
Sumber Energi Otot

- ATP
- Kreatin Fosfat
- Pemecahan Karbohidrat :
  - Anaerob
  - Aerob

Metabolisme Karbohidrat



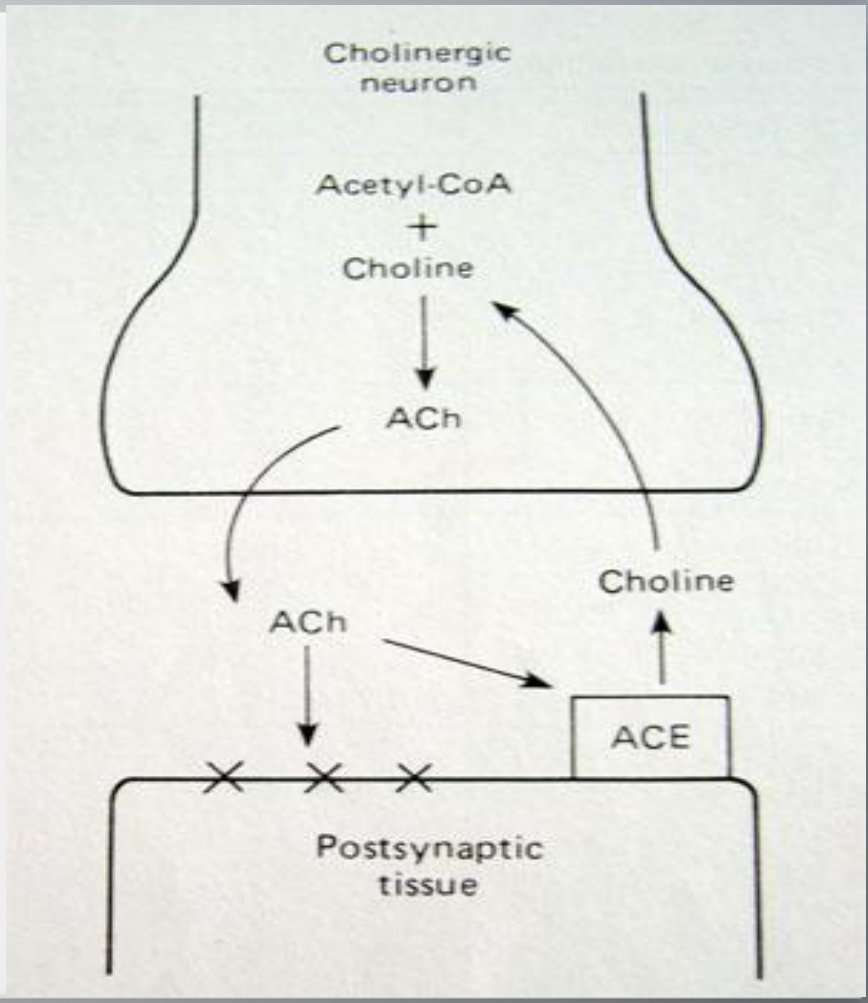
Hutang Oksigen (Oxygen Debt)



Aspek Kimia Neurotransmiter Asetilkolin

Asetilkolin :

- **Disintesa dari kolin + asetil Co-A**
- **Dikatalisa oleh enzim kolin asetiltransferase**
- **Dihidrolisis oleh enzim asetilkolinesterase**



Neuromuskular junction toxin

Jenis - jenis inhibitor asetilkolin pada neuromuskular junction

1. **Transmitter Release Inhibitors**
2. **Receptor Inhibitors**
3. **Acetylcholinesterase Inhibitors**

Acetylcholinesterase Inhibitors

Toxin	Synaptic protein hydrolyzed	Synaptic effect	Type of paralysis
Botulinum (Clostridium botulinum)	Synaptobrevin : (Bot. toxin B, D, F, G) Syntaxin : (Bot. toxin C) SNAP-25 : (Bot. toxin A, C & E)	Inhibits Ach release in NMJs and other synapses	Flaccid
Tetanus (Clostridium tetani)	Synaptobrevin	Inhibits glyciine & GABA release in CNS	Spastic

Receptor Inhibitors

Reseptor Asetilkolin :

Tipe Nikotinik

Terdapat pada neuromuskular junction dan ganglia otonom

Tipe Muskarinik

Terdapat pada sinaps parasimpatik pada organ jantung, pencernaan dan CNS

Inhibitor reseptor Asetilkolin

- **Natural ACh receptor inhibitors include: Curare: South American arrow poison produced from the vine, *Chondodendron tomentosum***
- **Atropine: from several plants, including Jimson weed (*Datura stramonium*), thornapple and nightshade (*Belladonna atropa)***
- **Scopolamine: from the henbane plant (*Hyoscyamus niger)***

Inhibitor reseptor Asetilkolin

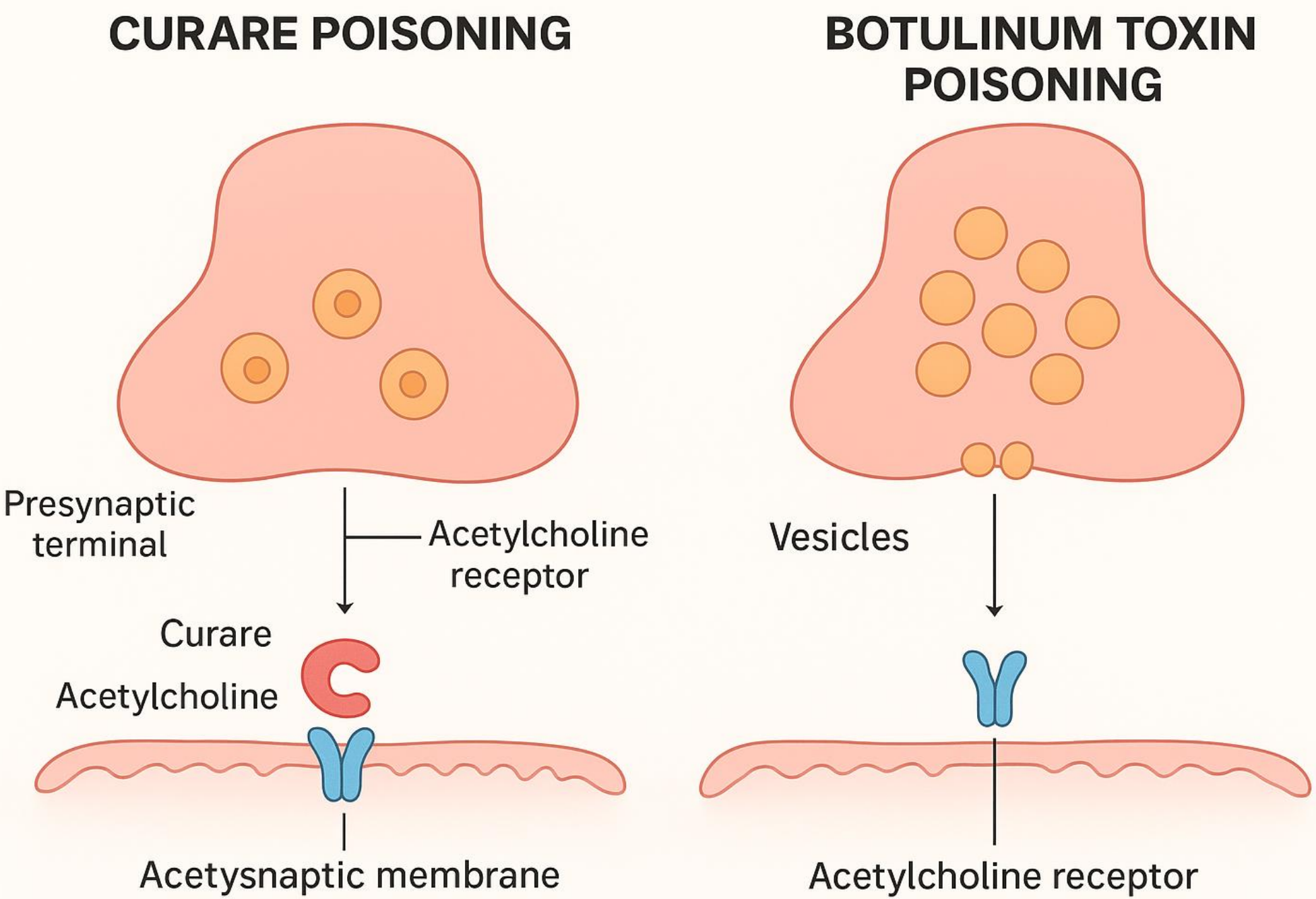
- Marine cone snail toxins: the venom from these snails contains dozens of different neurotoxins
- Alpha-bungarotoxin: produced by a snake, the banded krait
- Alpha-neurotoxin: made by the cobra

Atropine and scopolamine inhibit muscarinic receptors; the other toxins inhibit nicotinic types

Receptor Inhibitors

Toxin	Type of Ach Receptor Inhibited	Synapses and NMJs Affected	Toxin Effects
Curare	Nikotinic	NMJ	Paralyzes diaphragm, blocks respiration
Atropine	Muscarinic	Parasympathetic synapses with organs such as the heart & intestines. Also affects brain synapses	Inhibits parasympathetic nervous system, causing : rapid pulse, pupil dilation, coma & death

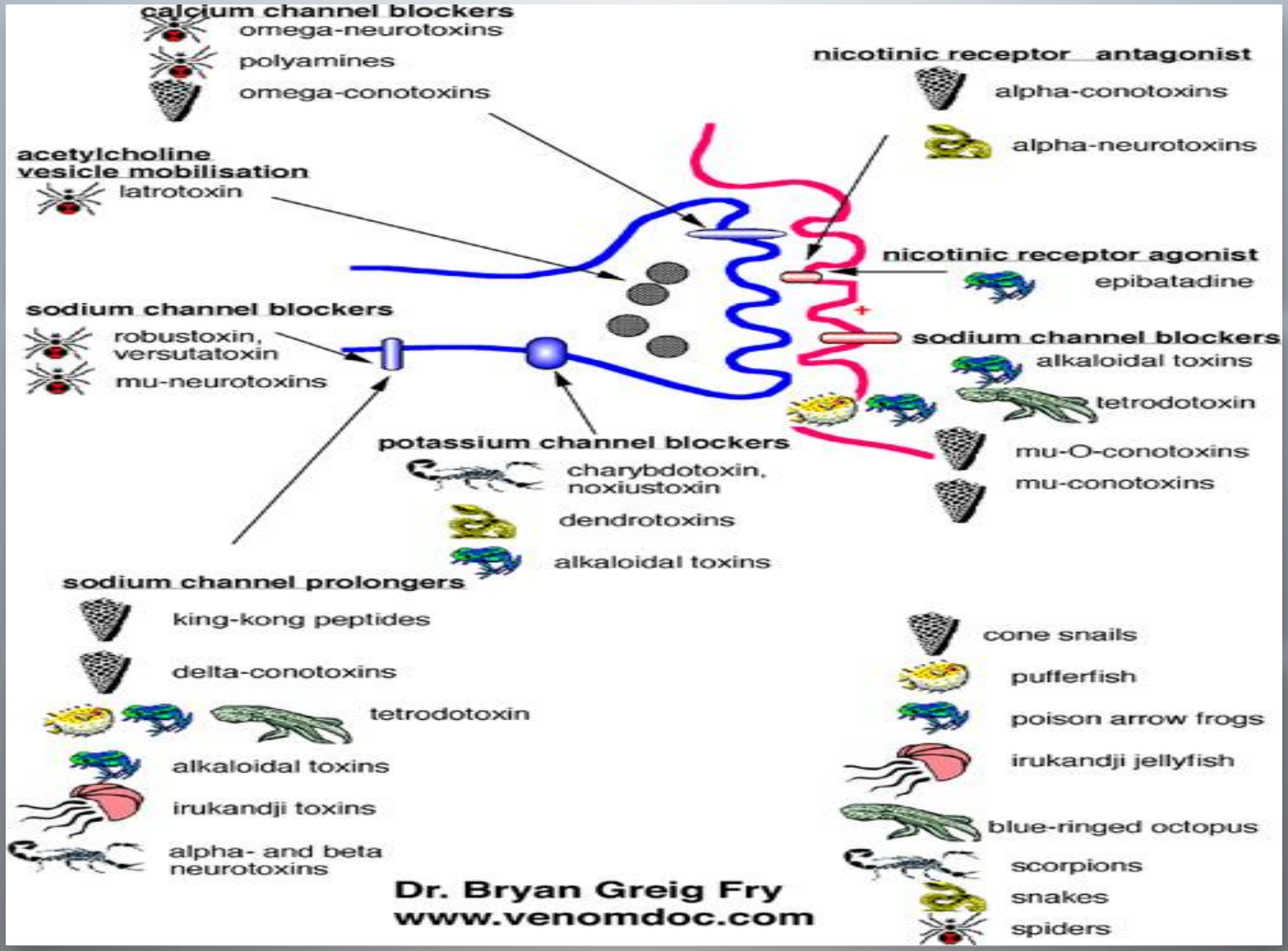
Aspek	Intoksikasi Kurare	Intoksikasi Botulinum
Lokasi gangguan	Post-sinaptik	Pre-sinaptik
Mekanisme utama	Blokade kompetitif reseptor ACh	Hambatan pelepasan ACh
Reseptor ACh	Normal tapi terblokir	Normal
Pelepasan ACh	Normal	Menurun drastis / tidak ada
Aktivitas otot	Lumpuh karena ACh tidak bisa berikatan	Lumpuh karena tidak ada ACh yang dilepas
Perubahan morfologi	Tidak signifikan	Penumpukan vesikel di ujung presinaptik


CURARE POISONING
BOTULINUM TOXIN POISONING
Presynaptic terminal
Acetylcholine receptor
Curare
Acetylcholine
Acetysnaptic membrane
Vesicles
Acetylcholine receptor

Acetylcholinesterase Inhibitors

Jenis – jenis Acetylcholinesterase Inhibitors

- **Physostigmine**
- **Organophosphates**
  - * **Organophosphorus insecticides**
  - * **Organophosphorus nerve gases**


calcium channel blockers
omega-neurotoxins
polyamines
omega-conotoxins
acetylcholine vesicle mobilisation
latrotoxin
nicotinic receptor antagonist
alpha-conotoxins
alpha-neurotoxins
nicotinic receptor agonist
epibatadine
sodium channel blockers
robustoxin, versutatoxin
mu-neurotoxins
sodium channel blockers
alkaloidal toxins
tetrodotoxin
mu-O-conotoxins
mu-conotoxins
potassium channel blockers
charybdotoxin, noxiustoxin
dendrotoxins
alkaloidal toxins
sodium channel prolongers
king-kong peptides
delta-conotoxins
tetrodotoxin
alkaloidal toxins
irukandji toxins
alpha- and beta neurotoxins
cone snails
pufferfish
poison arrow frogs
irukandji jellyfish
blue-ringed octopus
scorpions
snakes
spiders
Dr. Bryan Greig Fry
www.venomdoc.com

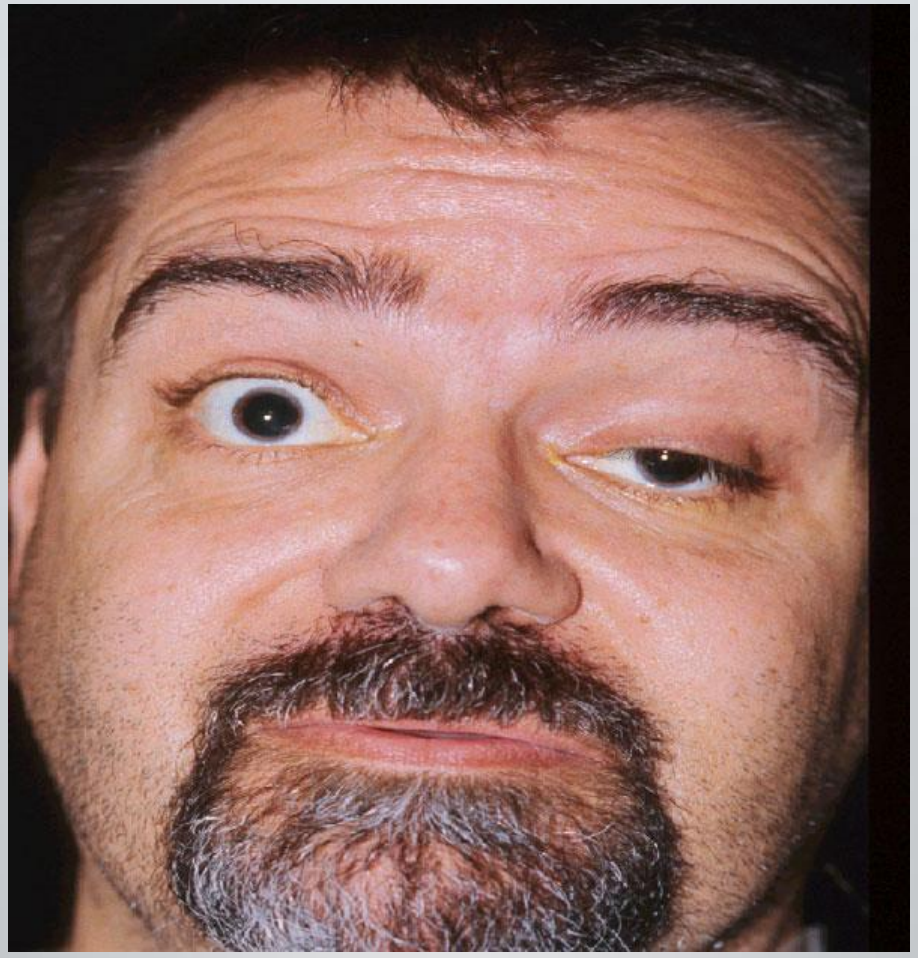
Kelainan pada otot

Myasthenia Gravis

- Autoimmune disorder
- Antibody yang merusak **reseptor asetilkolin pada post sinaps**
- Kelemahan pada otot yang progresif, kekuatan otot akan pulih sementara setelah **istirahat**
- Paling sering mengenai otot extraocular & bulbar

Myasthenia Gravis

- Gejala :
  - Kelemahan otot-otot wajah, termasuk ptosis
  - Penglihatan ganda (double vision)
  - Kesulitan bernapas, berbicara, mengunyah, & menelan
  - Kelemahan pada otot-otot ekstremitas
  - Kelemahan otot yang segera muncul setelah gerakan repetitif / berulang

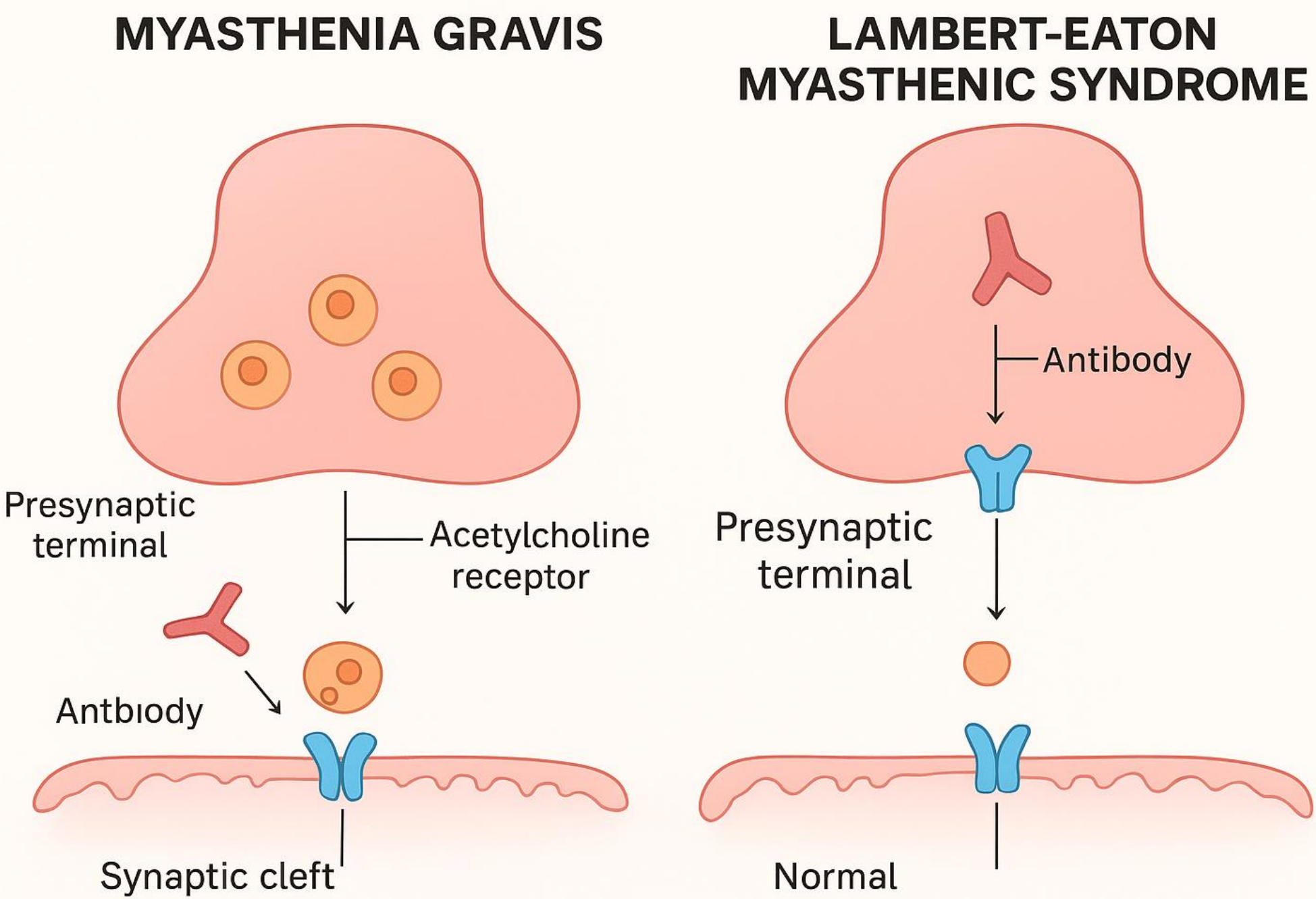


Myasthenia Gravis

Lambert Eaton Myasthenia Syndrome

- Antibody terhadap **voltage gate calcium di presinaps**
- Penurunan jumlah Ach ke celah sinaps
- Gejala mirip dengan Myasthenia gravis
- Amplitude compound muscle action potential (CMAP) rendah
- Kekuatan otot membaik setelah **gerakan repetitif**
- Dapat melibatkan gangguan fungsi otonom

Aspek	Myasthenia Gravis (MG)	Lambert-Eaton Myasthenic Syndrome (LEMS)
Lokasi gangguan	Post-sinaptik	Pre-sinaptik
Target antibodi	Reseptor asetilkolin (AChR)	Kanal kalsium voltase-gated (VGCC)
Jumlah ACh dilepaskan	Normal	Menurun
Reseptor ACh	Berkurang/rusak	Normal
Bentuk lipatan postsinaptik	Rata / menurun	Normal
Respons terhadap stimulasi berulang	Kelemahan bertambah	Kekuatan meningkat sementara


MYASTHENIA GRAVIS
Presynaptic terminal
Acetylcholine receptor
Antbıody
Synaptic cleft
LAMBERT-EATON MYASTHENIC SYNDROME
Antibody
Presynaptic terminal
Normal

Muscular Dystrophy

- Kelainan otot yang bersifat progresif yang bukan disebabkan karena proses inflamasi, kelainan saraf pusat atau perifer
- Terjadi degenerasi serabut otot
- Bersifat herediter : sex linked, autosomal resesif, & autosomal dominan

Muscular Dystrophy

- Klasifikasi :
  - Terkait sex :
    - Duchenne
    - Becker
    - Emery Dreyfuss

Muscular Dystrophy

- Autosomal dominant :
  - Facioscapulohumeral
  - Distal
  - Ocular
  - Oculopharyngeal
- Autosomal recessive : Limb Girdle Form

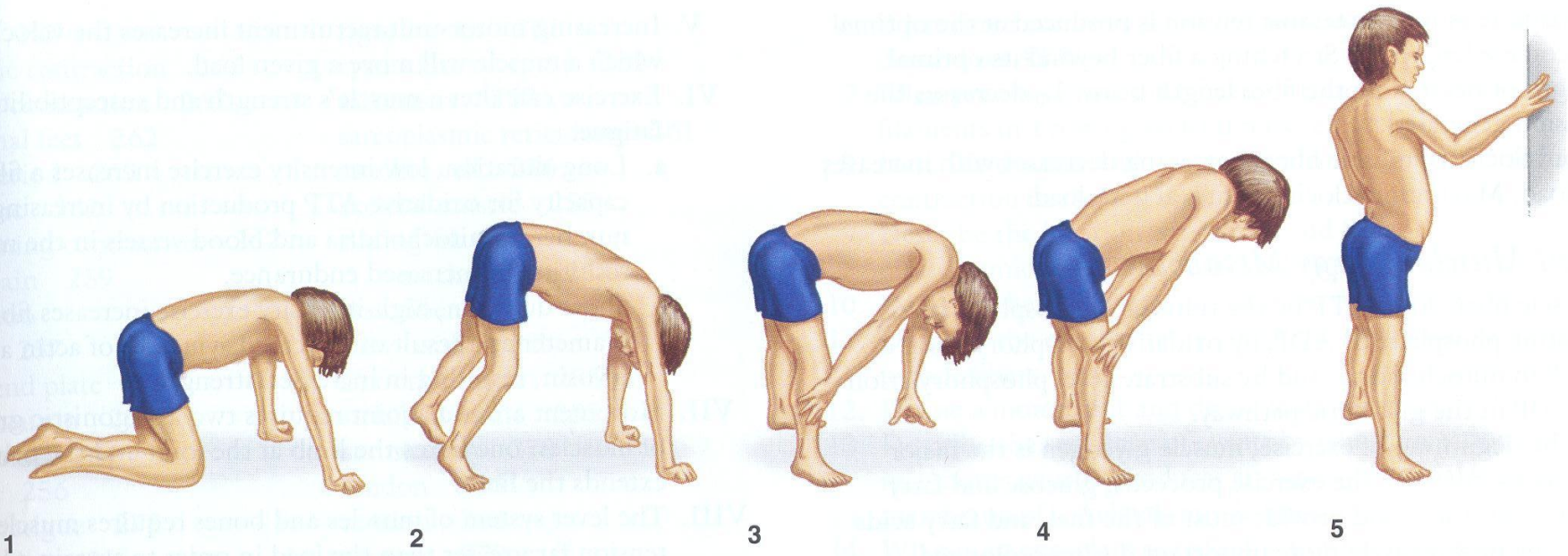
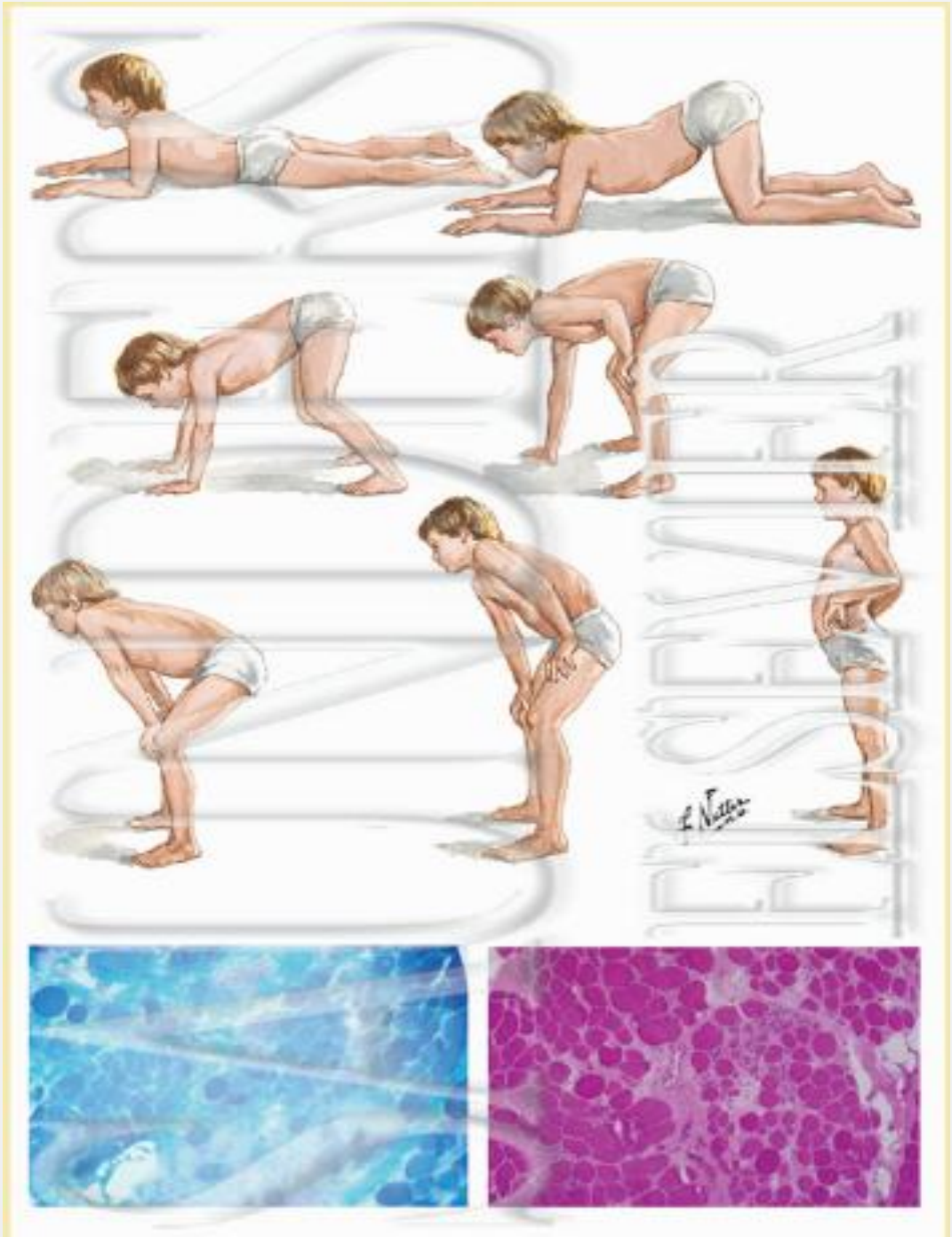
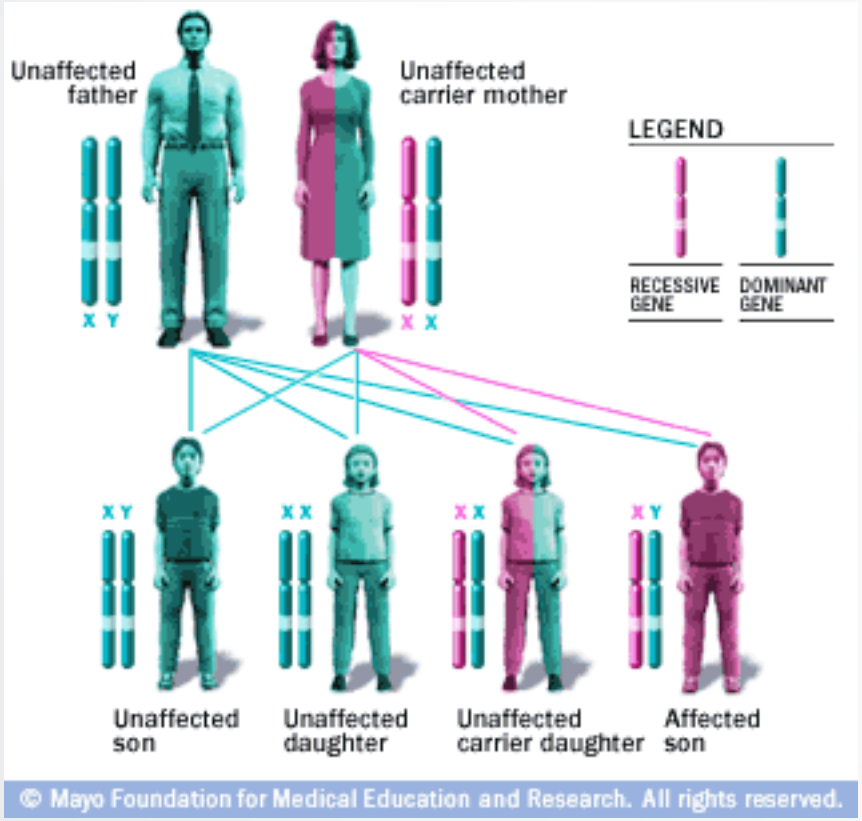
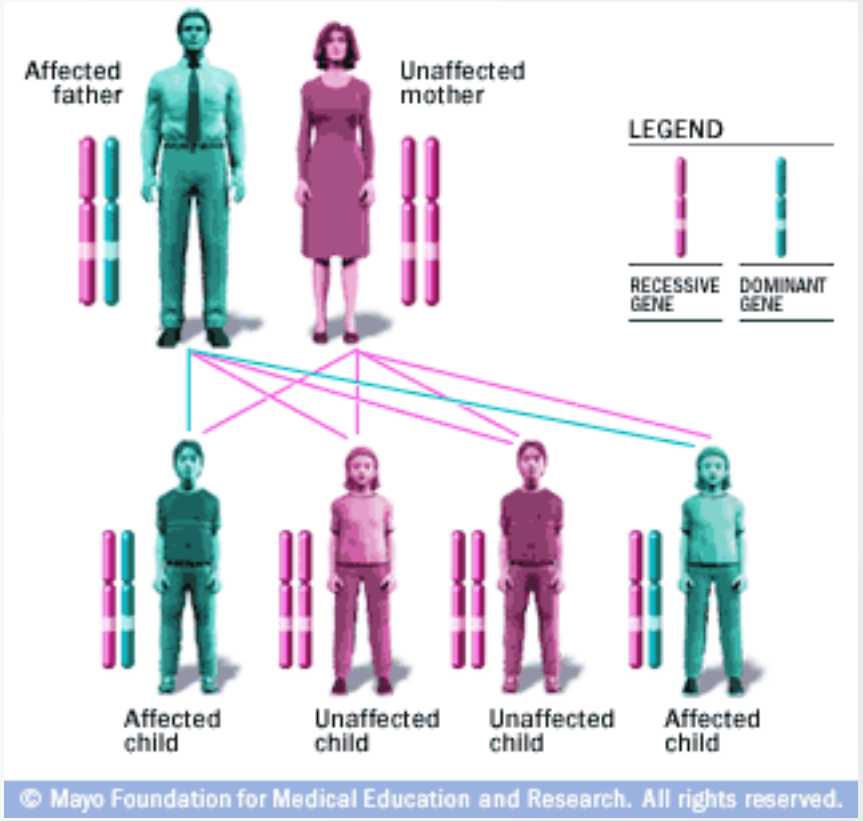


Figure 9–31

Boy with Duchenne muscular dystrophy. Muscles of the hip girdle and trunk are the first to weaken, requiring patients to use their arms to "climb up" the legs in order to go from lying to standing.







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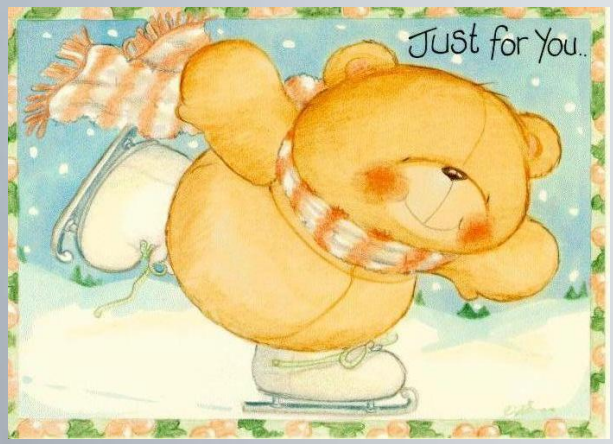

Terima Kasih