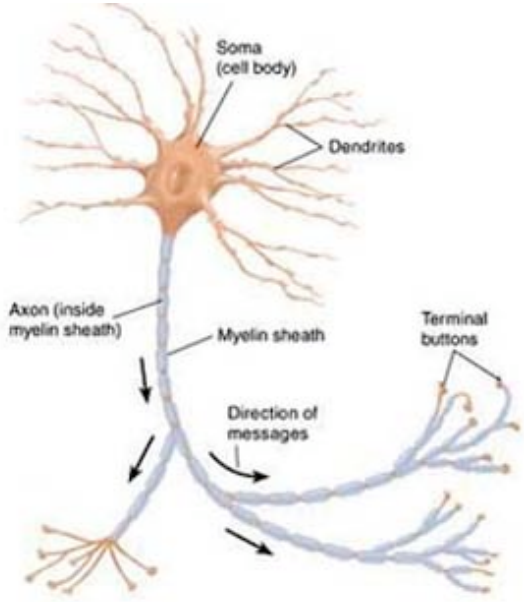
III. NEURO-HISTOLOGY

SANTIAGO RAMON Y CAJAL (Winner of the 1906 Nobel Prize in Medicine) came up with evidence that nerve fibers are not continuous, but rather contiguous, and that synapses separate them.

- He asserted the polarity of cells, with dendrites receiving and axons delivering.
- Also, he established the neuronal growth occurs at the proximal stump (nearest the cell body) during development, and not at the distal stump.

NEURON



CONTENTS OF THE NEURON SOMA: Only those things beyond the obvious.

- **NISSL BODIES:** Clusters of basophilic Rough ER, found in abundance in the neuron soma.
- **Phagosomes:** Waste-containing vacuoles that fuse with **primary lysosomes** to form **secondary lysosomes**.
- **DENSE BODY:** A **tertiary lysosome**, or a lysosomes that has already degraded much of its contents, but has non-digestible materials remaining.
  - Dense bodies contain **Lipofuscin**, which tends to accumulate with age.

DENDRITES

- They generally develop after the axons.
- No Golgi apparatus, and Nissl Bodies (i.e. Rough ER) diminish as you get away from the soma.
- Microtubules: The orientation of microtubules in dendrites is mixed, both plus to minus and minus to plus.

AXONS

- **Axon Hillock** is the initial segment of the axon, as it narrows down from the soma.
  - Nissl substances and Golgi can still be found at the hillock, but diminish as you move down the axon.
- Myelin Segments:
  - **Node of Ranvier:** The region of saltatory conduction where there is no myelin.
  - **Internode:** The myelinated regions between nodes of Ranvier.
  - **Paranode:** The region right next to a node of Ranvier.
- **Microtubules** and Neurofilaments: Histologically, they predominate throughout the axon.
  - For Microtubules, *the **plus-end** points away from the cell body.*
  - Mitochondria and smooth ER can also be found in axon. Other organelles are absent.
- **AXOLEMMA:** Membrane of the axon.

AXONAL TRANSPORT

- **Anterograde Transport:** Movement away from the soma, toward the axon terminal.
  - **Fast Anterograde Transport:** 200-400 mm / day. This is the majority of standard protein transport, of stuff from the Rough ER.
  - **Slow Anterograde Transport:**
    - Proteins transported by this mechanism are synthesized on **free polysomes** in the soma.
    - **Dynamin** is the name of the microtubule motor protein that functions in slow-component A.
    - Proteins include actin, spectrin, clathrin, and others.
    - Motor mechanism may utilize actin/myosin.
    - **Calcium-dependent proteases** function to disassemble the structure so that proteins can be utilized at their destination.
- **Retrograde Transport:** Movement toward the soma.
  - TWO FUNCTIONS:
  - Molecules transported: NGF, neurotoxins, viruses
  - **Horseradish peroxidase** = a retrograde tracer molecule.
  - **Dynein** moves things from the plus to the minus end of microtubules and is therefore responsible for retrograde transport.

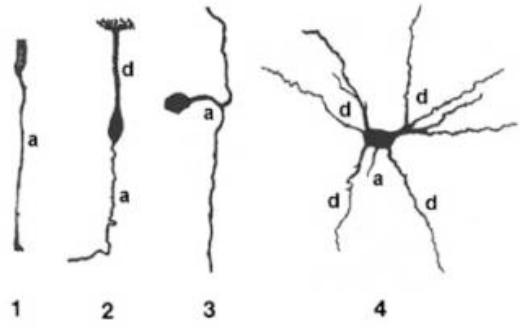
NEUROPIL: The interconnected and interwoven processes of dendrites, axons, and glia. (The neuronal environment).

Distinguishing Axons and Dendrites Histologically:

- Dendrites have a homogenous collection of microtubules, while axons have them in clumps.
- Axons may be myelinated. Dendrites aren't.
- The presence of synaptic vesicle indicates that it is an axon.

TYPES / CLASSIFICATIONS OF NEURONS

- According to function: Sensory / Motor
  - **Sensory:** The majority of neurons.
  - **Motor:** (The cell bodies are) found in three discrete places.
  - **Associative:** Interneurons, which make connection between other neurons.
- According to function: Mode of Action
  - **Excitatory**
  - **Inhibitory**
  - **Both Excitatory and Inhibitory**: Release neurotransmitters that excite some neurons but inhibit others.
- According to length
  - **Golgi Type I:** Long axons, as in PNS.
  - **Golgi Type II:** Short axons, as in CNS.
- According to number of processes

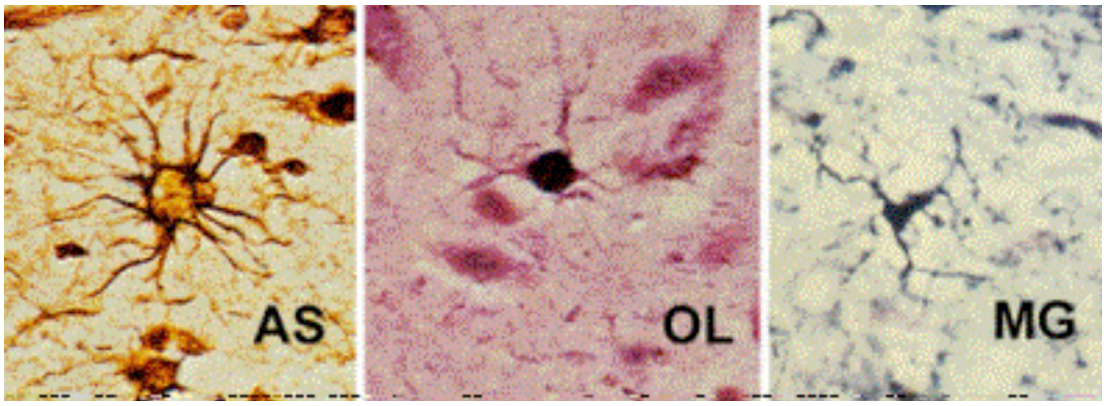


a: Axon d: Dendrite

  - **(1) Unipolar**—have a single process that may give rise many branches.
  - **(2) Bipolar**: Having a single axon and single dendrite coming out of the cell body.
  - **(3) Pseudounipolar**: Having the single process come off a stem attached to the soma.
  - **(4) Multipolar:** Most neurons. Multiple Axons and Dendrites

NEUROGLIA (NEUROGLIAL CELLS)

Central Neuroglia	Peripheral Neuroglia
Astrocyte - protoplasmic astrocyte - fibrous astrocyte **Oligodendrocyte** - perineuronal satellite cell - interfascicular cell **Microglia** **Ependymal Cell**	**Schwann Cell** - in peripheral nerve - and ganglion **Capsular (Satellite) Cell** - in ganglion

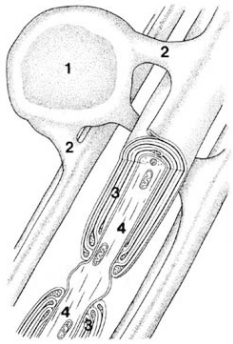


Astrocyte **Oligodendrocyte** **Microglia**

ASTROCYTES: STAR-LIKE NEUROGLIAL (NEURAL ACCESSORY) CELLS

- Functions:
  - Supportive role
  - Insulate synapse from each other
  - Regulate extracellular pH, K^+ concentration.
  - Induce formation of the blood-brain barrier
  - Interaction with immune system
  - Limited phagocytosis
- **GLIOSIS / ASTROCYTOSIS:** Astrocyte response to disease in the brain.
  - They proliferate and divide
  - They increase their concentration of GFAP-laden intermediate filaments.
  - They form a dense network termed a **glial scar**.
- Astrocyte Morphology / Histology
  - **Glial Fibrils:** The name of the intermediate filaments in astrocytes.
  - There are no microtubules in mature astrocytes.
  - **Perivascular Feet (Vascular End-Feet):** *Help form the blood brain barrier*.
  - Astrocytes are the largest of all the accessory neuronal cells.
- Two General Types of Astrocytes: The two types of astrocytes are really two morphological ends of a continuous spectrum.
  - **Fibrous Astrocytes:** Prominent in *white matter*.
  - **Protoplasmic Astrocytes:** Prominent in *grey matter*.
- Special Types of Astrocytes
  - **Bergmann Glial Cell:** Found in cerebellum, they have processes that extend all the way to the pial membrane, similar to early development.
  - **Muller Cell:** Found in retina, sharing features with both astrocytes and ependymal cells.
  - **Pituicute**.

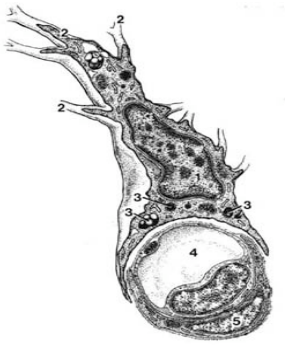
OLIGODENDROCYTES: Myelin forming cells in the CNS, and can myelinate multiple internodes



1. Nucleus of Oligodendrocyte
2. Process of Oligodendrocyte
3. Myelin Sheath
4. Axon

- Morphology:
  - They can have up to fifty processes. Each myelin sheath connects back to the oligodendrocyte by a single process.
  - They have no intermediate filaments.
  - They are smaller than astrocytes but larger than microglia.
- ORIGIN: *Neuroectodermal*
- Two types of Oligodendrocytes:
  - **Interfascicular Oligodendrocytes:** Oligodendrocytes found along and in between the axons they myelinate.
  - **Satellite Oligodendrocytes**: Oligodendrocytes found only in the grey matter of the CNS.

MICROGLIAL CELLS: The macrophages of the brain. They phagocytose debris in the CNS



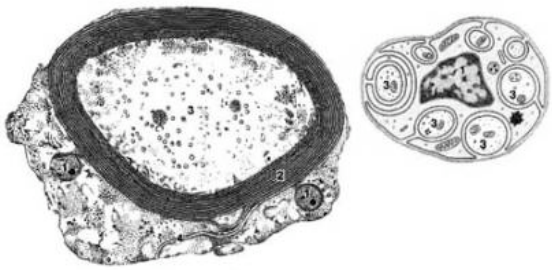
1. Nucleus of Microglia
2. Process of Microglia
3. Lysosome
4. Capillary
5. Pericyte

- Macrophage (Mononuclear Phagocytic) System
  - Mesenchymal Origin – Blood Monocyte
  - Increased in inflammation
- Morphology:
  - They are much smaller than Oligodendrocytes or Astrocytes.
  - They have short, highly branched Processes.
- These cells can get infected with HIV in individuals with HIV-dementia (presumably a possible but not essential manifestation of AIDS).

EPENDYMAL CELLS: Specialized Epithelial Cells that line the ventricles of the brain.

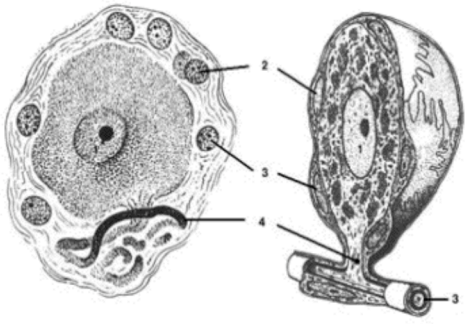
- Morphology:
  - *Cuboidal* or *Columnar Epithelium.*
  - They have polarity, and have a **junctional complex** near the luminal side. Junctional complex consists of Tanycytes.
  - **TANYCYTES**: Basal Processes found interdigitating with ependymal cells.
    - They are thought to be transporter molecules.
    - They contain GFAP.
    - Numerous in walls of 3rd Ventricle.
  - **CHOROID PLEXUS** Epithelial Cells:
    - Ion transporting cell.
    - Numerous mitochondria.

SCHWANN CELLS: Myelin forming cells in the PNS.



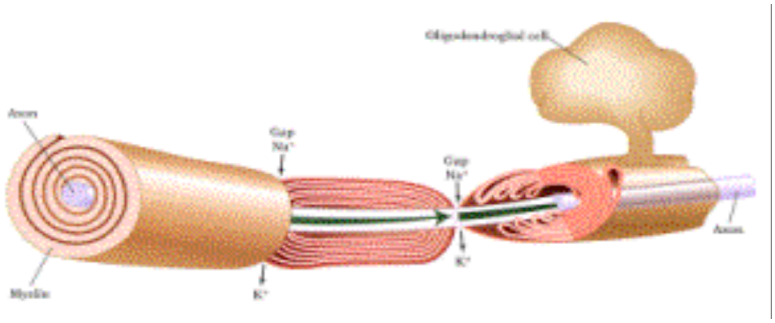
- Selender cells, found in Peripheral Nerves and Ganglions.
- Associated with the Myelin that it forms.
- Each Schwann Cell myelinates only one internode.
- ORIGIN: *Neural Crest Cell*
- Morphology: They do have intermediate filaments.

SATELLITE (Capsular) CELLS: Form a single layer around neuron soma, separating the soma from adjacent capillaries.



- Squamous Cells.
- Completely encircles pseudounipolar neuron in Spinal and Cranial Ganglions.
- They are morphologically similar to Schwann cells.
- They help to form the "Blood-Neuron Barrier" in the PNS.

MYELIN



- Myelin Sheath is formed by wrapped plasma membrane of:
  - **Oligodendrocyte in CNS**.
  - **Schwann Cells in PNS**.
- FORMATION: It is formed from two plasma membranes with cytoplasm in between. The two membranes juxtapose and role up like a jelly donut.
  - **Major Dense Line:** Fusion of the two *cytoplasmic* (**Inner**) faces of the lipid bilayer.
  - **Inter period Line:** Fusion of the two *extracellular* (**Outer**) faces of the lipid bilayer.
- **Mesaxon:** The cytoplasmic loop of myelin that is closest to the axolemma. Basically, the first layer of myelin that is immediately adjacent to the axon.
- SALTATORY CONDUCTION: Myelin is high resistance, and current jumps from one Node of Ranvier to the next. Advantages of Saltatory Conduction:
  - Higher conduction velocity at a much smaller nerve diameter.
  - Conserve tremendous amount of energy by concentrating Na^+ channels at the Nodes of Ranvier, so that the Na/K ATPases don't have to work as hard.

MULTIPLE SCLEROSIS: Lack of Myelin in cells. Auto-Antibody attack against Myelin.

HISTOLOGY OF SELECTIVE CNS PARTS

LAYERS OF THE RETINA: From the first layer that the light contacts, to the last layer that it contacts.

- **Choroid:** The material between the sclera and the beginning of the retina, through which the light travels.
- **Pigmented Epithelium:** Pigments in this layer absorbs a lot of the light initially.
  - It also supplies Vitamin-A to (and exchanges it with) the photoreceptor cells.
- **Outer Segment:** Contains the outer segment of *rods and cones*.
- **Inner Segment:** Containing the inner segment of *rods and cones*.
- **Outer Nuclear Layer:** Contains the nuclei of the *rods and cones*.
- **Outer Plexiform Layer:** Contains:
  - **Horizontal Cells**
  - **Bipolar Cells**
  - Processes and synapses from the *rods and cones.*
- **Inner Nuclear Layer:** Contains the nuclei and soma of the Bipolar, Amacrine, and Horizontal cells.
- **Inner Plexiform Layer:** Contains processes and synapses from the Bipolar, Amacrine, and Horizontal cells.
- **Ganglion Cell Layer:** Contains the **Ganglion Cells**, which ultimately converge on the Optic Nerve.
- **Nerve Fiber Layer:** Contains the axons of ganglion cells.
- **Inner Limiting Membrane**

CEREBELLUM LAYERS

- **MOLECULAR LAYER**: Outermost layer of grey matter, containing relatively few, unmyelinated fibers.
  - **Basket Cells:** They send out processes in the molecular layer that interconnect Purkinje cells.
- **PURKINJE CELLS**: Middle border layer containing huge neurons that have fine dendrites and axons extending beyond.
  - **Purkinje Dendrite** extends into the *molecular layer* (outer layer), where they receive efferent signals from the cerebellar cell bodies.
  - **Purkinje Axons** extends into the *granular layer* (inner layer), where they relay efferent signals ultimately to the white matter of the cerebellar core.
- **GRANULAR LAYER:** The innermost layer, containing numerous cells, and containing axons that extend into the molecular layer to meet up with the Purkinje dendrites.
- **WHITE MATTER:** Beneath the granular layer is the white matter core of the cerebellum, which is the interface between the cerebellum and the brainstem.
  - All incoming fibers have multiple connections in white matter and then make their way up to the cerebellar cortex, via the Purkinje cells.
  - Outgoing fibers go back to the white matter and down the brainstem, once again via Purkinje cells.

DORSAL ROOT GANGLION: Consists of **pseudounipolar** cells on the dorsal root (intervertebral foramen) of the spinal column. Both processes of a dorsal root ganglion cells are considered to be axons. Dorsal root ganglia are sensory neurons.

- **Central Process**: Transmits the sensory information into spinal column.
- **Peripheral Process:** Receives information from the periphery at the respective dermatomal level.

BLOOD-BRAIN BARRIER

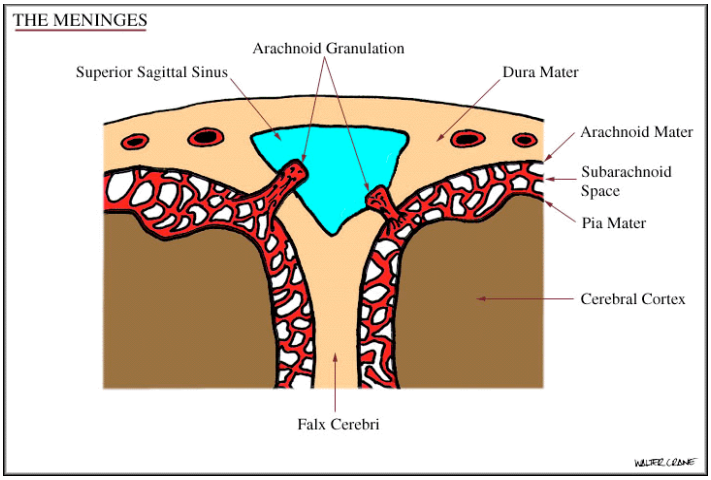
- Brain Arteries: They are covered by **Astrocyte End-Feet** and Pia Mater.
- Brain Capillaries: The primary barrier is the **Capillary Endothelium**, which has tight junctions.
  - Diffusion in and out of capillary is tightly regulated.
  - **Basement Membrane** surrounds the outside of the capillaries.
  - **Astrocyte End-Feet** are outside the basement membrane.

CEREBROSPINAL FLUID (CSF)

- The average production is 500 ml/day.
- Total amount in average adult is 100 to 150 ml. (only 25 ml. of CSF is available in ventricles).
- Functions:
  - Transport of glucose and other products to CNS.
  - Removes waste products and drugs
  - Supports and cushions the brain against trauma.
  - Carries hormones from the hypothalamus.

- Contents: It is made primarily in choroid plexus (70%), with some capillary ultrafiltrate (18%), and glucose oxidation products (12%).
- Properties:
  - Clear fluid, isotonic with Serum (290-295 mOsm/L).
  - PH = 7.33 (Less than blood PH = 7.36-7.40).
  - Concentration of Glucose and Protein is **lower** in CSF than in Serum. (Protein increases in CNS tumors).
  - Concentration of K^+, Ca^{2+} and HCO_3^- ions is **lower** in CSF than in Serum.
  - Concentration of Na^+, Cl^- and Mg^{2+} ions is **higher** in CSF than in Serum.
- Most of CSF returns to venous system (Superior Sagital Sinus) via Arachnoid Granulation.
- **CHOROID PLEXUS:** Contain numerous villi, made of ependymal cuboidal epithelial cells.
  - Located in each lateral ventricle, the third and forth ventricles.
  - The Ependymal cells have a basement membrane, and beneath that is the **stromal core**, in which the blood vessels are found.
  - Each choroid plexus is supplied by an artery.

BRAIN MENINGES

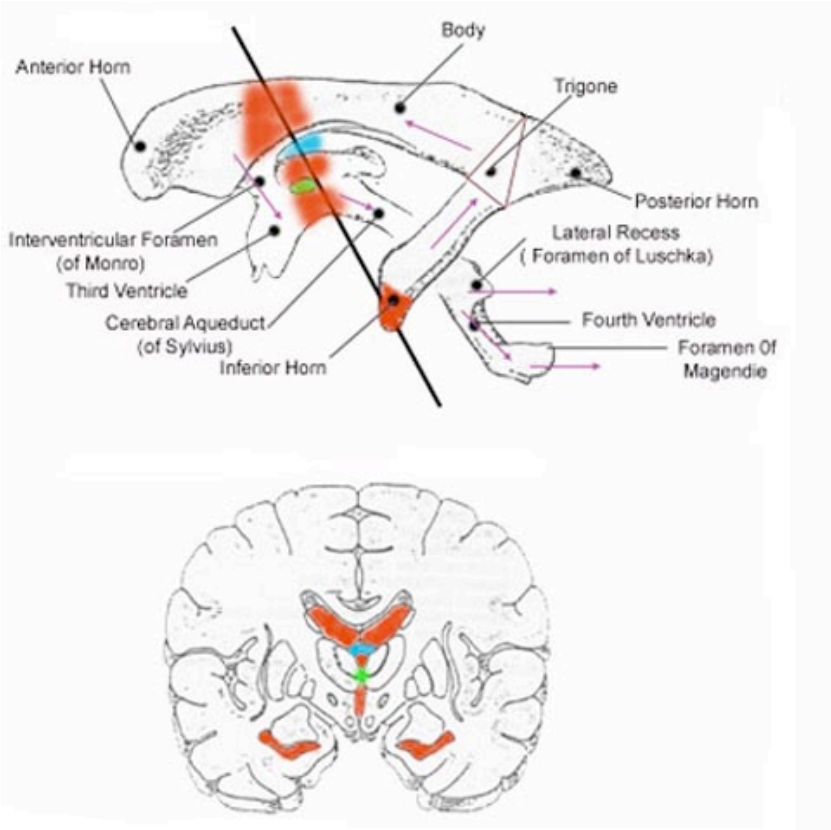


- **Dura Mater**: Attached to skull, made of collagen.
- **Arachnoid Mater:** Interdigitating fibers make it seem several layers of thick.
  - The arachnoid mater is **avascular**.
- **Subarachnoid Space:** Contains the cerebrospinal fluid.
  - **Arachnoid Trabecula** forms a web-like structure in this space.
- **Pia Mater:** Adherent to the brain.
  - The pia mater is **highly vascular**.
  - It follows vessels into the brain, forming reflections off of them as they enter brain.
  - **Glial Limitans** is just deep to the **pia mater**, separating brain from vessels. It is made of **astrocyte end-feet**.

VENTRICULAR SYSTEM

General Flow of CSF: The two LATERAL VENTRICLES ------> FORAMEN OF MONROE ------> THIRD VENTRICLE ------> CEREBRAL AQUEDUCT ------> FOURTH VENTRICLE

- **Foramen of Monroe:** Connects each Lateral Ventricle to the Third Ventricle.
- **Cerebral Aqueduct:** Connects the Third Ventricle to the Fourth Ventricle.
- **Central Canal:** The Central Canal of the Spinal Cord is formed as a continuation of the Fourth Ventricle, as it narrows through the Foramen Magnum.
- **Median Aperture (Foramen of Magendie):** Connects the Third Ventricle to the Subarachnoid Space, medially.
- **Lateral Aperture (Foramen of Luschka):** Connects the Third Ventricle to the Subarachnoid Space, laterally.
- **ARACHNOID GRANULATIONS:** This is how CSF leaves the Ventricles, to enter the **Superior Sagital Sinus**.
- **HYDROCEPHALUS:** Any blockage of the flow of cerebrospinal fluid will result in hydrocephalus.



LATERAL VENTRICLES: They are the primary makers of CSF, and they have four major parts, corresponding to the cerebral hemispheres.

- **Anterior Horn:** That part in the Frontal Lobe.
- **Body:** That part in the Parietal Lobe.
- **Inferior Horn:** That part in the Temporal Lobe.
- **Posterior Horn:** That part in the Occipital Lobe.

BLOOD SUPPLY TO THE CNS

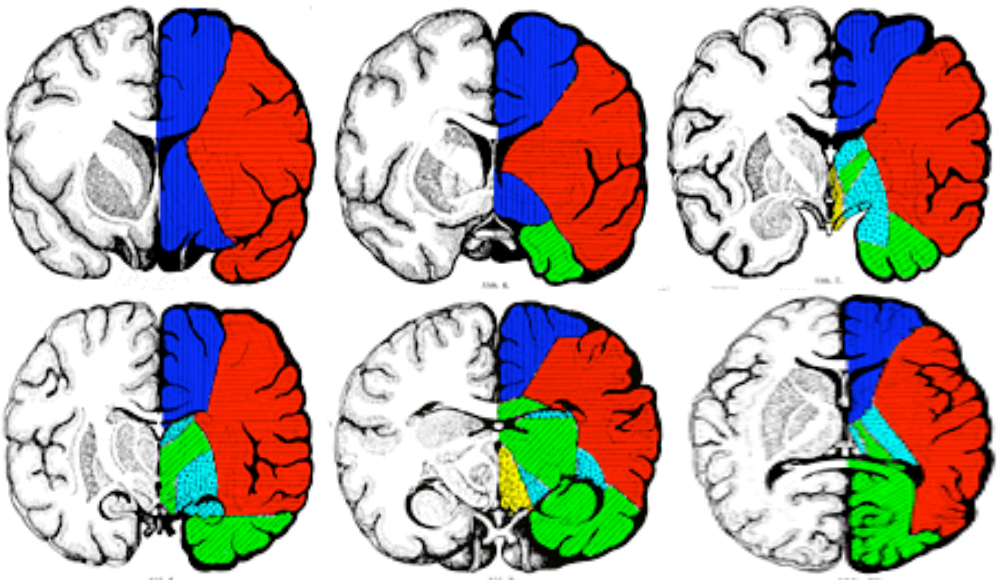
ANTERIOR CIRCULATION: Basically the Carotid System.

- Supplies:
  - The Eye (via **Ophthalmic Arteries**) off of Internal Carotid.
  - The **anterior (forebrain) deep structures** (via Anterior Cerebral) of each cerebral hemisphere.
  - The **lateral surface** of each cerebral hemisphere (via Middle Cerebral)
  - The **medial forebrain**, as far back as the Parieto-Occipital Sulcus (via Anterior Cerebral)

- FOUR SEGMENTS OF THE INTERNAL CAROTID:
  - **Cervical Segment:** From Bifurcation to The Carotid Canal
  - **Petrous Segment:** As it goes through the Carotid Canal, in Petrous Temporal bone.
  - **CAROTID SIPHON (S-SHAPED):** An S-Shape is made from two segments:
    - BRANCHES = a few small branches to supply the dura mater in the cavernous sinus.
    - BRANCHES = **Middle Cerebral Artery** and **Anterior Cerebral Artery**.

BRANCHES OF THE INTERNAL CAROTID

  - Ophthalmic Artery: The eye, anastomosis with supraorbital face, Meninges and Falx Cerebri.
  - Posterior Communicating Artery joins the Posterior Cerebral Artery
  - **Anterior Choroidal Artery**: Supplies the choroid plexus in the anterior horn of the lateral ventricle.
  - Anterior Cerebral Artery
  - Middle Cerebral Artery



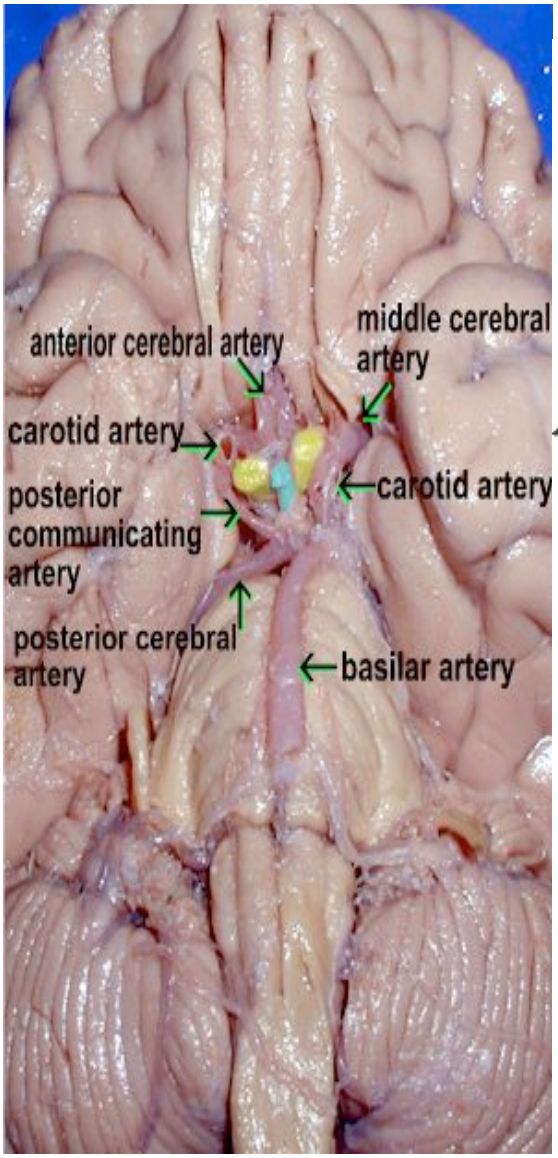
Anterior Cerebral Artery **Middle Cerebral Artery**
Posterior Cerebral Artery **Basilar Artery** **Anterior Choroidal Artery**

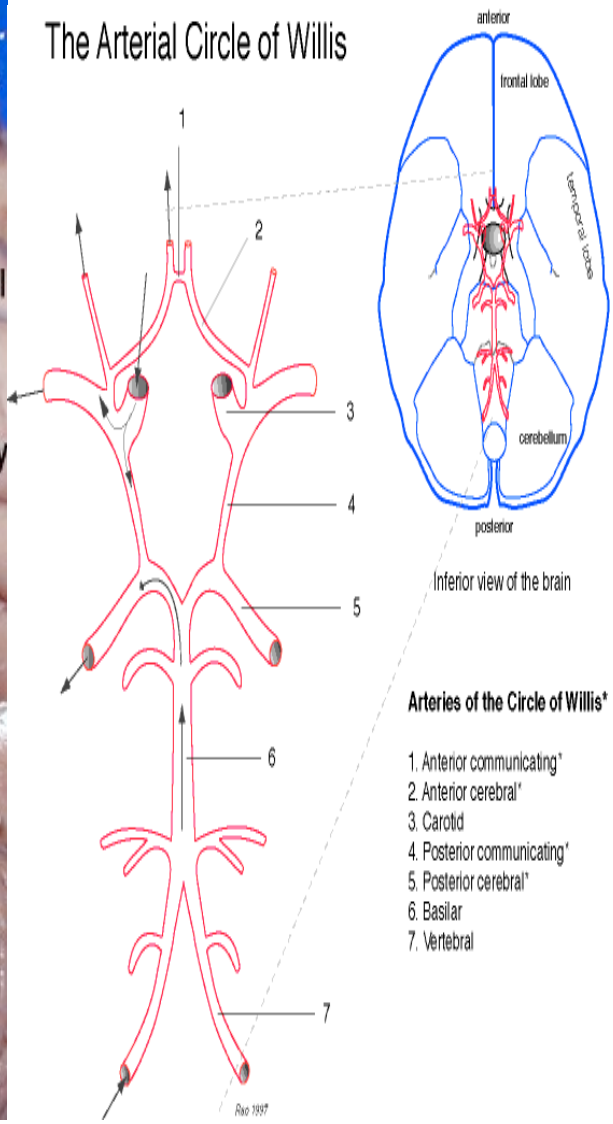
- **ANTERIOR CEREBRAL ARTERY:** Enters cranial cavity at the **Longitudinal Fissure**.
  - Anastomoses with other anterior cerebral artery via the Anterior Communicating.
  - TWO SEGMENTS:
    - Gives off the **anteromedial and medial striate arteries** through the anterior perforating substance.
    - It divides into branches to supply the **medial, frontal cerebral cortex** up to the parieto-occipital fissure.
  - SUPPLIES **the entire medial surface of each cerebral hemisphere, except for the Occipital Pole.**
- **MIDDLE CEREBRAL ARTERY:** Enters the **Sylvian Fissure** and then bifurcates into two main branches (Anterior and Posterior)
  - SUPPLIES

POSTERIOR CIRCULATION: Basically the vertebral system.

- Supplies:
  - The Spinal Cord.
  - The Brain Steam: Medulla, Pons, most of Mesencephalon
  - All of the Cerebellum
- SEGMENTS OF THE VERTEBRAL ARTERIES:
  - Soft Tissue Segment: Subclavian Arteries ------> **C6 Foramen Transversarium**, i.e. until the point when they enter the interior of the vertebral canal.
  - Intervertebral Segment: Inside the vertebral canal, from C6 ------> Atlas ------> Foramen Magnum
  - Intracranial Segment: That portion within the dura, distal to the foramen magnum.
    - **POSTERIOR INFERIOR CEREBELLAR ARTERY (PICA)** supplies the *lateral medulla* and part of the cerebellum. Paired arteries.
  - **BASILAR ARTERY:** The terminal segment of the Vertebral Arteries, where the two vertebras join each other.
    - **ANTERIOR INFERIOR CEREBELLAR ARTERY (AICA)**: Sends numerous branches to **caudal Pons** and **Rostral Medulla**.
    - **SUPERIOR CEREBELLAR ARTERY (SCA):** Superior aspect of Cerebellum, given off before the Basilar joins the Circle of Willis
    - **POSTERIOR CEREBRAL ARTERY (PCA):** Given off in the Circle of Willis
- **Anterior Inferior Cerebellar Artery (AICA):**
  - Supplies the Pontomedullary Junction
  - Then ascend to cerebellum to supply its named part.
- **POSTERIOR CEREBRAL ARTERIES**: The terminal branch of the Basilar Artery. *These arteries officially begin the posterior limb of the Circle of Willis*.

CIRCLE OF WILLIS: THE ANASTOMOTIC ARTERIAL CONNECTIONS SUPPLYING THE CRANIAL CAVITY. THE TWO MAIN SUPPLIES TO THE BRAIN ARE THE *INTERNAL CAROTID* AND *VERTEBRAL ARTERIES*, AND THEY COMMUNICATE THROUGH THE CIRCLE OF WILLIS.





- *All three of the Cerebral Arteries are given off in the Circle of Willis*, while the Cerebellar Arteries are given off before the Circle of Willis.
  - **POSTERIOR CEREBRAL ARTERIES:** Terminal Branches of the Basilar.
  - **MIDDLE CEREBRAL ARTERIES**: Branches off at the point where the Internal Carotids join the circle.
  - **ANTERIOR CEREBRAL ARTERIES**: The junction of the Anterior Communicating and Internal Carotid Arteries.
- **Posterior Communicating Artery** connects the Posterior Cerebral (from Basilar) to the Internal Carotid Artery. This is the *major anastomosis between the Carotid and Vertebral arterial channels*.
- **Anterior Communicating Artery:** Connects the Anterior Cerebellar Arteries to each other. This is the *major anastomosis of the Right and Left Internal Carotids with each other*.
- UNEVEN DISTRIBUTION: It is not uncommon to find one side of the Circle-of-Willis arteries too much larger than the other, carrying the majority of blood-flow.