

Neurohistology II:

Synapses, Meninges, & Receptors

Overall Objectives: To understand the concept of the synapse; to understand the concept of axonal transport; to learn to identify the three layers of the meninges; and to understand how receptors are classified.

I. The Synapse:

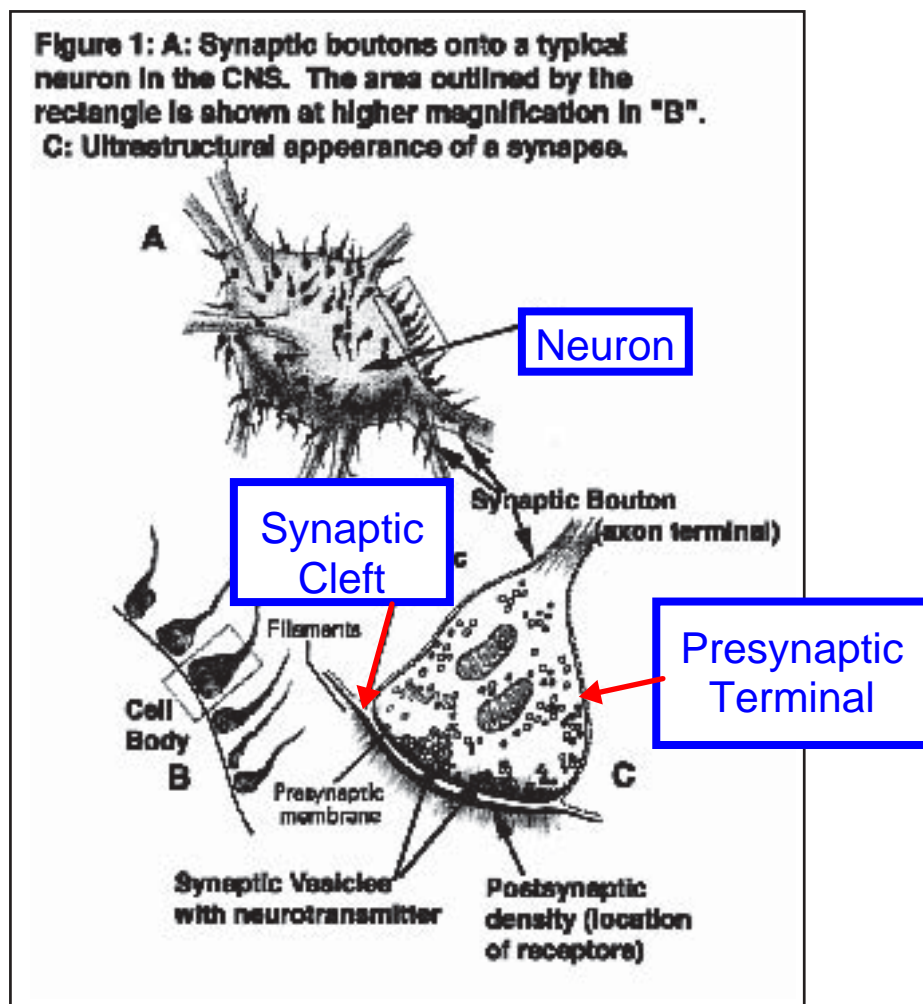
The synapse is a specialized point of functional contact between neurons or between a neuron and a target organ (i.e., muscle) that allows neurons to communicate with one another or with their target cells.

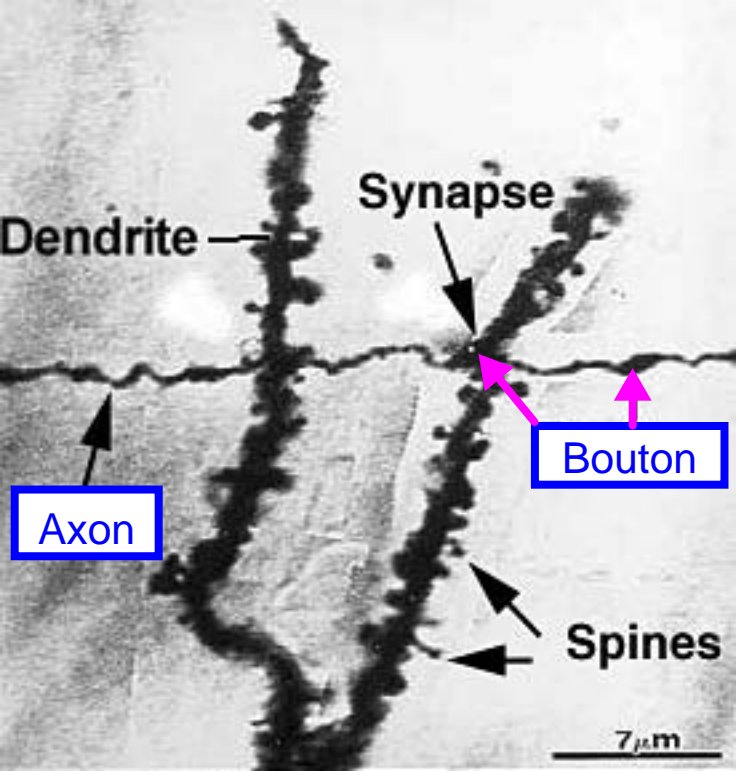
Synaptic Anatomy . . .

The synapse is a site of apposition between a presynaptic element of one neuron and a postsynaptic membrane of a target neuron (or an effector organ); where, typically, a presynaptic axon enlargement releases transmitter molecules that diffuse across a synaptic cleft and bind to receptor channels in the postsynaptic membrane.

Synapses are comprised of three elements:

- Presynaptic nerve terminal — contains synaptic vesicles which house a chemical neurotransmitter that is released after vesicle fusion with the presynaptic terminal plasma membrane.
- Postsynaptic element — a dendrite, a cell body, or a target cell receiving the synaptic input. Receptor protein molecules, to which neurotransmitter molecules bind, are embedded in the postsynaptic plasma membrane.
- Synaptic Cleft — a gap between pre- and post-synaptic elements into which neurotransmitter molecules are released.





Dendrite

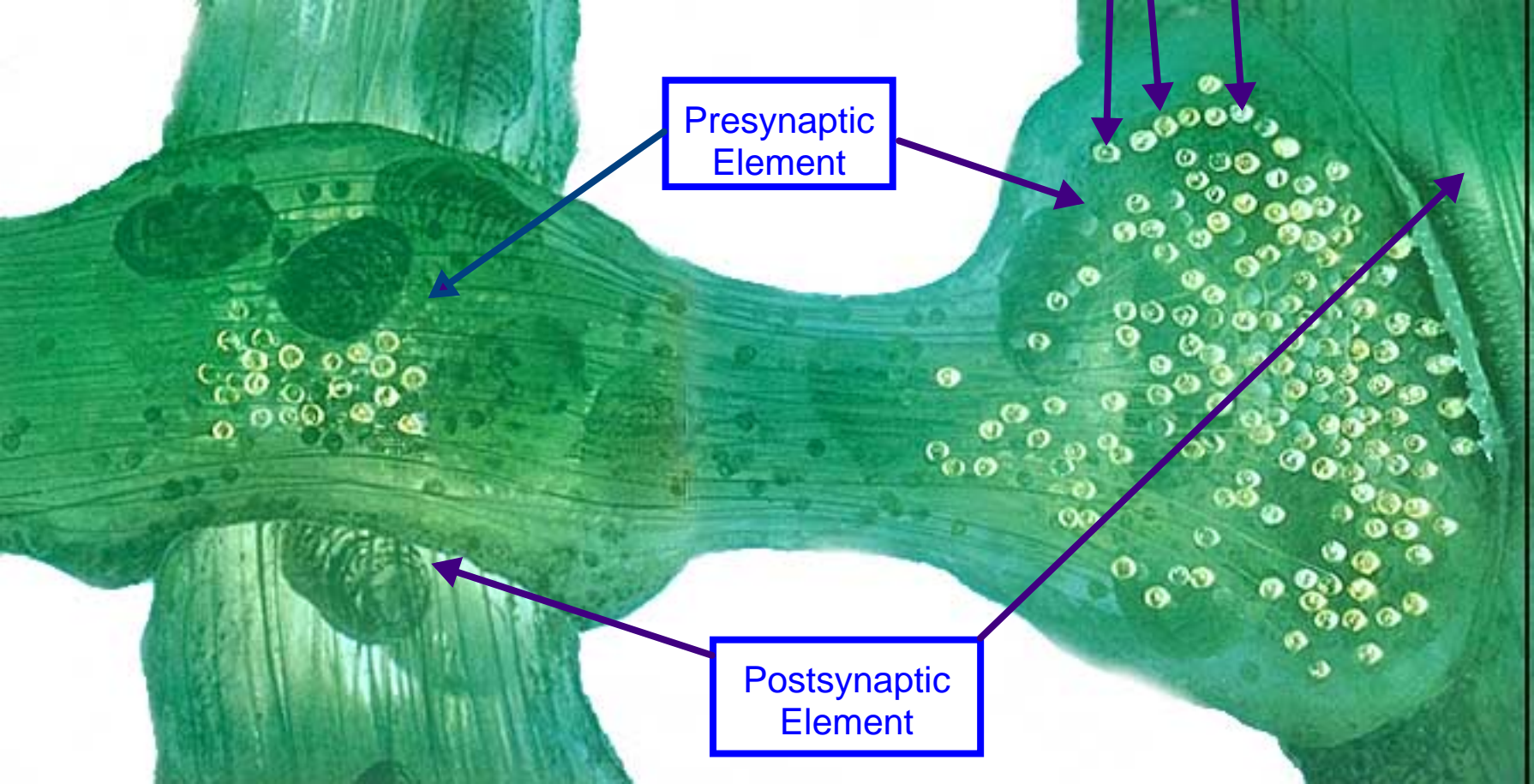
Synapse

Axon

Bouton

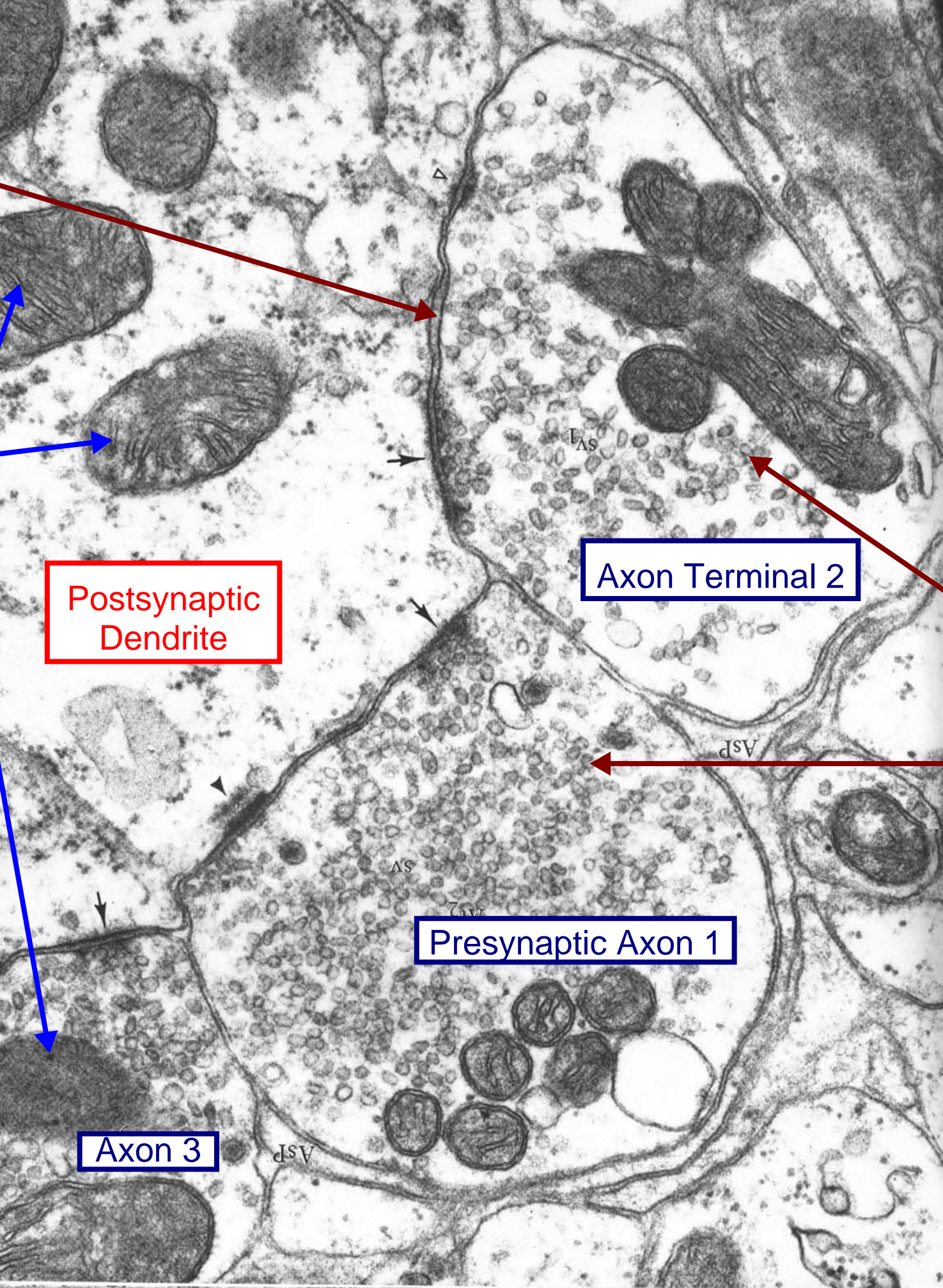
Spines

$7\mu\text{m}$



Presynaptic
Element

Postsynaptic
Element



Postsynaptic Dendrite

Axon Terminal 2

Presynaptic Axon 1

Axon 3

Common presynaptic arrangements:

- 1) axon terminal branches have terminal enlargements (called boutons or bulbs)
- 2) axon terminal branches feature varicosities (for synapses “in passing”)
- 3) neuromuscular synapse: axon branches have terminal ramifications that form motor end plates on skeletal muscle fibers.



Classification of synaptic types:

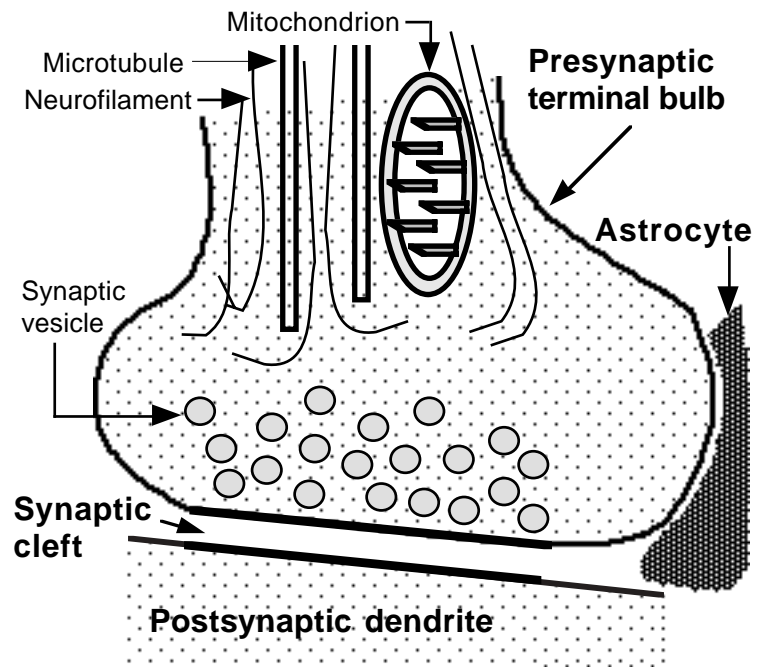
- 1] axodendritic — axon terminal branch (presynaptic element) synapses on a dendrite;
- 2] axosomatic — axon terminal branch synapses on a soma (cell body);
- 3] axoaxonic — axon terminal branch synapses on another axon terminal branch (for presynaptic inhibition) or beside the initial segment of an axon;
- 4] dendrodendritic — dendrite synapsing on another dendrite (very localized effect).

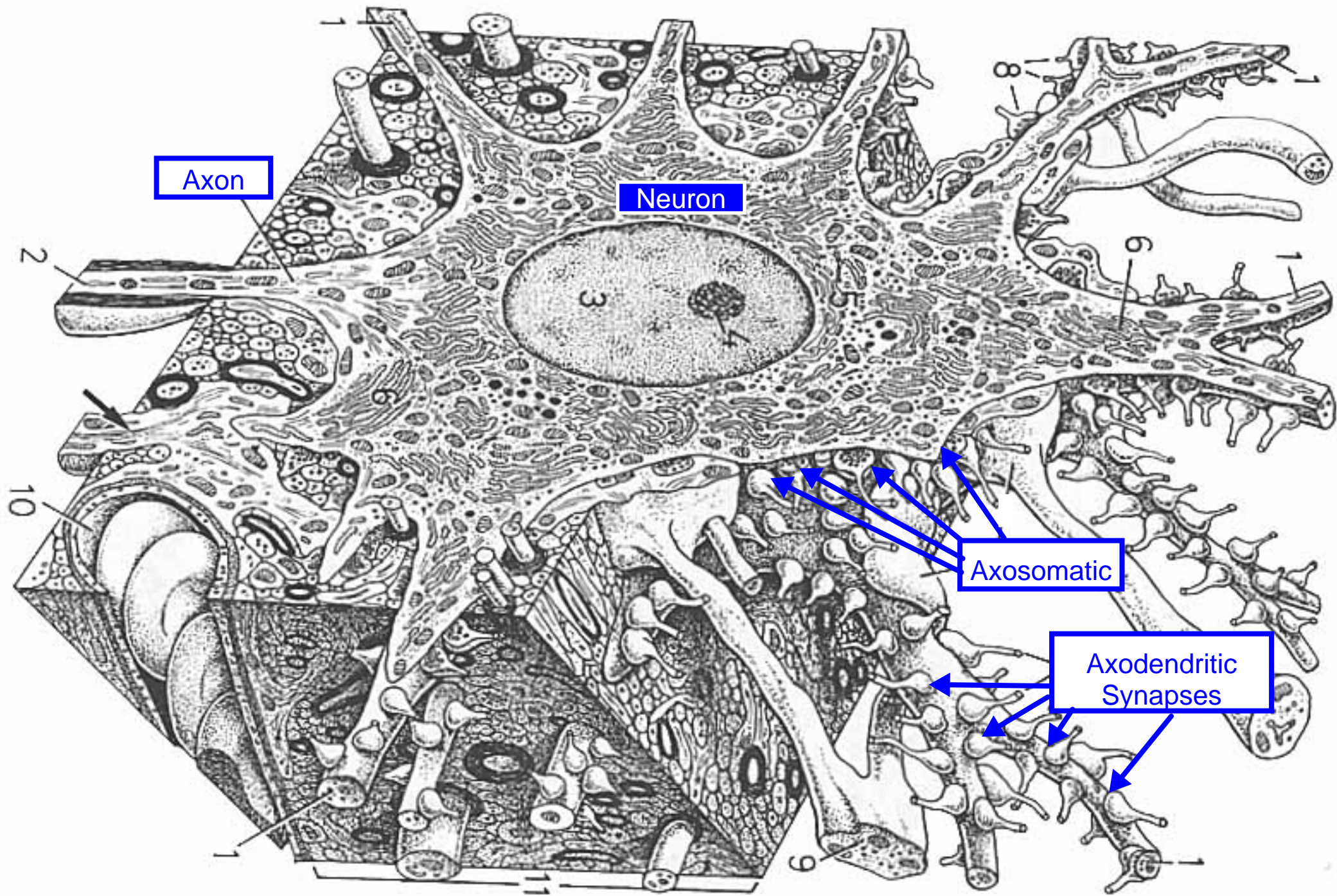
Synaptic ultrastructure:

- The presynaptic enlargement (bouton, varicosity, or end plate) contains synaptic vesicles (20 nm diameter), clustered around an electron dense active zone (protein-rich plasma membrane). Vesicles are anchored in place by actin microfilaments.

- Pre- and postsynaptic plasma membranes are separated by a synaptic cleft (20 nm wide). The cleft contains glycoprotein linking material and is surrounded by glial cell processes.

- The postsynaptic plasma membrane may appear unremarkable or thickened (electron dense). Receptor proteins (typically ligand-gated channels) are embedded in the plasma membrane.





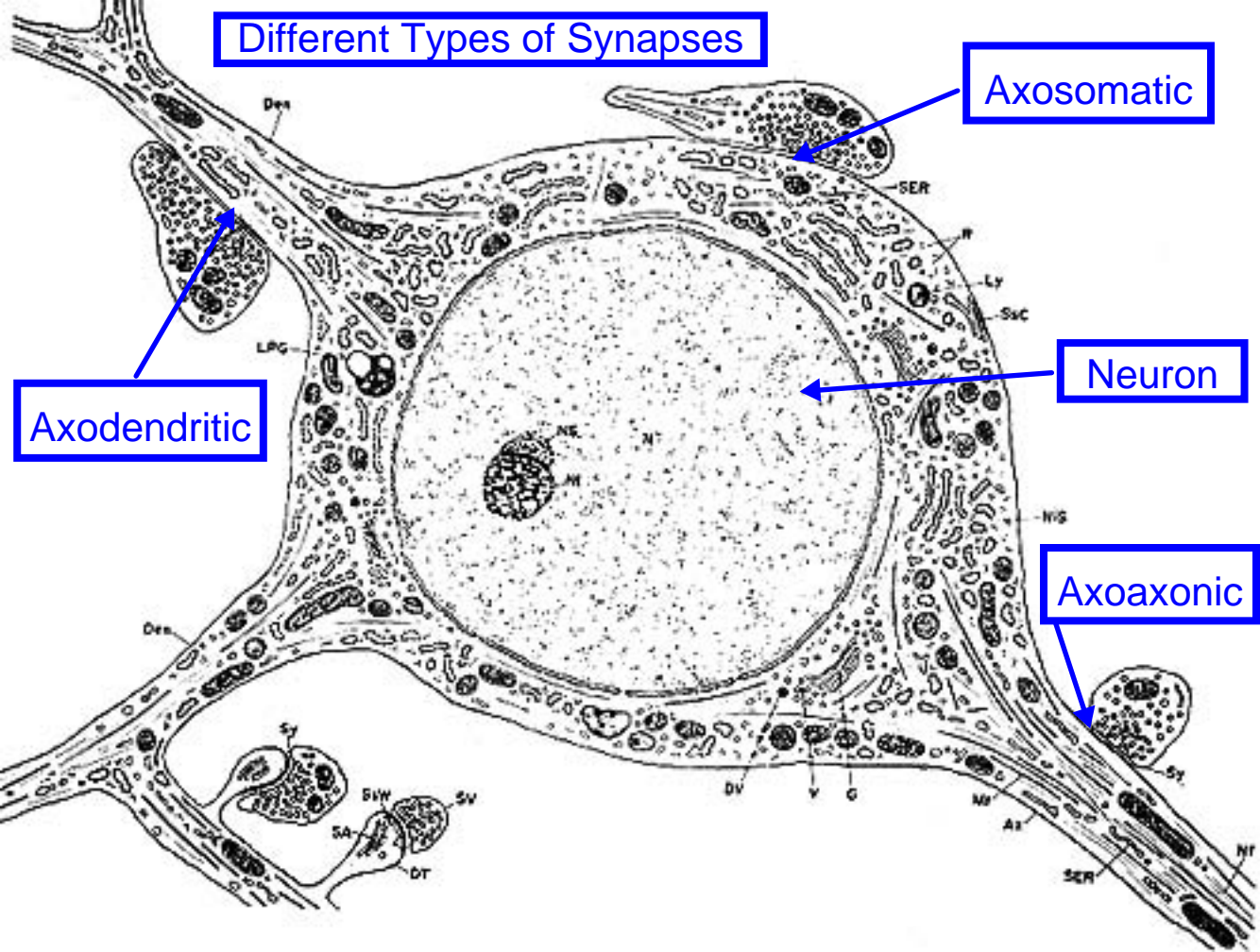
Different Types of Synapses

Axosomatic

Neuron

Axoaxonic

Axodendritic



Common presynaptic arrangements:

- 1) axon terminal branches have terminal enlargements (called boutons or bulbs)
- 2) axon terminal branches feature varicosities (for synapses “in passing”)
- 3) neuromuscular synapse: axon branches have terminal ramifications that form motor end plates on skeletal muscle fibers.



Classification of synaptic types:

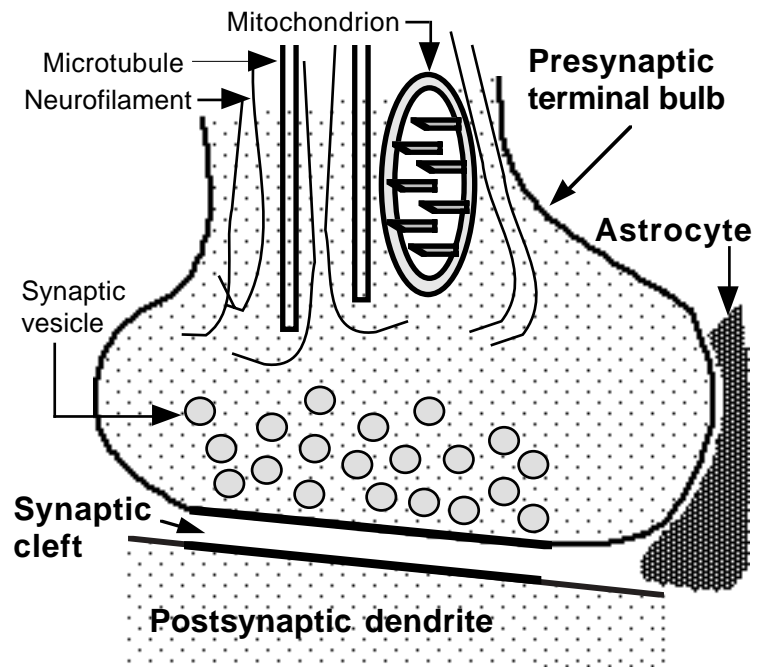
- 1] axodendritic — axon terminal branch (presynaptic element) synapses on a dendrite;
- 2] axosomatic — axon terminal branch synapses on a soma (cell body);
- 3] axoaxonic — axon terminal branch synapses on another axon terminal branch (for presynaptic inhibition) or beside the initial segment of an axon;
- 4] dendrodendritic — dendrite synapsing on another dendrite (very localized effect).

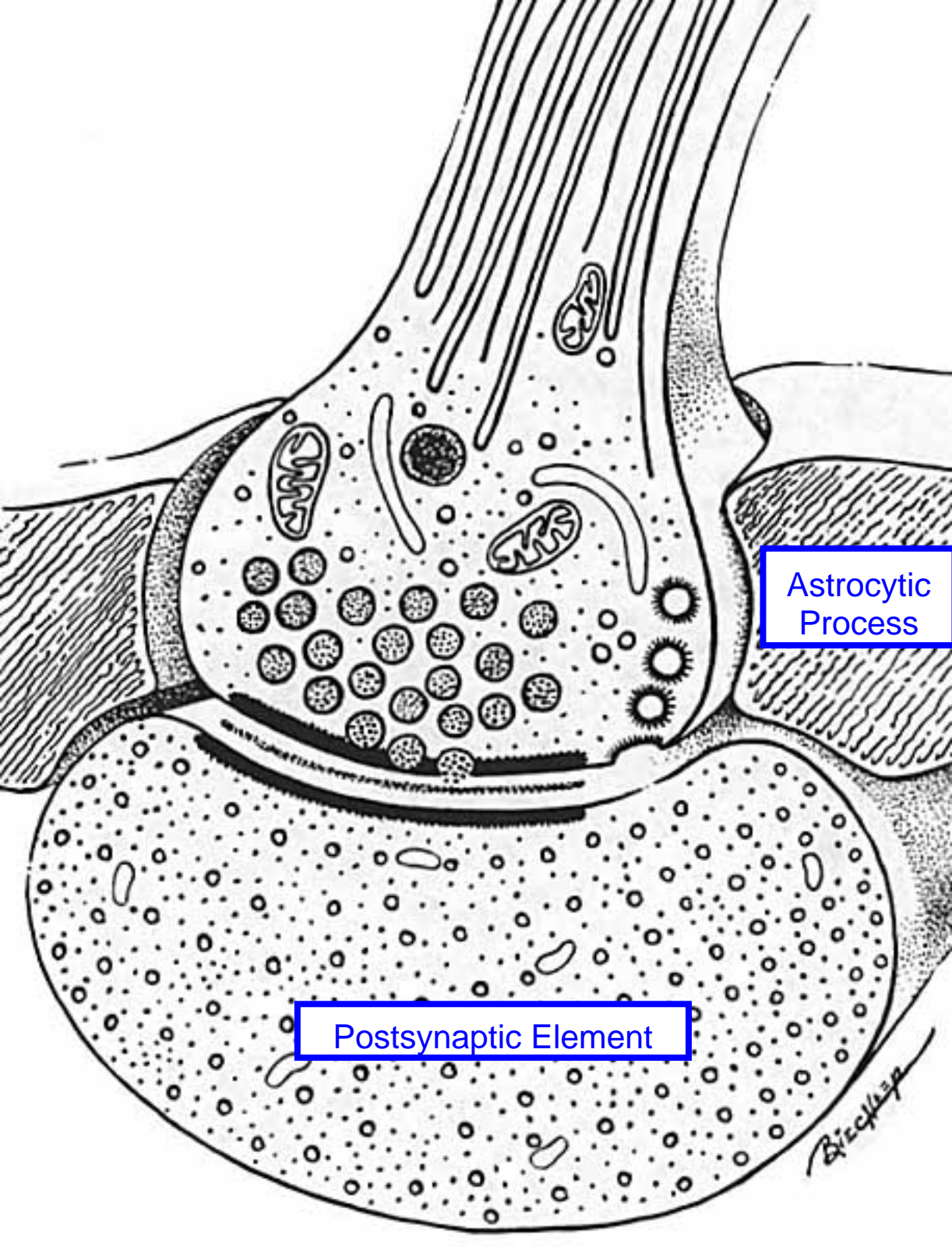
Synaptic Ultrastructure:

- The presynaptic enlargement (bouton, varicosity, or end plate) contains synaptic vesicles (20 nm diameter), clustered around an electron dense active zone (protein-rich plasma membrane). Vesicles are anchored in place by actin microfilaments.

- Pre- and postsynaptic plasma membranes are separated by a synaptic cleft (20 nm wide). The cleft contains glycoprotein linking material and is surrounded by glial cell processes.

- The postsynaptic plasma membrane may appear unremarkable or thickened (electron dense). Receptor proteins (typically ligand-gated channels) are embedded in the plasma membrane.

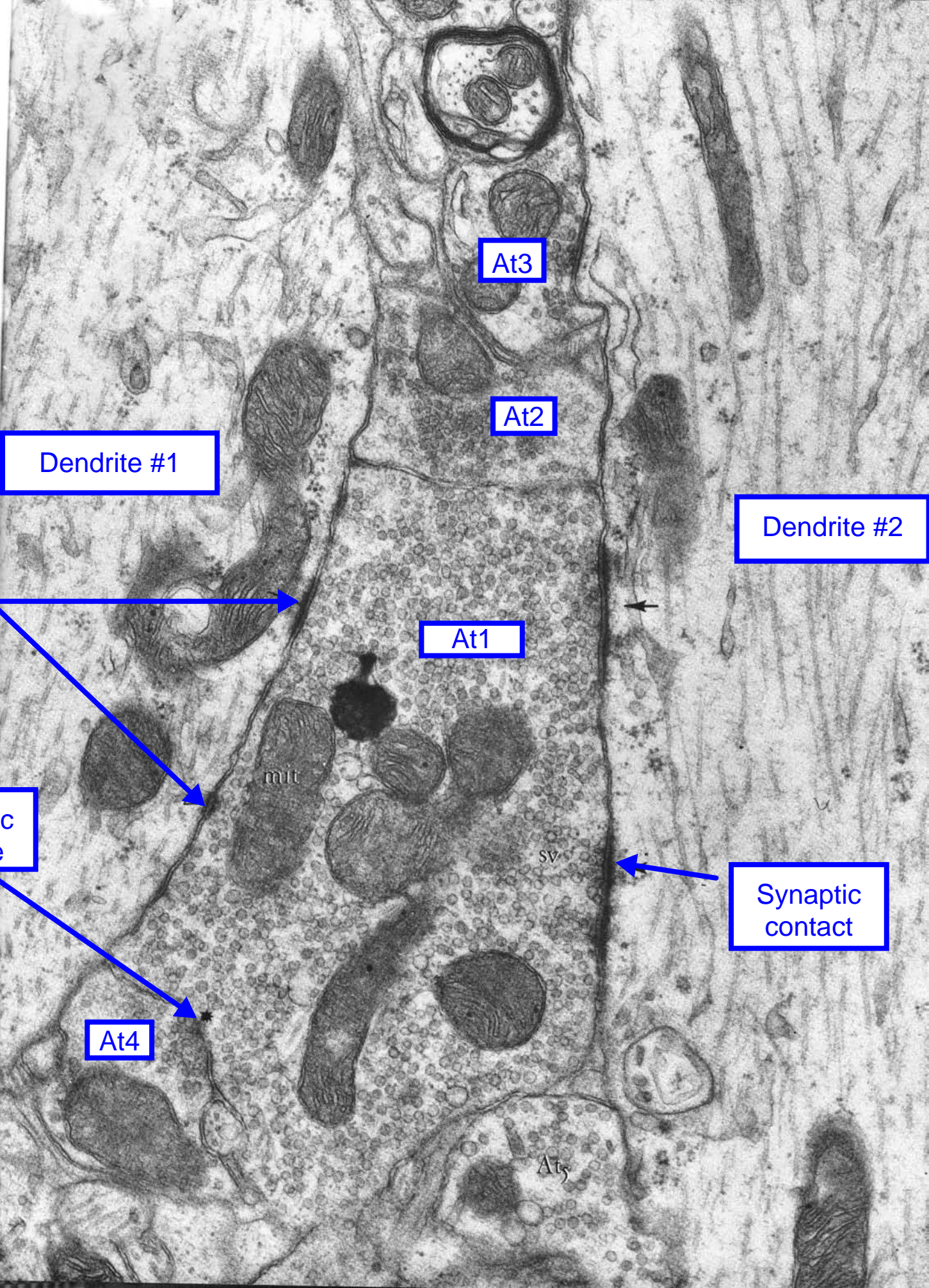




Astrocytic Process

Postsynaptic Element

Bjorklyp



At3

At2

Dendrite #1

Dendrite #2

At1

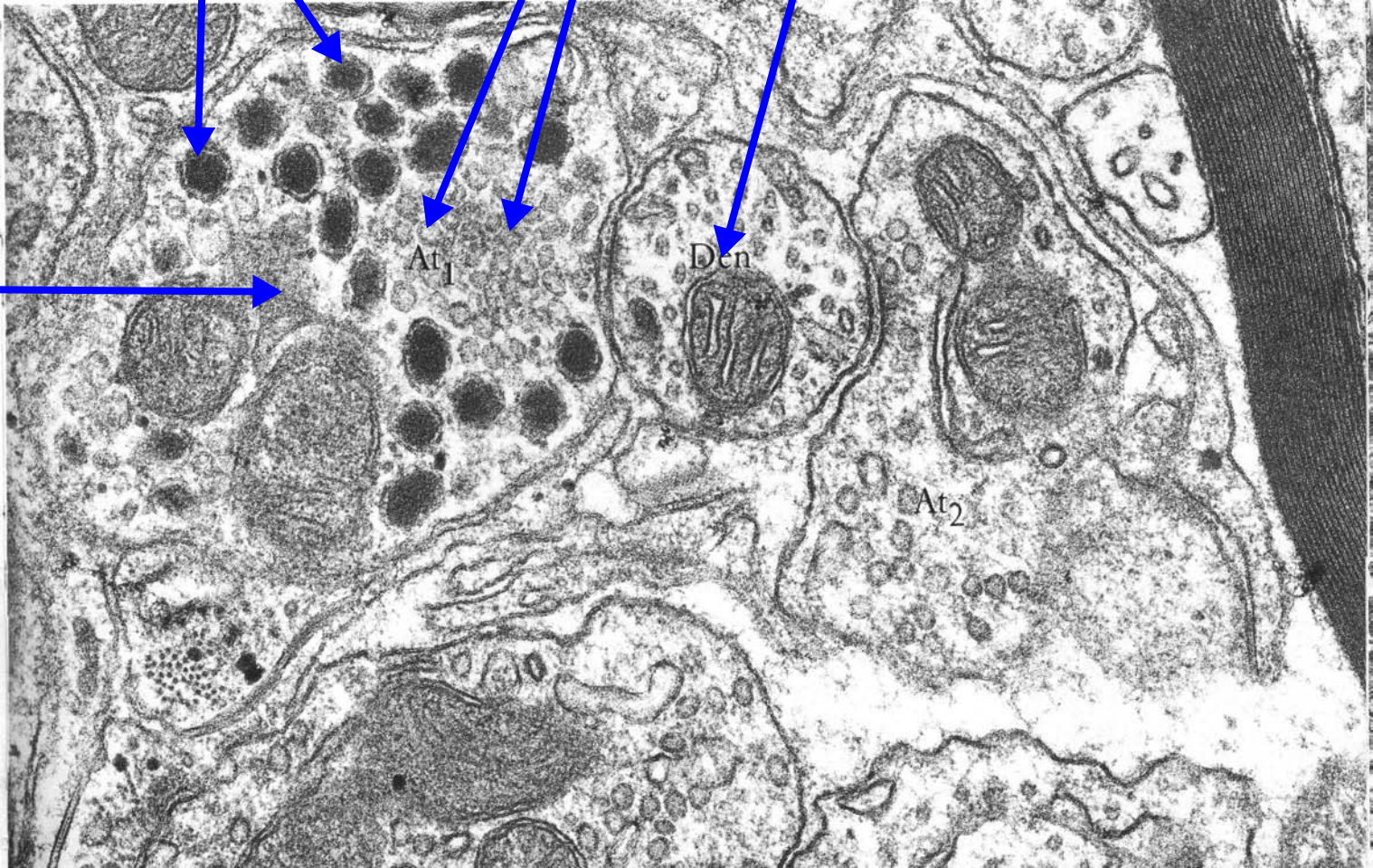
mit

sv

Synaptic contact

At4

At5



Presynaptic events:

Neurotransmitter molecules are released in proportion to the amount of Ca^{++} influx, in turn proportional to the amount of presynaptic membrane depolarization, i.e.,

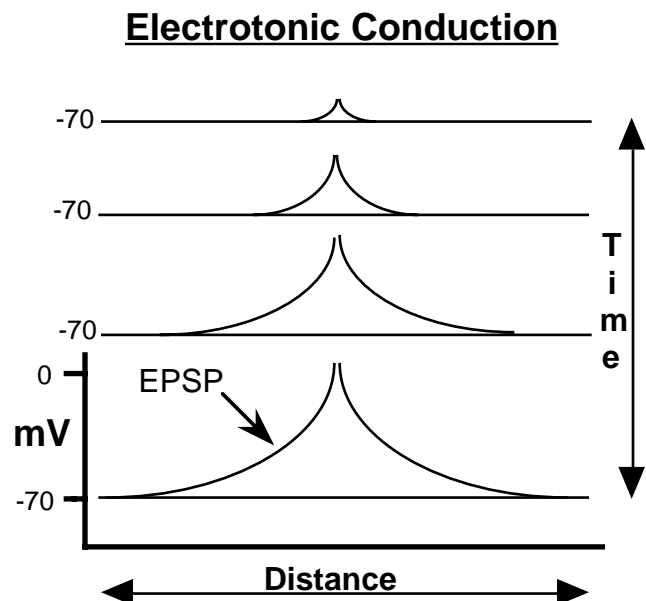
- in the resting state, the presynaptic membrane is polarized
- when an action potential arrives at the end of the axon, the adjacent presynaptic membrane is passively depolarized (toward zero transmembrane potential)
- voltage-gated Ca^{++} channels allow Ca^{++} influx (driven by $[\text{Ca}^{++}]$ gradient).
- elevated $[\text{Ca}^{++}]$ triggers vesicle mobilization and docking with the plasma membrane
- a number of vesicles fuse with presynaptic plasma membrane and release neurotransmitter molecules (about 5,000 per vesicle) by exocytosis.
- transmitter molecules diffuse across the cleft & bind with postsynaptic receptor proteins
- neurotransmitter molecules are eliminated from synaptic clefts via pinocytotic uptake by presynaptic or glial processes and/or via enzymatic degradation at the postsynaptic membrane. The molecules are recycled.
- subsequently, presynaptic plasma membrane repolarizes (due to K^+ channel conductance).

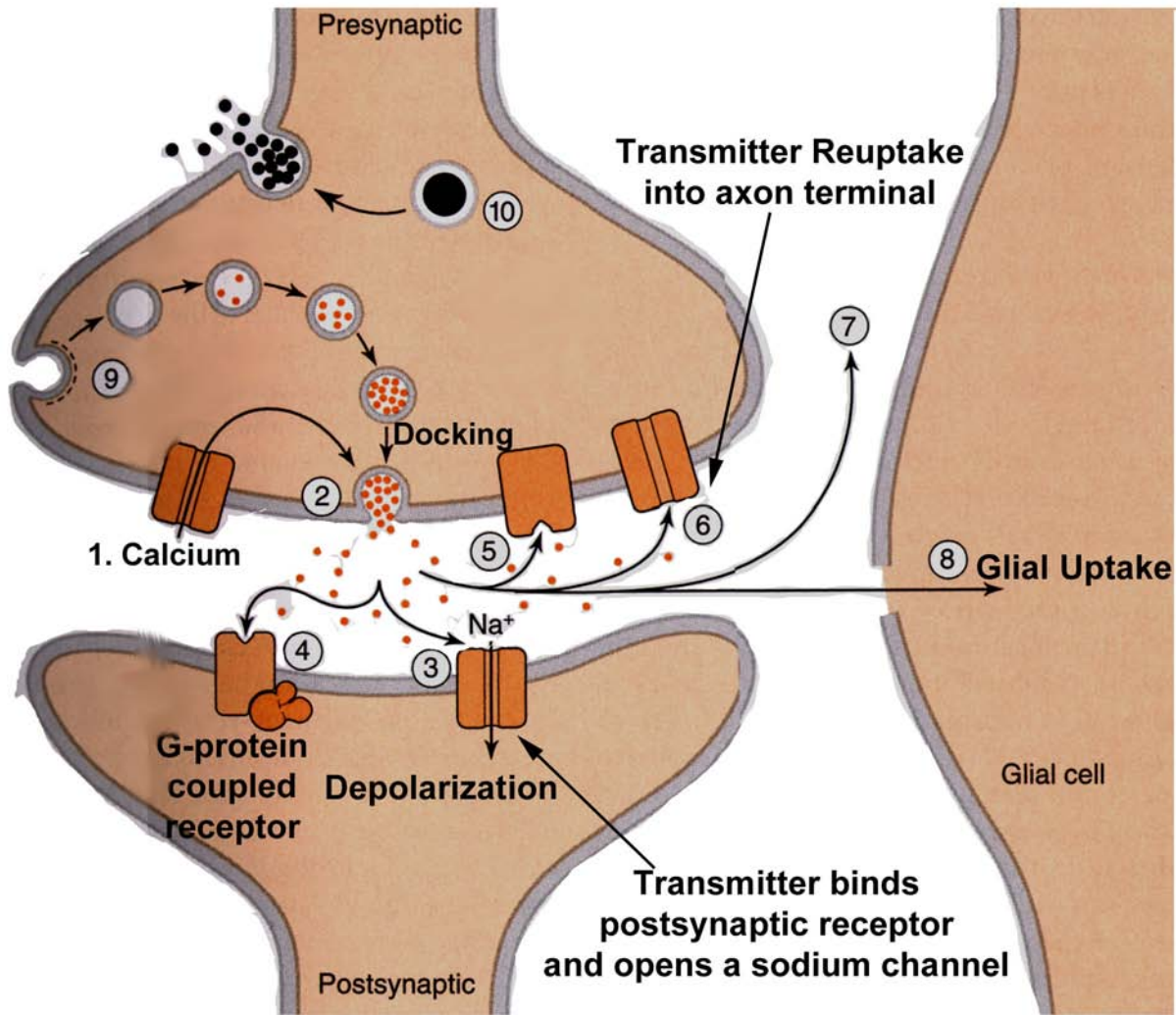
Postsynaptic events:

Neurotransmitter binding results in a proportional ion flux across the postsynaptic membrane. The particular excitability effect depends on the nature of the ion flux which depends on the nature of the ion channels in the particular postsynaptic membrane, i.e.,

- in the resting state, postsynaptic plasma membrane is polarized (voltage activated K^+ channels dominate conductance)
- arriving neurotransmitter molecules bind briefly/repeatedly to ligand-gated receptors, which opens ion channels directly or by means of second messengers
 - activation of $[\text{Na}^+ \& \text{K}^+]$ channels \rightarrow leads to depolarization toward zero potential;
 - activation of Cl^- or K^+ channels \rightarrow hyperpolarization of postsynaptic membrane.
- a postsynaptic potential (PSP) results from the altered membrane conductance
 - EPSP** = Excitatory PSP = depolarization toward zero potential, excites the postsynaptic cell
 - IPSP** = Inhibitory PSP = hyperpolarization (serves to cancel EPSPs), inhibits the postsynaptic cell
- following the removal/degradation of neurotransmitter molecules, the postsynaptic membrane is re-polarized (K^+ channel conductance again dominates.)

Note: **PSPs** constitute *electrotonic conduction*, a passive voltage spread (in contrast to the regenerative conduction of which axons are capable). **PSPs** decay exponentially, over distance and with time. The magnitude of a **PSP** depends on the number of open ion channels which, in turn, depends on the amount of neurotransmitter released.





Synaptic Physiology . . .

Presynaptic events:

Neurotransmitter molecules are released in proportion to the amount of Ca^{++} influx, in turn proportional to the amount of presynaptic membrane depolarization, i.e.,

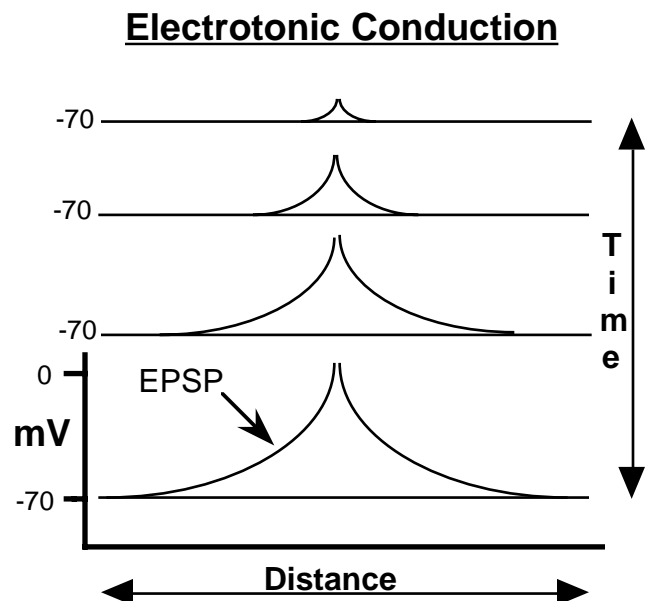
- in the resting state, the presynaptic membrane is polarized
- when an action potential arrives at the end of the axon, the adjacent presynaptic membrane is passively depolarized (toward zero transmembrane potential)
- voltage-gated Ca^{++} channels allow Ca^{++} influx (driven by $[\text{Ca}^{++}]$ gradient).
- elevated $[\text{Ca}^{++}]$ triggers vesicle mobilization and docking with the plasma membrane
- a number of vesicles fuse with presynaptic plasma membrane and release neurotransmitter molecules (about 5,000 per vesicle) by exocytosis.
- transmitter molecules diffuse across the cleft & bind with postsynaptic receptor proteins
- neurotransmitter molecules are eliminated from synaptic clefts via pinocytotic uptake by presynaptic or glial processes and/or via enzymatic degradation at the postsynaptic membrane. The molecules are recycled.
- subsequently, presynaptic plasma membrane repolarizes (due to K^+ channel conductance).

Postsynaptic Events

Neurotransmitter binding results in a proportional ion flux across the postsynaptic membrane. The particular excitability effect depends on the nature of the ion flux which depends on the nature of the ion channels in the particular postsynaptic membrane, i.e.,

- in the resting state, postsynaptic plasma membrane is polarized (voltage activated K^+ channels dominate conductance)
- arriving neurotransmitter molecules bind briefly/repeatedly to ligand-gated receptors, which opens ion channels directly or by means of second messengers
 - activation of $[\text{Na}^+ \& \text{K}^+]$ channels \rightarrow leads to depolarization toward zero potential;
 - activation of Cl^- or K^+ channels \rightarrow hyperpolarization of postsynaptic membrane.
- a postsynaptic potential (PSP) results from the altered membrane conductance
 - EPSP** = Excitatory PSP = depolarization toward zero potential, excites the postsynaptic cell
 - IPSP** = Inhibitory PSP = hyperpolarization (serves to cancel EPSPs), inhibits the postsynaptic cell
- following the removal/degradation of neurotransmitter molecules, the postsynaptic membrane is re-polarized (K^+ channel conductance again dominates.)

Note: **PSPs** constitute *electrotonic conduction*, a passive voltage spread (in contrast to the regenerative conduction of which axons are capable). **PSPs** decay exponentially, over distance and with time. The magnitude of a **PSP** depends on the number of open ion channels which, in turn, depends on the amount of neurotransmitter released.



Additional Comments

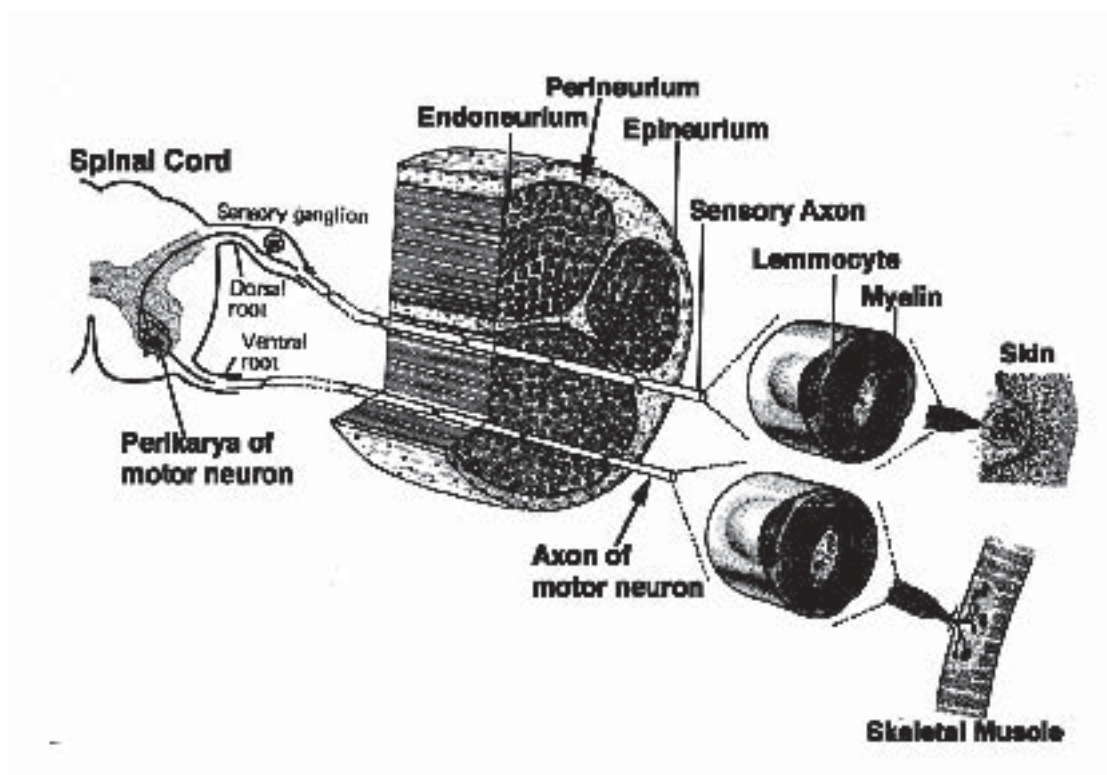
- synaptic transmission is unidirectional (vesicles are located on only one side).
- glutamate is the major excitatory neurotransmitter in the nervous system; GABA and glycine are the major inhibitory neurotransmitters.
- synaptic transmission is slower than axonal conduction; each synapse introduces delay into a neural pathway (at least 0.5 msec/synapse).
- synapses are more susceptible to fatigue, hypoxia, and drug effects than are axons (generally pathways fail first at synapses).
- different kinds of drugs (tranquilizers, anesthetics, narcotics, anticonvulsants, muscle relaxants, etc.) work by modifying activity selectively among the different kinds of chemical synapses.
- certain diseases are manifestations of selective synaptic dysfunction; e.g., Parkinson's disease, tetanus, myasthenia gravis, various intoxications, etc.

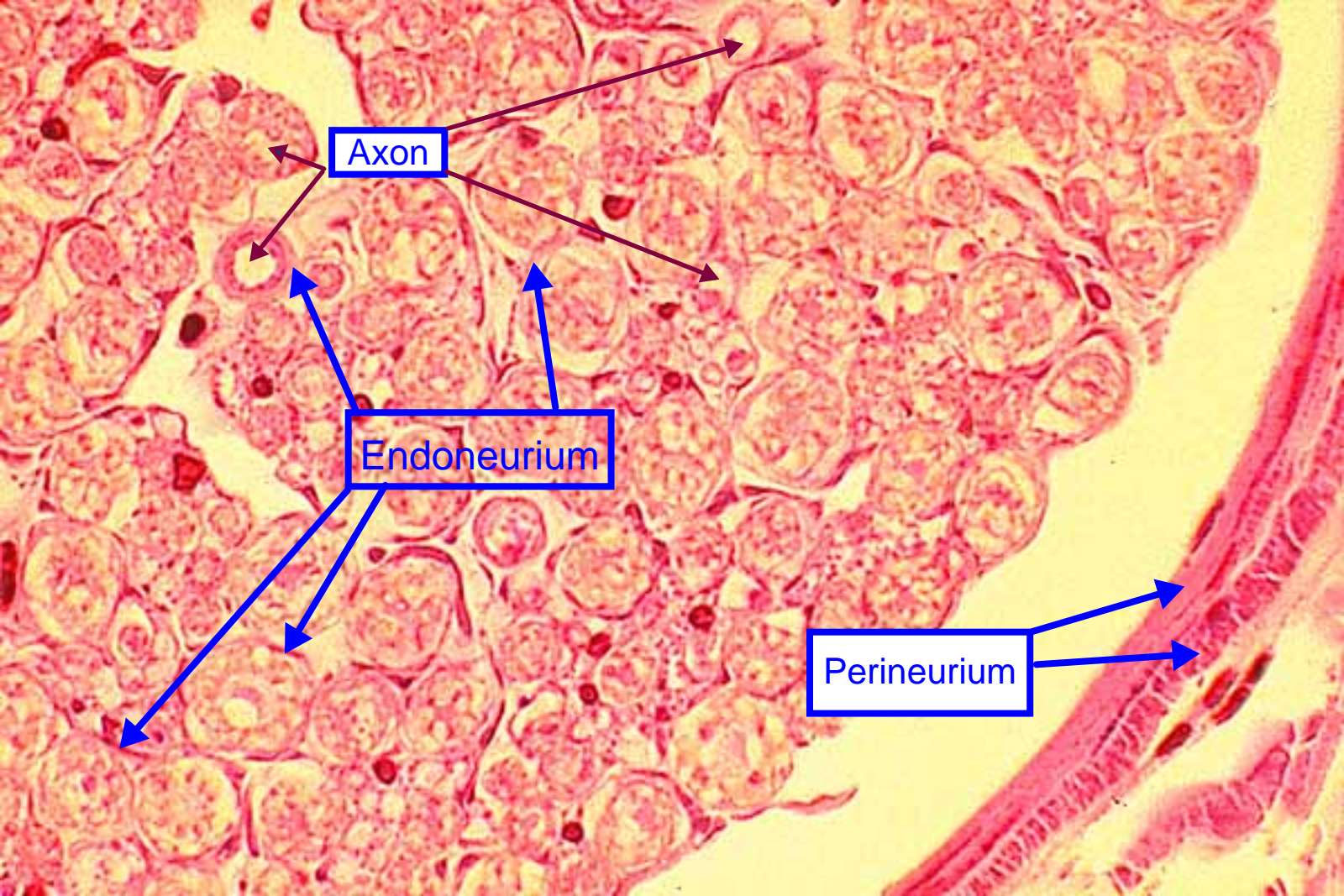
II. Connective Tissue Coverings of Axons in the PNS:

1. **Endoneurium**-- surrounds each myelinated axon, or a group of nonmyelinated axons.

2. **Perineurium**— surrounds each nerve fascicle (a bundle of axons); consists of a **perineural epithelium** and associated collagenous connective tissue. The perineurium participates in forming a blood-nerve barrier which limits the passage of water-soluble substances and proteins from blood into the endoneurial compartment. (The integrity of this barrier is altered in certain neuropathies and following nerve trauma.)

3. **Epineurium**— surrounds the entire nerve





Axon

Endoneurium

Perineurium

III. Axonal Transport:

1. The net movement of substances along the axon; 2 rates:

A. Fast Axonal Transport—100-500 mm/day

B. Slow Axonal Transport—1-10 mm/day

2. *Anterograde Transport*—transport of materials down the axon away from the cell body; important for renewing proteins along the axon and thus maintaining the axon.

3. *Retrograde Transport*—transport from the axon terminal toward the cell body; *important mechanism by which virus particles (rabies) and neurotoxins (tetanus toxin) gain access to the CNS.* [Note: Tetanus and Botulinum toxins are proteases which cleave neuronal SNARE-proteins.]

IV. Meninges: protective connective tissue sheaths surrounding the brain and spinal cord.

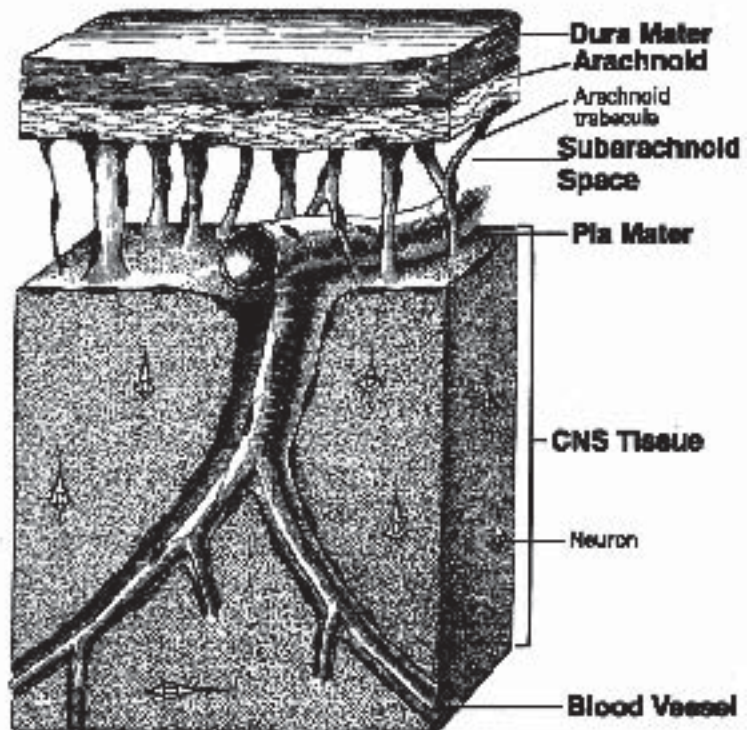
There are three layers of meninges:

1. **Dura Mater**— the outermost layer consisting of coarse, irregular connective tissue; composed of collagen and elastic fibers.

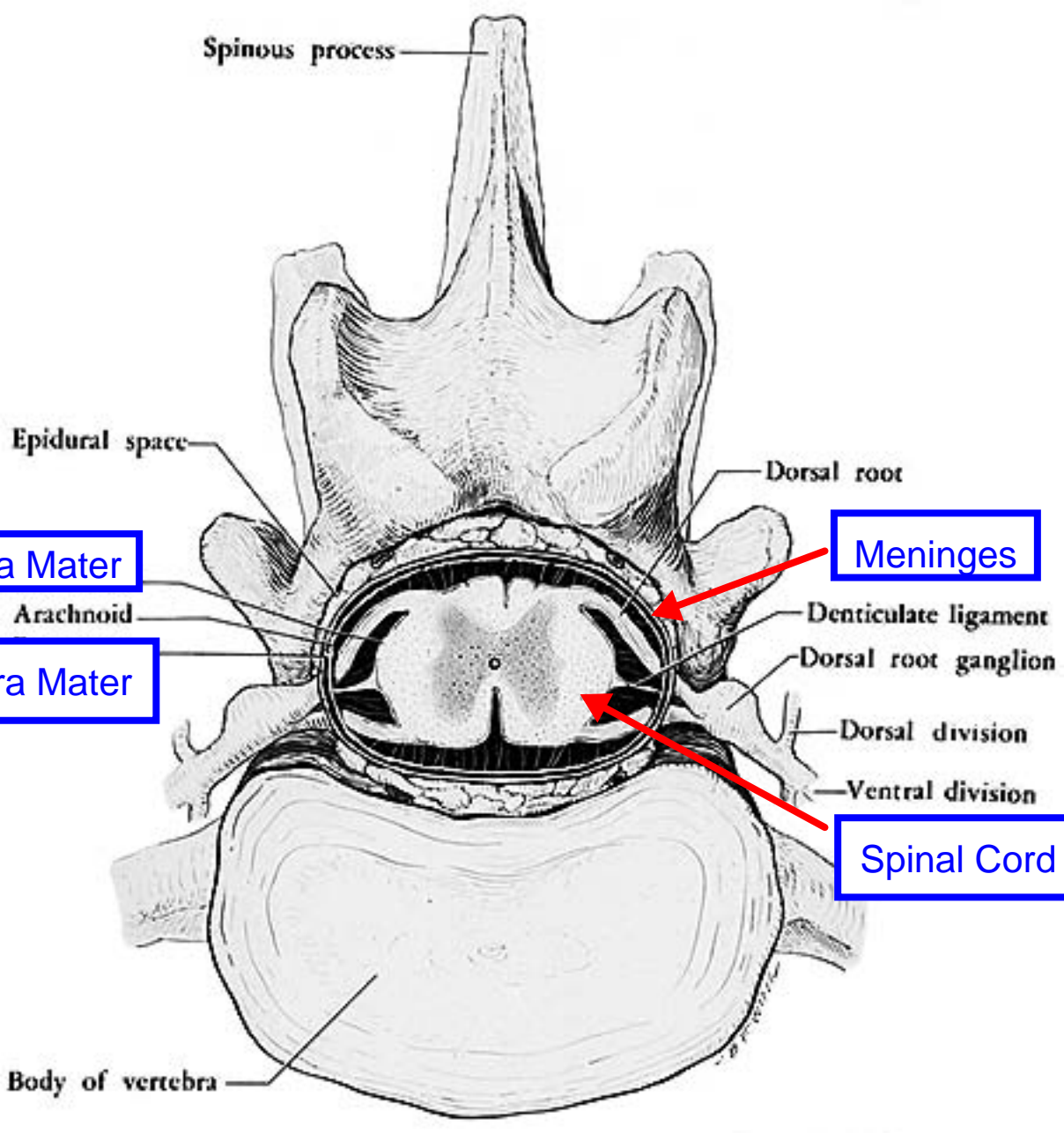
2. **Arachnoid**— middle layer of the meninges; it consists of a distinct membrane and numerous fibrous trabeculae on its inner surface. This trabecular network forms the structural framework for the subarachnoid space which lies between the arachnoid proper and the underlying pia mater.

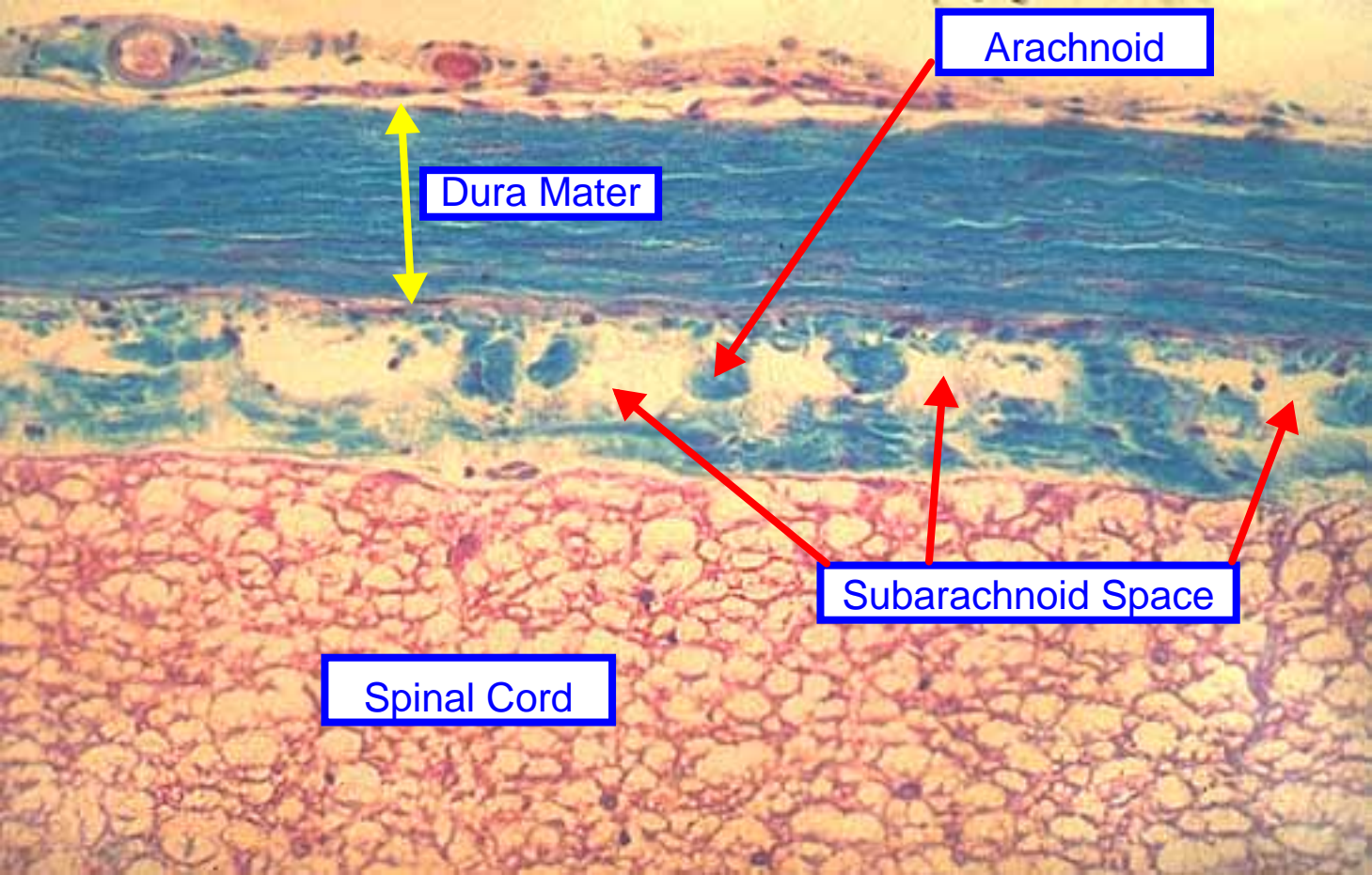
The **subarachnoid space** contains cerebrospinal fluid (CSF). At certain points the subarachnoid space is dilated and forms “cisterns”. The *cisterna magna* and lumbar cisterns are important clinically because that is where CSF taps are performed.

[Note: CSF is a clear colorless fluid that surrounds and permeates the entire central nervous system. It functions to protect, support and nourish the CNS.]



3. **Pia Mater**—(from the latin term meaning “tender mother”), the innermost layer of the meninges, it forms a thin protective membrane which adheres to the surface of the brain and spinal cord. It consists of flattened fibrocytes superficial to elastic and collagen fine fibers that extends into the numerous depressions and fissures on the surface of the brain and cord. It is very vascular.



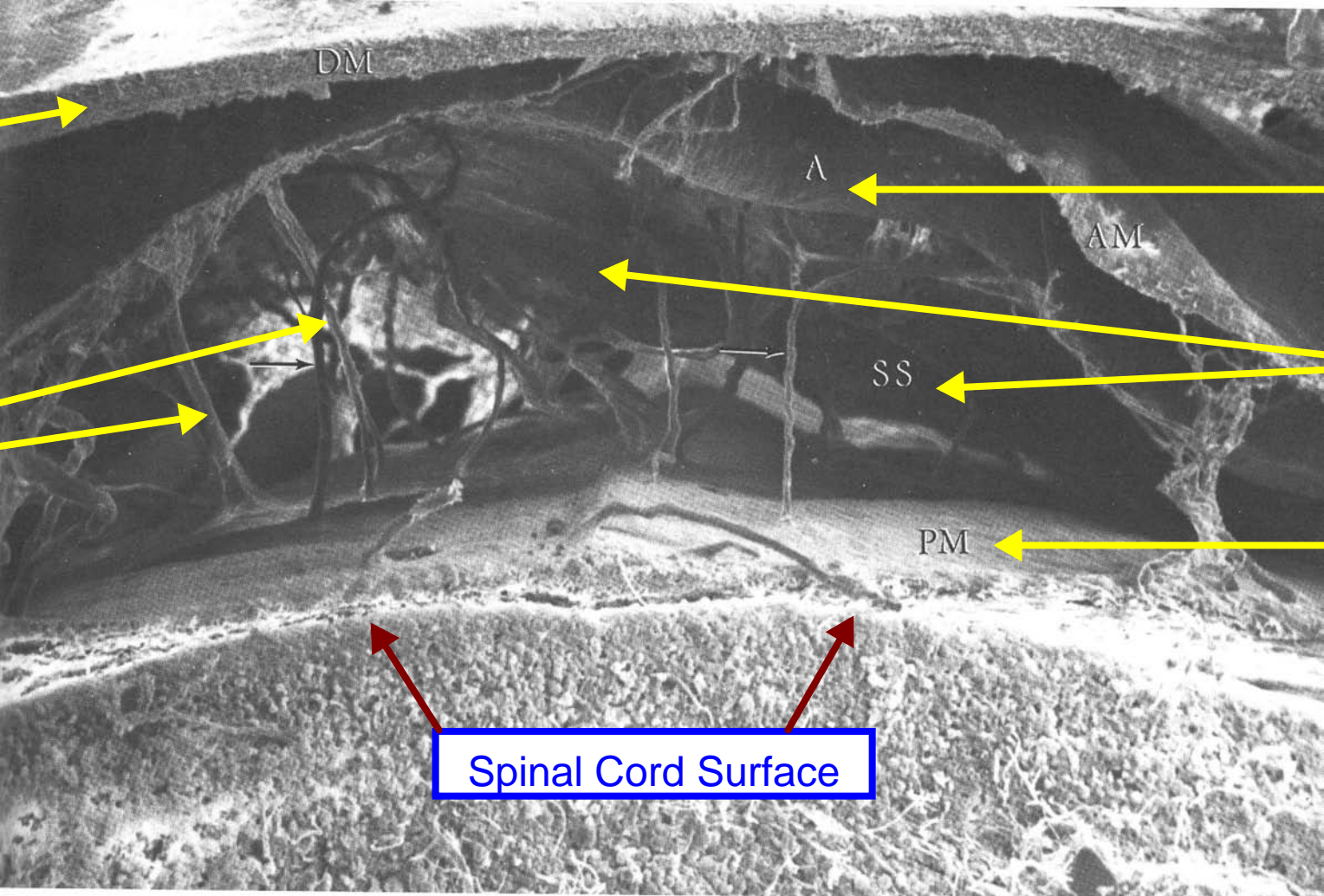


Arachnoid

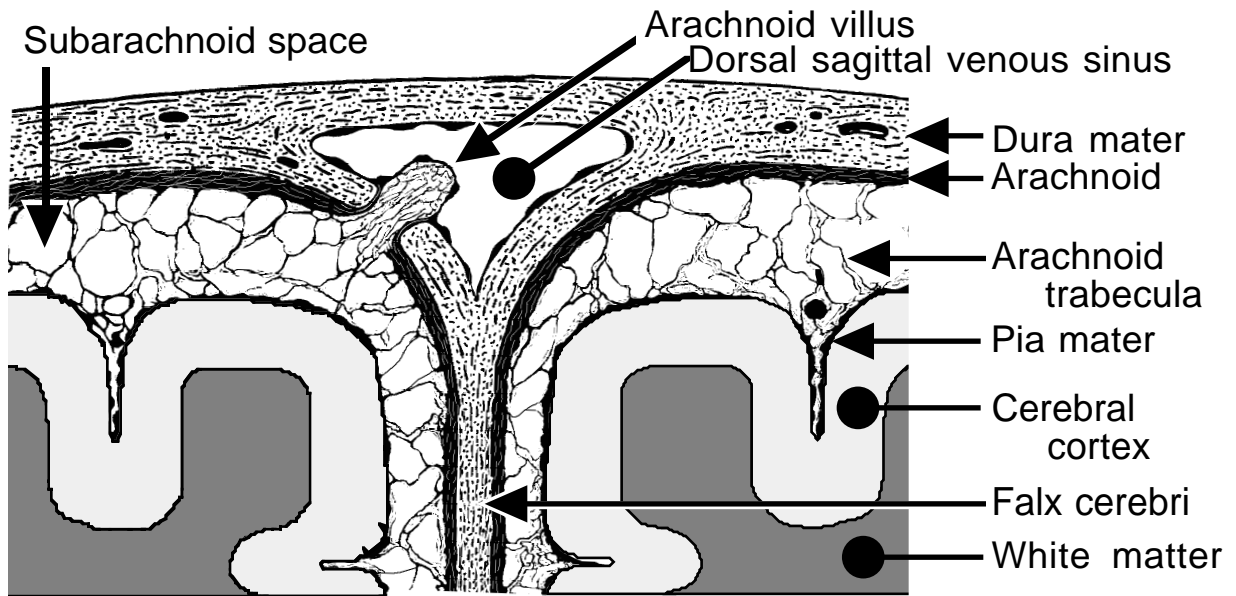
Dura Mater

Subarachnoid Space

Spinal Cord



Cranial Meninges



V. Receptors:

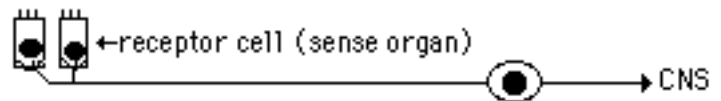
- 1. Receptor** = a specialized region located on a peripheral terminal branch of an axon of a primary afferent neuron, that can serve as a *transducer*—converting environmental energy (sensory stimuli) into depolarizing ionic current (nerve signals). The number of receptors per neuron ranges from several (small receptive field) to several dozen (large receptive field).

vs.



Sense organ = an organized collection of receptor cells, with which the dendritic zones of afferent neurons synapse. The excitability of receptor cells is modified by environmental energy, i.e., the receptor cells act as transducers.

Sense organs are: retina, cochlea, vestibular apparatus, taste buds, and olfactory epithelium. Neurons that synapse with receptor cells are *SSA* or *SVA* in type and commonly bipolar rather than unipolar.



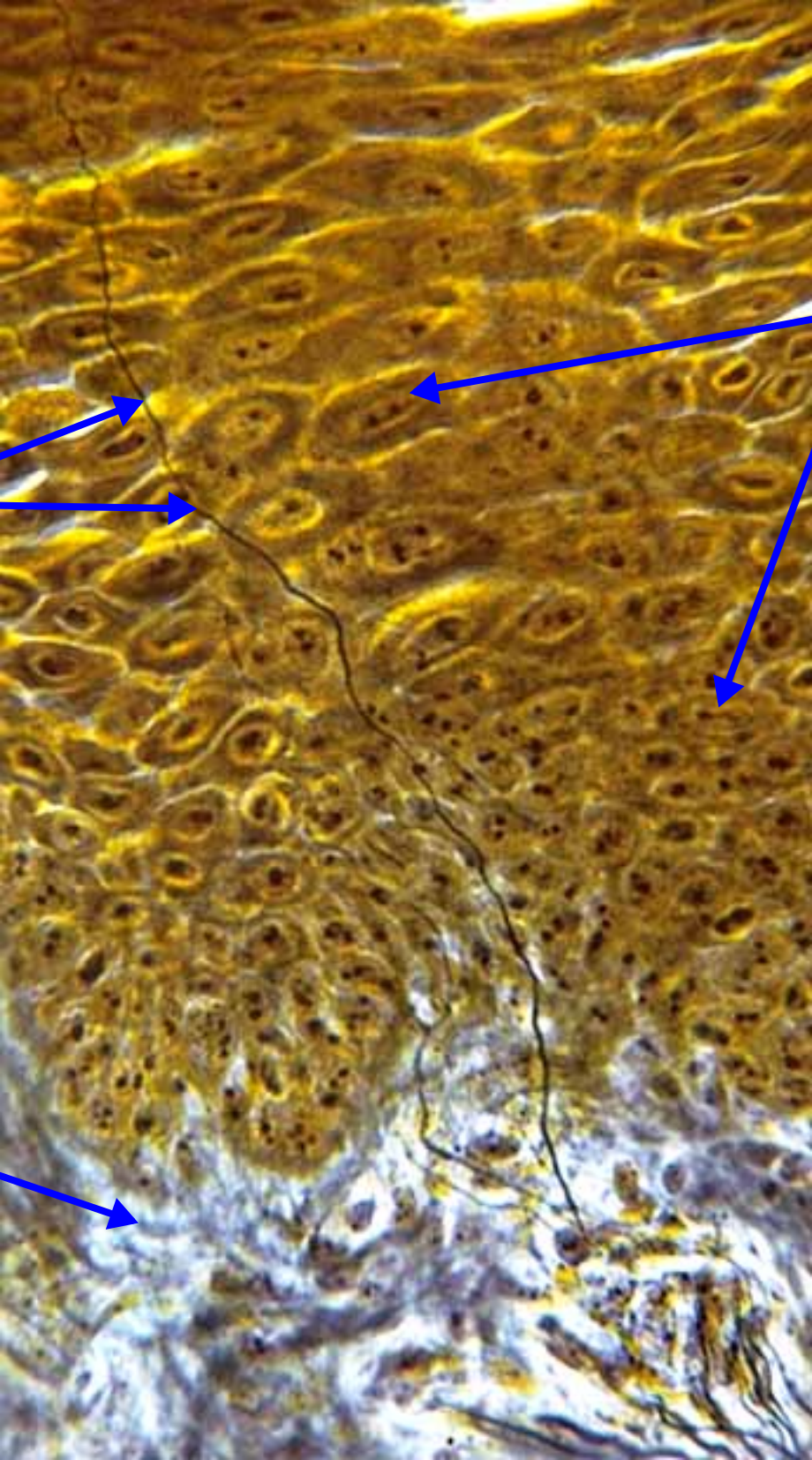
2. Classification of receptor populations:

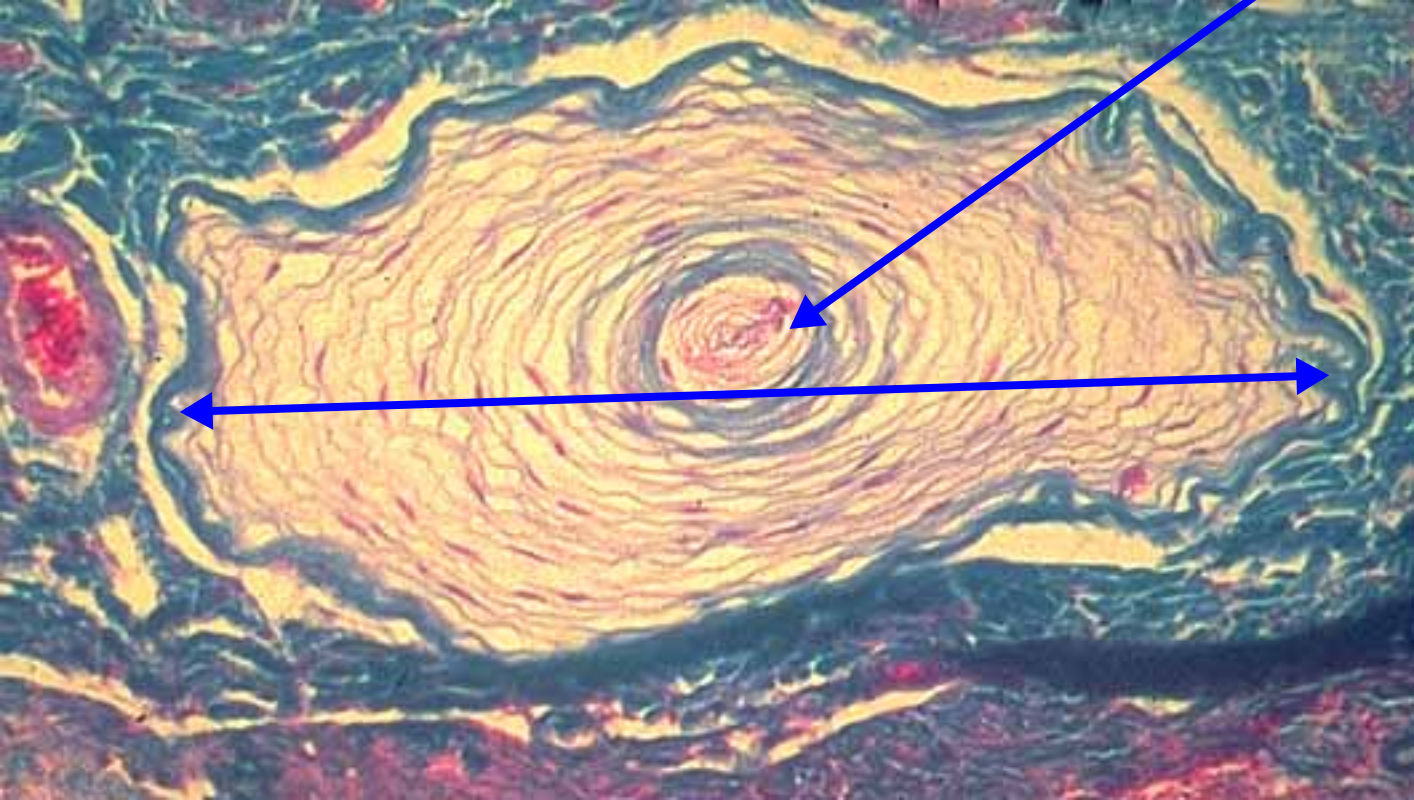
Receptor classification based on *Morphology*:

- 1) free nerve endings—terminal branches ramifying among epithelial cells, very common especially in the skin (mediate pain sensation, itch thermal sensations).
- 2) tactile discs—consists of a terminal expansions of an afferent axon which are joined to modified epidermal cells (found in skin and mucous membranes).
- 3) encapsulated—each receptor is encapsulated by lemmocytes and perineural epithelium (examples: pacinian corpuscles, tactile corpuscles, muscle spindles).

Receptor classification based on *Location*:







- 1) Exteroceptors—associated with skin and subcutaneous tissue (GSA)
- 2) Proprioceptors—associated with muscles, tendons and joints (GSA)
- 3) Interoceptors—located in viscera (GVA)

Receptor and sense organ classification based on *Modality* (energy sensitivity):

- 1) mechanoreceptors—detect mechanical deformation (touch, pressure, vibration)
- 2) thermoreceptors—detect changes in temperature (some detect warmth, some detect cold)
- 3) nociceptors—detect damage to tissue (pain receptors); also detect itch
- 4) electromagnetic—detect light on the retina of the eye
- 5) chemoreceptors—detect chemical molecules, including: taste receptors, olfactory receptors, arterial oxygen receptors in the aortic arch and carotid bodies, blood osmolarity in the hypothalamus and blood glucose and fatty acid receptors in the hypothalamus.

Schematic diagram illustrating various types of peripheral receptors:

