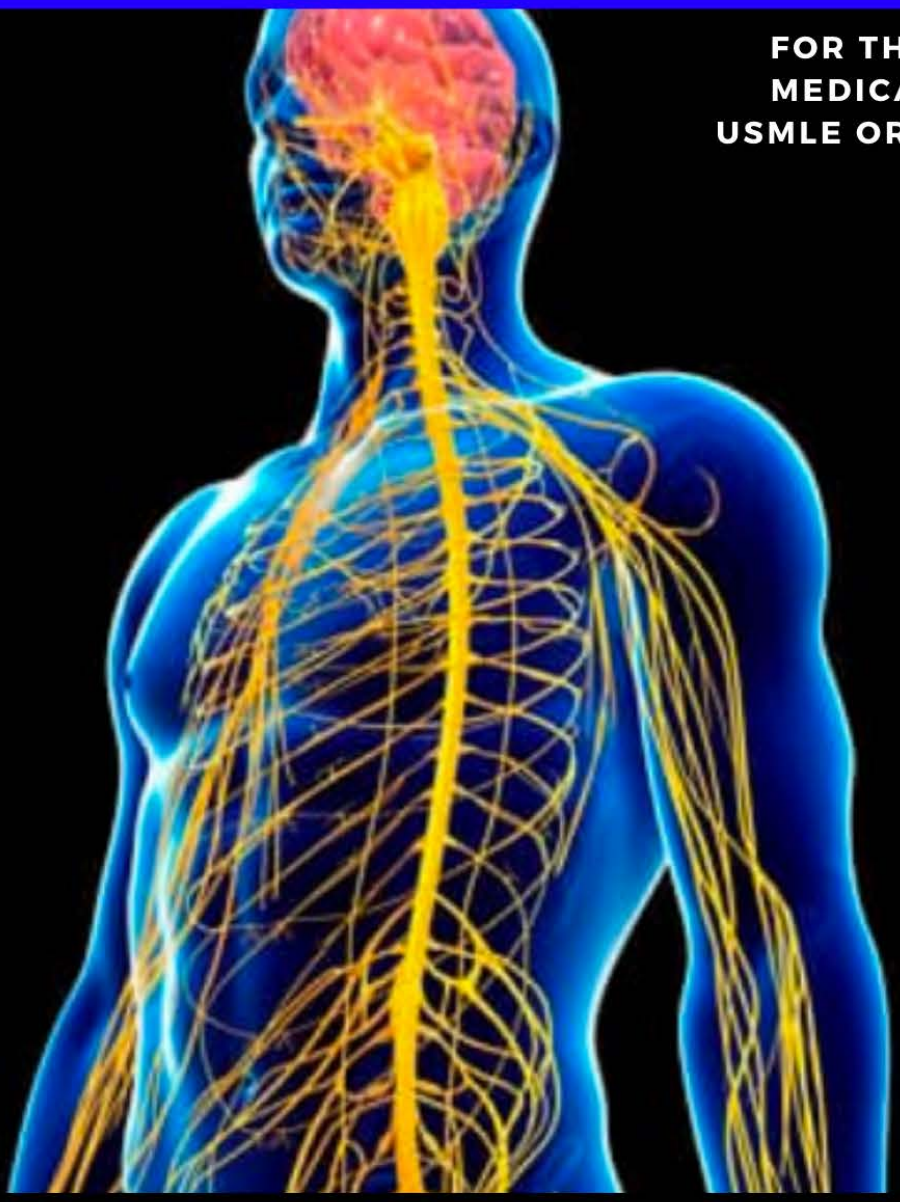
ANATOMY, PHYSIOLOGY & PATHOLOGY NOTES
OF THE

NERVOUS SYSTEM

AND SPECIAL SENSES

PRE-SUMMARIZED
READY-TO-STUDY
HIGH-YIELD NOTES

FOR THE TIME-POOR
MEDICAL, PRE-MED,
USMLE OR PA STUDENT



REGENT STUDIES

MEDICAL NOTES
(MBBS, MD, MBChB, USMLE, PA, & Nursing)
Anatomy, Physiology, Pathophysiology, Pathology, Histology & Treatments

www.regentstudies.com/medicalnotesmbbs

Table Of Contents:

What's included: Ready-to-study anatomy, physiology and pathology notes of the nervous system & special senses presented in succinct, intuitive and richly illustrated downloadable PDF documents. Once downloaded, you may choose to either print and bind them, or make annotations digitally on your iPad or tablet PC.

Free Bonus: 'Neurology', 'Neurosurgery & 'Ophthalmology' chapters of Toronto Notes for reference and further detailed reading.

File List:

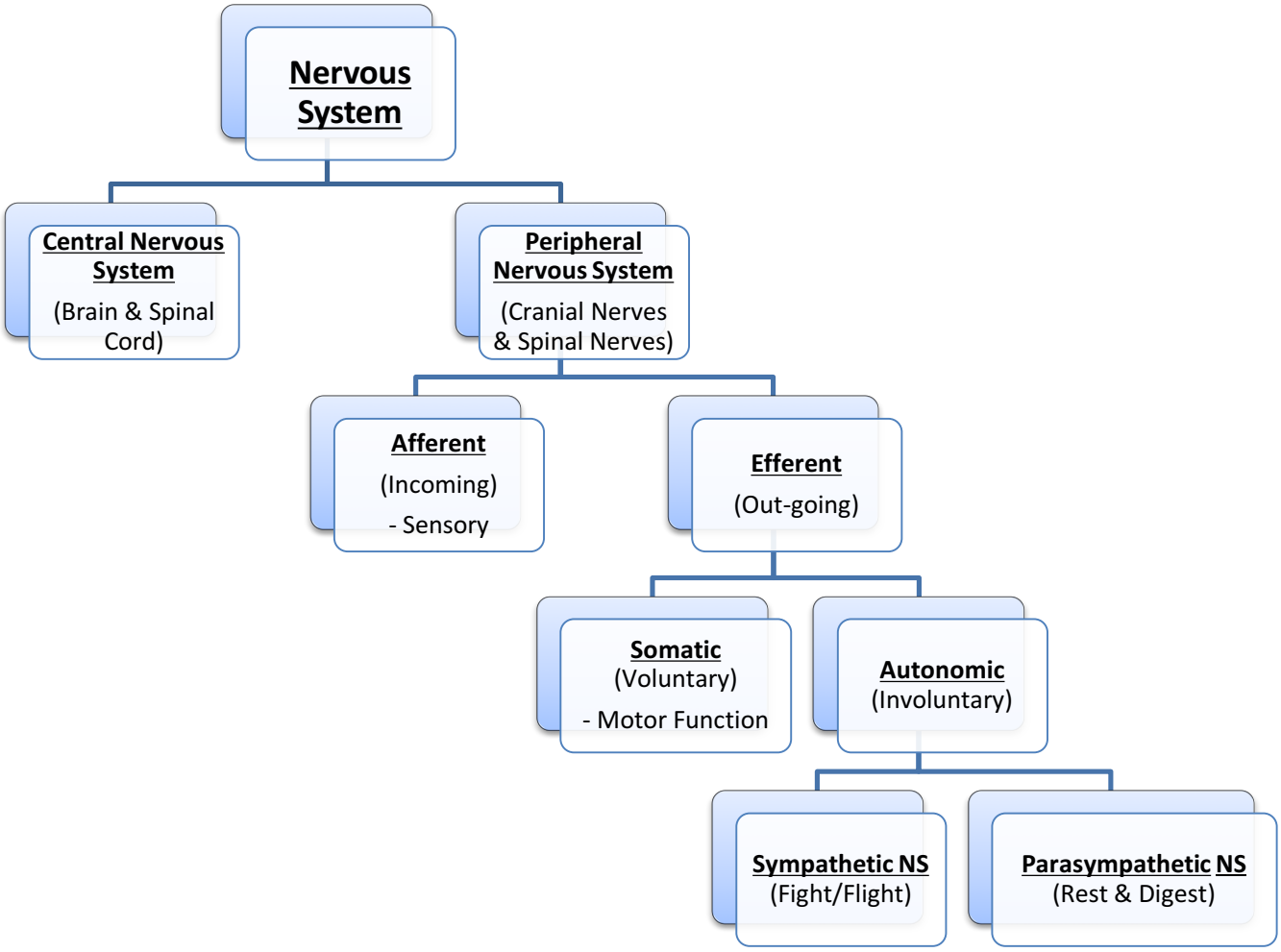
Neuroscience Notes
Development & Organisation of the Nervous System

The Nervous System - Overview:

- **Macro Structures:**
  - Brain
  - Spinal Chord
  - Peripheral Nerves
  - Sense Organs
    - Eyes
    - Ears
    - Tongue
    - Olfactory bulbs
    - Skin
- **Functions:**
  - Detection of stimuli (external/internal)
  - Response to stimuli
  - Coordinates activity of other organs & systems

Organisation of the Nervous System:

- **Central Nervous System (the "CPU" & "Motherboard")**
  - Brain
  - Spinal Cord
- **Peripheral Nervous System (the "Cables")**
  - Cranial Nerves & Spinal Nerves
  - Communication between CNS & rest of body

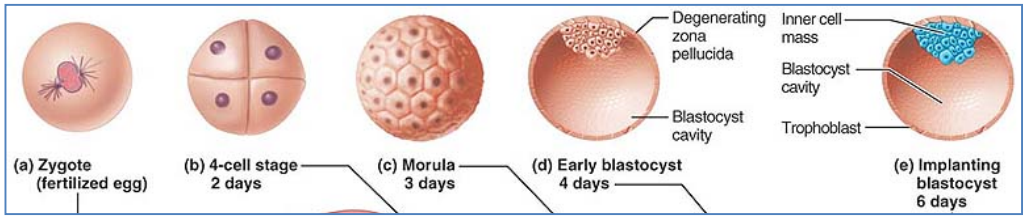


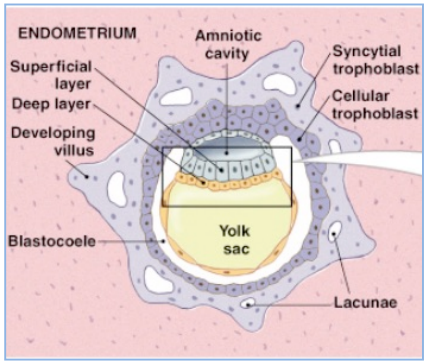
General Embryonic Development is Described as Either:

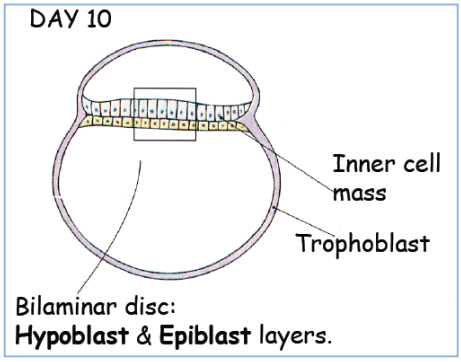
- **Trimesters** (3x 3-Month Periods)**:**
  - **First:** - *Foundations* of Major Organs
  - **Second:** - *Development* of Organs
  - **Third:** - *Rapid Growth* & *Fully Functional Organs*.
- **OR... Anatomical Stages: ****(These are more relevant)
  - **Pre-Embryonic Period: 0-2 Weeks**
    - Fertilisation
    - Blastocyst Formation & Implantation
    - Gastrulation
  - **Embryonic Period: 3-8 Weeks**
    - Development & Differentiation of 3 Germ Layers into foundations of Organs.
  - **Foetal Period: 9 Weeks → Birth.**
    - Period of *Growth*, NOT Differentiation.

Embryonic Development of the Nervous System:

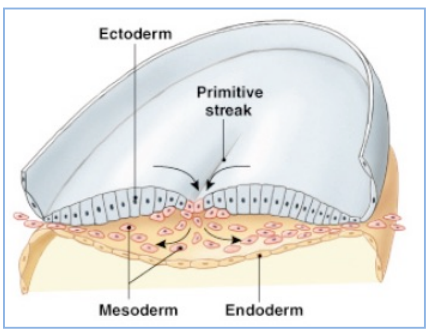
1. **Blastocyst: (Pre-Embryonic Period)**
   a. A fertilised egg reaches the **Morula** stage (Day 3), differentiates into a **Blastocyst** (Day 7) and then implants in the endometrium.
   b. The implanted **Blastocyst** consists of an 'Inner-Cell Mass' surrounded by Trophoblasts.
   c. This 'Inner-Cell Mass' differentiates to form the **'Bilaminar Disc'** (2 layers of cells)
      i. **Epiblast Layer:** The *top* layer of *Columnar Cells*.
      ii. **Hypoblast Layer:** The *bottom* layer of *Cuboidal Cells*.



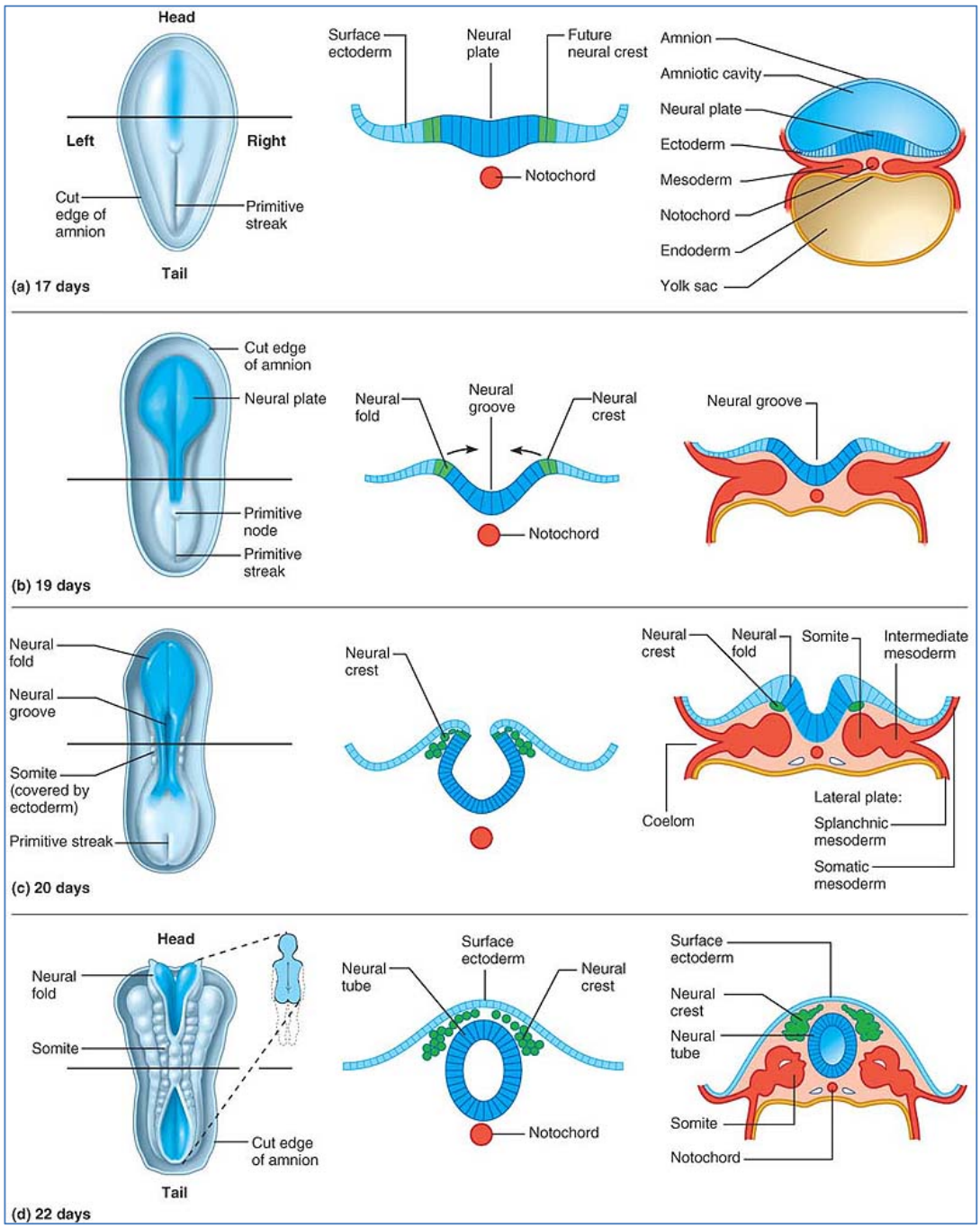




2. **Gastrulation: (Embryonic Period [wk 3+])**
   a. Gastrulation = the process that establishes the **3 Primary Germ Layers** in the Embryo.
   b. Begins with formation of the **Primitive Streak** (a shallow midline groove) along the caudal/tail half of bilaminar disc.
   c. At the cephalic/head end of the Primitive Streak is the **Primitive Node** which surrounds the small **Primitive Pit**. Cells of the **Epiblast** proliferate & migrate *through* the **Primitive pit** into the gap between the Epiblast & the Hypoblast. This is known as **Invagination.**
   d. The **Epiblast** then becomes the **Ectoderm**, the invaginated cells become the **Mesoderm** and the **Hypoblast** becomes the **Endoderm**.

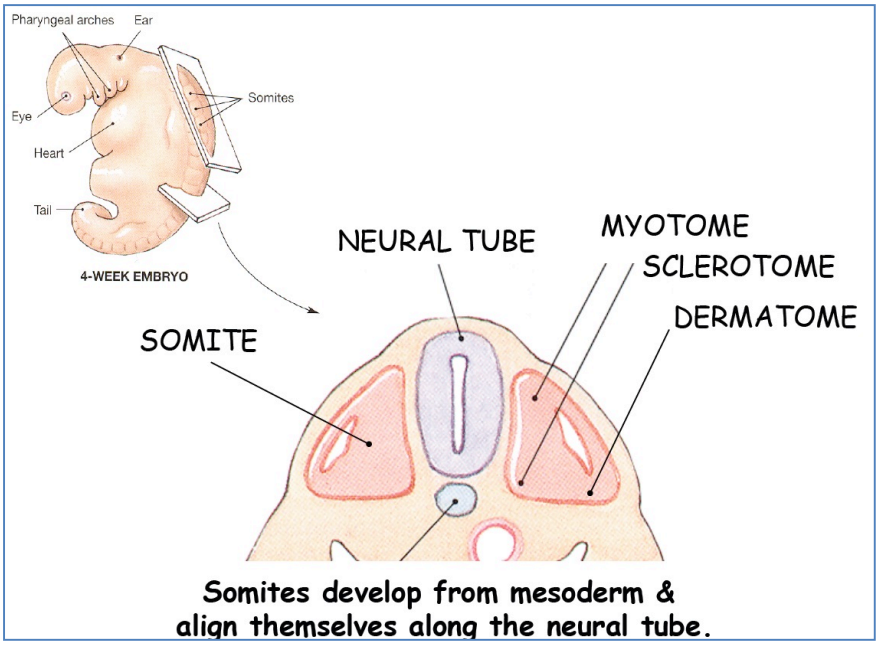


3. **Neurulation:**
   a. Neurulation = Where the ectoderm around the midline thickens to form an elevated **Neural Plate.**
   b. This **Neural Plate** invaginates to form a **Neural Groove** down the midline, flanked by 2 **Neural Folds.** The **Notochord**, a flexible rod of mesoderm-derived cells, defines the primitive axis of the embryo.
   c. The outer edges of the 2 **Neural Folds** continue folding towards the midline where they fuse together to form the **Neural Tube**. (NB: Initially this happens around the centre of the embryo, leaving open Neural Grooves at both the Cephalic & Caudal ends. However, these Neural Grooves, aka **Neuropores**, close off by around wk 6 of development. Failure of a **Neuropore** to close can result in Neural Tube Defects such as Spina-Bifida)
   d. The hollow part inside the **Neural Tube** is called the **Neurocoele.**
   e. The **Neural Tube** then separates from the **Ectoderm** and sinks down to the level of the Mesoderm.
      i. The Mesoderm that flanks the sunken Neural Tube develops into **The Somites**, which eventually become the Skin, Skeletal Muscle & Vertebrae+Skull.
   f. Next, some cells on the top of the **Neural Tube** differentiate and separate to form the **Neural Crest.** Cells of the **Neural Crest** eventually migrate & give rise to **Peripheral Sensory Neurons, Autonomic Neurons & Sensory Ganglia** of the spinal nerves.



The Somites:

- **Somites** = The Mesoderm Tissue directly adjacent to Neural Tube.
    - The Mesoderm that flanks the sunken Neural Tube develops into **The Somites**, which eventually become the Skin, Skeletal Muscle & Vertebrae+Skull.
- Somites grow in association with the developing nervous system → establish early connections.
- **Somites** differentiate into **3 regions:**
    - **Sclerotome:** Becomes the **Vertebral Column** & **Skull**
    - **Myotome:** Becomes **Skeletal Muscle**
    - **Dermatome:** Becomes **Skin**
- Hence, the **Somites** determine the distribution of *Nervous Supply* to all Mesoderm-Derived Tissue.

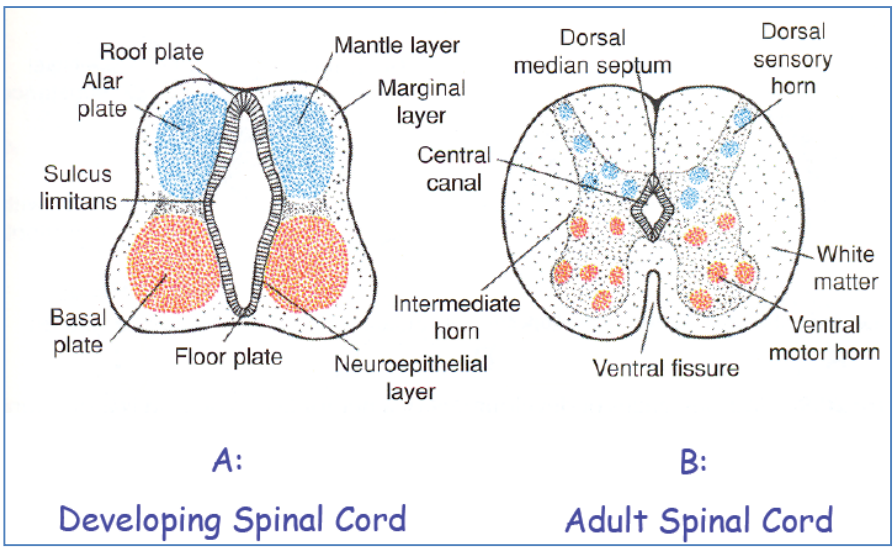


Somites develop from mesoderm & align themselves along the neural tube.

Development of the Neural Tube Into the Spinal Cord:

1. Once the **Neural Tube** closes, the cells differentiate into **Neuroblasts.**
2. These **Neuroblasts** give rise to 2 concentric layers, **The Mantle Layer** (Inner) and **The Marginal Layer** (Outer).
    a. **Mantle Layer:** Later forms the *Grey-Matter* of the Spinal Cord. (Ventral & Dorsal 'Horns')
    b. **Marginal Layer:** Later forms the *White-Matter* of the Spinal Cord.
3. The Dorsal & Ventral regions of the **Mantle Layer** thicken forming 2x**Basal Plates**, and 2x**Alar Plates**.
    a. **Basal Plates:** (Motor Plates) Develop into *Motor Neurons* innervating skeletal muscles.
        i. Become the **Ventral Horns**
    b. **Alar Plates:** (Sensory Plates) Develop into *Sensory Neurons*.
        i. Become the **Dorsal Horns**

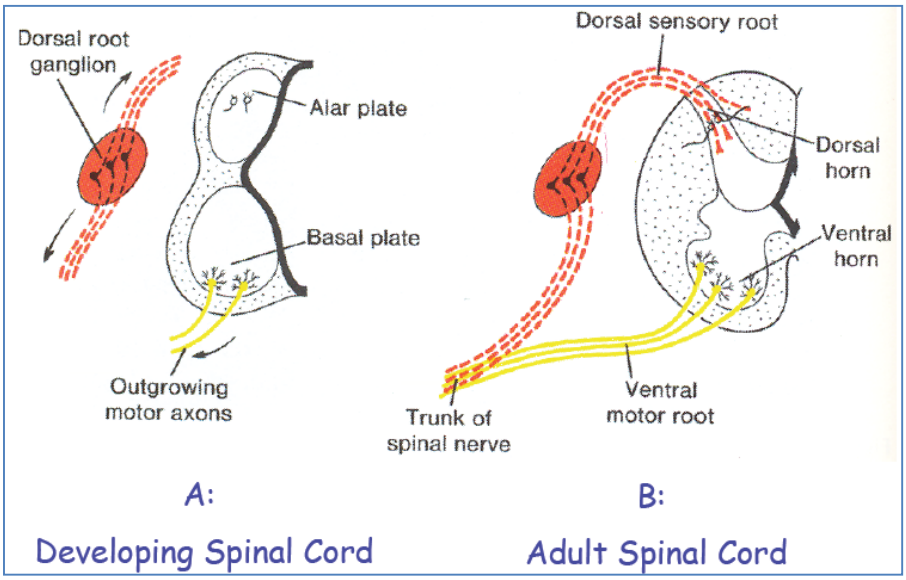
- NB: The **Lateral Horns** in the Thoracic & Lumbar Regions of the Spinal Cord are **Autonomic Motor Neurons** and their Axons exit via the Ventral Roots.



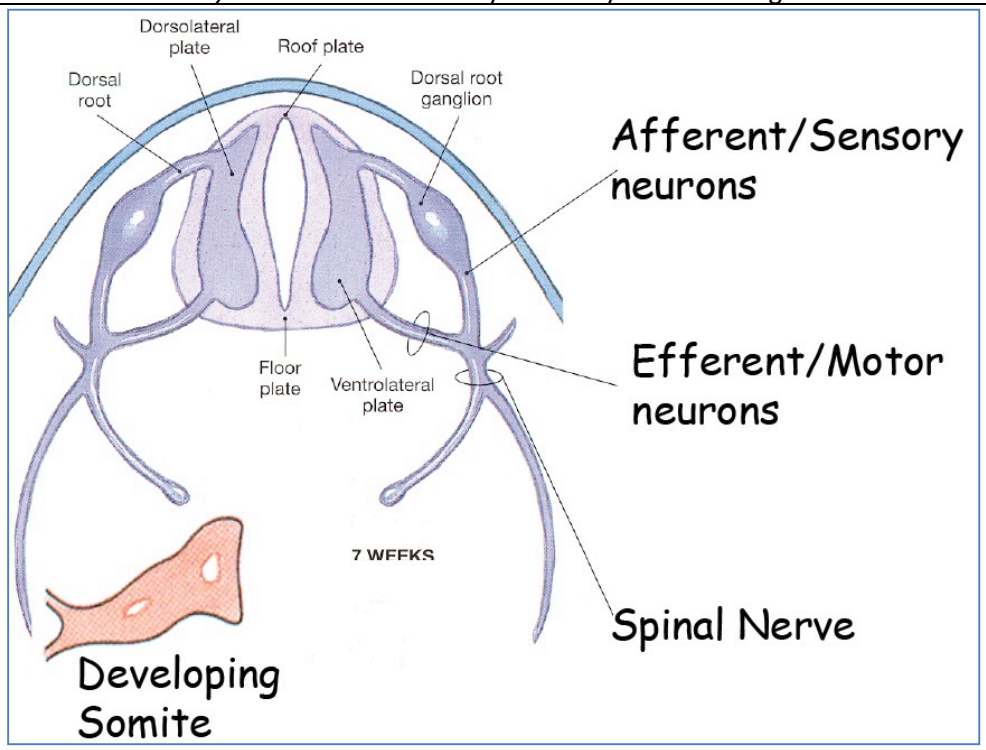
Development of the Neural Crest cells Into the Sensory ('Dorsal-Root') Ganglia of PNS:

1. **Neural Crest** Cells also differentiate into N**euroblasts** which become the **Sensory** ('Dorsal-Root') **Ganglia.**
2. The **Neuroblasts** of the Dorsal-Root Ganglia develop 2 processes:
    a. Penetrates into the **Alar Plate** of the Neural Tube AND/OR into the **Marginal Layer** & up to brain.
    b. Grows distally (outwards) and integrates with the Ventral Motor Root, forming the **Trunk** of the **Spinal Nerve.** These neurons eventually terminate in the sensory receptors in skin/muscle/tendons.

    NB: These Dorsal-Root Ganglia Processes form the ***'Sensory PseudoUnipolar'*** Nerve-Type.



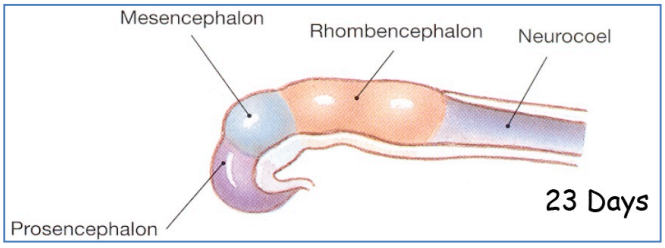
NB: By Wk 7 we have a *Nearly-Functional* Nervous System very similar in Organisation to Adult Anatomy.



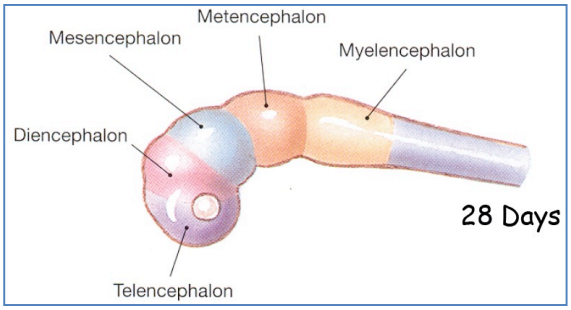
Development of the Head & Brain:

1. **Neural-Tube Enlargement (Cephalic End):**
   a. At around 3-4wks, the Cephalic portion of the **Neural Tube** enlarges to form 3 regions; the **Primary Brain Vesicles**:
      i. **Prosencephalon** (Fore Brain)
      ii. **Mesencephalon** (Mid Brain)
      iii. **Rhombencephalon** (Hind Brain)

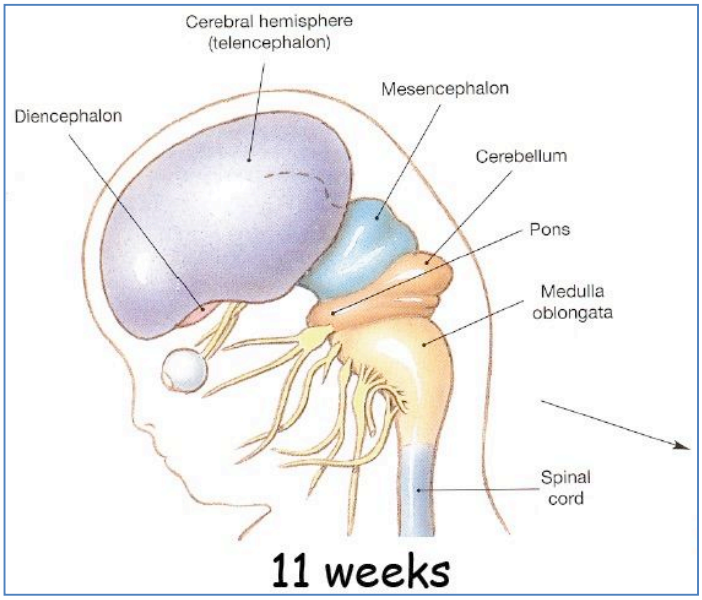
      NB: The Cephalic Flexure between the Prosencephalon & Mesencephalon – important in humans for **Bipedalism** (Brain @ 90^0 to Spinal Cord).

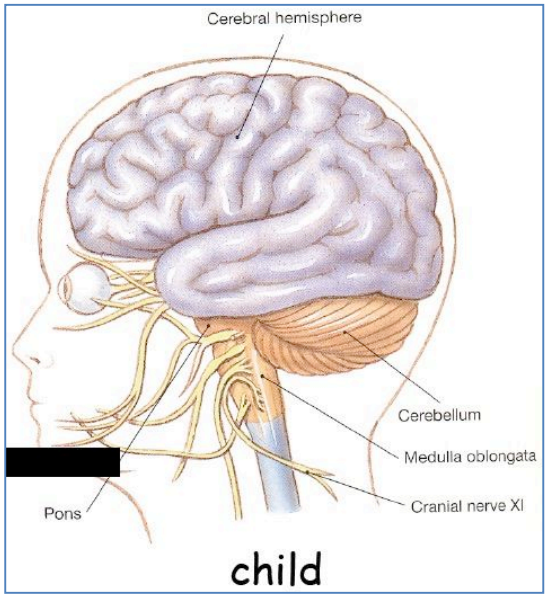


   b. By around 4-5wks, the **Primary Brain Vesicles** develop further:
      i. **Prosencephalon** (Fore Brain) develops into:
         1. **Telencephalon** (Future Cerebral Hemispheres)
         2. **Diencephalon** (Future Thalamus & Hypothalamus)
      ii. **Mesencephalon** (Mid Brain)
      iii. **Rhombencephalon** (Hind Brain) develops into:
         1. **Metencephalon** (Future Pons & Cerebellum)
         2. **Myelencephalon** (Future Medulla)

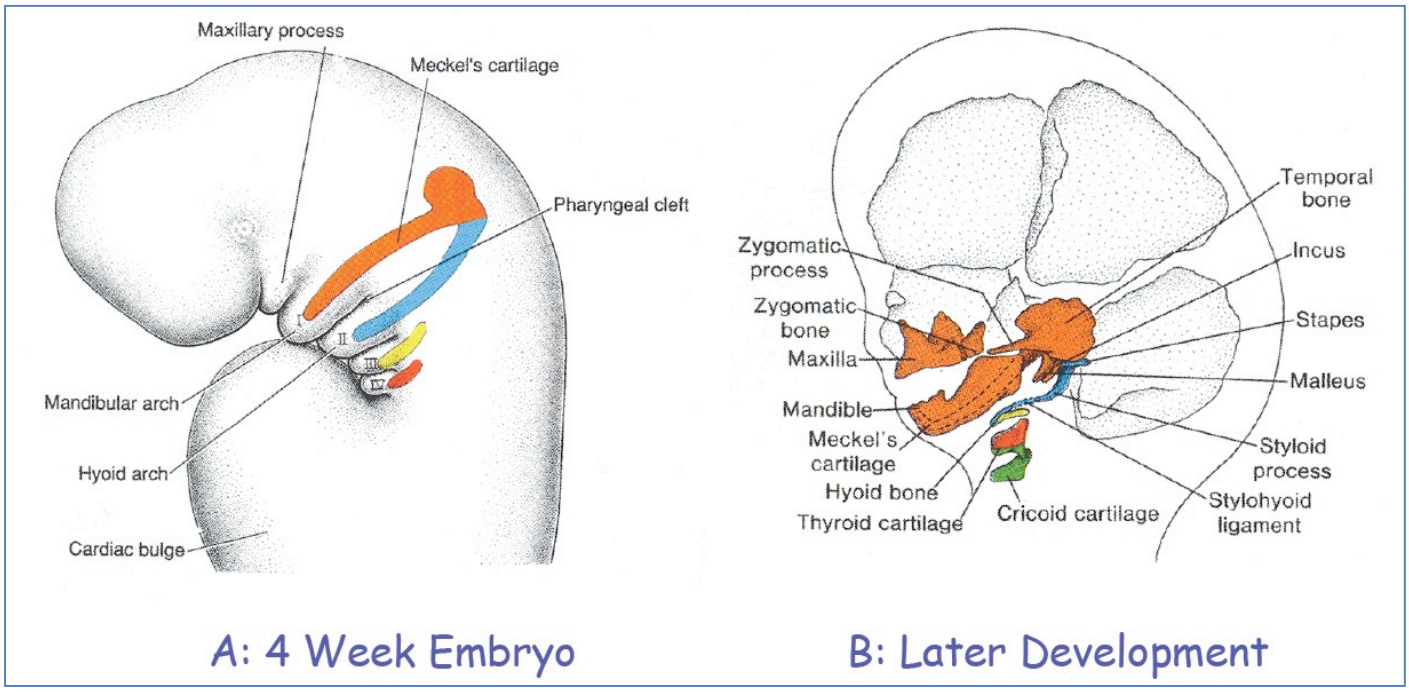


2. **Brain Formation:**
   a. At around 11wks, there is massive **Proliferation** of **Neuroblasts** in Cephalic Neural Tube, causing folding due to lack of space within the cranium.

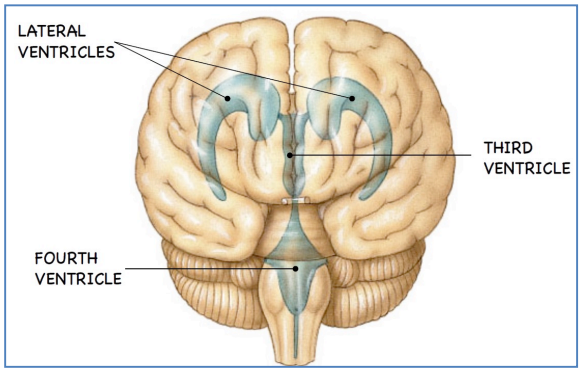


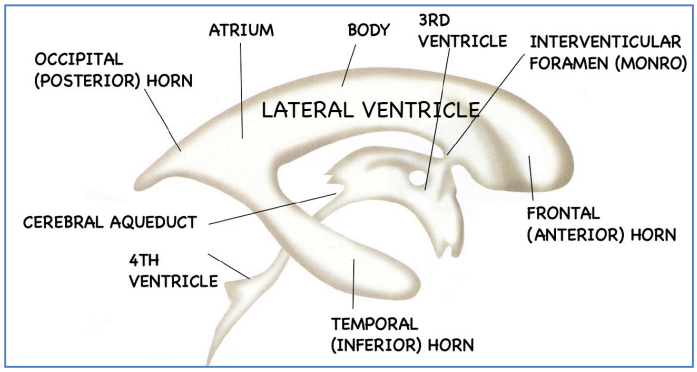


3. **Pharyngeal Arches & Cranial Nerves:**
    a. **Pharyngeal Arches =** Similar to the **Somites** in lower parts of embryo. Each Pharyngeal Arch consists of:
        i. **Ectoderm Tissue** → Cranial Nerves & Skin of Face.
        ii. **Mesenchyme** (Mesoderm) **Tissue** → Musculature of Face & Neck
        iii. **Endoderm Tissue** → Pharyngeal Epithelium.
    b. NB: Essentially, this results in *Segmental Development* of the Head & Neck, similar to Somites.



4. **Formation of Ventricles:**
    a. The **Neurocoel** of the Neural Tube becomes the **Ventricles** of the Adult Brain.





i. **Lateral Ventricles (Vent. 1 & 2):**
    1. Sits in the Cerebral Hemispheres (Telencephalon)
    2. Are shaped due to folding of brain during development.
    3. Each Consists of:
        a. An Frontal (Anterior) Horn
        b. A 'Body'
        c. An Occipital (Posterior) Horn
        d. A Temporal (Inferior) Horn

ii. **Third Ventricle:**
    1. Sits in the Diencephalon
    2. Lateral Walls formed by Thalamus & Hypothalamus
    3. Connects with the 4th Ventricle via the **Cerebral Aqueduct.**

iii. **Fourth Ventricle:**
    1. Sits in the Brainstem
    2. Is Continuous with the **Spinal Canal (Central Canal).**

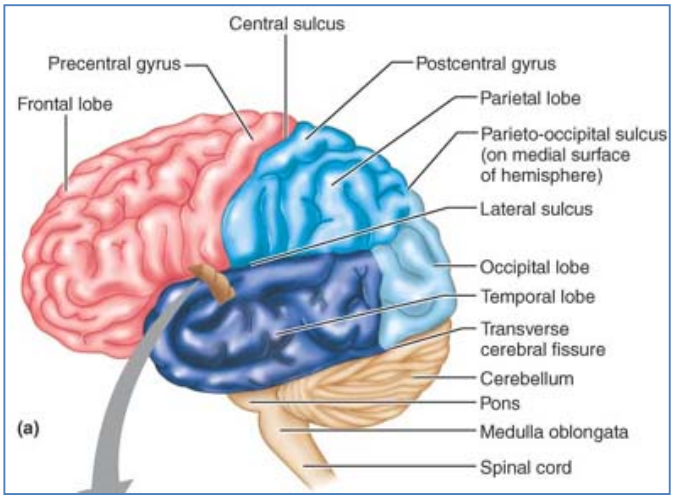
GLS STUFF:

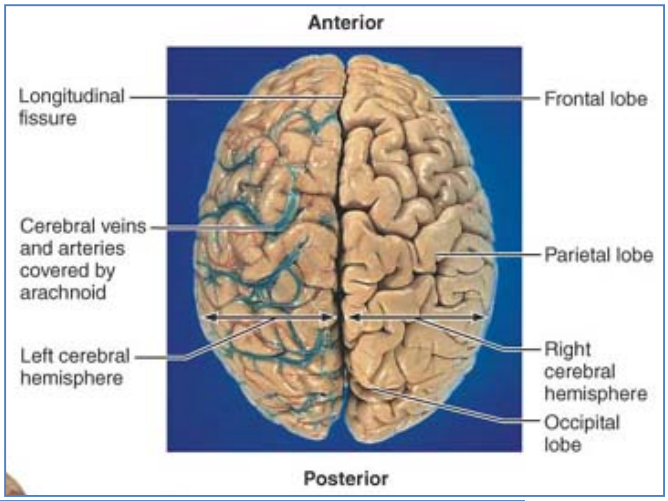
Terminology:

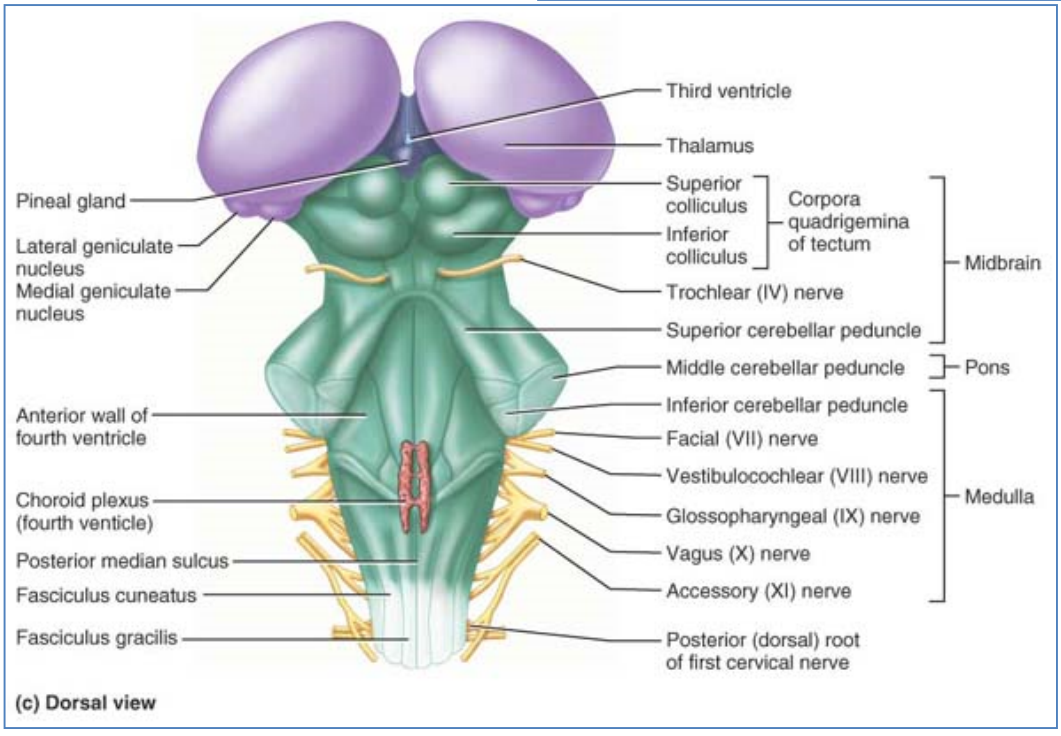
- **"Rostral" = Head**
- **"Caudal" = Tail**
- **"Dorsal" = Back**
- **"Ventral" = Front**
- **"Ganglia" = Groups of Nerve-Cell Bodies**
- **"Gyrus" = Elevations (Crests) of the folds on the Cerebral Cortex.**
- **"Sulcus" = Grooves / Furrows between the Gyri on the Cerebral Cortex.**

Anatomy of the Brain:

- **Surface Anatomy**
  - **Dorsal Landmarks:**
    - **Longitudinal Fissure:** Separates Left & Right Hemispheres
    - **Central Sulcus:** Separates the Frontal & Parietal Lobes.
    - **Lateral Sulcus:** Separates the Temporal Lobe from the Other Lobes.
    - **Occipital Lobe:** Most Caudal Lobe (Visual Cortex)
    - **Colliculi:** Nestled in between the Cerebrum & Cerebellum.
      - **2x Superior:** Controls eye movements
      - **2x Inferior:** Part of Auditory Pathway

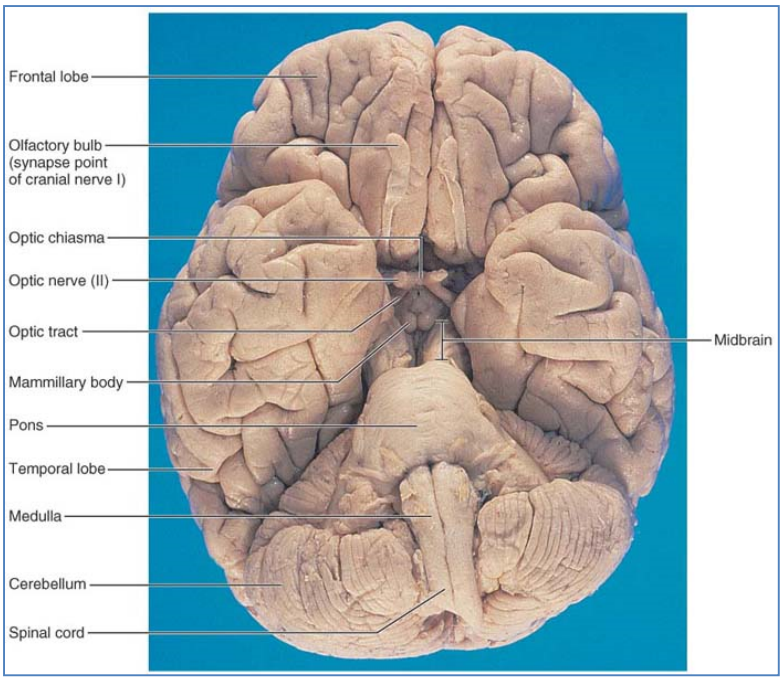




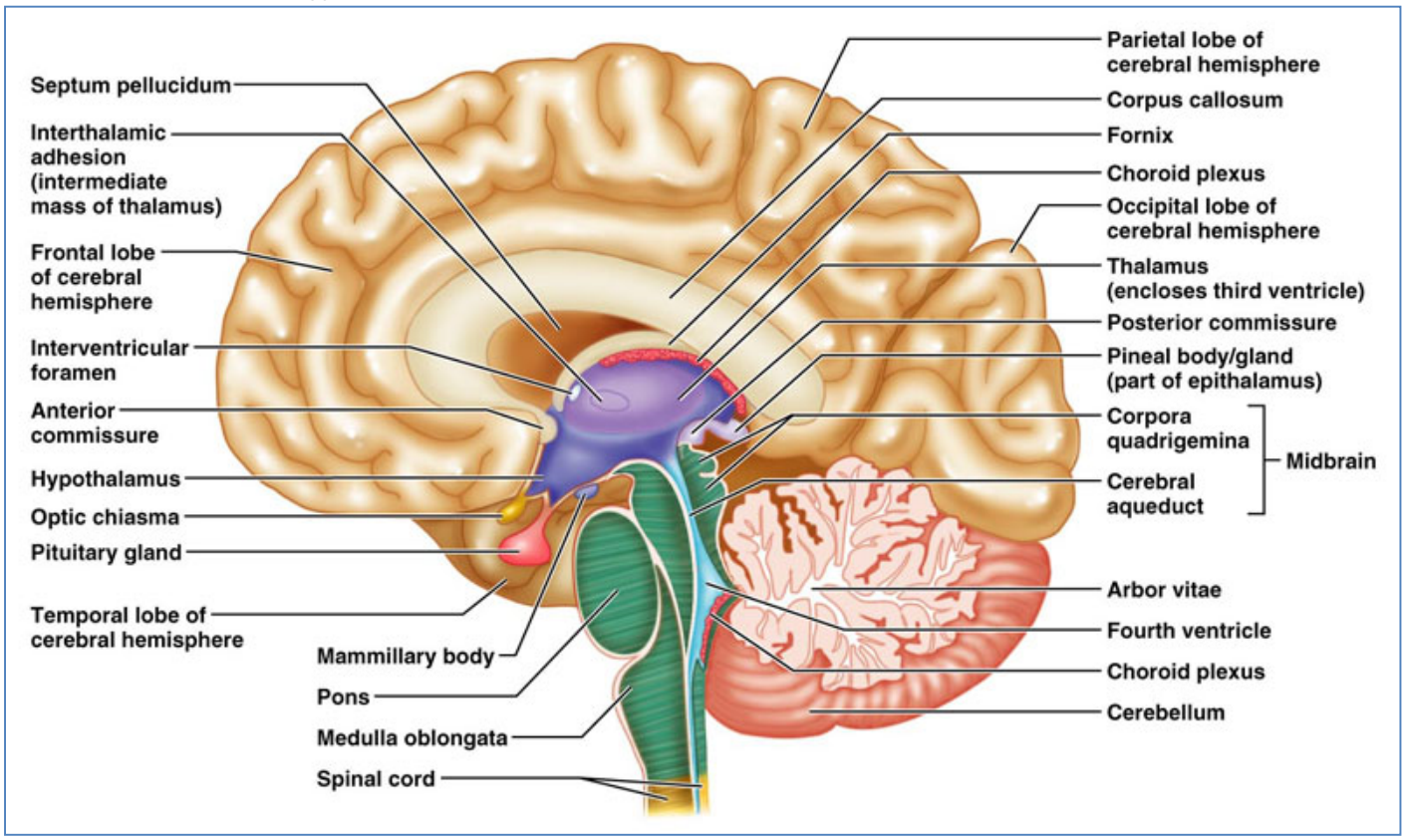


Brain Stem (Note the Colliculi – Superior & Inferior)

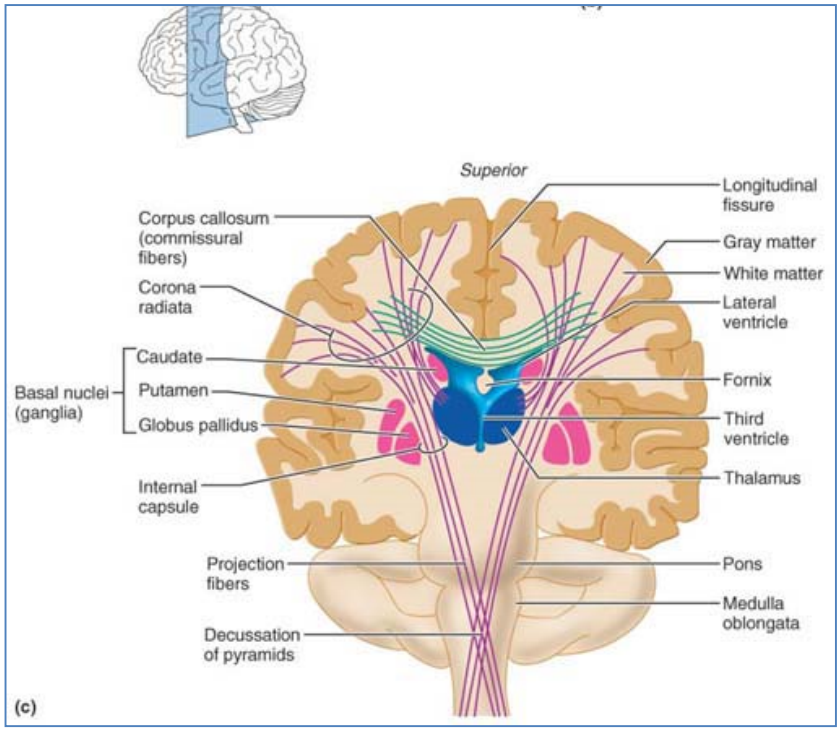
- **Ventral Landmarks:**
  - **Optic Chiasm ("Optic Crossing"):** 'X'-shaped crossing-over of Optic Nerves.
  - **Hypothalamus:**
  - **Infundibulum:** Connection between Pituitary & Hypothalamus.
  - **Pituitary:**
  - **Olfactory Bulbs:**
  - **Mamillary Bodies:**



- **Medial Landarks (Ie. On Sagital Section):**
  - **Cingulate Gyrus**
  - **Corpus Callosum**
  - **Lateral Ventricle**
  - **Pineal Body**
  - **Thalamus**
  - **Hypothalamus**



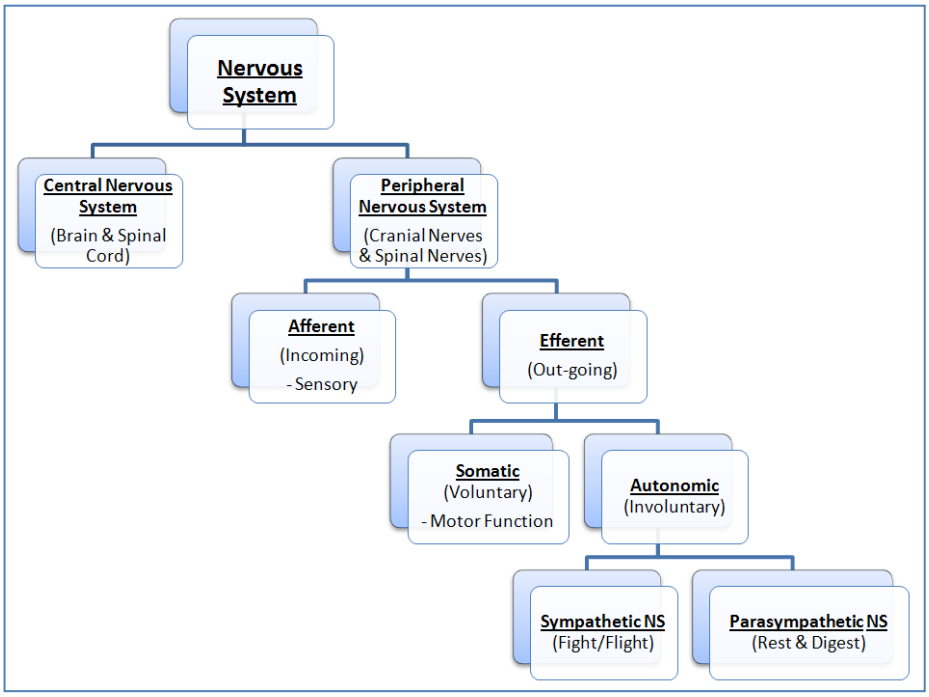
- **Coronal Section Landmarks:**
  - **Cortex (Grey Matter)**
  - **White Matter**
  - **Lateral Ventrcile**
  - **Caudate Nucleus**
  - **Corpus Striatum**
  - **Thalamus**
  - **Massa Intermedia:** The Bridge between the Left & Right Thalamus.
  - **Hippocampus**



System: Neurological

Nervous System:

- **Central Nervous System (CNS)**
  - Brain & Spinal Chord
  - Integrating command centre
- **Peripheral Nervous System (PNS)**
  - Outside the CNS
  - Nerves extending to and from the periphery and CNS



The Neuron:

Structural Features:

a) **Receptive Field: *Dendrites***
   - Stimulated by inputs

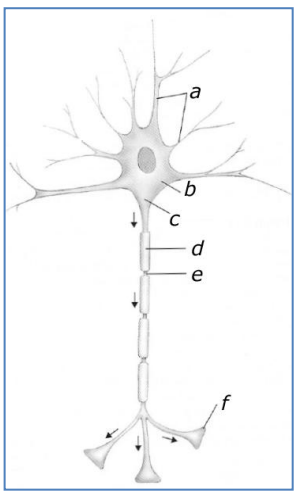
b) **Cell Body: *Soma***
   - Responds to graded inputs

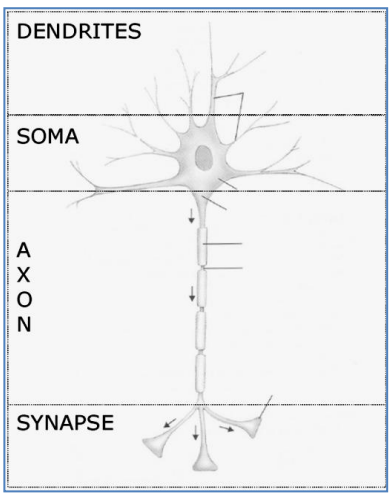
c) **Efferent Projection: *Axon (and axon hillock)***
   - Conducts nerve impulses to target
   - Myelinated and unmyelinated

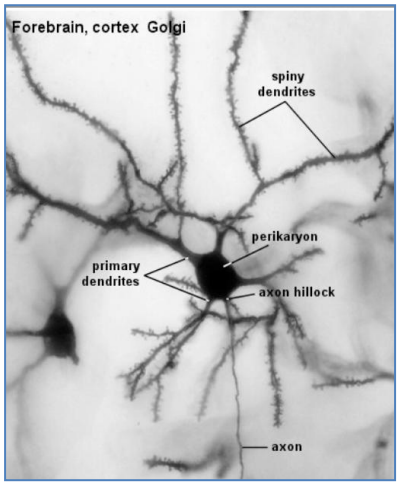
d) **Efferent Projection: *Myelin Sheath***

e) **Efferent Projection: *"Nodes of Ranvier"***

f) **Output: *Synaptic Terminals***

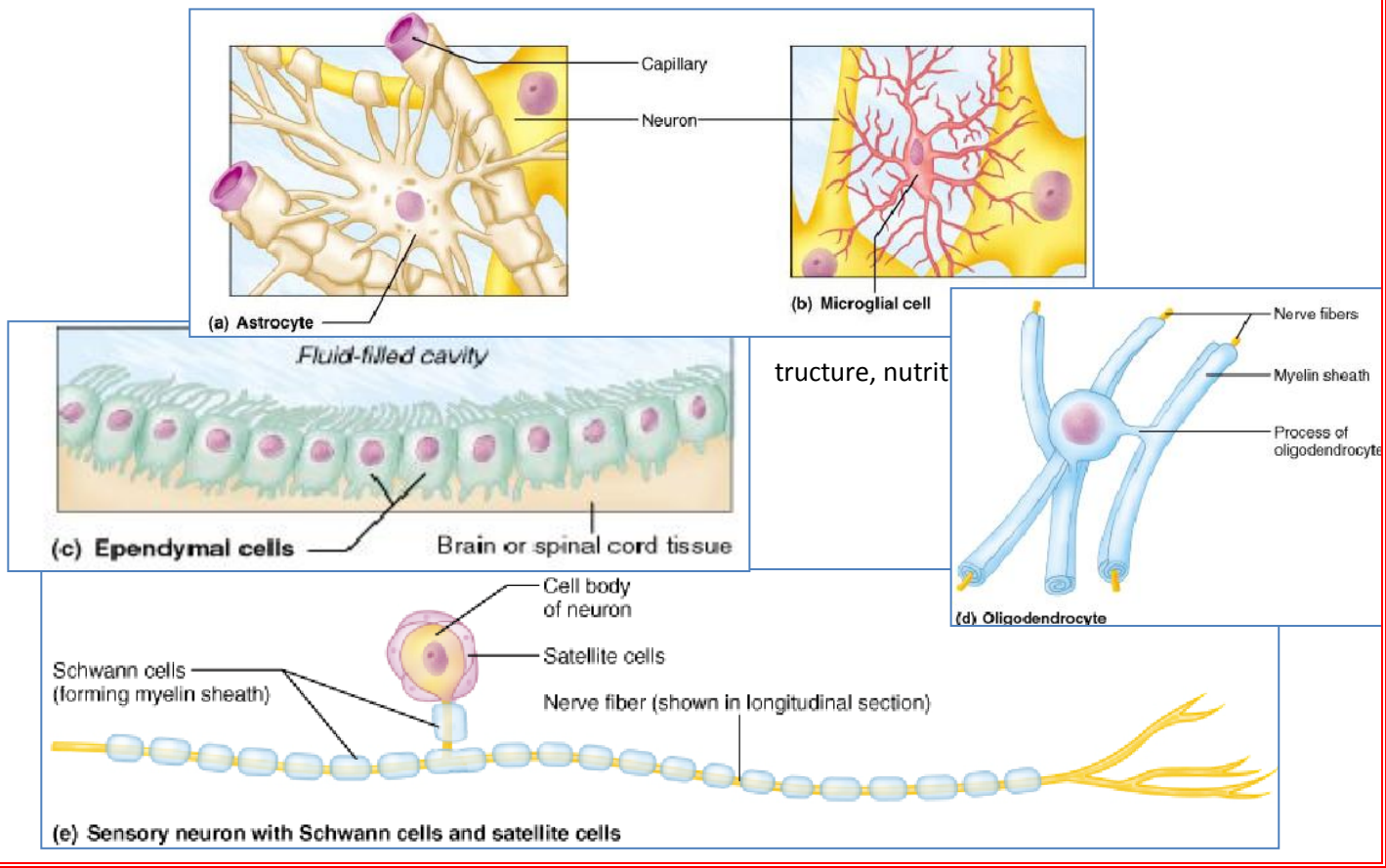






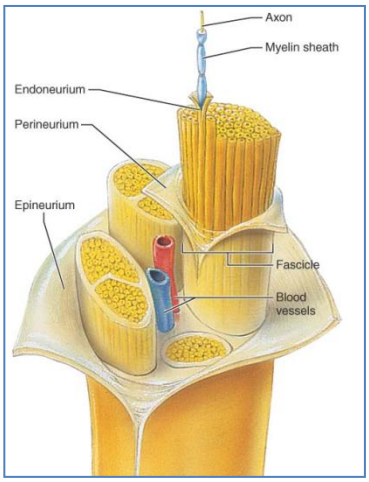
Supporting Cells:

- **Neuroglia (Glia)**
  - Smaller **support cells** of NS
  - Outnumber neurons 10:1
  - Structural & mechanical support
  - Roles in maintaining homeostasis
  - Myelination
  - Immune responses via phagocytosis.
  - **Types of neuroglia:**
    - **CNS:**
      - **Astrocytes**
        - Nutrient bridge between neuron & capillaries
        - Guide migrating young neurons
        - Synapse formation
        - Mop up excess K^+ ions + neurotransmitters
      - **Oligodendrocytes**
        - Myelin formation in CNS
      - **Microglia**
        - Long thorny processes
        - Monitors neuron health
        - Senses damaged neurons
        - Migrates to damaged neuron
        - Phagocytoses microbes & debris (immune cells are denied access to CNS)
      - **Ependymal Cells**
        - Lines central cavities of brain + spinal chord
        - Blood-brain barrier
        - Beating cilia circulates cerebrospinal fluid
    - **PNS:**
      - **Schwann Cells**
        - Myelin Formation – wrap around axon
        - Regeneration of damaged neurons
      - **Satellite cells**
        - Surround neuron bodies



Connective Tissue Sheaths on Peripheral Nerves:

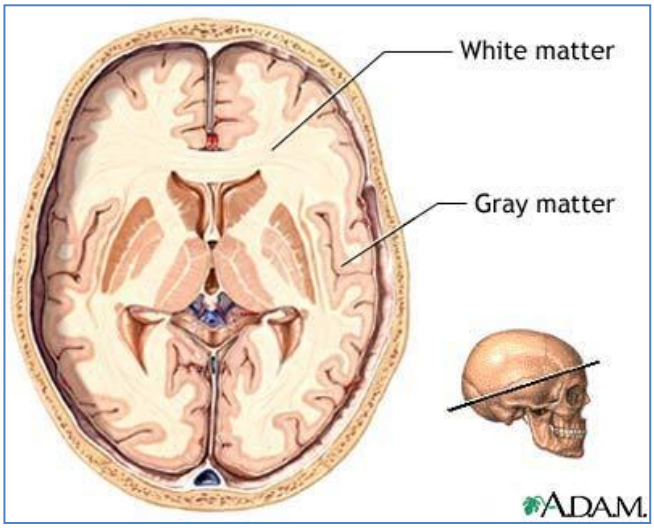
- **Endoneurium**
  - Delicate connective tissue layer
  - Surrounds each axon
- **Perineurium**
  - Coarser connective tissue layer
  - Bundles groups of fibres into **fascicles**
- **Epineurium**
  - Tight, fibrous sheath
  - Bundles fascicles into a **single nerve**.
  - Houses blood vessels



Grey Matter & White Matter:

- **Grey Matter**
  - Neuron bodies (Soma)
  - Imbedded in neuroglial cells
  - Eg:
    - Cortex of Brain
    - Centre of Spinal Chord
    - Ganglia/nuclei

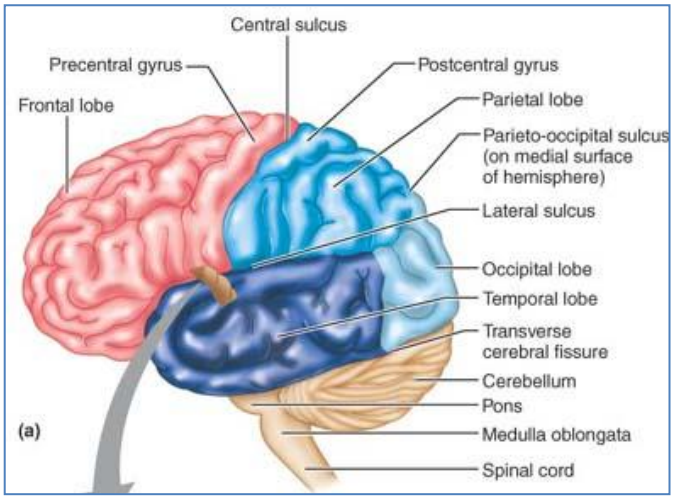
- **White Matter**
  - Neuron fibres (axons & dendrites
  - White due to myelin
  - Eg:
    - Peripheral Nerves & Plexuses
    - Central fibre tracts

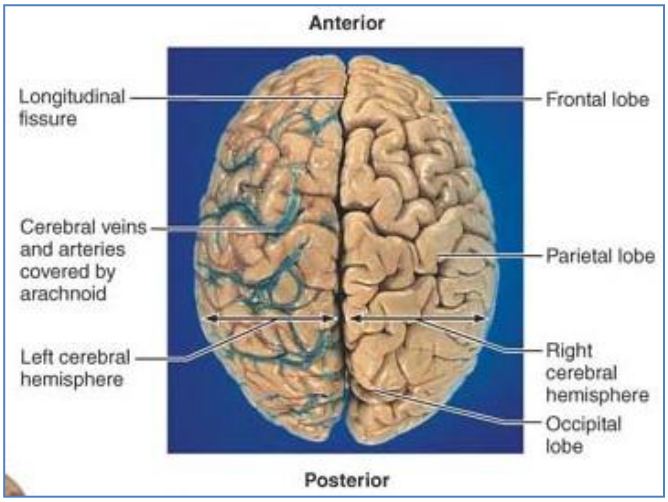


Anatomy of the Brain:

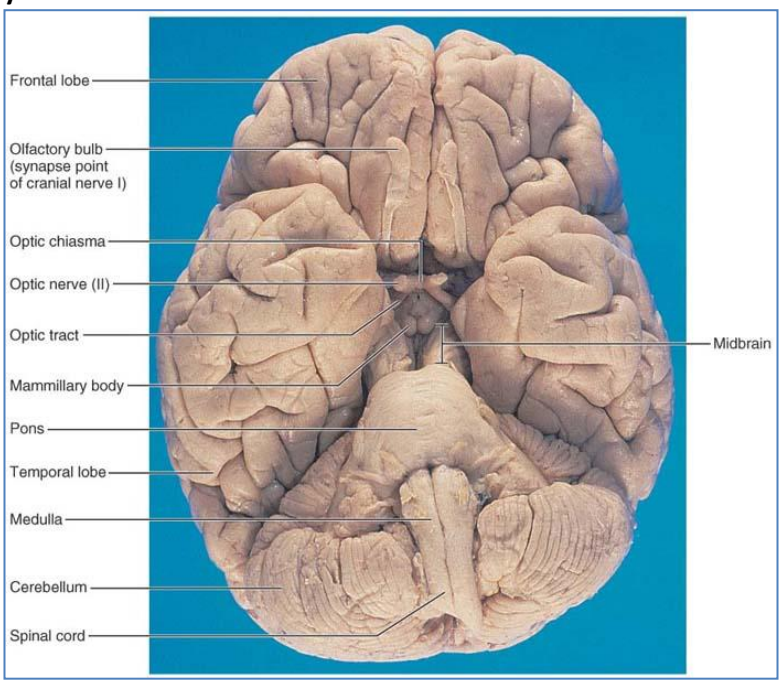
Surface Anatomy

- **Dorsal Landmarks:**
  - **Longitudinal Fissure:** Separates Left & Right Hemispheres
  - **Central Sulcus:** Separates the Frontal & Parietal Lobes.
  - **Lateral Sulcus:** Separates the Temporal Lobe from the Other Lobes.
  - **Occipital Lobe:** Most Caudal Lobe (Visual Cortex)
  - **Colliculi:** Nestled in between the Cerebrum & Cerebellum.
    - **2x Superior:** Controls eye movements
    - **2x Inferior:** Part of Auditory Pathway

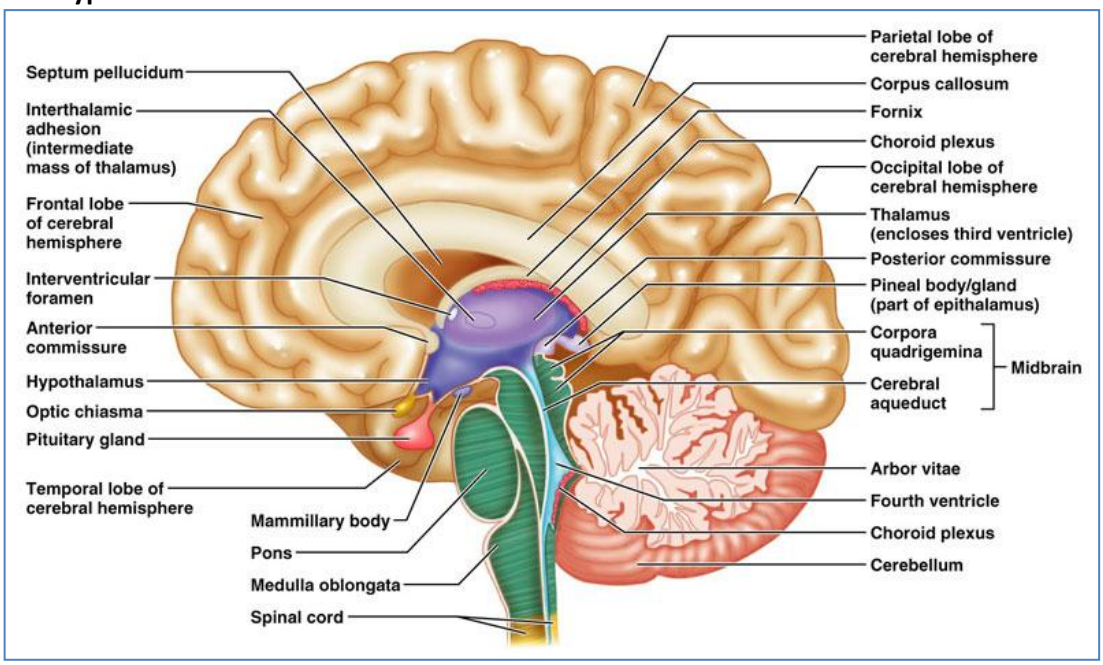




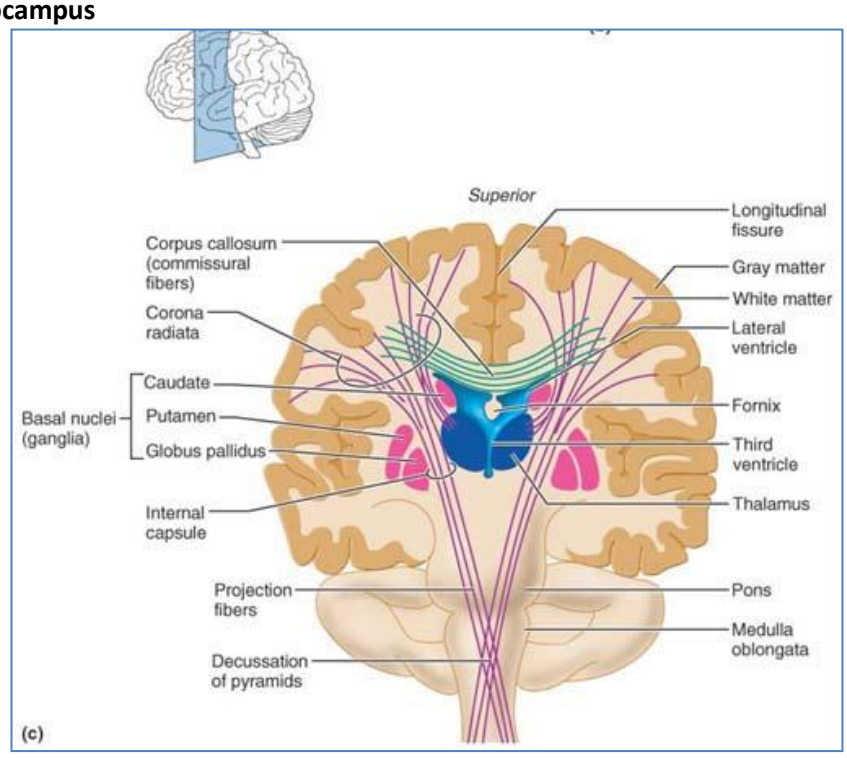
- **Ventral Landmarks:**
  - **Optic Chiasm ("Optic Crossing"):** 'X'-shaped crossing-over of Optic Nerves.
  - **Hypothalamus:**
  - **Infundibulum:** Connection between Pituitary & Hypothalamus.
  - **Pituitary:**
  - **Olfactory Bulbs:**
  - **Mamillary Bodies:**



- **Medial Landarks (Ie. On Sagital Section):**
  - **Cingulate Gyrus**
  - **Corpus Callosum**
  - **Lateral Ventricle**
  - **Pineal Body**
  - **Thalamus**
  - **Hypothalamus**



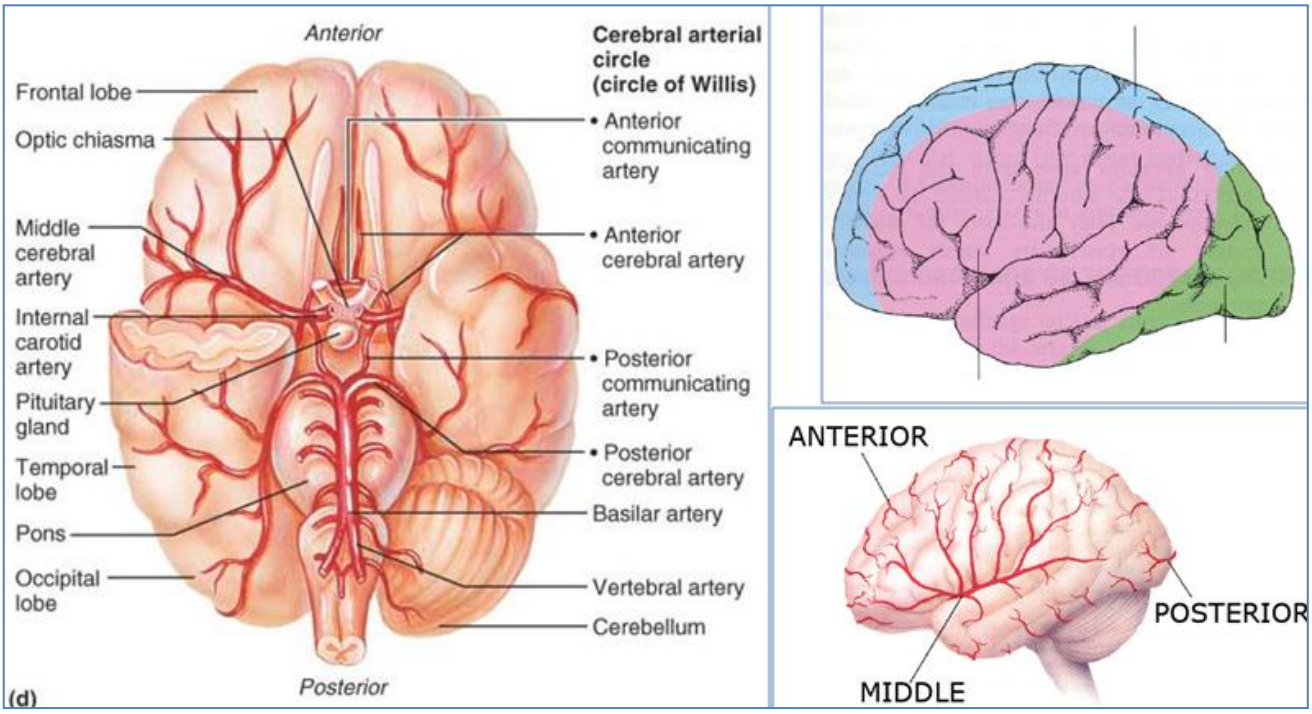
- **Coronal Section Landmarks:**
  - **Cortex (Grey Matter)**
  - **White Matter**
  - **Lateral Ventrcile**
  - **Caudate Nucleus**
  - **Corpus Striatum**
  - **Thalamus**
  - **Massa Intermedia:** The Bridge between the Left & Right Thalamus.
  - **Hippocampus**



Blood Vessels & Blood Flow to the Brain

Arterial Supply of the Brain:

- **Brain is Supplied by 2 Arterial Systems:**
  - 2x Vertebral Arteries → 1x Basilar Artery → Circle of Willis
  - 2x Internal Carotid Arteries → Circle of Willis
- **'Circle of Willis', The Anastomosis of the Brain:**
  - (The *'Roundabout'* of Arteries on the underside of the Brain with multiple *'Roads'* coming off it)
  - (Encircles the Optic Chiasma, The Pituitary Gland & the Mammillary Bodies.)
  - **The *'Roads'*: (Anterior → Posterior)**
    - 2x Anterior Cerebral Arteries
    - *1x Anterior Communicating Artery*
    - **2x Internal Carotid Arteries**
    - 2x Middle Cerebral Arteries
    - *2x Posterior Communicating Arteries*
    - 2x Posterior Cerebral Arteries
    - **1x Basilar Artery**
  - **NB:** Communicating Arteries are always patent, but generally not functional (no blood flow) when blood flow from both Carotids & Basilar Arteries is normal. However, if blood flow from one of the major arteries is impeded, blood is shunted through the Communicating Arteries to compensate.

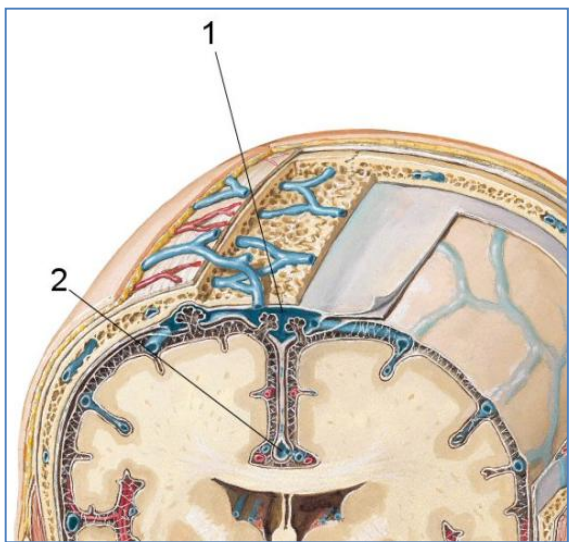


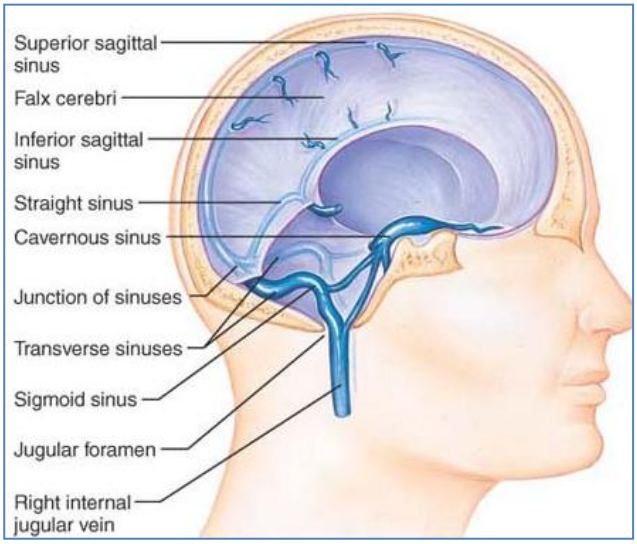
Distribution of Cerebral Arteries:

- **Anterior Cerebral Arteries:**
  - (Travels up and over the Corpus Callosum, sprouting branches outwards towards the cortex)
  - Medial Portion of Frontal Lobe (Incl. Cortex)
  - Medial Portion of Parietal Lobe (Incl. Cortex)
  - Corpus Callosum
- **Middle Cerebral Arteries:**
  - (Travels through the Lateral Fissure/Sulcus and emerges onto the Lateral Surface of the Brain)
  - Lateral Portion of the Frontal Lobe (Incl. Cortex)
  - Lateral Portion of the Parietal Lobe (Incl. Cortex)
  - Entire Temporal Lobe (Incl. Cortex)
- **Posterior Cerebral Arteries:**
  - (Travels along the Inferior brain surface between the Cortex and the Cerebellum)
  - Inferior Portion of Temporal Lobe (Incl. Cortex)
  - Posterio-Medial Portion of Parietal Lobe (Incl. Cortex)
  - Entire Occipital Lobe (Incl. Cortex)

Venous Drainage of the Brain – Via "Dural Sinuses":

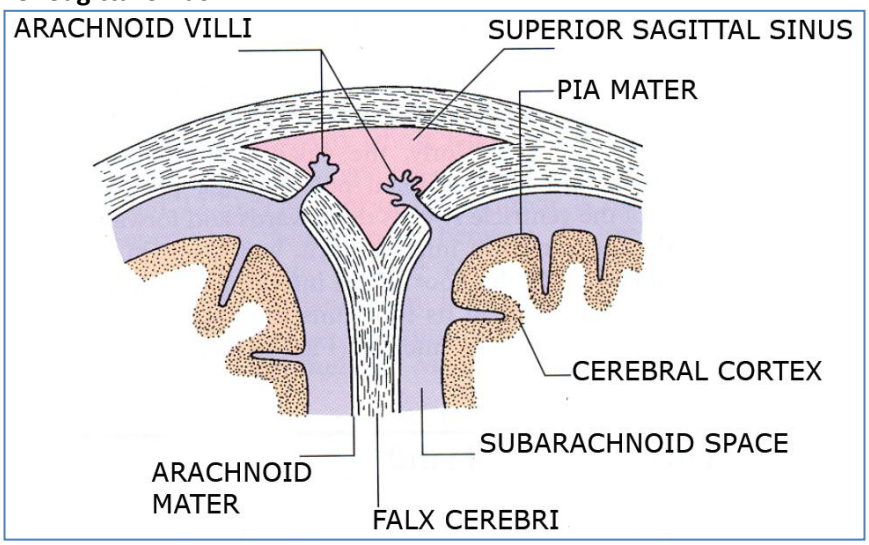
- Venous Drainage begins with venous blood collecting in small venous channels known as "Dural Sinuses".
- **Sinuses Sit Within The Dura-Mater:**
    - The Dura-Mater is the thickest & outermost of the 3 Meninges of the brain. It extends deep into the brain in **2 locations,** the ***Falx Cerebri*** & the ***Tentorium Cerebelli*****:**
        - **1. Falx Cerebri:**
            - The Dura Mater folds deep into the Longitudinal Fissure (Falx Cerebri) of the brain, where it forms 2 Sinuses:
                - 1. A Triangular **'Superior Sagittal Sinus'** at the top of the dural fold.
                - 2. A lower **'Inferior Sagittal Sinus'** at the bottom of the dural fold.
        - **2. Tentorium Cerebelli:**
            - The Dura Mater folds deep into the Transverse Cerebral Fissure (Tentorium Cerebelli) of the brain, where it forms a pair of sinuses:
                - **The R.&L. "Transverse Sinuses"**.
                - NB: All blood from Sup. & Inf. Sagittal Sinuses and the Straight Sinus empties into these Transverse Sinuses.
    - The L.&R. Transverse Sinuses then become the L.&R. **Sigmoid Sinuses** (Respectively).
    - These **Sigmoid Sinuses** turn Inferiorly and become the **Internal Jugular Veins.**



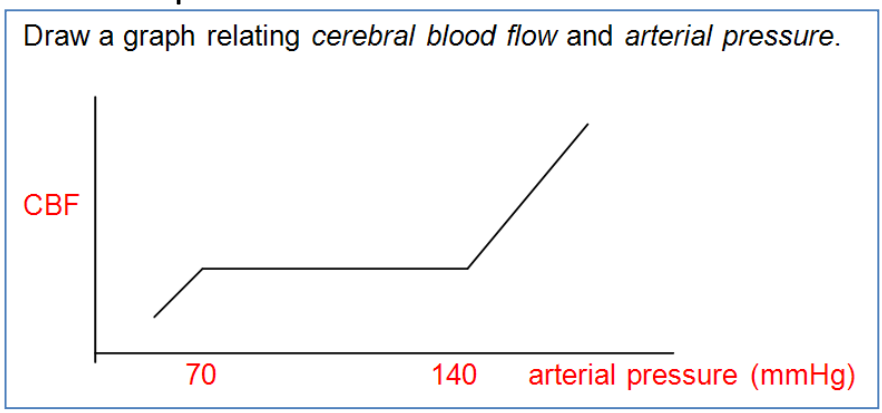


Reabsorption of CSF into the Dural Sinuses:

- NB: CSF is constantly being produced, and therefore must also be constantly drained to prevent a rise in intracranial pressure. Therefore:
- **CSF is Reabsorbed** into the **Venous System** via diffusion through **Arachnoid Villi.**
    - **Arachnoid Villi** are invaginations of Arachnoid Mater **through the Dura Mater** and **into the Superior Sagittal Sinus**.



- **Cerebral Blood Flow And Intracranial Pressure:**
  - Cerebral blood flow is carefully regulated under normal conditions.
  - **Cerebral Blood Flow:**
    - **What percentage of cardiac output goes to the cerebral circulation *at rest*?**
      - 750ml/min (15% of cardiac output)
    - **Relationship Between Cerebral Blood Flow & Arterial Pressure:**

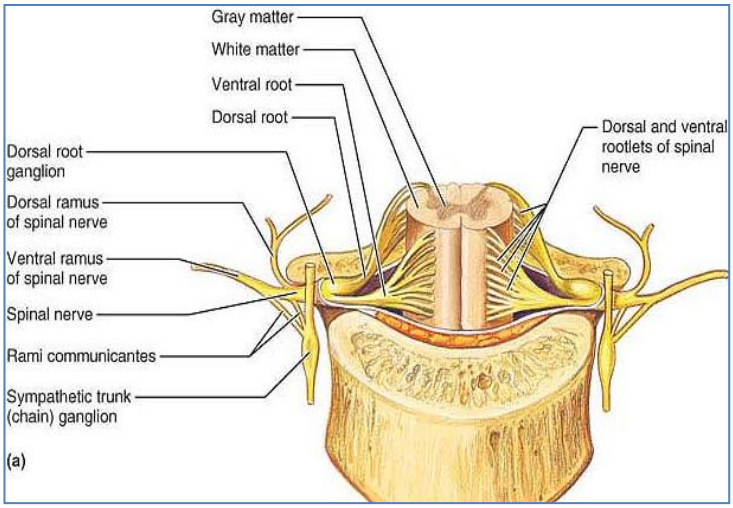


  - **Autoregulation of Cerebral Blood Flow:**
    - **What effect does a *high* P_{CO2} have on cerebral blood flow?**
      - Hypercarbia → Vasodilation → ↑Cerebral Blood Flow.
    - **What effect does a *very low and very high* P_{O2} on cerebral blood flow?**
      - Very High O2 → Vasoconstriction
      - Very Low O2 → Vasodilation
    - **What implication does this have for the *management* of a patient with an acute head injury/cerebral oedema?**
      - You want to prevent any hypercapnia because any vasodilation will → Takes up more room → ↑Intracranial Pressure.
      - You want to maintain PO2

  - **Kelly-Monroe Doctrine:**
    - States that the Cranial Compartment is Incompressible, and the Volume is Fixed.
    - The Cranial Constituents (Blood, CSF, and Brain Matter) create a state of Volume Equilibrium:
      - Any increase in Volume of one of the constituents must be compensated by a decrease in volume of another.
    - **Volume Buffers:**
      - Both **CSF and**, to a lesser extent, **Blood** Volume.
      - (Eg. In Extradural Haematoma → CSF & Venous Blood Volumes are Decreased)
      - → Maintain normal ICP
      - Buffer Capacity ≈ 100-120mL

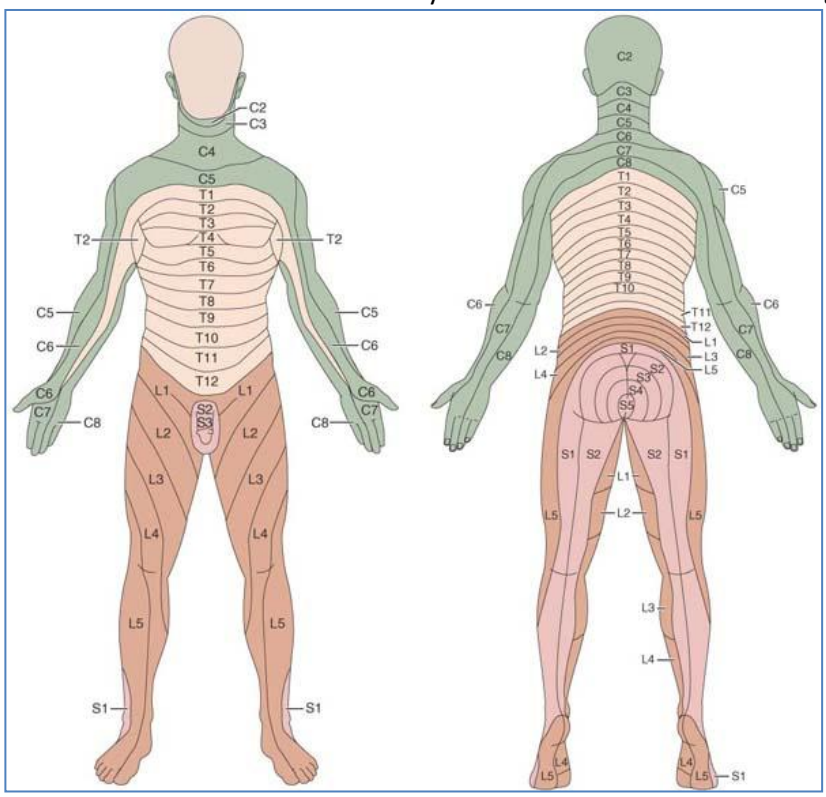
Ganglia

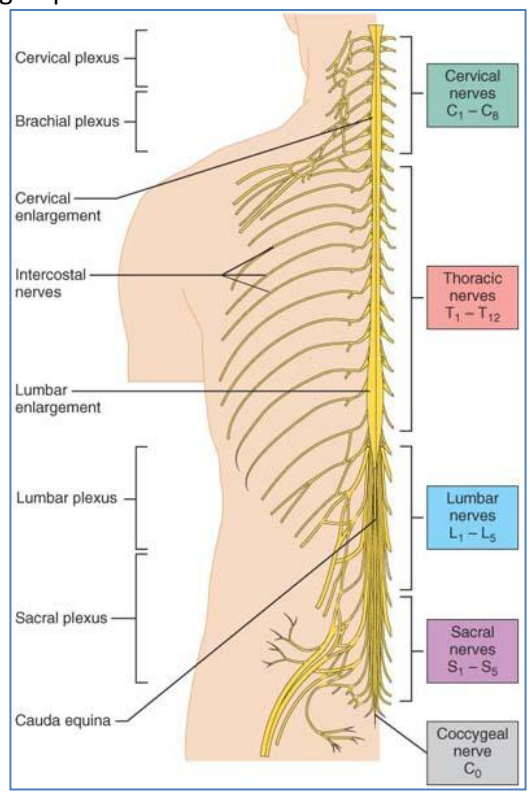
- **Collections** of neuron **cell bodies** in **PNS**
  - **Afferent** Spinal Nerves:
    - Cell bodies of sensory neurons
    - 'Dorsal root ganglion'
  - **Efferent** Spinal Nerves:
    - Cell bodies of autonomic nerve fibres
    - 'Sympathetic trunk ganglion'
  - **In Central Nervous System:**
    - Called: **Basal Nuclei / Nuclei**



Spinal Nerves:

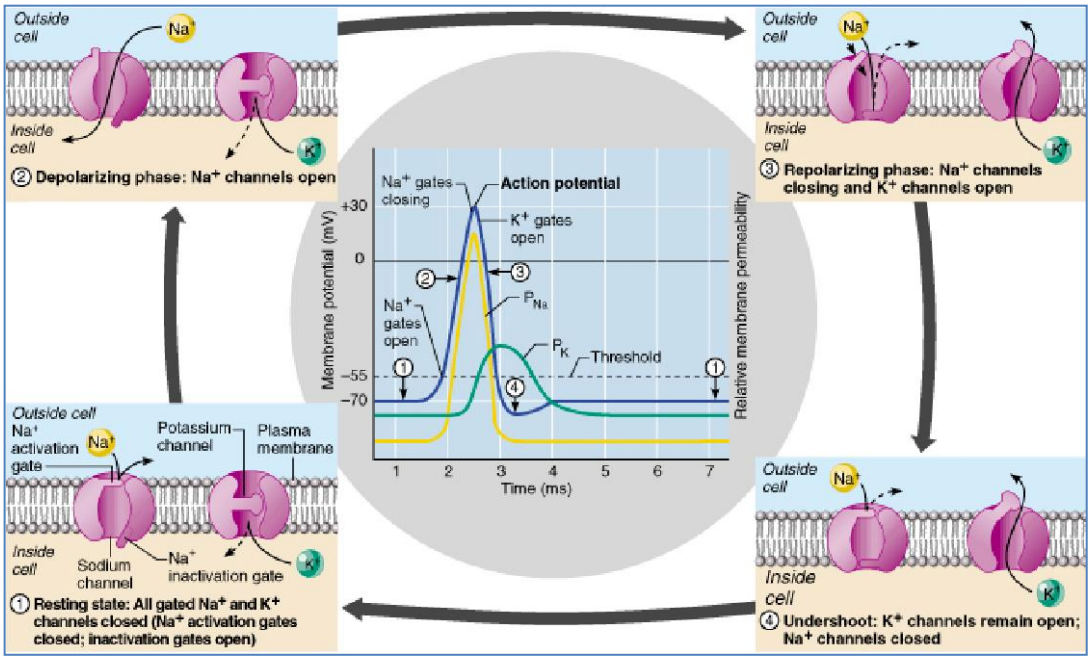
- **Innervation of the Skin:**
  - **Dermatomes:**
    - A portion of the mesoderm (skin, sensory receptors, sebaceous glands, blood vessels) innervated by the cutaneous branches of a single spinal nerve.





Neuronal Action Potentials:

- **4 Phases:**
  - **1 – Resting Phase:**
    - Membrane is **much** more permeable to K^+ than to Na^+.
    - Greater diffusion of K out than Na in
    - Therefore inside is negative/Ouside is positive.
    - **Both Na & K voltage gated channels are CLOSED.**
  - **2 – Depolarisation Phase:**
    - Mechanical/chemical/vibratory/other stimulus opens some Na^+ channels such that Na^+ flows into the cell.
    - Therefore membrane potential becomes less negative (ie. It depolarises)
    - If the MP reaches approx. **-55mV (threshold)**, the **voltage gated Na^+ channels open**.
    - Na^+ influx increases dramatically – until MP reaches approx. **+30mV** where the voltage-gated Na^+ channels close.
  - **3 – Repolarisation Phase:**
    - @ approx. +30mV K^+ voltage gated channels open. (perm. of K increases & Na decreases)
    - Large outflow of K^+ → membrane potential becomes more negative (repolarises) and returns to -70mV.
  - **4 – Hyperpolarisation (undershoot) Phase:**
    - K^+ channels remain open past -70mV and MP becomes more negative than at rest.
    - K^+ channels close and Na/K ATPase returns the MP to normal (-70mV)



Refractory Periods During the Action Potential:

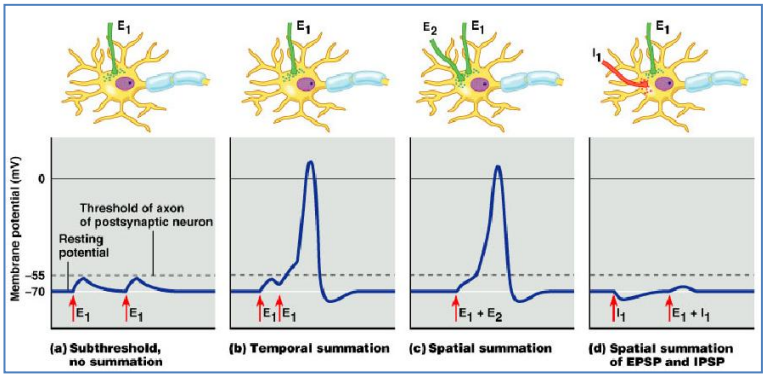
- Basically the total time between a stimulus creating an action potential and the MP returning to rest.
  - Determines how soon a neuron can respond to another stimulus.
- Divided into 2 sub-periods:
  - **Absolute Refractory Period –** no additional stimulus (no matter how large) can initiate a further action potential.
  - **Relative Refractory Period –** If an additional stimulus is to initiate another action potential during this time, it must be larger in order to reach threshold.

Speed of impulse: Dependent upon:

- 1. Axon Diameter → Larger = Quicker
- 2. Presence of Myelin (white matter) → Impulse jumps from exposed axon-region to the next instead of having to open & close ion channels across the axon's entire length (which would be slow)

Phases of Neurotransmission:

1. **Action potential** reaches axon terminal, opens voltage-gated **Ca^+ channels.**
   - **Influx of Ca^+** into axon terminal causes **vesicles** of neurotransmitter to migrate to the axon terminal.
   - **'Neurotransmitter'** released by exocytosis from the sending (**pre-synaptic) neuron.**
   - **Neurotransmitter** (acetylcholine/nor adrenaline/dopamine/glutamate/gaba/etc) diffuses across **synaptic cleft** between 2 neurons.
2. Neurotransmitters bind to **ligand-gated ion channels**, causing change in MP of **post-synaptic neuron** (dendrite) → creating **graded potentials**.
   -Short-lived, localised changes in membrane potential.
   -Current flow decreases in magnitude with distance.
   -The stronger the stimulus, the greater the GP (and further distance)
   - If GP **depolarises** membrane, it is **excitatory**
   - If GP **hyperpolarises** membrane, it is **inhibitory.**



   - The **sum** of the GP may cause MP to reach threshold, triggering an action potential on the next neuron.
3. **Neurotransmitter Inactivation** stops continued stimulation of post-synaptic neuron.
   - Neurotransmitter is either broken down by enzymes (eg. ACh-Esterase) or reabsorbed by pre-synaptic terminal.

2 Types of Post-Synaptic Receptors:

- **Ionotropic:** **(Ligand-Gated Ion Channels)**
  - **Mech:** Binding of Neurotransmitter → Opening of Ion Channel → Excitation/Inhibition of Cell.
    - **Excitatory: Na^+/Ca^+ Channel** – opening → Na^+/Ca^+ Influx → Depolarisation of Membrane → → *"Excitatory Post-Synaptic Potential" (EPSP)*
    - **Inhibitory: Cl^- Channel** – opening → Cl^- Influx → Hyperpolarisation of Membrane → **K^+ Channel** – opening → K^+ Efflux → Hyperpolarisation of Membrane → → *"Inhibitory Post-Synaptic Potential" (IPSP)*
- **Metabotropic:** **(G-Protein Linked Receptors)**
  - **Mech:** Binding of Neurotransmitter → Activates G-Protein → Activates 'Effector' Proteins → Activate secondary Messengers (Eg. cAMP) → Regulates Ion Channels/Activates Enzymes/Alters Metabolism.

Actions of Neurotransmission:

- **Direct Physiological Action:**
  - Eg. Neuromuscular Junction → Muscle Contraction
  - Eg. Sympathetic Synapse @ SA-Node → ↑Heart Rate
- **Links in a Chain:**
  - Eg. Peripheral Sensory Neuron → Spinal Cord → Ascending Sensory Pathways → Thalamus → Cortex
- **Modulation:**
  - Ie. Exerting a +ve/-ve influence on transmission *by another neuron.*

The Neurotransmitters

The Major Neurotransmitters (Classified by Structure):

- ****Amines ("Classical Neurotransmitters"):**
  - Acetylcholine (ACh)
  - Dopamine
  - Noradrenaline/Norepinephrine (NA/NE)
  - Serotonin/5-Hydroxyl Tryptamine (5-HT)
- **Amino Acids:**
  - Glutamate (#1 Excitatory Neurotransmitter of the Brain)
  - GABA (γ-Amino Butyric Acid) (#1 Inhibitory Neurotransmitter of the Brain)
  - Glycine
- **Peptides:**
  - Cholecystokinin
  - Enkephalins (Eg. Endorphins, Opioids) (Turn off Nociceptive/pain Pathways)
  - Vasoactive Intestinal Peptide (VIP)

Memories

Short-Term Memory (STM):

- ***Based in Hippocampus***.
- **Lasts Seconds → Several Hours MAX.** (AKA: "Crammers" Memory)
- **Limited to ≈7-8 "Chunks"** of Info.
- **Amnesia** ≈ Damage to Connection between STM & LTM.

Long-Term Memory (LTM):

- **Limitless Capacity:**
- **Usually Requires STM Input:**
  - Generally LTM-Creation requires the info to pass through STM first.
- **LTM Creation – Improved by:**
  - Positive/Powerful Emotional State
  - Rehearsal
  - Association of New data with Old Data.
  - The Belief that the Memory is Important
- **By Remodelling the Neuron** (Functionally/Structurally)
- More Specifically, **Synaptic Remodelling:**
- **Long-Term Potentiation (LTP):**
  - **Definition:** "A Long-Lasting Post-Synaptic Depolarisation, induced through Repetitive Stimulation & Summation of Excitatory Post-Synaptic Potentials."
    - Simply – "A Persistent Increase in Synaptic Strength"
  - **The #1 Neurotransmitter:**
    - **Glutamate** → binds to ***NMDA*** and/or ***AMPA*** Receptors.
  - **3 Phases of LTP:**
    - **1. Induction** - (Synaptic *Plasticity*)
    - **2. Expression** - (Synaptic *Augmentation*)
    - **3. Maintenance -** (Long Term Loss/Continuation of LTP)
- **2 Types of Long-Term Memory:**
  - **1. Declarative (EXPLICIT):**
    - **Brain Regions:**
      - Hippocampus
      - Para-Hippocampal Regions (Medial Temporal Lobe)
      - Areas of Cerebral Cortex
      - Thalamus + Hypothalamus
    - **Learning "*WHAT*"**:
      - Facts/Words/Ideas/Concepts/Events
  - **2. Non-Declarative (IMPLICIT):**
    - Learning ***"HOW"***: - How to do things/How to recognise things.
      - **Motor:** Motor Cortex, Cerebellum,
      - **Emotional Responses:** Amygdala

- **Seven 'Sins of Memory' – (Types of Memory Deficits):**
  - **1. Transience**
    - – Memory 'Fade'
  - **2. Absent-Mindedness**
    - – Brushing teeth when already brushed them
  - **3. Blocking**
    - – When a memory is on the 'Tip of the tongue'.
  - **4. Misattribution**
    - – Where you Misremember where you saw/heart something, or even if.
  - **5. Suggestibility**
    - **-** Where someone suggests that you saw/heard something (when you didn't) and you 'remember' seeing/hearing it.
  - **6. Bias (Negative Bias)**
    - **-** Tend to recall only the Negative Things.
  - **7. Persistence**
    - - Remember a *Single Failure* rather than multiple successes (eg. Post Exam Briefings)
  - ...**8. Confabulation –** When you elaborate on a memory.

Intelligence - Theories:

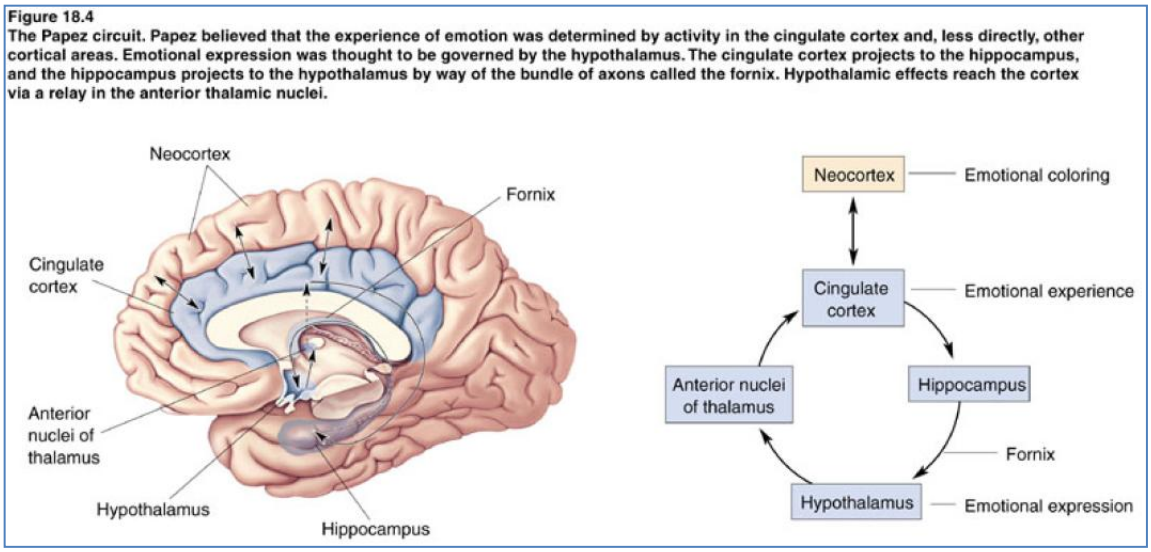
- **Theory of Multiple Intelligences:**
  - **7 Intelligences:**
    - **Linguistic:** **-** Good with words/dates/names/places.
    - **Logical-Mathematical** **-** Good with numbers/abstract/puzzles/logic/computers
    - **Spatial** - Good with pictures/directions/jigsaws/construction/drawing
    - **Musical** - Good with sounds/notes/rhythms.
    - **Bodily-Kinaesthetic** - Good with motor/sports/mimicking/fine craft
    - **Interpersonal** **-** Good with people/leading /manipulation/streetwise/team/Co-op
    - **Intrapersonal** **-** Independent/Loner/sense of self-worth/individual/opinionated

- **Emotional Intelligence:**
  - **Properties:**
    - Knowing your feelings/strengths/weaknesses.
    - Managing your emotions/motives/behaviour
    - Persisting despite setbacks
    - Empathy (good at reading other's emotions)
  - **Indicators of EI:**
    - Optimism
    - Taking Initiative
    - Achievement Motivation
  - **3 Adaptive Abilities:**
    - Appraisal & Expression of Emotion
    - Regulation of Emotion
    - Utilisation of Emotion

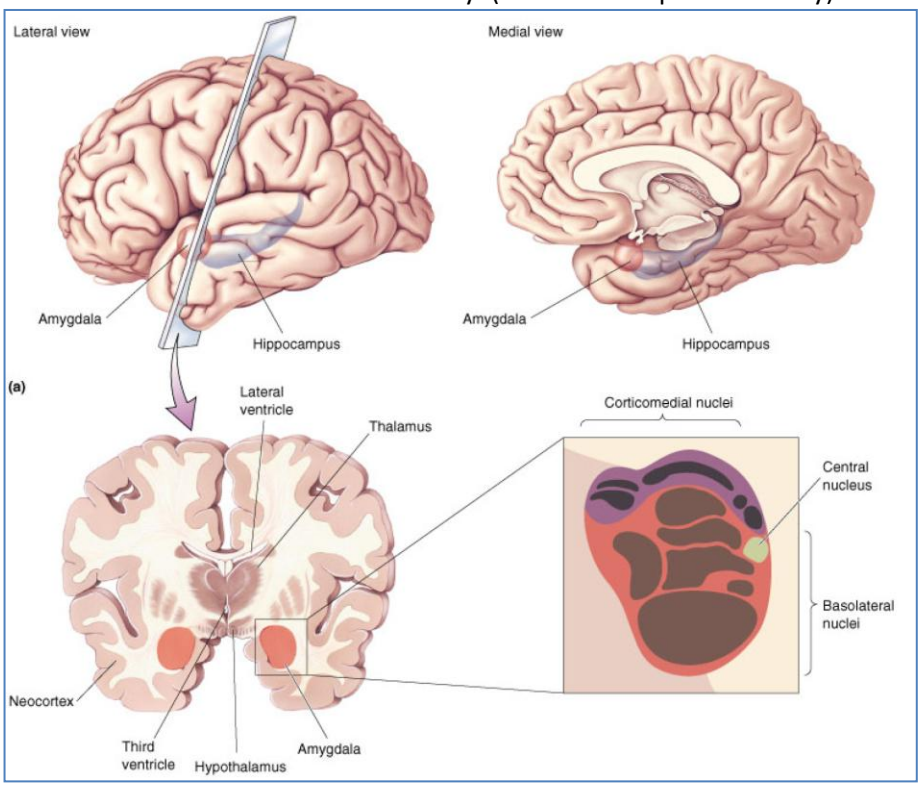
Neurobiology of Emotions

Neuroanatomy of Emotion – The Limbic System:

- **The Papez Circuit:**
  - **1. Thalamus** relays Sensory Input to Cingulate Cortex.
  - **2. Cingulate Cortex** - gives you the Emotional Experience
    - also relays to the **Neocortex**, which gives Context/Colouring to the Emotion.
    - also relays to the **Hippocampus** →
  - **3. Hippocampus** Relays to the Hypothalamus – Causes the Emotional Expression (Visceral Response)



- ***Amygdala***:**
  - #1 Structure involved in Emotion → The "Heart" of the Limbic System.
  - "The Fight/Flight Centre"
  - Linked to all but 8 areas of the Cortex → :. Thought to be #1 integrator of Cognitive & Emotional Info.
  - **Regulates:**
    - Fear & Aggression
    - Vigilance & Attention
    - Recognition of Emotion (in Self & Others)
    - Emotional Contribution to Memory. (Emotional Implicit Memory)



Neurotransmitters & Emotion:

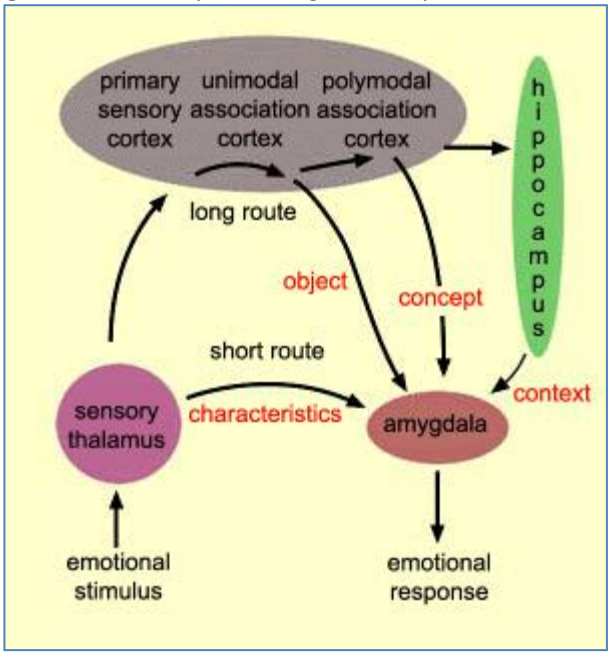
- ***Noradrenaline:**
  - **Activated By:**
    - Novel, Unexpected Stimuli
  - **Released By:**
    - ***Locus Coeruleus*** (A Nucleus In the Pons involved with physiological responses to stress & panic.)
- ***Serotonin:**
  - **Activated By:**
    - General activity/arousal
  - **Released By:**
    - Raphe Nuclei (A group of Nuclei In the brainstem)

What we target in treating Depression.

- ***Dopamine:**
  - **Activated By:**
    - Pleasurable Activities
  - **Released By:**
    - Ventral Tegmental Area (VTA)
    - Substantia Nigra
- **Glutamate & GABA:**
  - Reduces Anxiety

Fear:

- **Brain Structures Involved:**
  - Thalamus →
    - Amygdala
  - Thalamus →
    - Primary Sensory Cortex
    - Association Cortices
- **Long & Short Pathways:**
  - **Long:**
    - Info processed by higher brain centres & Hppocampus.
    - Results in a more complex response
  - **Short:**
    - Info sent straight to Amygdala
    - Results in a basic response (Recoil from stimulus/Freeze)
    - **Advantage =** *No cortical processing means quicker reaction times → ↑Survival.*

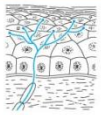
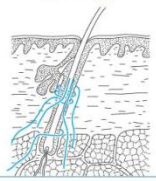
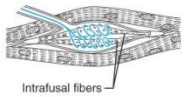
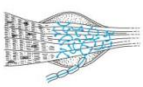


Somatosensory Processing

Sensory Receptors:

- **Classifying Sensory Receptors:**
  - **Type of Stimulus:**
    - **Mechano:** deformation & mechanical force (touch/pressure/vibration/stretch)
    - **Thermo:** temperature changes
    - **Photo:** light energy
    - **Chemo:** changes in aqueous chemistry of interstitial fluid/smell/taste
    - **Nociceptor:** sense potentially damaging stimuli →pain (heat/cold/pressure/chemicals)
  - **Location in Body:**
    - **Exteroceptors:** near the body surface – touch/pressure/pain/temperature/ the senses
    - **Interoceptors (viscero ceptors):** stimuli within the body [viscera/blood vessels] – (chemical changes/tissue stretch/temperature) →pain/discomfort/hunger/thirst
    - **Proprioceptors:** occur in skeletal muscles/tendons/joints/ligaments/muscle sheaths
  - **Structural Complexity:**
    - **Simple:** absolute majority – modified dendritic endings of sensory neurons.
    - **Complex:** minority – sense **organs** = collections of cells associated with the "special senses" (vision/hearing/smell/taste)
- Once sensory input enters CNS, it travels to the **Thalamus** (sorting station of the brain)
  - Impulses are sorted on the basis of **where they came from** and the **type of sensation**
  - They are then sent to their **relative functional areas** on the **cortex (brain surface)**.
- **Response:** If a response is required, then a discrete area of the brain will activate it.
  - **Primary motor cortex:** voluntary motor
  - **Language & Speech Centres:** vocalisation
  - **Hypothalamus & Brain Stem:** visceral responses (chest/abdominal – pulse/sweat/B.Pressure)

Receptor Types:

STRUCTURAL CLASS	ILLUSTRATION	FUNCTIONAL CLASSES ACCORDING TO LOCATION (L) AND STIMULUS TYPE (S)	BODY LOCATION
UNENCAPSULATED			
Free nerve endings of sensory neurons		L: Exteroceptors, interoceptors, and proprioceptors S: Thermoreceptors (warm and cool), chemoreceptors (itch, pH, etc.), mechanoreceptors (pressure), nociceptors (pain, hot, cold, pinch, and chemicals)	Most body tissues; most dense in connective tissues (ligaments, tendons, dermis, joint capsules, periostea) and epithelia (epidermis, cornea, mucosae, and glands)
Modified free nerve endings: Merkel discs (tactile discs)		L: Exteroceptors S: Mechanoreceptors (light pressure); slowly adapting	Basal layer of epidermis of skin
Hair follicle receptors		L: Exteroceptors S: Mechanoreceptors (hair deflection); rapidly adapting	In and surrounding hair follicles
ENCAPSULATED			
Meissner's corpuscles (tactile corpuscles)		L: Exteroceptors S: Mechanoreceptors (light pressure, discriminative touch, vibration of low frequency); rapidly adapting	Dermal papillae of hairless skin, particularly nipples, external genitalia, fingertips, soles of feet, eyelids
Pacinian corpuscles (lamellated corpuscles)		L: Exteroceptors, interoceptors, and some proprioceptors S: Mechanoreceptors (deep pressure, stretch, vibration of high frequency); rapidly adapting	Dermis and hypodermis; periostea, mesentery, tendons, ligaments, joint capsules; most abundant on fingers, soles of feet, external genitalia, nipples
Ruffini endings		L: Exteroceptors and proprioceptors S: Mechanoreceptors (deep pressure and stretch); slowly or nonadapting	Deep in dermis, hypodermis, and joint capsules
Muscle spindles		L: Proprioceptors S: Mechanoreceptors (muscle stretch, length)	Skeletal muscles, particularly those of the extremities
Golgi tendon organs		L: Proprioceptors S: Mechanoreceptors (tendon stretch, tension)	Tendons
Joint kinesthetic receptors		L: Proprioceptors S: Mechanoreceptors and nociceptors	Joint capsules of synovial joints

Receptors: Nature of Activity:

- **When Are They Active?**
  - **Tonic Receptors:**
    - Continually Firing
    - – Eg. Proprioceptors
  - **Phasic Receptors:**
    - Fire only with a ***Change*** in the Environment.
    - – Eg. Thermoreceptors
- **When Do They Inactivate? (How Quickly do they "Adapt"?):**
  - **NB: "Adaptation" = *Time Taken*** for receptor to ***Stop Firing*** during ***Sustained Stimulation***
    - **RARs – Rapidly Adapting Receptors:**
      - Receptor quickly stops firing under continuous stimulus
      - - Eg. Touch Receptors (Can't feel clothes after a while)
    - **SARs – Slowly Adapting Receptors:**
      - Receptor maintains firing under continuous stimulus
      - - Eg. Muscle Stretch Receptors (Proprioceptors)

Receptive Fields:

- **A Receptive Field:** The Area Monitored by 1x Receptor.
  - Ie. Touch anywhere in that field, the sensation will come from the entire receptive field.

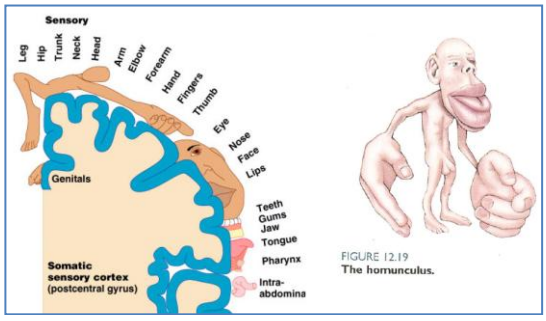
Functional Sensory Areas of the Brain:

- **Primary visual area** – receives visual information from the retina of the eye.
- **Primary motor area** – controls voluntary skilled movements of our skeletal muscles
- **Pre-motor cortex** – controls learned motor skills (musical instruments/typing/etc)
- **Primary auditory area** – sound energy stimulates hearing receptors and is interpreted as pitch/vol/location.
- **Primary somatosensory area** – receives information from the general (somatic) sensory receptors.
- **Primary gustatory area** – perception of taste stimuli.
- **Primary Olfactory area** – info from smell receptors

Sensory Association Areas – info flows from sensory receptors to a specific primary sensory cortex, then to a specific association area. Association areas give meaning to the received information, store it in memory, relate it to past experiences & decide on plan of action

Somatosensory Processing:

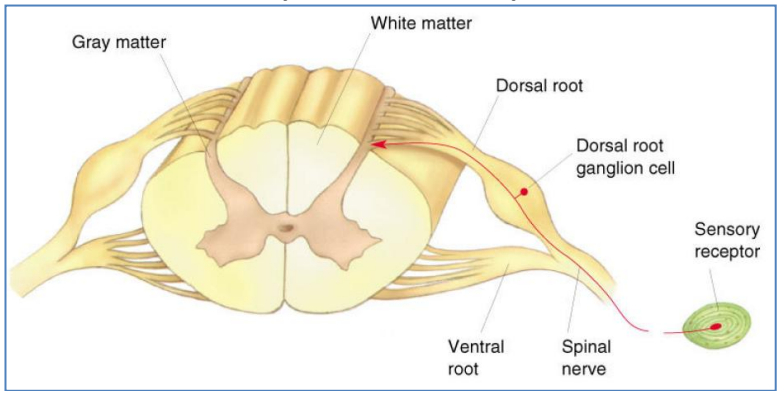
- **Somatosensory Cortex:**
  - **Roles:**
    - Detection of Sensation & Conscious Awareness of Sensation
    - Feature/Quality Recognition (ie. Texture/Size/Shape)
  - Exhibits ***'Somatotopy'*** (Body Mapping)
    - – ie. Specific Cortical Areas responsible for Particular Body Regions
  - Receptor Density in a Body Region determines the Size of the respective Cortical Area. – See Below:



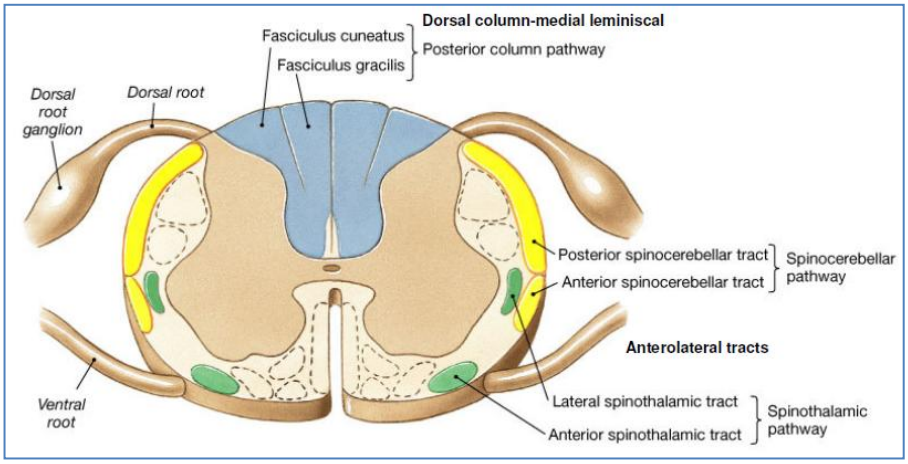
- **Somatosensory Association Area:**
  - The Somatosensory Cortex has Connections to the Somatosensory Association Areas
  - **Role:**
    - Compares Received Stimulus to Past Experiences.

Somatosensory Pathways:

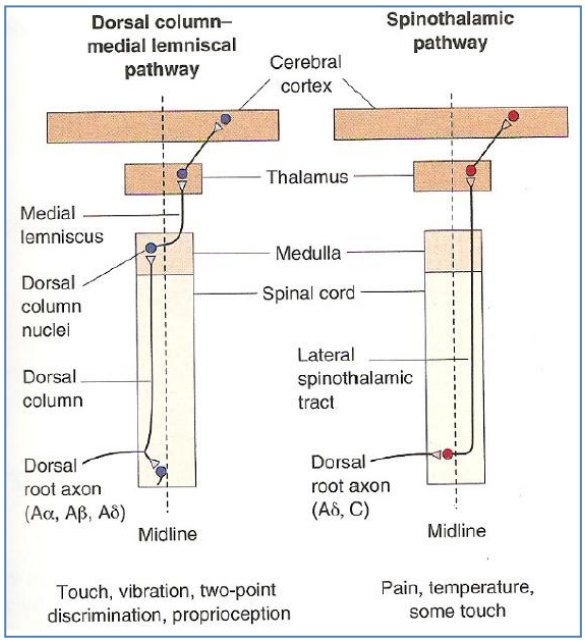
- **First Order Neurons (Peripheral Afferent Nerves):**
  - (Eg. Dorsal Root of Spinal Nerves & Sensory Cranial Nerves)
  - ***Enter Spinal Cord*** via Dorsal Nerve Root → Terminate in ***Dorsal Horn***.
  - ***NB: Cell-Bodies*** of the ***Pseudounipolar-Neuron Receptors*** culminate in the ***Dorsal Root Ganglion***

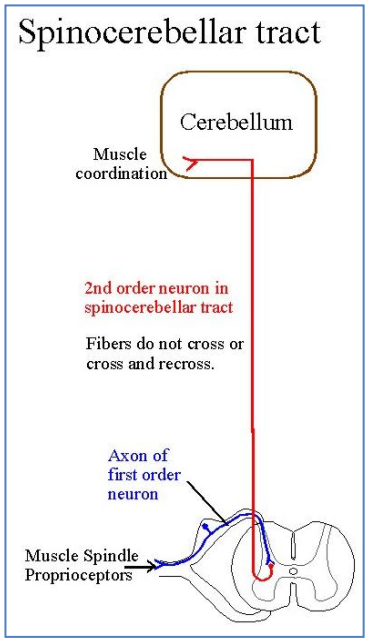


- **Second Order Neurons (Ascending Pathways of Spinal Cord):**
  - Once inside the Spinal Cord, ***1st-Order Neurons → Synapse with 2nd-Order Neurons***
  - ***2nd-Order Neurons*:**
    - Often responsible for ***Decussation*** (Crossing of Fibre-Tracts to the Other Side of the Body)
      - Different Sensory Info takes Different Ascending Pathways to the Brain.



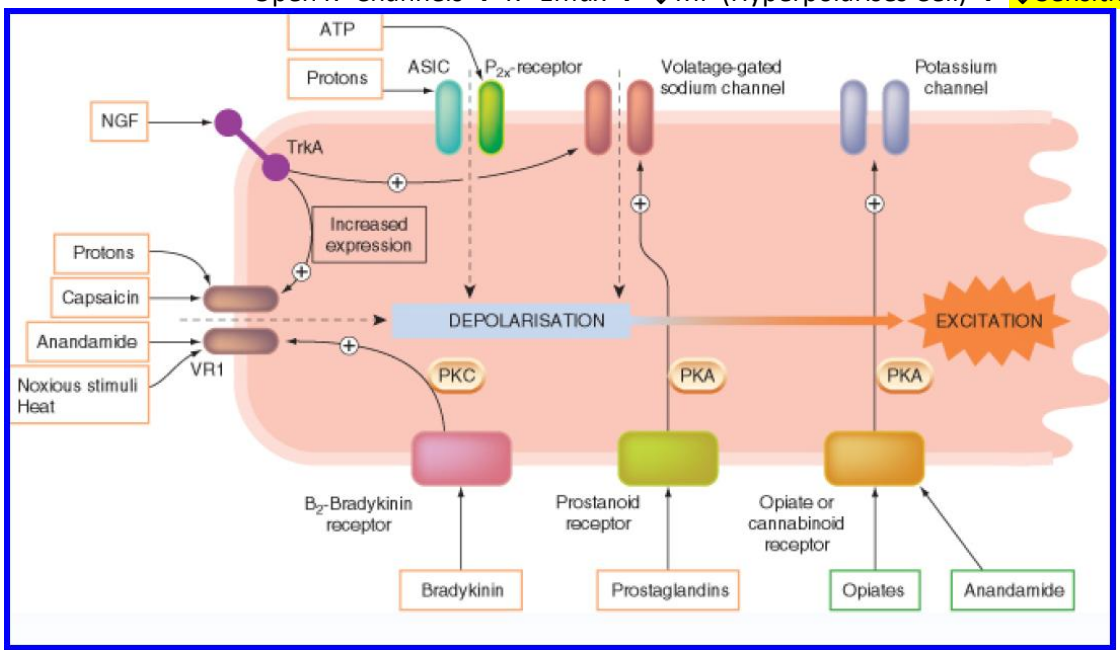
- **Third Order Neurons:**
  - **NB:** 3rd-Order Neurons are only Relevant to the Posterior Column & The SpinoThalamic Pathways.
    - The SpinoCerebellar Pathway terminates in the Cerebellum with 2nd-Order Neurons.
  - Carry ***Sensory Info*** from ***Thalamus*** → to ***Primary Somatosensory Cortex*** in Parietal Lobe.
    - ***Thalamus –*** Sorts incoming Sensory Info → Sends it to Cortex.





- **Neurotransmitters & Receptors:**
  - **NTs/Receptors @ The Sensory Nerve:**
    - ***TRPV$_1$-Receptor (Ca$^+$ Channel)("TRP Vanilloid Receptor$_1$"). Opened by:**
      - Capsaicin (from hot chillies)
      - Heat
      - Mechanical (Mechanism unclear)
      - H$^+$ (Acid)(Often a result of inflammation)
    - **Bradykinin Receptors:**
      - Bradykinin Receptor Activates TRPV$_1$-Receptor → Depolarisation → Nociception.
    - **Prostanoid Receptors:**
      - Sensitive to Prostaglandins.
      - Open Na$^+$ Channels →
      - Inhibit K$^+$ Channels →
      - Open TRPV$_1$-Receptors →

      } → ↑MP → :. Lowers Threshold → ↑Sensitivity
    - **ASIC – ("Acid Sensitive (gated) Ion Channel"):**
      - Acid →ASIC-Stimulation → Depolarisation of Cell → Nociception
    - **Opiate/Cannabinoid Receptors:**
      - Sensitive to Opioid & Cannabinoids.
      - Open K$^+$ Channels → K$^+$-Efflux → ↓MP (Hyperpolarises Cell) → ↓Sensitivity



  - **NTs/Receptors @ The Dorsal Horn:**
    - **Afferent Pathway:**
      - ***Substance-P**
      - ***Glutamate** (AMPA & NMDA Receptors)
    - **Efferent Pathway – Sensory Modulation Via Pain-Gate Mechanism:**
      - ***OPIOIDS*:**
        - Activate Descending Inhibitory Pathways & Directly inhibit Dorsal Horn Synapse.
      - ***Noradrenaline**
        - Directly Inhibits Dorsal-Horn Synapse
      - ***Serotonin (5-HT):**
        - Directly Inhibits Dorsal-Horn Synapse
      - ***Enkephalins:**
        - Directly Inhibits Dorsal-Horn Synapse
      - **NB:** Low-Dose Tri-Cyclic Anti-Depressants can treat Neuropathic pain by blocking re-uptake of NE, 5-HT, & Enkephalins in Dorsal Horn Synapse.

Motor Processing

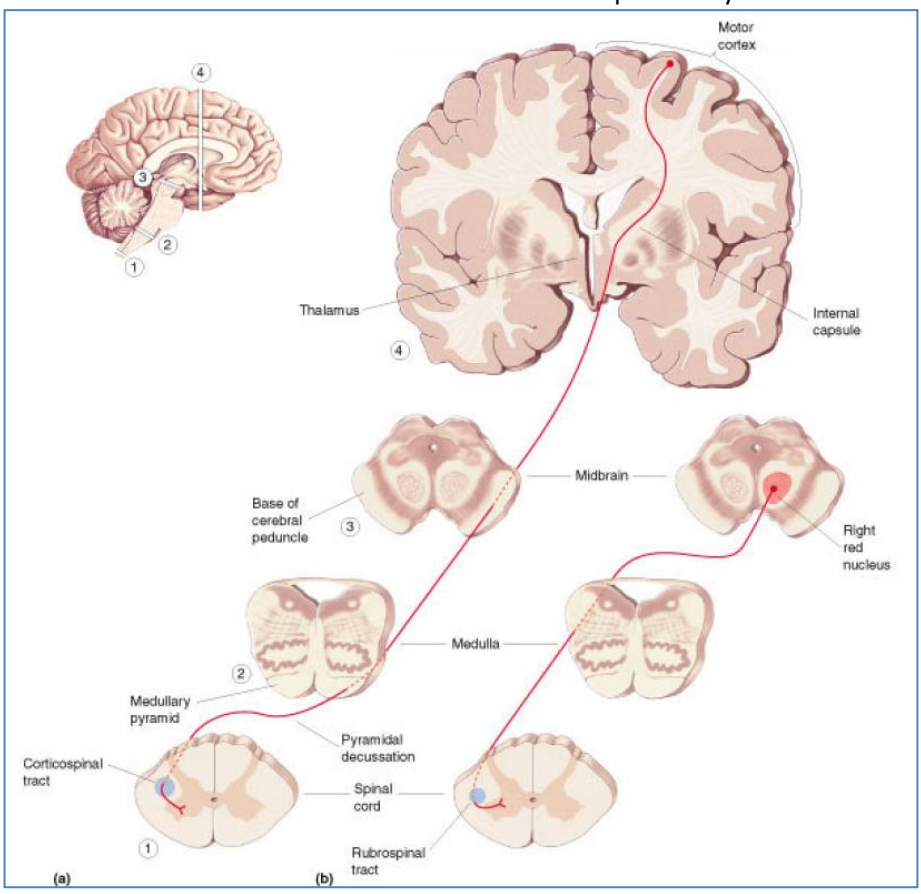
Motor Processing Hierarchy - The Levels of Motor Control:

- **1. Ready (*Strategy*) – Deciding 'What to do':**
  - Prefrontal Cortex
  - Basal Ganglia (NB: Basal Ganglia are the interface between 'Strategy' & 'Tactics'.)
- **2. Set (*Tactics*) – Deciding 'How to do it':**
  - Pre-Motor Area (PMA)
- **3. Go (*Execution*) – 'Action':**
  - Primary Motor Cortex (M1)
  - Cerebellum
  - Brainstem
  - Descending Tracts
  - Spinal Nerves
  - Peripheral Motor Neurons

Descending Tracts Involved in Motor Function:

- **Descending Motor Pathways:**
  - **Lateral Pathways:**
    - **Roles:**
      - Both Tracts – Voluntary Movement of Distal Extremities (Particularly Hands & Feet)
    - **2 Divisions:**
      - **Corticospinal Tract:**
        - Originates in Primary Motor Cortex
        - Run through the ***Internal Capsule*** to the Brainstem.
        - **Decussate** in Medullary Pyramids (Medulla)
      - **Rubrospinal Tract:**
        - Originates in Red Nucleus of Midbrain.
        - Decussate immediately below Red Nucleus (In the Pons)

        →→
        - Continue down the spinal cord in the Lateral White Matter.
        - Terminate in Ventral Horn of Spinal Grey Matter



- **Ventromedial (Indirect/Extrapyramidal) Pathways:**
  - **4 Divisions:**
    - Tectospinal (AKA: Colliculospinal) Tract
    - Vestibulospinal Tract
    - Pontine Reticulospinal Tract
    - Medullary Reticulospinal Tract
  - **Specific Functions:**
    - Tectospinal/Colliculospinal: Visual Tracking (Head/Eye Coordination)
    - Vestibulospinal: Maintain Balance During Standing & Moving
    - Pontine Reticulospinal: Maintains Muscle Tone & Visceral Motor Functions
    - Medullary Reticulospinal: Maintains Muscle Tone & Visceral Motor Functions

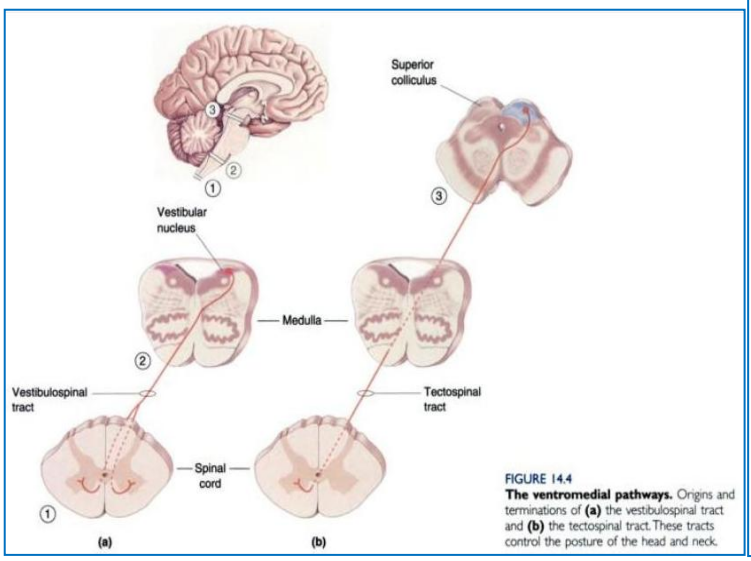


FIGURE 14.4
The ventromedial pathways. Origins and terminations of **(a)** the vestibulospinal tract and **(b)** the tectospinal tract. These tracts control the posture of the head and neck.

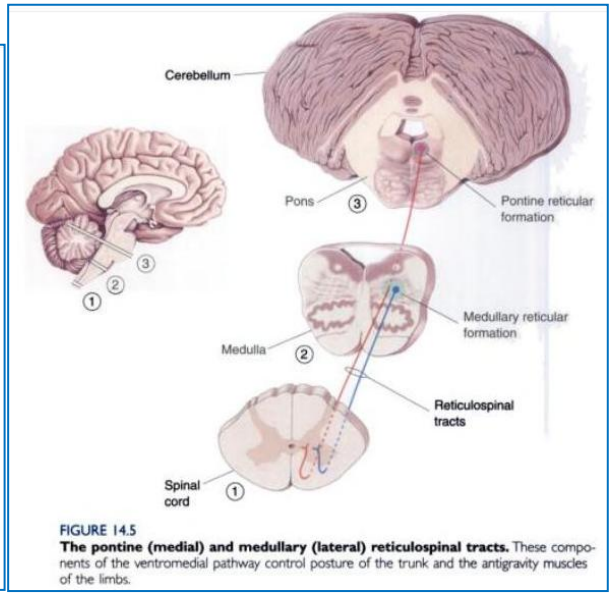
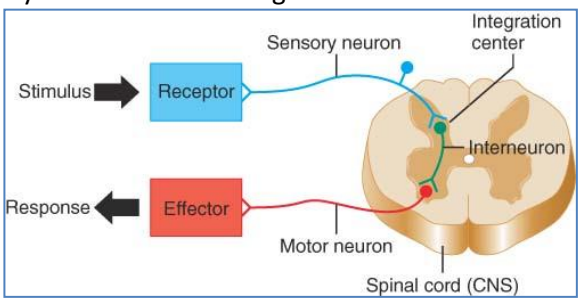


FIGURE 14.5
The pontine (medial) and medullary (lateral) reticulospinal tracts. These components of the ventromedial pathway control posture of the trunk and the antigravity muscles of the limbs.

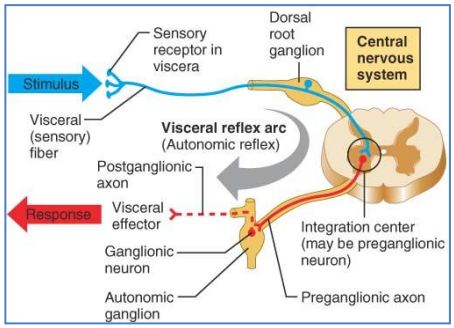
Reflexes:

- Rapid, automatic responses to stimuli.
- Occur over neural pathways called **reflex arcs**.
- **Components of a reflex arc:**
  - Receptor → Sensory neuron → CNS integration centre→ Motor neuron→ Effecter



Visceral Reflexes:

- Similar to the Somatic-NS, the ANS also has reflex arcs;
- **Visceral Reflex Arcs Components:**
  - Visceral Sensory Neurons (Chemical Changes/Stretch/Irritation of Viscera) → Integration Centre →Motor Neuron → Effector



The Autonomic Nervous System:

Divisions of the Autonomic NS:

- The 2 Divisions of the ANS (Sympathetic & Parasympathetic) serve the same visceral organs, but cause Opposite Effects. This ***Dual Innervation*** counterbalances each division's activities → Maintains Homeostasis.
- **Sympathetic:**
  - "Fight/Flight"
  - Mobilizes the body during activity
  - Effects are Widespread
- **Parasympathetic:**
  - "Rest/Digest"
  - Conserves Body Energy & Promotes Maintenance Functions.
  - Has relatively Short-Lived Effects (Due to short-acting nature of Acetylcholine)
  - Effects are relatively Localised

Effectors:

TABLE 14.5 Effects of the Parasympathetic and Sympathetic Divisions on Various Organs

TARGET ORGAN OR SYSTEM	PARASYMPATHETIC EFFECTS	SYMPATHETIC EFFECTS
Eye (iris)	Stimulates sphincter pupillae muscles; constricts pupils	Stimulates dilator pupillae muscles; dilates pupils
Eye (ciliary muscle)	Stimulates muscles, which results in bulging of the lens for close vision	Weakly inhibits muscles, which results in flattening of the lens for far vision
Glands (nasal, lacrimal, gastric, pancreas)	Stimulates secretory activity	Inhibits secretory activity; causes vasoconstriction of blood vessels supplying the glands
Salivary glands	Stimulates secretion of watery saliva	Stimulates secretion of thick, viscous saliva
Sweat glands	No effect (no innervation)	Stimulates copious sweating (cholinergic fibers)
Adrenal medulla	No effect (no innervation)	Stimulates medulla cells to secrete epinephrine and norepinephrine
Arrector pili muscles attached to hair follicles	No effect (no innervation)	Stimulates to contract (erects hairs and produces "goosebumps")
Heart muscle	Decreases rate; slows heart	Increases rate and force of heartbeat
Heart: coronary blood vessels	Weakly dilates coronary vessels	Causes vasodilation*
Bladder/urethra	Causes contraction of smooth muscle of bladder wall; relaxes urethral sphincter; promotes voiding	Causes relaxation of smooth muscle of bladder wall; constricts urethral sphincter; inhibits voiding
Lungs	Constricts bronchioles	Dilates bronchioles*
Digestive tract organs	Increases motility (peristalsis) and amount of secretion by digestive organs; relaxes sphincters to allow movement of foodstuffs along tract	Decreases activity of glands and muscles of digestive system and constricts sphincters (e.g., anal sphincter)
Liver	No effect (no innervation)	Stimulates release of glucose to blood*
Gallbladder	Excites (gallbladder contracts to expel bile)	Inhibits (gallbladder is relaxed)
Kidney	No effect (no innervation)	Causes vasoconstriction; decreases urine output; promotes renin release
Penis	Causes erection (vasodilation)	Causes ejaculation
Vagina/clitoris	Causes erection (vasodilation) of clitoris	Causes contraction of vagina; increases mucus secretion
Blood vessels	Little or no effect	Constricts most vessels and increases blood pressure; constricts vessels of abdominal viscera and skin to divert blood to muscles, brain, and heart when necessary; NE constricts most vessels when necessary; epinephrine dilates vessels of the skeletal muscles during exercise*
Blood coagulation	No effect (no innervation)	Increases coagulation*
Cellular metabolism	No effect (no innervation)	Increases metabolic rate*
Adipose tissue	No effect (no innervation)	Stimulates lipolysis (fat breakdown)*

*Effects are mediated by epinephrine release into the bloodstream from the adrenal medulla.

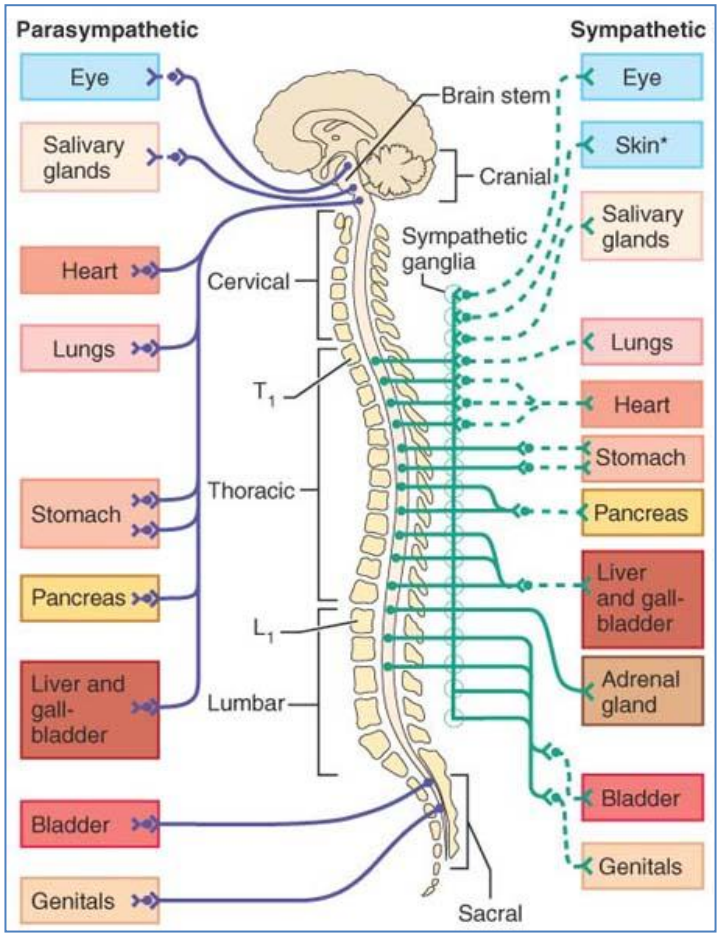
Efferent Pathways & Ganglia:

- As opposed to the Somatic-NS which uses a mono-synaptic system (& Hence Lacks Ganglia), the Autonomic-NS uses a 2-Neuron-Chain system.
- **1. The Pre-Ganglionic Neuron:**
  - The Cell-Body of the first neuron
  - Resides in the Brain or Spinal Cord
  - Synapses with a Ganglionic Neuron.
- **2. The Ganglionic Neuron:**
  - Resides in an 'Autonomic Ganglion' outside the CNS.
  - Extends from the Ganglion to the Effector Organ.

Sympathetic & Parasympathetic Divisions Differ Anatomically in 3 Ways:

- 1. Site of Origin
- 2. Fibre Lengths
- 3. Location of Ganglia

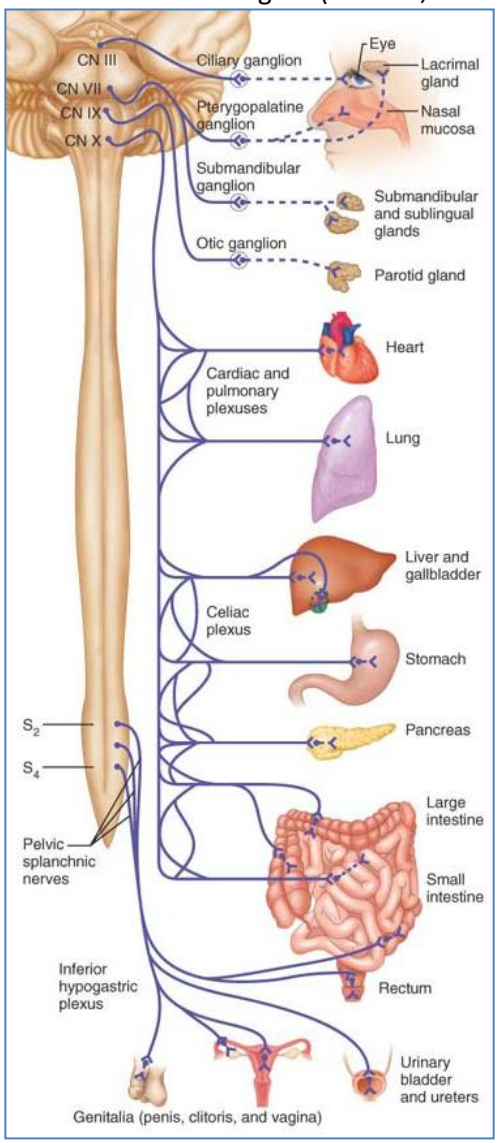
CHARACTERISTIC	PARASYMPATHETIC	SYMPATHETIC
Origin	Craniosacral outflow: brain stem nuclei of cranial nerves III, VII, IX, and X; spinal cord segments S_2–S_4	Thoracolumbar outflow: lateral horn of gray matter of spinal cord segments T_1–L_2
Location of ganglia	Ganglia in (intramural) or close to visceral organ served	Ganglia within a few centimeters of CNS: alongside vertebral column (sympathetic trunk, or chain, ganglia) and anterior to vertebral column (collateral, or prevertebral, ganglia)
Relative length of pre- and postganglionic fibers	Long preganglionic; short postganglionic	Short preganglionic; long postganglionic



Anatomy: The Parasympathetic (Craniosacral) Division:

- **Fibres originate from:**
  - Brain Stem
  - Sacral Region of Spinal Cord
- **Fibre Lengths:**
  - Preganglionic Fibres – Extend nearly all the way to the structures to be innervated.
  - Postganglionic Fibres – Very Short; Extend from the ***Terminal Ganglia*** & synapse with Effector Cells.
- **Ganglia Location:**
  - The ***'Terminal Ganglia'*** are located *Very Close To* or *Within* the Target Organs.

- **The Cranial Outflow:**
  - Fibres Originate From Cranial-Nerve Nuclei in the Brain Stem.
  - Fibres Extend to their Terminal Ganglia via 4 of the paired Cranial Nerves:
    - III – Oculomotor Nerves → Pupil Constriction & Lens Accommodation (close sight)
    - VII – Facial Nerves → Stimulate large Glands in the head (Nasal/Lacrimal/Submandibular & Sublingual Salivary)
    - IX – Glossopharyngeal Nerves → Stimulate Parotid Salivary Glands
    - X – Vagus Nerves → Serves virtually all organs of the thoracic & abdominal Cavities (Except Distal Large Intestine)
- **The Sacral Outflow:**
  - Fibres Originate from Neurons in the Lateral Gray Matter of Spinal Cord Segments S2-S4.
  - Fibres Extend to their Terminal Ganglia via ***Splanchnic Nerves*** of the ***Pelvic Plexus***.
  - Serve Distal Large Intestine & the Pelvic Organs (Bladder, Ureters, Repro. Organs)



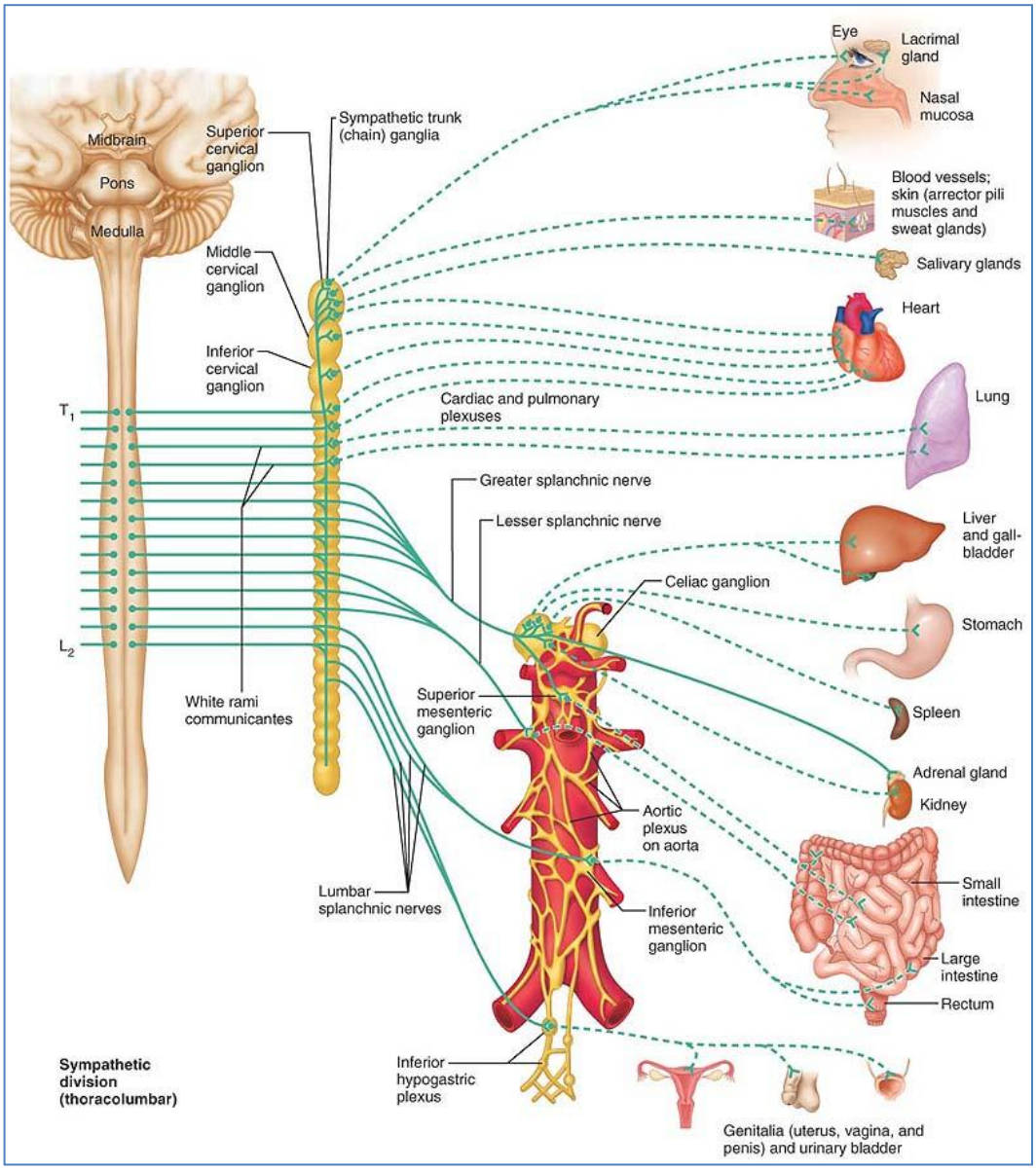
Anatomy: The Sympathetic (Thoraco-Lumbar) Division:

- NB: Sympathetic-NS innervates more organs than the Parasympathetic, and its effects are longer-lasting.
- **Fibres originate from:**
  - Cell bodies of Preganglionic Neurons in the ***Lateral Horns Spinal Cord Segments T1 → L2***.
- **Fibre Lengths:**
  - Preganglionic Fibres – Exit the Spinal Cord via the ***Ventral Root*** → Then pass through a ***White Ramus Communicans*** → Synapse adjoining ***Sympathetic Trunk (Chain) Ganglion***. (NB: These fibres are short)
  - Postganglionic Fibres – Exit the Sympathetic Ganglion at/below/above their spinal level via a ***Gray Ramus Communicans*** → Then enters the Ventral Spinal Nerve at that level → Effector Organs.

  NB: The Colour of the Rami Communicans reveals whether or not their fibres are myelinated.
  Preganglionic Fibres = Myelinated Postganglionic Fibres = Unmyelinated

- **Ganglia Location:**
  - Sympathetic Trunks (Chains of Ganglia) Flank each side of the Vertebral Column from the Neck to Pelvis.

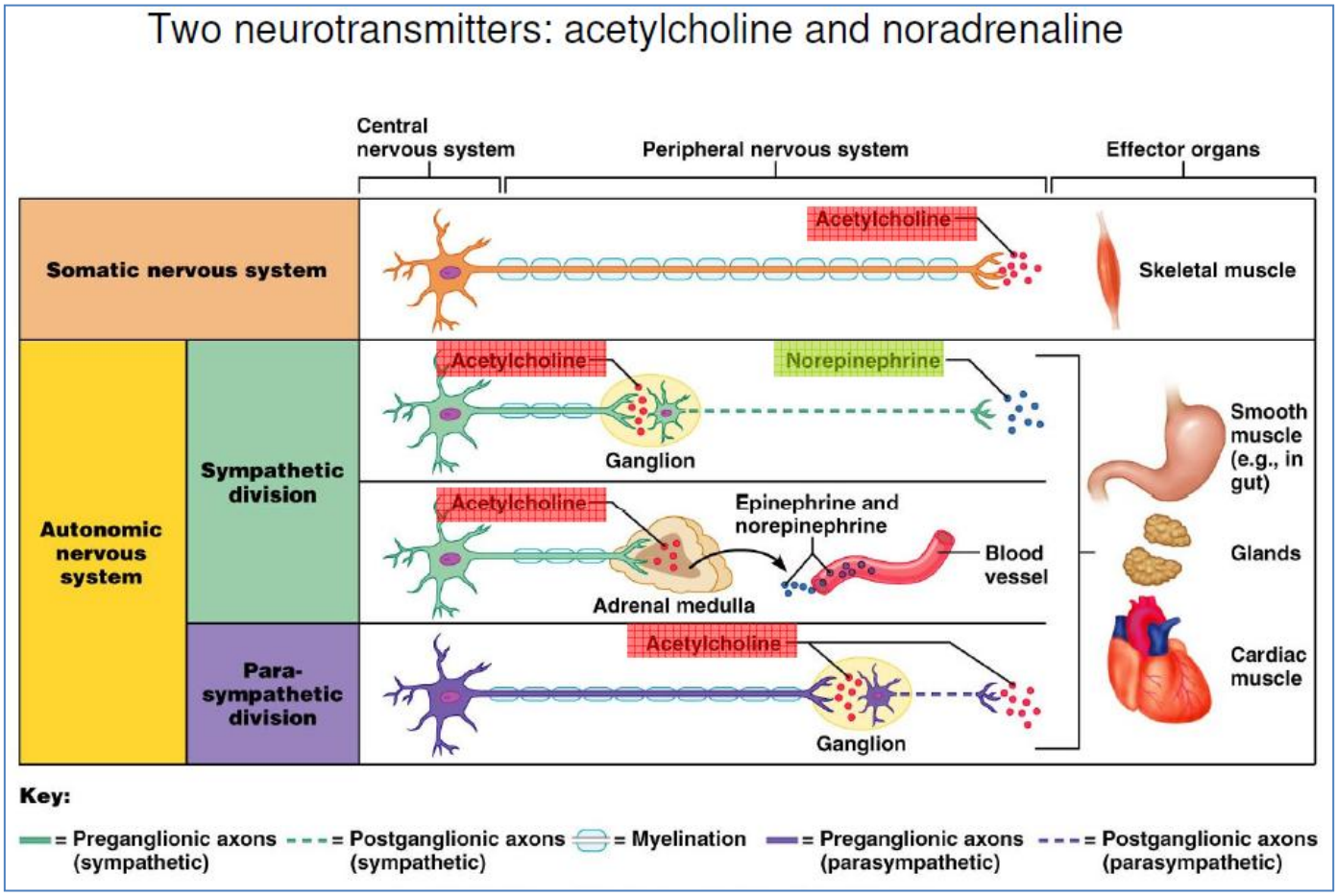
  NB: Although the Sympathetic *Trunks* exist along the length of the spinal cord, the *Fibres* arise only from Thoracic & Lumbar cord segments.



Physiology of the Autonomic NS:

Neurotransmitters of the PNS:

- **Afferent (Sensory):** *Glutamate*/Calcitonin-Gene-Related Peptide/Substance P
- **Efferent (Motor):**
  - **Somatic/Voluntary (Skeletal Muscle):** Acetylcholine (ACh)
  - **Autonomic:**
    - **Sympathetic:**
      - **Preganglionic:** Acetylcholine (ACh) →Stimulates Ganglia & Adrenal Medulla
      - **Postganglionic:** Norepinephrine
      - **→Adrenal Medulla:** Stim. by Acetylcholine (ACh) to release Epinephrine & NE into Blood.
    - **Parasympathetic:**
      - **Preganglionic:** Acetylcholine (ACh)
      - **Postganglionic:** Acetylcholine (ACh)



Sympathetic & Parasympathetic Tone:

- **Sympathetic (Vasomotor) Tone:**
  - The continual state of Partial Constriction of the Vascular System that Maintains BP (even @ rest)
  - During Activity, a Higher BP is needed → the ***Vasomotor Fibres*** fire more rapidly → Vasoconstriction.
  - **NB:** Alpha-Blockers dull the effects of the Sympathetic/Vasomotor Tone → Control Hypertension.
- **Parasympathetic Tone:**
  - Slows the heart, sets the *Normal* activity levels of the Digestive & Urinary Systems, & Stimulates Glandular Secretion (Except Adrenal Glands & Skin Glands)
  - NB: The Sympathetic division an override this during times of stress.
  - **NB:** Drugs that block Parasympathetic Responses → ↑HR, Faecal/Urinary Retention & ↓Glandular Secretion.

Cranial Nerves:

I. **Olfactory**
   - Smell

II. **Optic**
   - Vision (Visual Acuity)

III. **Oculomotor ('eye-mover')**
   - Controls 4 of the 6 eye muscles.

IV. **Trochlear ('pulley')**
   - Controls 1 of the extrinsic eye muscles – pulley shaped

V. **Trigeminal**
   - 3-branched (Opthalmic, Maxillary, Mandibular) sensory fibres to the face & cornea + Mastication

VI. **Abducens ('abduct')**
   - Controls the extrinsic eye muscle that abducts the eyeball (lateral rotation)

VII. **Facial**
   - Facial expression (Furrow Brow, Shut Eyes, Smile)

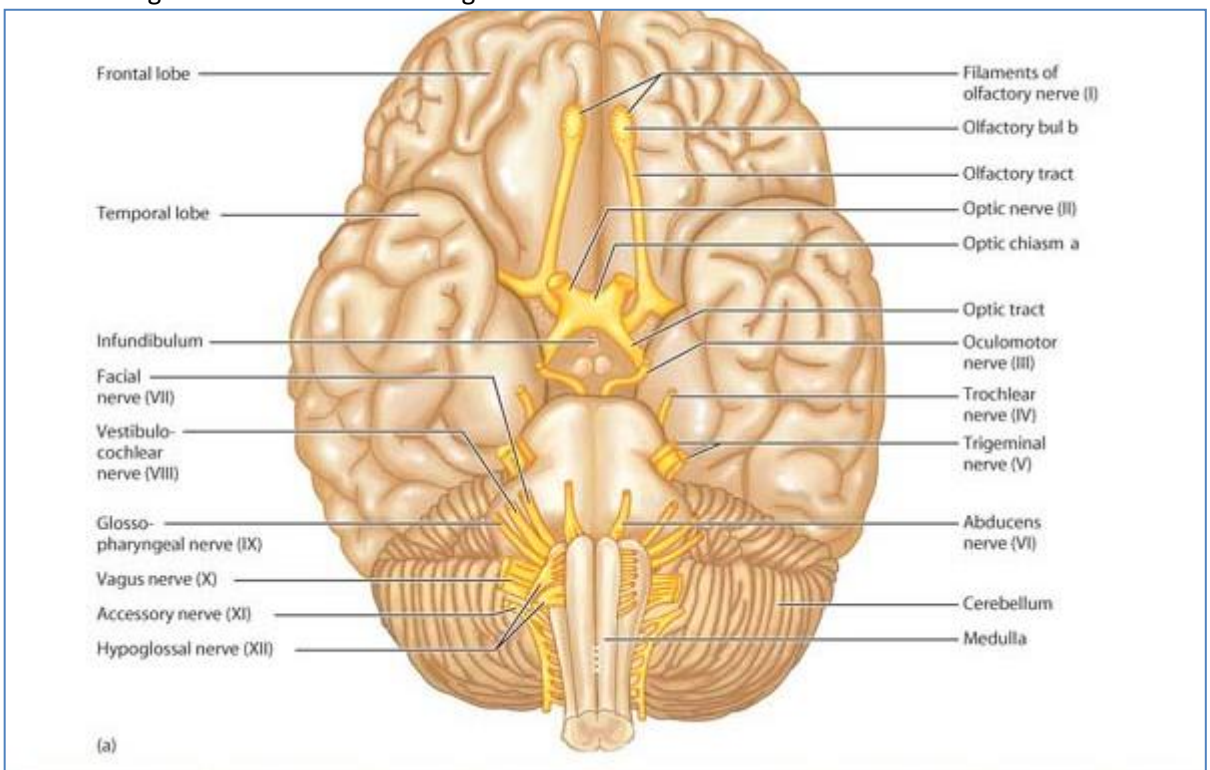
VIII. **Vestibulocochlear**
   - Hearing and balance (formerly the auditory nerve)

IX. **Glossopharyngeal ('tongue & pharynx')**
   - Sensory Tongue and pharynx (Gag reflex)

X. **Vagus ('the wanderer')**
   - Mouth motor + parasympathetic effects in the thorax & abdomen.

XI. **Accessory**
   - Neck and shoulder muscles

XII. **Hypoglossal ('under-tongue')**
   - tongue movement – Poke tongue out

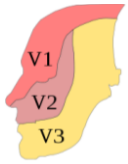
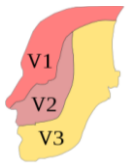
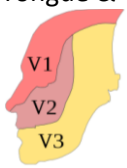


(a)

Cranial nerves I – VI	Sensory function	Motor function	PS* fibers
I Olfactory	Yes (smell)	No	No
II Optic	Yes (vision)	No	No
III Oculomotor	No	Yes	Yes
IV Trochlear	No	Yes	No
V Trigeminal	Yes (general sensation)	Yes	No
VI Abducens	No	Yes	No

Cranial nerves VII – XII	Sensory function	Motor function	PS* fibers
VII Facial	Yes (taste)	Yes	Yes
VIII Vestibulocochlear	Yes (hearing and balance)	Some	No
IX Glossopharyngeal	Yes (taste)	Yes	Yes
X Vagus	Yes (taste)	Yes	Yes
XI Accessory	No	Yes	No
XII Hypoglossal	No	Yes	No

(b) *PS = parasympathetic

Nerve	Functional Components	Location of Nerve Cell Bodies	Cranial Exit Point	Functions (major)
I Olfactory nerve	Special Sensory	Olfactory Epithelium	Cribriform Plate of The Ethmoid Bone	Smell
II Optic nerve	Special Sensory	Retinal Ganglion	Optic Canal	Vision and associated reflexes
III Oculomotor nerve	Somatic Motor	Midbrain	Superior Orbital Fissure	Movements of eyes (Superiorly, Inferiorly & Medially)
	Visceral Motor (parasympathetic)	**Presynaptic:** Midbrain **Postsynaptic:** *Ciliary* Ganglion		Pupillary constriction and lens accommodation (parasympathetic)
IV Trochlear nerve	Somatic Motor	Midbrain	Superior Orbital Fissure	Movements of eyes (Inferolaterally)
V Trigeminal nerve				
- V1 Opthalmic Division	General Sensory	Trigeminal Ganglion	Superior Orbital Fissure	Sensation from Cornea, & V_1 Dermatome 
- V2 Maxillary Division			Foramen Rotundum	Sensation from Maxillary Teeth, Nasal Mucosa, Maxillary Sinuses, Palate, & V_2 Dermatome 
- V3 Mandibular Division			Foramen Ovale	Sensation from Mandibular Teeth, Mucosa of Mouth, Tongue & V_3 Dermatome 
	Branchial Motor	Pons		Muscles of Mastication & Swallowing
VI Abducent nerve	Somatic Motor	Pons	Superior Orbital Fissure	Lateral Rectus Muscle - Abduction (Lateral Rotation) of the Eye
VII Facial nerve	Branchial Motor	Pons	Internal Acoustic Meatus; Facial Canal; Stylomastoid Foramen	Facial Muscles + Some Muscles of Mastication
	Special Sensory	Geniculate Ganglion		Taste (Anterior 2/3 of Tongue)
	Visceral Motor (Parasympathetic)	**Presynaptic:** Pons **Postsynaptic:** Pterygopalatine Ganglion; Submandibular Ganglion		Stimulation of Submandibular & Sublingual Salivary Glands, & Lacrimal Glands.

VIII Vestibulocochlear				
- Vestibular Division	Special Sensory	Vestibular Ganglion	Internal Acoustic Meatus	Position of the Head & Balance (The body's Gyro)
- Cochlear Division	Special Sensory	Spiral Ganglion		Hearing (Via Spiral Organ)
IX Glossopharyngeal	Branchial Motor	Medulla	Jugular Foramen	Stylopharyngeus Muscle (Assists with swallowing)
	Visceral Motor	**Presynaptic:** Medulla **Postsynaptic:** *Otic* Ganglion		Stimulates Parotid Salivary Gland
	Visceral Sensory	Superior Ganglion		Visceral Sensation from Parotid Gland, Carotid Sinus, Pharynx & Middle Ear
	Special Sensory	Inferior Ganglion		Taste(Posterior 1/3 of Tongue)
	General Sensory	Inferior Ganglion		Cutaneous Sensation of External Ear
X Vagus	Branchial Motor	Medulla	Jugular Foramen	Constrictor Muscles of Pharynx, Muscles of Larynx, Palate & Upper 2/3 Esophagus
	Visceral Motor	**Presynaptic:** Medulla **Postsynaptic:** Viscera		Maintains Smooth Muscle Tone in Trachea & Bronchi, Peristalsis in GIT & ↓HR.
	Visceral Sensory	Superior Ganglion		Visceral Sensation from Base of Tongue, Pharynx, Larynx Trachea, Bronchi, Heart, Esophagus, Stomach & Intestine → L-Colic Flexure.
	Special Sensory	Inferior Ganglion		Taste (Epiglottis & Palate)
	General Sensory	Superior Ganglion		Sensation from the External Ear.
XI Spinal Accessory	Somatic Motor	Spinal Cord	Jugular Foramen	Sternocleidomastoid & Trapezius Muscles
XII Hypoglossal	Somatic Motor	Medulla	Hypoglossal Canal	Intrinsic & Extrinsic Muscles of the Tongue.

- **Spinal Cord**
  - Extends from Foramen Magnum
  - Resides in the vertebral canal
  - Bathed in cerebrospinal fluid
  - Terminates at the 'conus medullaris' (cone of medulla) – approx L1 in adults.
  - **Cauda Equina:**
    - Nerve rootlets of lower-lumbar & sacral regions extend further down vertebral canal.
  - **Filum Terminale:**
    - Conn. Tissue anchors Cauda Equina to the base of vertebral canal.

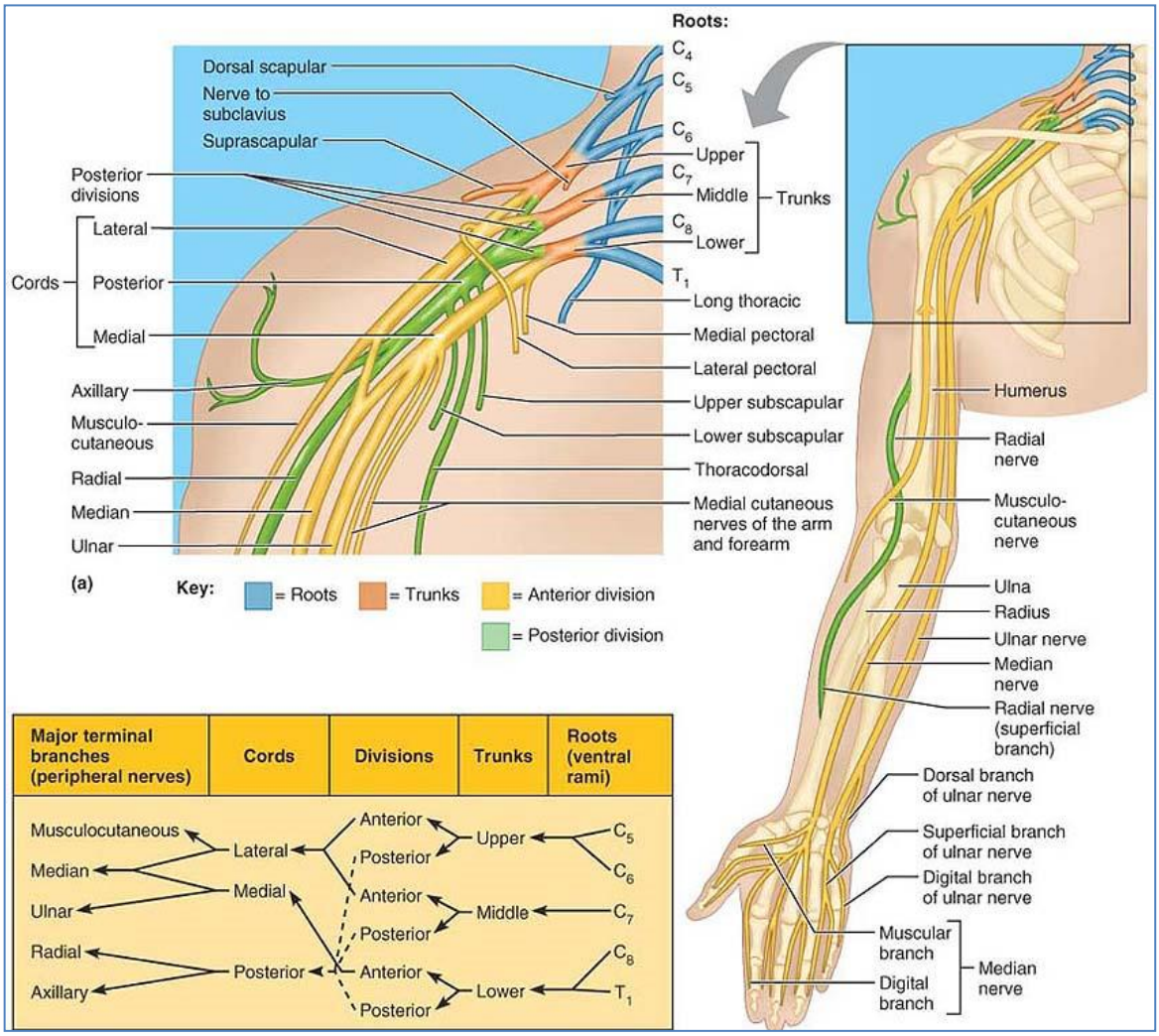
Internal Structure:	**External Structure:**
• **Grey Matter:** ○ All neuronal cell bodies ○ 2 Dorsal Horns ▪ Nerve cells that receive sensory information from body ▪ Via the dorsal root fibres. ○ 2 Ventral Horns ▪ Contain motor nerve cells ▪ Cell axons leave through ventral root fibres. ○ Lateral Horns: ▪ Present in thoracic & upper lumbar regions ▪ Autonomic motor nerves from sympathetic nervous system ▪ Exit spinal cord through the ventral roots • **White Matter:** ○ Ascending and descending fibre tracts.	• **Spinal Nerves:** ○ Merging of the Dorsal & Ventral root fibres ○ Carry mixed sensory & motor info to relevant body area • **Branches of Spinal Nerves:** ○ **Ventral Rami:** "ventral branch" ○ **Dorsal Rami:** "dorsal branch" • **Sympathetic Chain** • **Sympathetic Ganglia:**

Information Pathways: Central → Peripheral

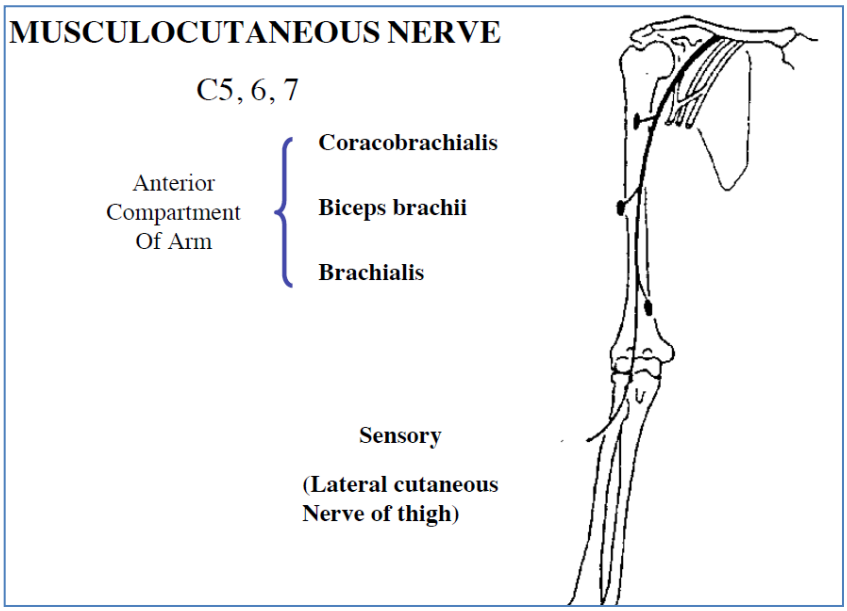
Somatic:	
• **Afferent (Sensory Info)** ○ Receptor cells in periphery ○ Info conveyed along peripheral axon → Soma (in dorsal root ganglion) ○ Info conveyed along proximal axon → spinal cord (CNS) ○ Info → ascending fibres (white matter) → brain for processing	• **Efferent (Skeletal Muscle)** ○ Neuronal cell bodies in ventral horn of grey matter. ○ Cell axon leaves spinal cord through ventral root → spinal nerve ○ Axon flows out of Ventral Rami ○ Directly innervates muscle @ neuromuscular junction

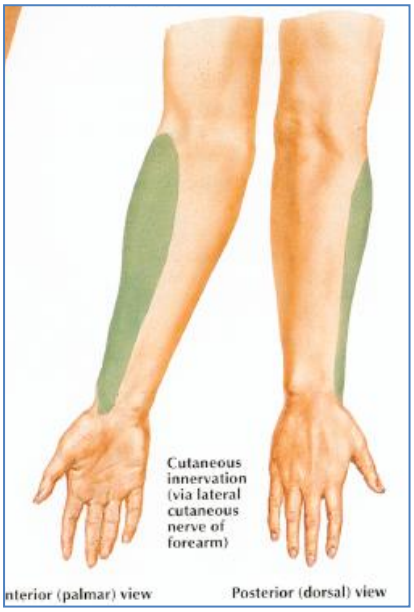
Visceral:	
• **Afferent (Sensory Info)** ○ Receptors in viscera ○ Info conveyed along peripheral axon → Soma (in dorsal root ganglion) ○ Info conveyed along proximal axon → spinal cord (CNS) ○ Info → ascending fibres (white matter) → brain for processing	• **Efferent (Smooth Muscle)** ○ Neuronal cell bodies in lateral horn of grey matter. ○ Cell axon leaves spinal cord through ventral root → spinal nerve ○ Axon flows out of Ventral Rami ○ Axon synapses with peripheral ganglia ○ Peripheral ganglia innervates internal viscera: ▪ smooth muscle/glandular tissue/cardiac muscle

Shoulder Girdle Nerves

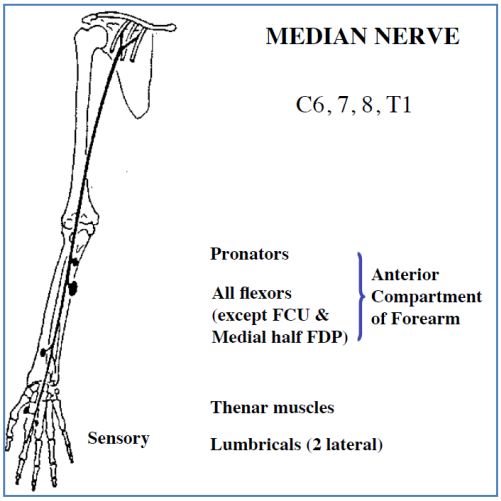


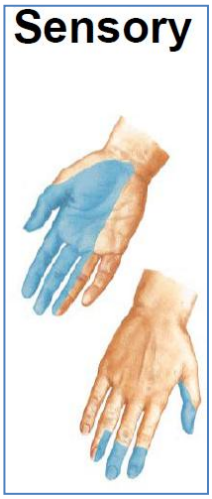
- **(Ant) Musculocutaneous**
  - Innnervates:
    - Flexors of Arm:
      - Biceps Brachii
      - Brachialis
      - Coracobrachialis
    - Skin of Anterio-Lateral Forearm



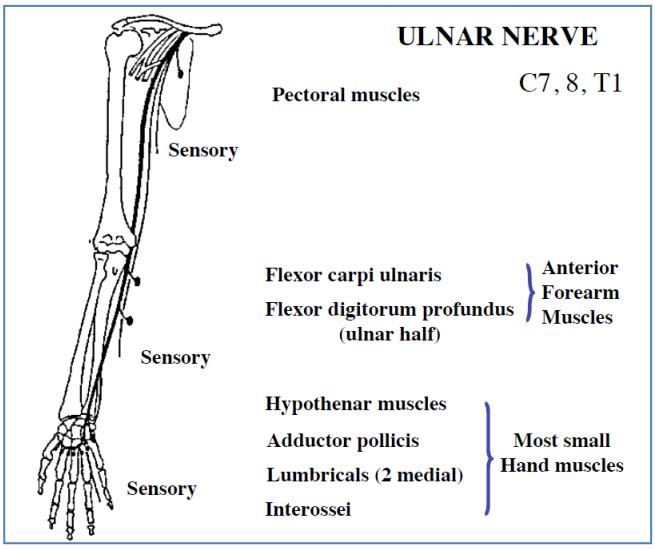


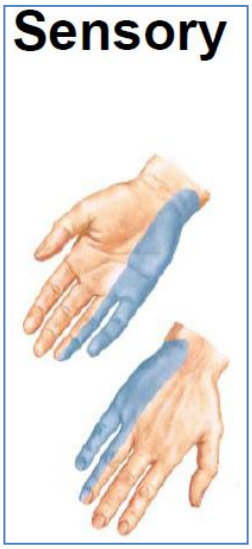
- **(Ant) Median**
  - Innervates:
    - Flexors of Anterior Forearm:
      - Palmaris Longus
      - Flexor Carpi Radialis
      - Flexor Digitorum Superficialis
      - Lateral ½ of Flexor Digitorum Profundus
      - Flexor Pollicis Longus
      - Pronator Teres
      - Pronator Quadratus
      - Thenar Muscles (Intrinsic muscles of Lateral Palm)
      - Lumbricals #1 & #2
      - Digital Branches to Fingers
    - Skin of Lateral 2/3 of Hand, Palm Side & Dorsum of Fingers 2 & 3



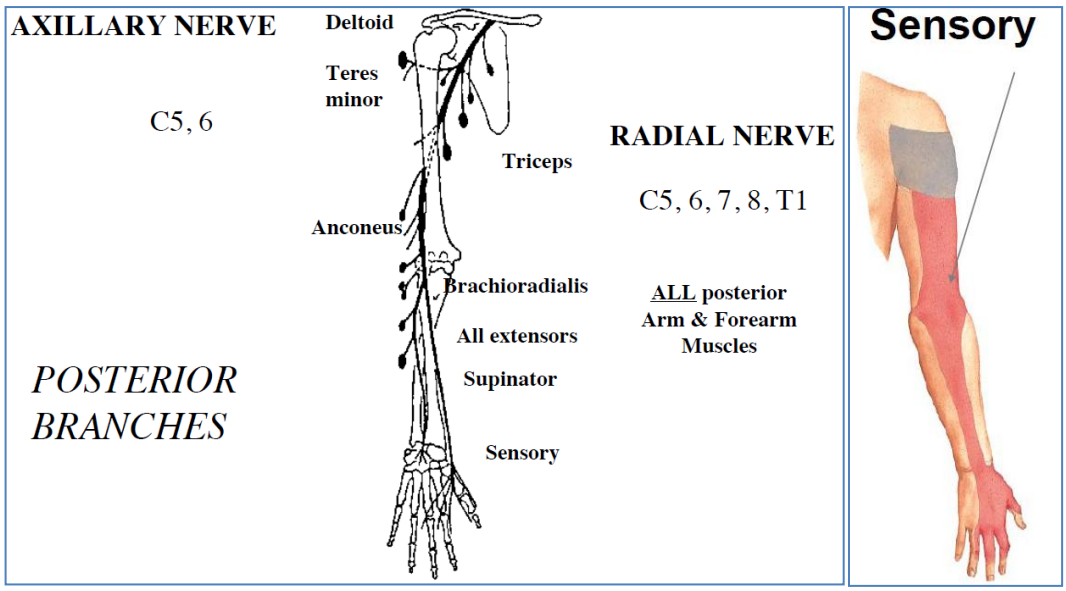


- **(Ant) Ulnar**
  - Innervates:
    - Flexors of Anterior Forearm:
      - Flexor Carpi Ulnaris
      - Medial part of Flexor Digitorum Profundus
      - Majority of Intrinsic Muscles of Hand
        - Adductor Pollicis
        - Flexor Digiti Minimi Brevis
        - Abductor Digiti Minimi
        - Opponens Digiti Minimi
        - Lumricals #3 & #4
        - Interossei
    - Skin of Medial 1/3 of Hand (Ant & Post).

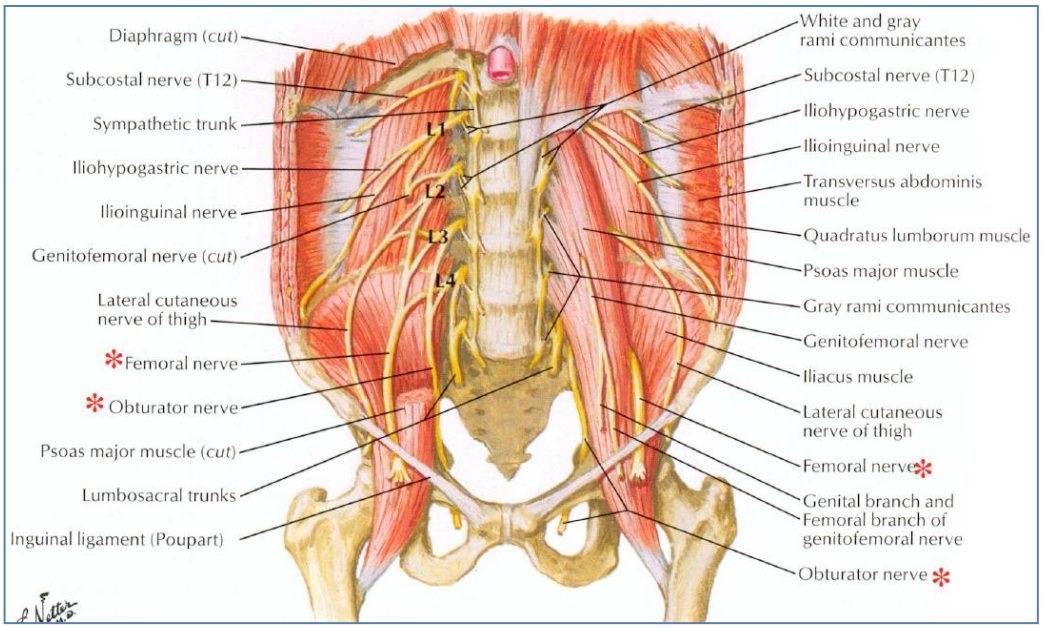




- **(Post) Axillary**
  - Innervates:
    - Deltoid
    - Teres Minor
    - Skin & Joint Capsule of Shoulder
- **(Post) Radial**
  - ALL Posterior Upper-Arm & Forearm Muscles.
    - Extensor Muscles of Arm, Forearm & Hand:
      - Triceps Brachii
      - Anconeus
      - Supinator
      - Brachioradialis
      - Extensor Carpi Radialis Brevis
      - Extensor Carpi Radialis Longus
      - Extensor Carpi Ulnaris
      - Abductor Pollicis Longus
      - Extensor Pollicis Brevis
      - Extensor Pollicis Longus
      - Extensor indicis
      - Extensor Digitorum
      - Extensor Digiti Minimi
    - Skin of Entire Latero-Posterior Arm & Forearm & Hand (except dorsum of fingers 2 & 3)



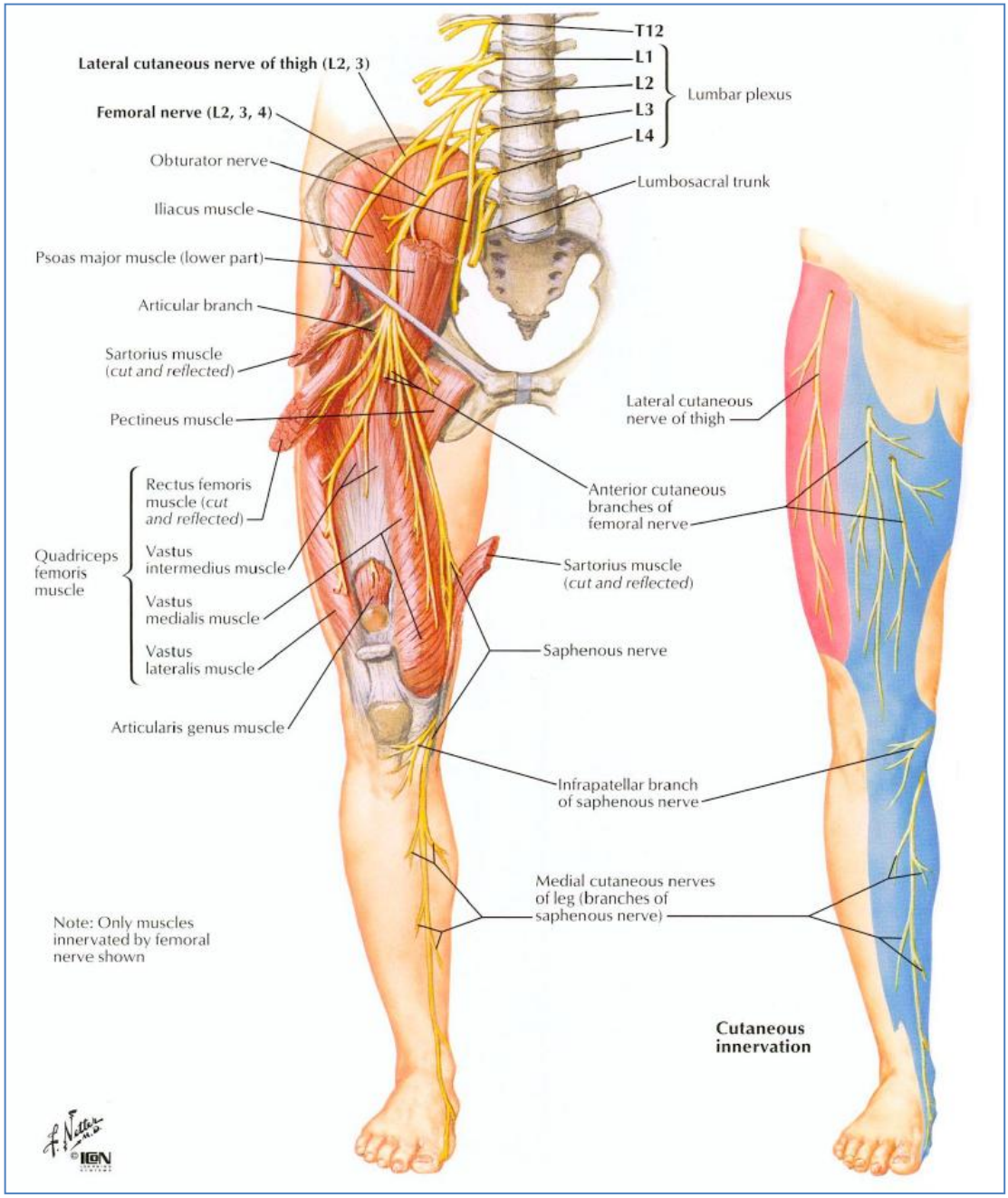
- **Lumbar Plexus:**



NB: Know:

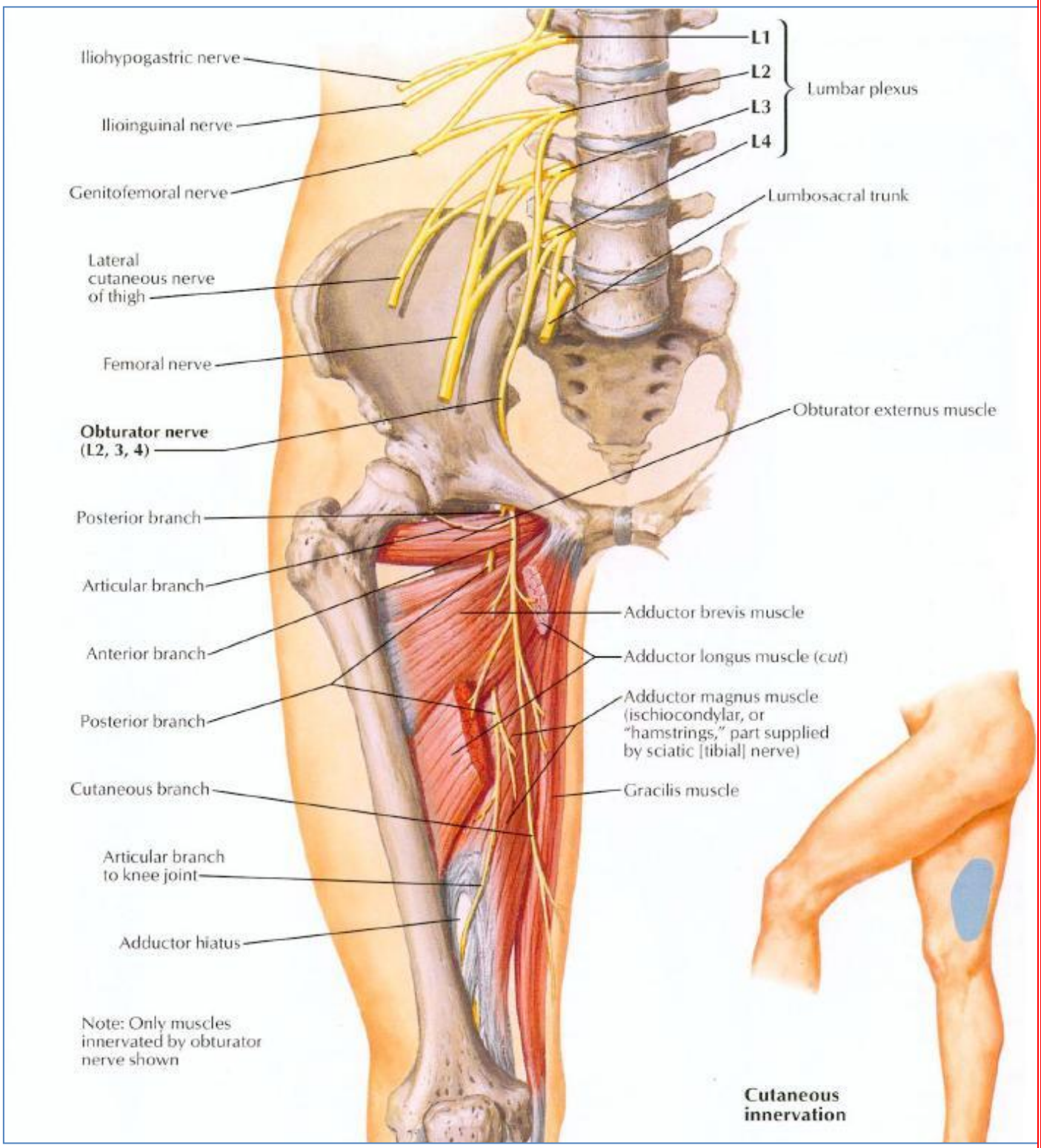
Lumbosacral Trunk – Communicates between Lumbar & Sacral Plexus

- **Femoral Nerve:**
  - Branches off L_2, L_3 & L_4
  - Runs between Psoas Major & Iliacus → beneath Inguinal Ligament → Thigh → Splits in 2:
    - Anterior Division
      - Cutaneous Branches
      - Muscular Branches → Pectineus & Sartorius
    - Posterior Division
      - Cutaneous Branch – *Saphenous Nerve*
      - Muscular Branches → Quadriceps Femoris
  - Innervates:
    - Pectineus
    - Sartorius
    - Rectus Femoris
    - Vastus Lateralis
    - Vastus Intermedius
    - Vastus Lateralus
    - Skin of Anterio-Medial Thigh & Lower Leg + Medial Aspect of Foot

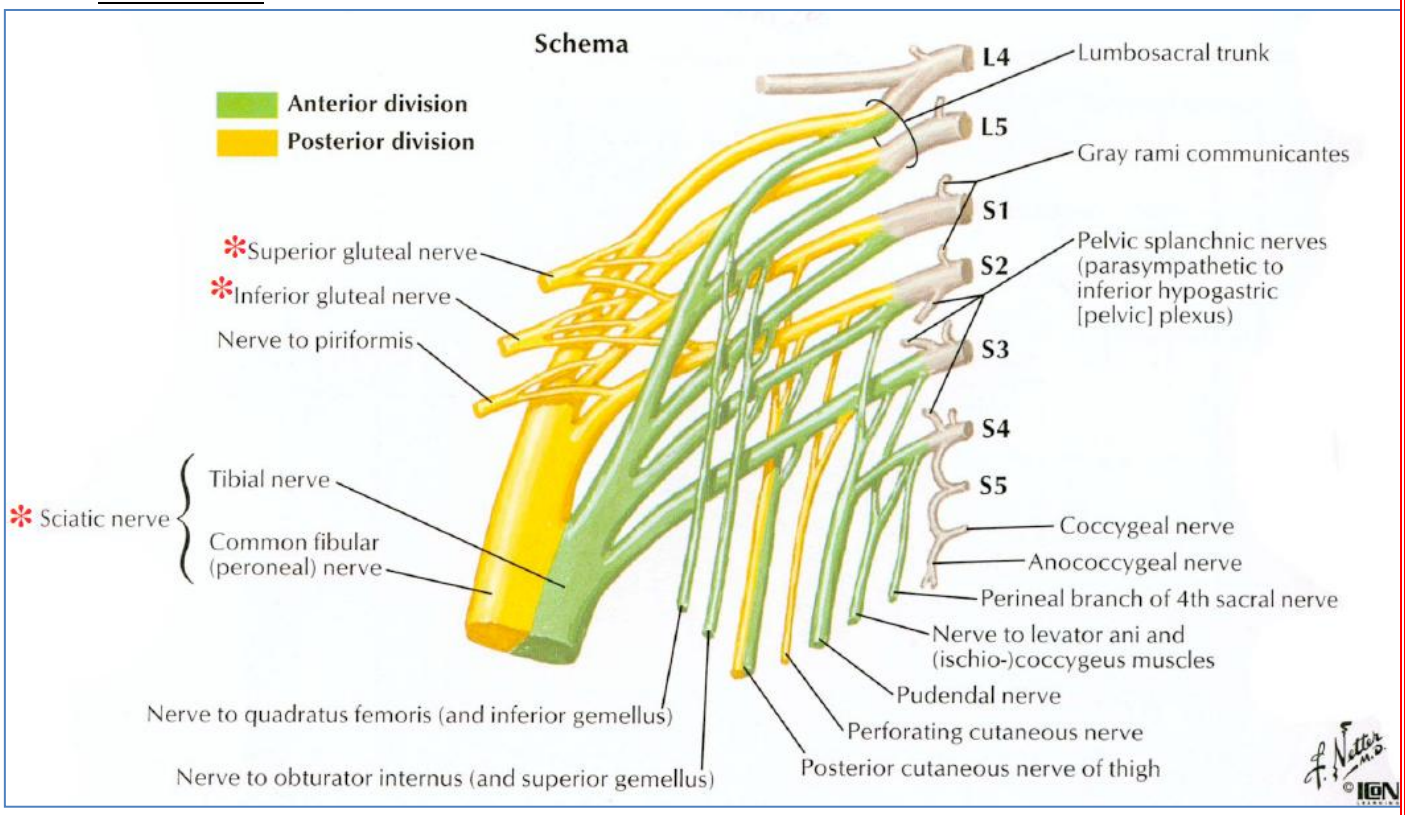


NB: Cutaneous Innervation – In blue

- **Obturator Nerve:**
  - Branches off L_2, L_3 & L_4
  - Runs medial to Psoas Major, down along the inside wall of lesser pelvis → through Obturator Canal (in obturator membrane) through Obturator Foramen → Thigh
  - Innervates:
    - External Obturator
    - Adductor Longus
    - Adductor Brevis
    - Adductor Magnus
    - Gracilis
    - Skin of medial aspect of thigh

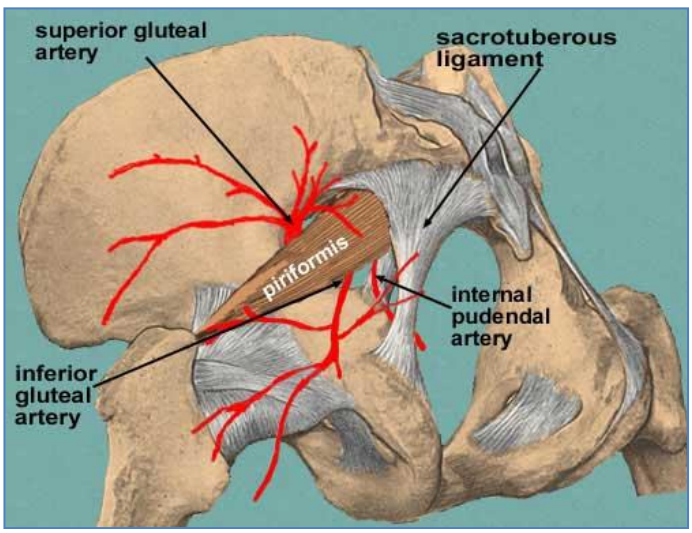


- **Sacral Plexus:**

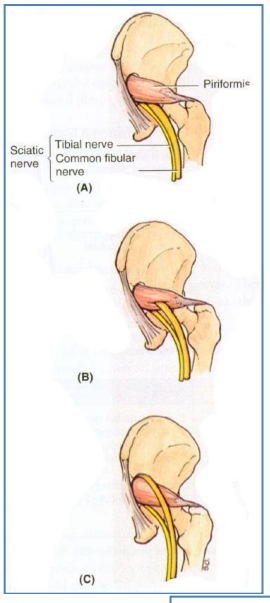


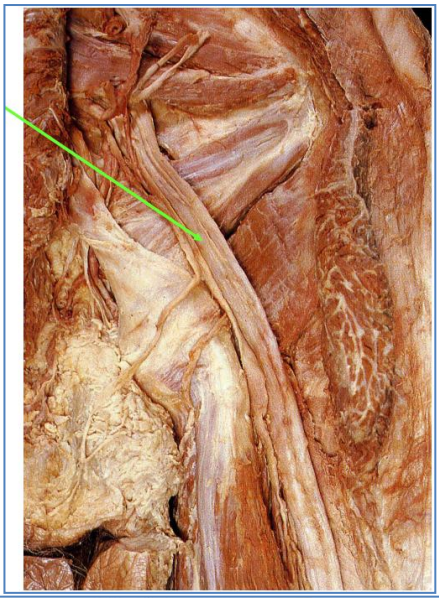
  - **Superior Gluteal Nerve:**
    - Branches off L_4, L_5 & S_1
    - Runs from Dorsal Roots → leaves pelvis through Greater Sciatic Foramen above Piriformis → Gluteus Medius, Gluteus Minimus & Tensor Fasciae Latae.
      - Accompanied by Superior Gluteal Vein & Artery.
    - Innervates:
      - Gluteus Medius
      - Gluteus Mimimus
      - Tensor Fasciae Latae

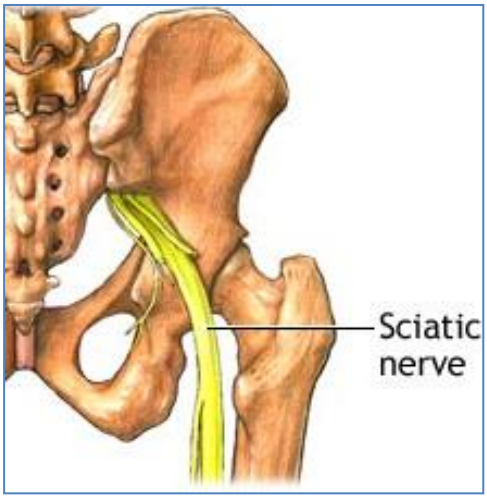
  - **Inferior Gluteal Nerve:**
    - Branches off L_5, S_1 & S_2
    - Runs from Dorsal Roots → leaves pelvis through Greater Sciatic Foramen above Piriformis → Gluteus Maximus.
    - Innervates:
      - Gluteus Maximus

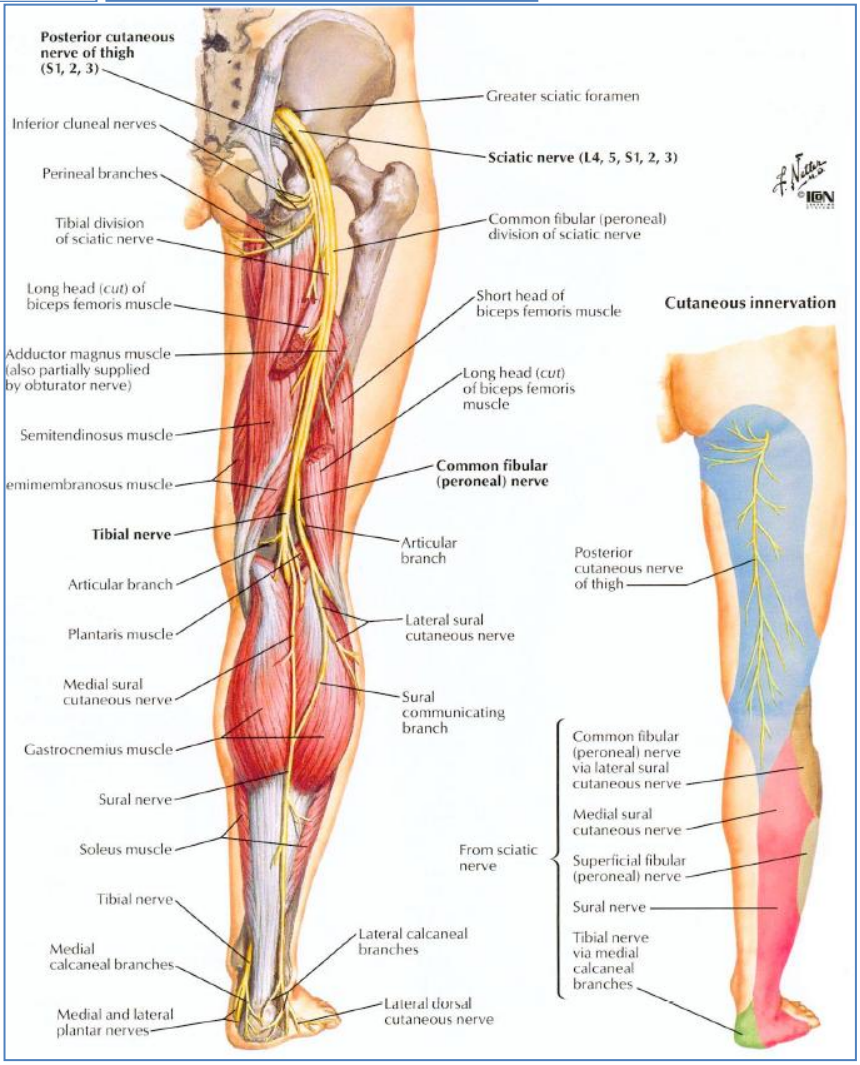


- **Sciatic Nerve:**
  - Branches off L_4, L_5, S_1, S_2 & S_3
  - Runs from inside pelvis → through Greater Sciatic Foramen (below piriformis) → descends along the posterior thigh to about its lower third → ***Divides into 2 Branches: Tibial & Common Fibular Nerves.*** (some variation)
  - Innervates:
    - Hamstrings
    - ½ of Adductor Magnus

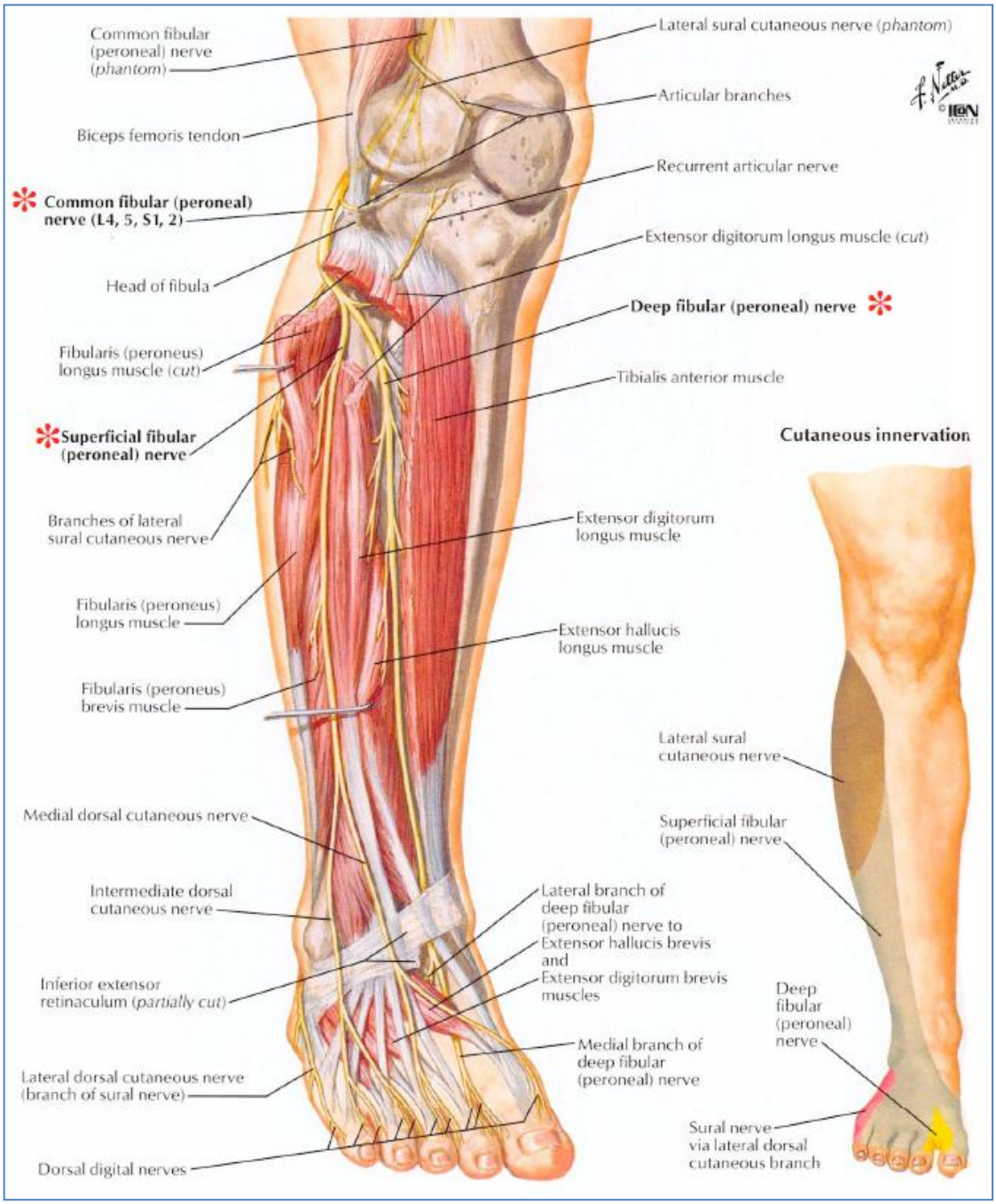




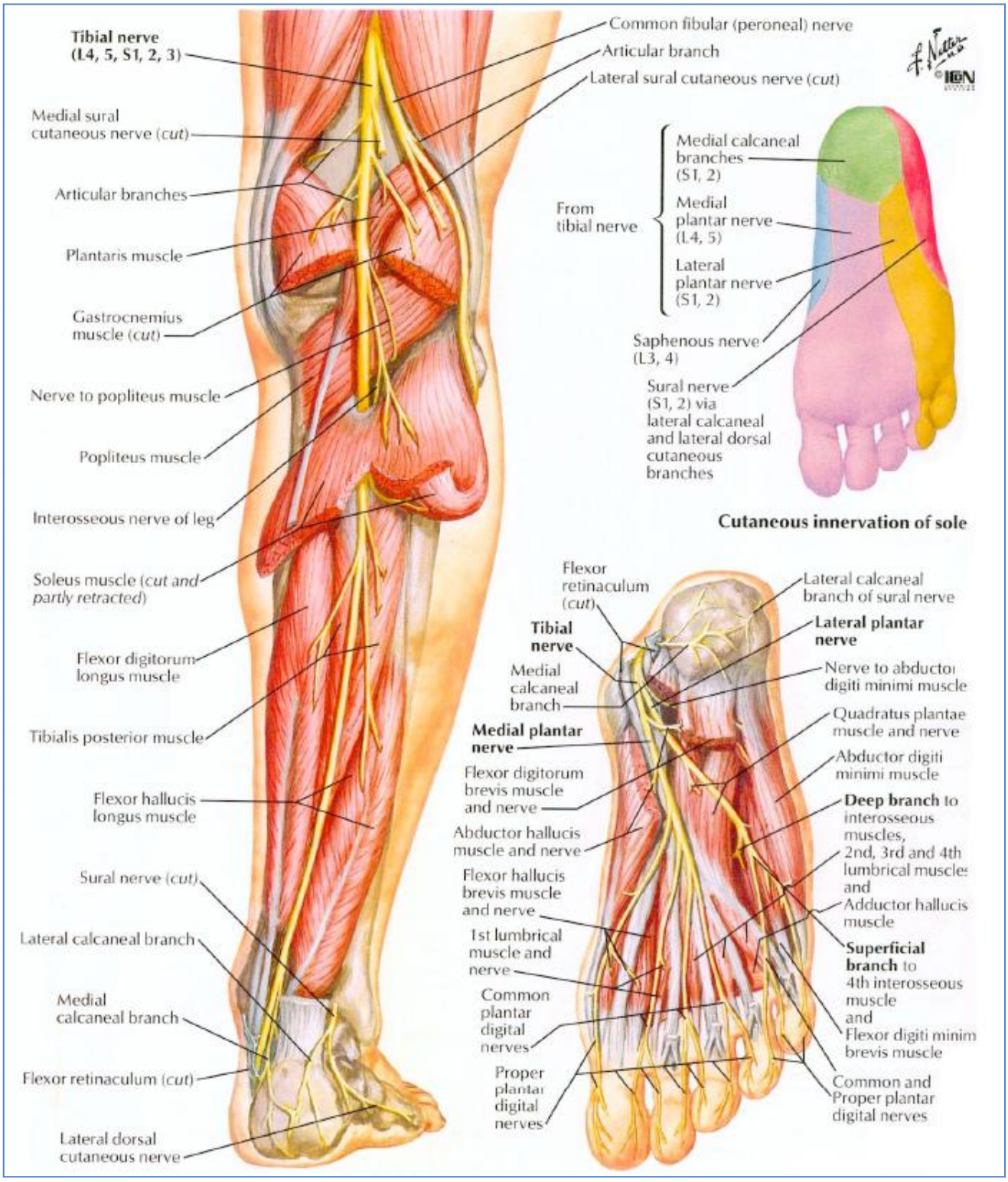




- **Sciatic Nerve: Common Fibular (Peroneal) Nerve:**
  - Branches off Sciatic Nerve
  - Runs obliquely along the lateral side of the Popliteal Fossa → Head of the Fibula Adjacent to the Medial Margin of the Biceps Femoris → Winds around neck of Fibula → **divides into Deep & Superficial Fibular (peroneal) Nerves**
  - Innervates:
    - Skin of Lateral Aspect of Lower Leg
    - Skin of Dorsum of Foot
  - **Deep Fibular Nerve:**
    - Innervates:
      - Tibialis Anterior
      - Extensor Digitorum Longus
      - Fibularis Tertius
      - Extensor Hallucis Longus
  - **Superficial Fibular Nerve:**
    - Innervates:
      - Fibularis Longus
      - Fibularis Brevis



- **Tibial Nerve:**
  - Branches off Sciatic Nerve
  - Runs through Popliteal Fossa → Then follows the Tibia to the ankle → passes into Foot (below medial malleolus) → Terminates as Medial & Lateral Plantar Nerves
  - Innervates:
    - Gastrocnemius
    - Popliteus
    - Soleus
    - Plantaris
    - Tibialis Posterior
    - Flexor Digitorum Longus
    - Flexor Hallucis Longus



Neuroscience Notes
Blood Vessels & Blood Flow to the Brain

Why Does the Brain Need Blood?

- Consumes **15-20%** of **the body's total energy needs**, (and receives 15% of Cardiac Output), despite being only **2% of total body mass.**
- **Neurons require high ATP to:**
  - Maintain Ion Gradients across Plasma Membrane
  - Regulate Neurotransmitter synthesis/re-uptake.
- **Neurons have NO ANAEROBIC CAPACITY** → Therefore the brain *absolutely depends on* Oxygenated Blood.
  - Hence, any deficit in blood supply is detrimental (≈30^{+}sec lack of blood/O_2 to brain → unconscious)

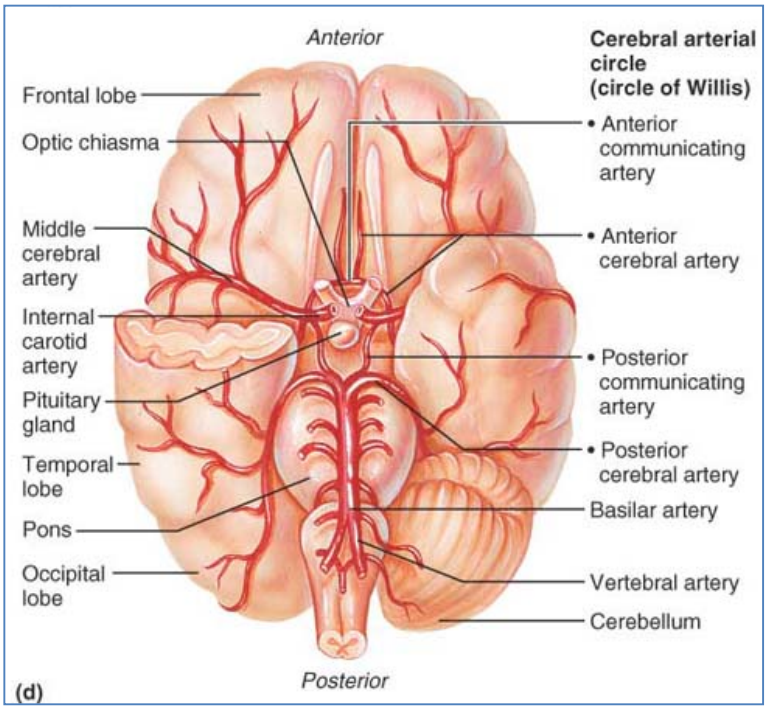
Blood Supply to the Brain is an ANASTOMOSIS:

- **Anastomosis:** Where *Multiple Arteries* Supply the *Same Region of Tissue.* ***Ie. A Dual Blood-Supply.***
- **The Advantage:** If one of the arteries becomes blocked/damaged, the other artery will compensate for it.

Arterial Supply of the Brain:

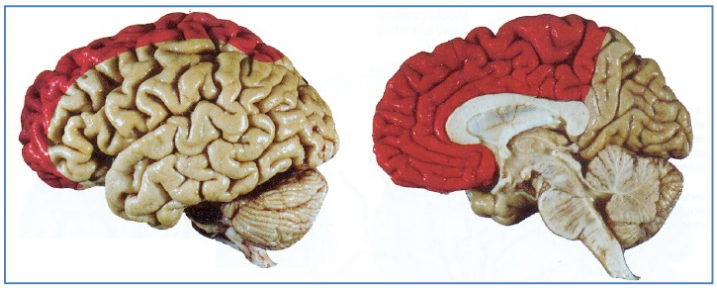
- **Brain is Supplied by 2 Arterial Systems:**
  - 2x Vertebral Arteries → 1x Basilar Artery → Circle of Willis
  - 2x Internal Carotid Arteries → Circle of Willis
- **'Circle of Willis', The Anastomosis of the Brain:**
  - (The *'Roundabout'* of Arteries on the Ventral Surface of the Brain with multiple *'Roads'* coming off it)
  - (Encircles the Optic Chiasma, The Pituitary Gland & the Mammillary Bodies.)
  - **The *'Roads'*: (Anterior → Posterior)**
    - 2x Anterior Cerebral Arteries
    - *1x Anterior Communicating Artery*
    - **2x Internal Carotid Arteries**
    - 2x Middle Cerebral Arteries
    - *2x Posterior Communicating Arteries*
    - 2x Posterior Cerebral Arteries
    - **1x Basilar Artery**

  - **NB:** Communicating Arteries are always patent, but generally not functional (no blood flow) when blood flow from both Carotids & Basilar Arteries is normal. However, if blood flow from one of the major arteries is impeded, blood is shunted through the Communicating Arteries to compensate.

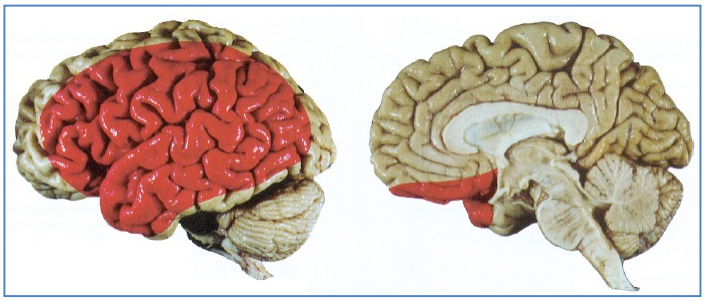


Distribution of Cerebral Arteries:

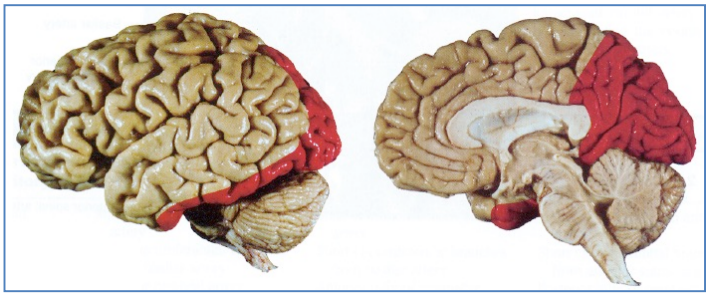
- **Anterior Cerebral Arteries:**
  - (Travels up and over the Corpus Callosum, sprouting branches outwards towards the cortex)
  - Medial Portion of Frontal Lobe (Incl. Cortex)
  - Medial Portion of Parietal Lobe (Incl. Cortex)
  - Corpus Callosum

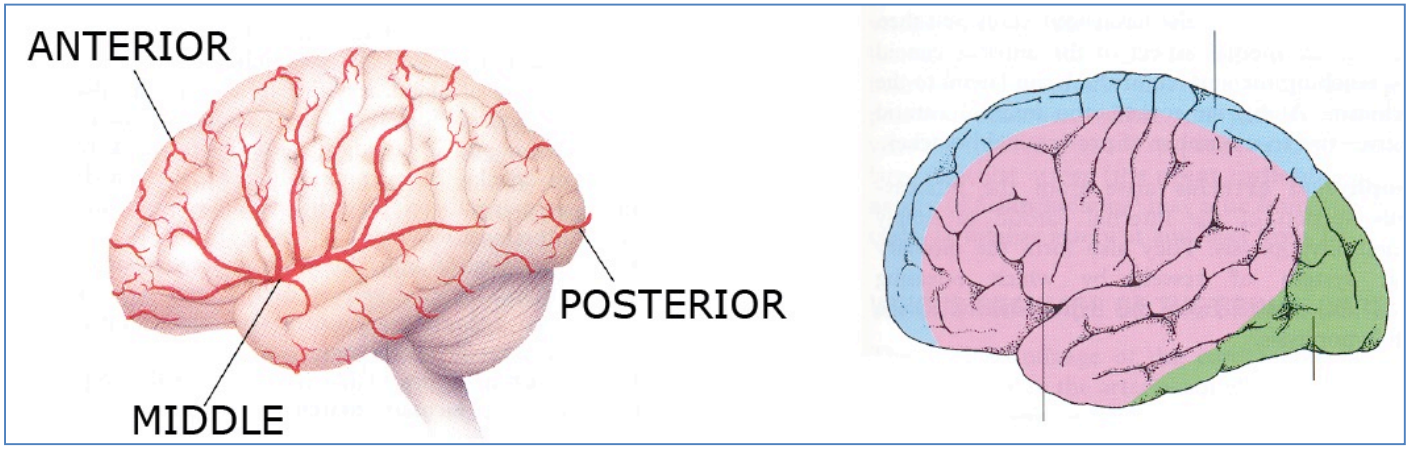


- **Middle Cerebral Arteries:**
  - (Travels through the Lateral Fissure/Sulcus and emerges onto the Lateral Surface of the Brain)
  - Lateral Portion of the Frontal Lobe (Incl. Cortex)
  - Lateral Portion of the Parietal Lobe (Incl. Cortex)
  - Entire Temporal Lobe (Incl. Cortex)



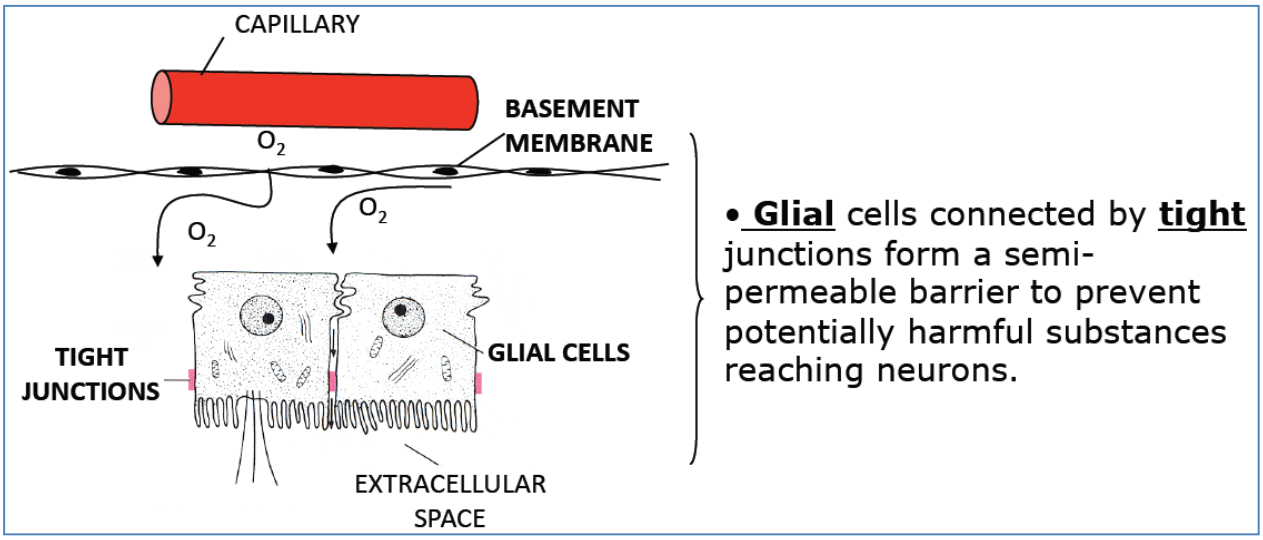
- **Posterior Cerebral Arteries:**
  - (Travels along the Inferior brain surface between the Cortex and the Cerebellum)
  - Inferior Portion of Temporal Lobe (Incl. Cortex)
  - Posterio-Medial Portion of Parietal Lobe (Incl. Cortex)
  - Entire Occipital Lobe (Incl. Cortex)



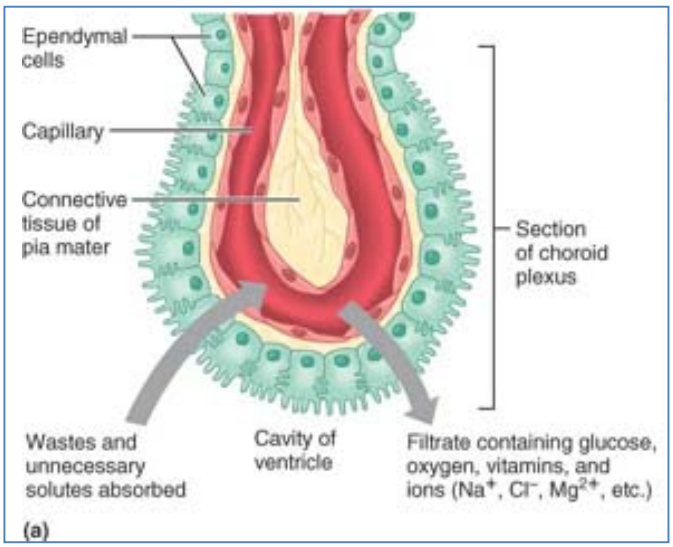


The Blood-Brain Barrier:

- Isolates Brain from Blood to provide a **Stable Environment**, necessary for control & function of CNS Neurons.
- **How?:**
  - 1. The **Endothelial Cells** of the CNS Capillaries are seamlessly joined by **Tight Junctions**.
    - This prevents diffusion of most materials except dissolved gasses & lipid-soluble compounds.
    - Therefore, any required water-soluble compound must be transported across the BBB.
  - 2. **Thick Basement Membrane of Capillary**



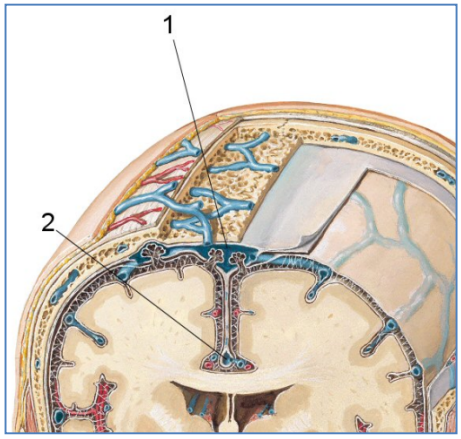
  - **NB:** In the **2 Choroid Plexuses**, the BBB is formed by **Tight Junctions between Glial (Eppendymal) Cells** as the capillaries in this region are Fenestrated & highly leaky.



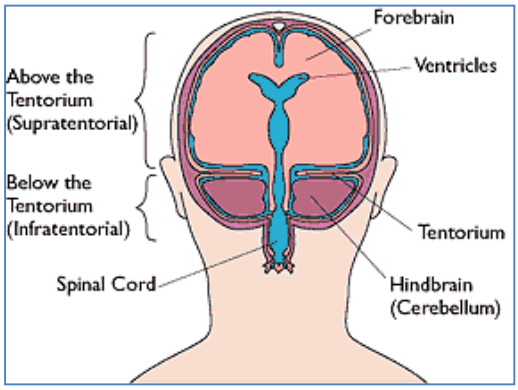
- **The BBB exists everywhere except:**
  - Hypothalamus – (Monitors chemical composition of blood. Ie. Hormone levels, water balance, etc)
  - Vomiting Centre - (Monitors poisonous substances in blood)

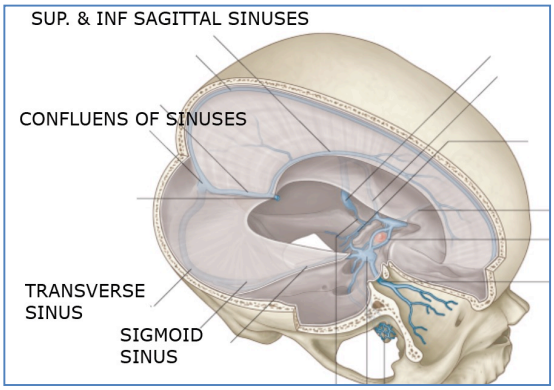
Venous Drainage of the Brain – Via "Dural Sinuses":

- Venous Drainage begins with venous blood collecting in small venous channels known as "Dural Sinuses".
- **Sinuses Sit Within The Dura-Mater:**
  - The Dura-Mater is the thickest & outermost of the 3 Meninges of the brain. It extends deep into the brain in **2 locations,** the ***Falx Cerebri*** & the ***Tentorium Cerebelli*****:**
    - **1. Falx Cerebri:**
      - The Dura Mater folds deep into the Longitudinal Fissure (Falx Cerebri) of the brain, where it forms 2 Sinuses:
        - 1. A Triangular **'Superior Sagittal Sinus'** at the top of the dural fold.
        - 2. A lower **'Inferior Sagittal Sinus'** at the bottom of the dural fold.
          - **NB:** Inf. Sagittal Sinus merges to form the '**Straight Sinus'.**

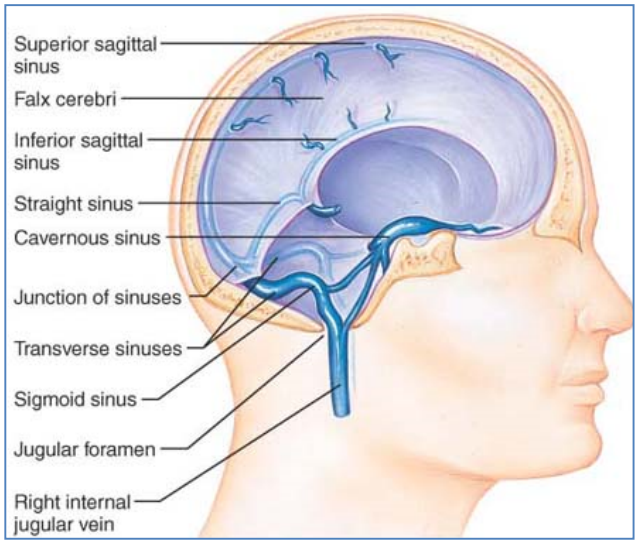


    - **2. Tentorium Cerebelli:**
      - The Dura Mater folds deep into the Transverse Cerebral Fissure (Tentorium Cerebelli) of the brain, where it forms a pair of sinuses:
        - **The R.&L. "Transverse Sinuses"**.
        - NB: All blood from Sup. & Inf. Sagittal Sinuses and the Straight Sinus empties into these Transverse Sinuses.



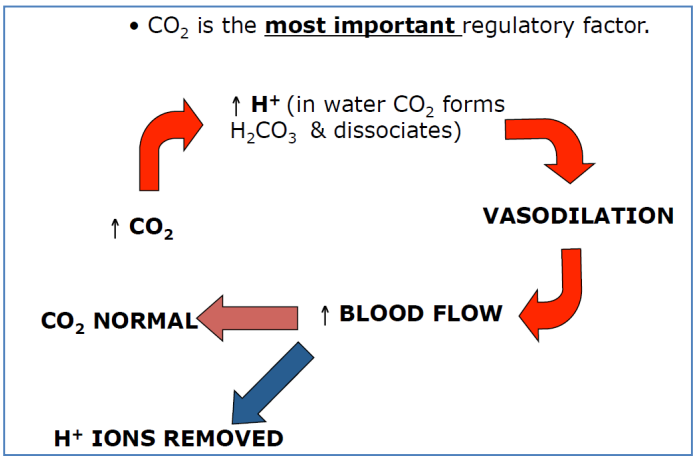


  - The L.&R. Transverse Sinuses then become the L.&R. **Sigmoid Sinuses** (Respectively).
  - These **Sigmoid Sinuses** turn Inferiorly and become the **Internal Jugular Veins.**



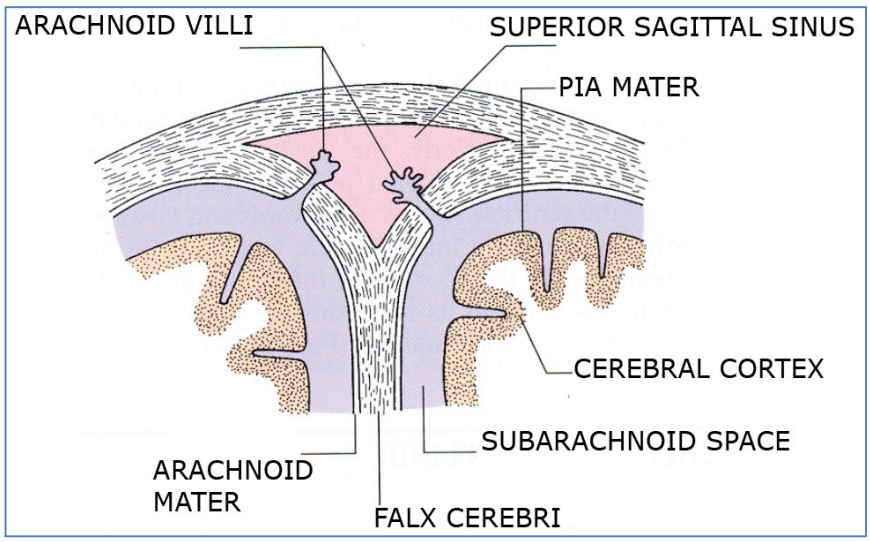
***Regulation* of Blood Flow to the Brain:**

- **Blood Flow to the Brain is *AUTOREGULATED:***
  - Ie. BP in the Brain is kept constant, despite systemic BP fluctuations.
  - It also means different areas of the brain control their blood flow depending on metabolic activity.
- **The *Myogenic* Autoregulation of Blood Flow to the Brain:**
  - When Mean Arterial Pressure rises, the SNS constricts the larger arteries of the brain to prevent damaging high pressures in the smaller, more delicate vessels. (Important for preventing Stroke)
- **The 3 *Metabolic* Autoregulatory Factors Affect Blood Flow to the Brain:**
  - ****1. Blood [CO_2]:**
    - ↑[CO_2] → Vasodilation (to ↑ Blood Flow)
    - ↓[CO_2] → Vasoconstriction (to ↓ Blood Flow)
  - **2. Blood/CSF pH:**
    - ↑[CO_2] → ↑[H^+] via carbonic anhydrase → ↓pH → Vasodilation (to ↑ Blood Flow)
    - ↓[CO_2] → ↓[H^+] via carbonic anhydrase → ↑pH → Vasoconstriction (to ↓ Blood Flow)
  - **3. Blood/CSF [O_2]:**
    - ↓[O_2] → Vasodilation (to ↑ Blood Flow)
    - ↑[O_2] → Vasoconstriction (to ↓ Blood Flow)



Reabsorption of CSF into the Dural Sinuses:

- NB: CSF is constantly being produced, and therefore must also be constantly drained to prevent a rise in intracranial pressure. Therefore:
- **CSF is Reabsorbed** into the **Venous System** via diffusion through **Arachnoid Villi.**
  - **Arachnoid Villi** are invaginations of Arachnoid Mater **through the Dura Mater** and **into the Superior Sagittal Sinus**.
- **Water Diffuses from Arachnoid Villi → Sup. Sagittal Sinus Due To:**
  - 1. Higher **Hydrostatic Pressure** in Sub-Arachnoid Space.
  - 2. Higher **Colloid-Osmotic Pressure** of the Venous Blood in the Sinus.



Intracranial Pressure:

- **What is it?**
  - The pressure within the cranium created by the cerebrospinal fluid (CSF), and exerted on the brain tissue & the brain's blood circulation vessels.
- **Determinants:**
  - CSF Production/Resorption (Eg. ↑Production + ↓Resorption)
  - Brain Tissue (Eg. Tumour / Inflammation)
  - Blood (Eg. Haemorrhage)
- **High Intracranial Pressure:**
  - Compresses the Cerebral Arteries → Decreased Blood Supply → Brain Damage
  - Can also displace the brain.
- **Symptoms of High ICP:**
  - Altered Consciousness
  - Changes in BP & HR
  - Changes in Eye Responses
  - Changes in Motor Function

Cerebral Oedema:

- **What is it?**
  - An excess accumulation of water in the intracellular and/or extracellular spaces of the brain.
- **Types of Cerebral Oedema:**
  - **Vasogenic:**
    - (Extracellular Oedema)
    - Due to a breakdown of tight endothelial junctions which form the BBB.
    - Eg. Hydrostatic Cerebral Oedema – where acutely high cerebral capillary pressure results in fluid moving from Capillary to ECF.
  - **Cytotoxic:**
    - (Intracellular Oedema)
    - Due to a defect in cellular metabolise → inadequate functioning of the Na/K-ATPase in the cell membrane → cellular retention of H_2O
  - **Osmotic:**
    - (Extracellular Oedema)
    - Where a drop in Plasma Osmolality (compared to CSF Osmolality) causes water to flow from the Venous Sinuses back into the Sub-Arachnoid Space.

Migraines:

- **What are They?**
  - Incapacitating Neurovascular disorder characterized by unilateral, throbbing headaches, photophobia, phonophobia, nausea & vomiting.
- **What Causes Them?**
  - Decrease in ***Serotonin*** Levels → ↑Sensitivity to Migraine Triggers + Cerebral Vasoconstriction → ↓cerebral blood flow → Raphe Nuclei in Brain-Stem release Serotonin → Cerebral Vasodilation + Release of ProInflammatory Mediators from ***Trigeminal Nerve*** & Spinal Nerves → Perivascular Cerebral Inflammation → Pain.
- **Classic Vs. Common:**
  - **Classic:**
    - Associated with **'Aura'**. (A visual symptom, such as an arc of sparkling (scintillating) zig-zag lines or a blotting out of vision or both)
  - **Common:**
    - Migraine without 'Aura' (Only 20% of sufferers experience aura. Most bypass the aura phase)
- **Migraines as a Risk Factor:**
  - ↑ Risk of Silent Post. Cerebral Infarcts.
  - ↑ Risk of Stroke & CVD (Women)
  - ↑ Risk of MI (Men)

CVA's – Cerebro-Vascular Accidents (Strokes):

- 3rd largest cause of death
- **What is it?**
  - "The rapidly developing loss of brain function(s) due to disturbance in the blood supply to the brain."
  - The specific functional loss caused by a stroke depends on *which artery/s* and functional areas of the brain are affected/occluded.

- **2 Forms of Stroke:**
  - **Ischaemic:**
    - Thrombotic
    - Embolic
  - **Haemorrhagic:**
    - Bleeding → short-circuits blood flow + increases Intra-Cranial Pressure → Compresses other Cerebral Arteries → Stroke.
      - NB: Haemorrhages in the brain can lead to perfusion deficits → ↑CO_2 + ↓pH → Vasodilation of cerebral arteries → More blood flow to the bleeding area → more bleeding → ↑Intracranial Pressure.

- **3 Common Causes of Stroke:**
  - **Atherosclerosis –**
    - Atherosclerotic Plaque within a cerebral artery ruptures causing thrombosis (blood clotting) → ↓Blood Flow → Cerebral Ischaemia → Stroke.
    - Part of an Atherosclerotic Plaque that has broken off lodges in a cerebral artery → ↓Blood Flow → Cerebral ischaemia → Stroke
  - **Heart Disease –**
    - Eg. Atrial Fibrillation can cause clotting → thrombo-emboli lodging in cerebral artery → ↓Blood Flow → Cerebral ischaemia → Stroke
  - **Hypertension –**
    - Puts high stress on blood vessel walls → blood vessel to thicken and break down→ stroke.
    - Can cause clots or plaques to break off artery walls → block a brain artery → stroke.
    - In rare cases it can cause a haemorrhagic stroke in people who were born with irregular formation of the blood vessel walls in the brain.

Measuring Brain Injury – The Glasgow Coma Scale:

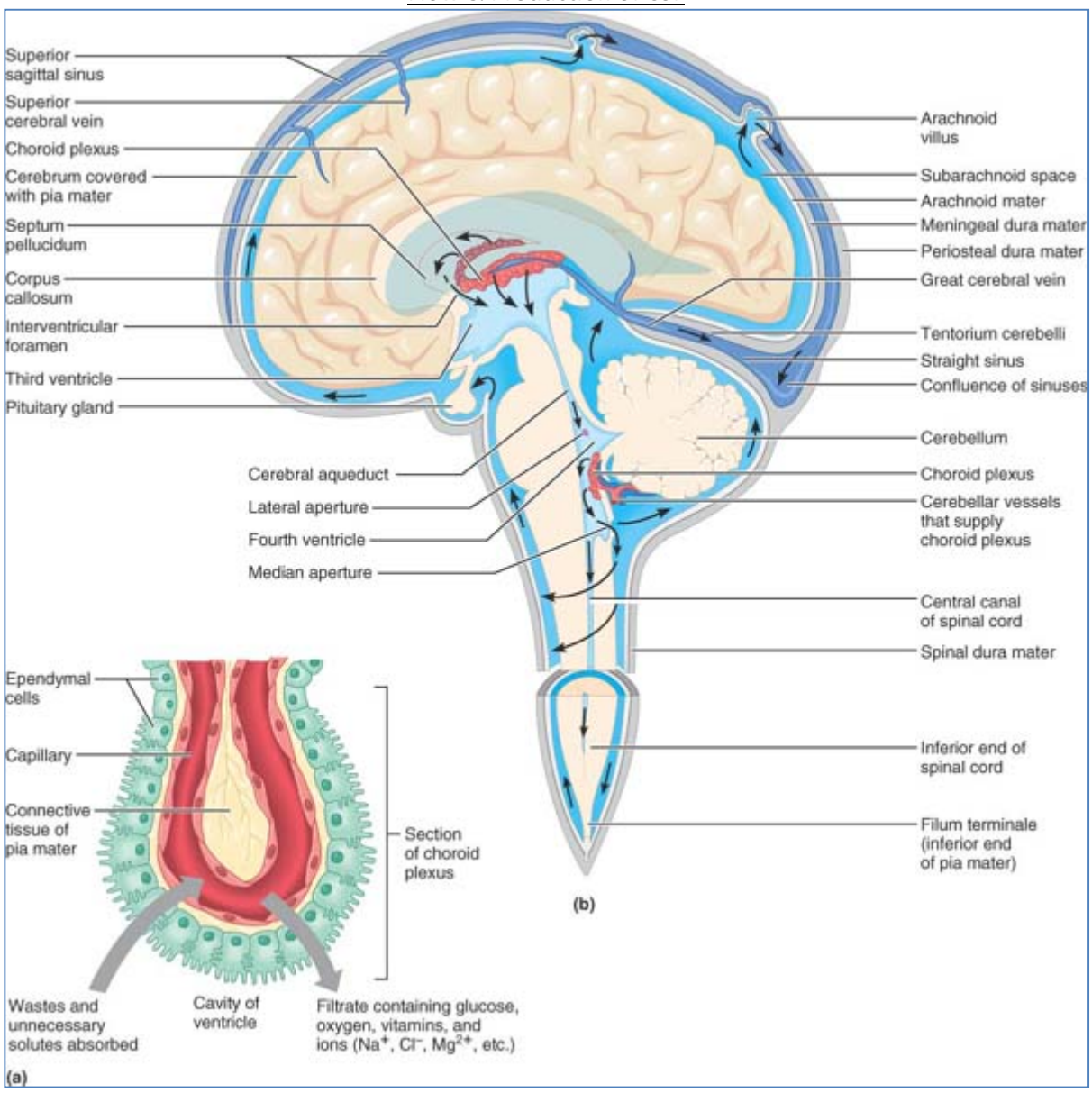
- A scale that measures the conscious state of a person against certain criteria, and the resulting points give a patient score between 3 (indicating deep unconsciousness) and 15 (full consciousness).

Glasgow Coma Scale

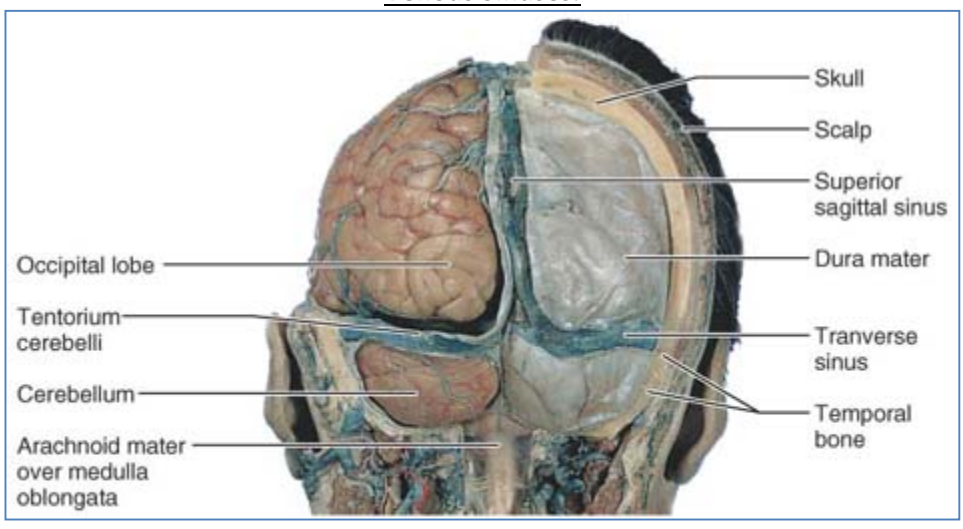
	1	2	3	4	5	6
Eyes	Does not open eyes	Opens eyes in response to painful stimuli	Opens eyes in response to voice	Opens eyes spontaneously	N/A	N/A
Verbal	Makes no sounds	Incomprehensible sounds	Utters inappropriate words	Confused, disorientated	Oriented, converses normally	N/A
Motor	Makes no movements	Extension to painful stimuli	Abnormal flexion to painful stimuli	Flexion / Withdrawal to painful stimuli	Localizes painful stimuli	Obeys commands

Pictures for Your Interst/Reference:

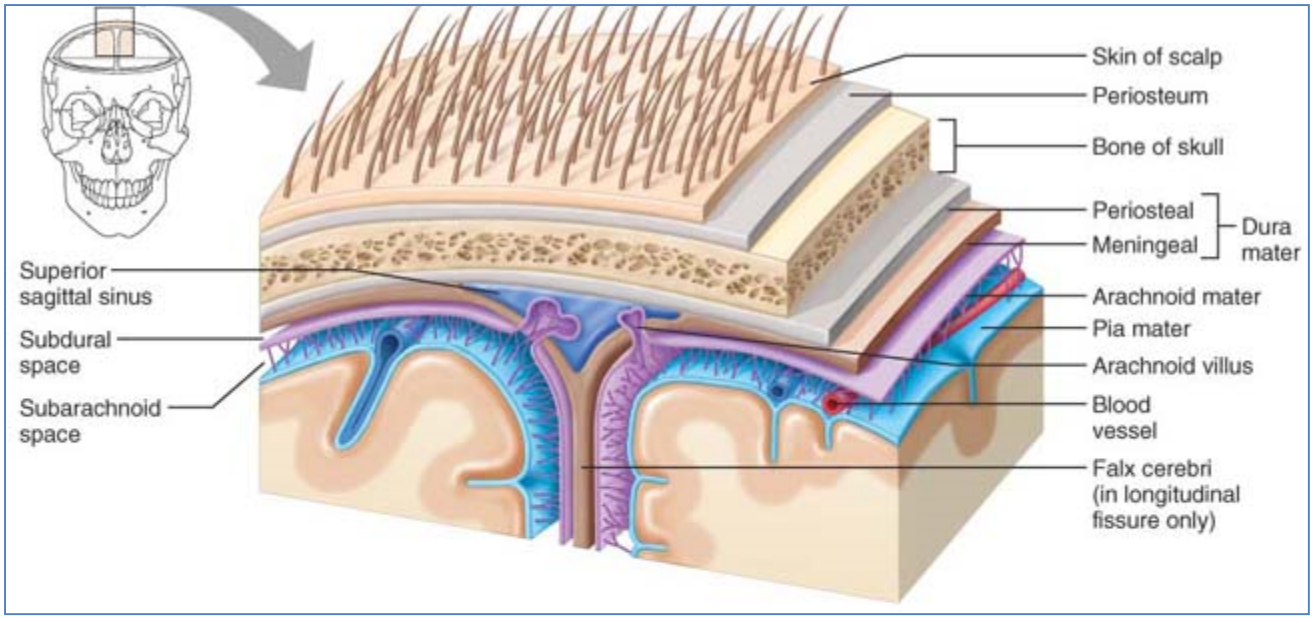
Flow & Production of CSF



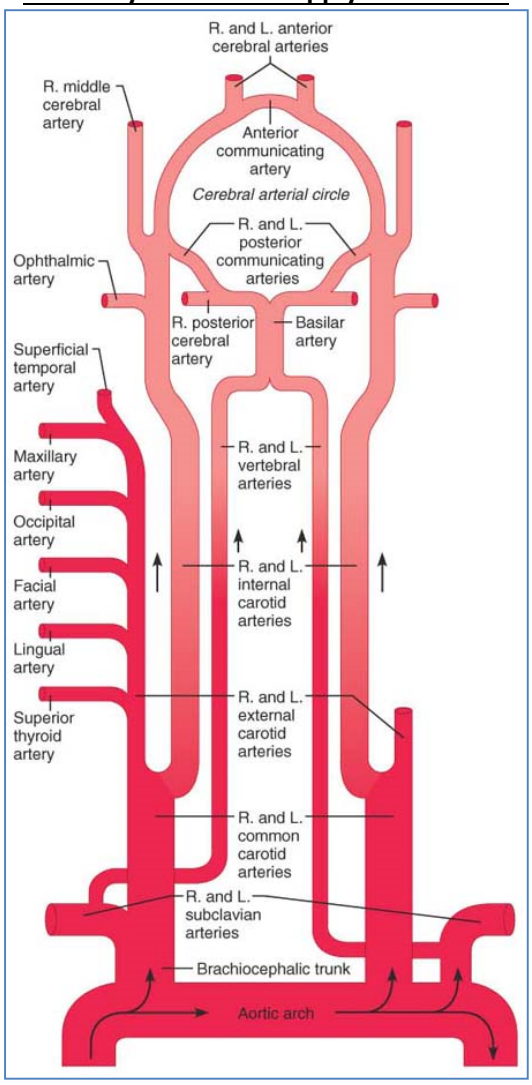
Venous Sinuses:



Meninges of the Brain



Summary of Arterial Supply of the Brain



Neuroscience Notes
Neurotransmission

What is Neurotransmission?:

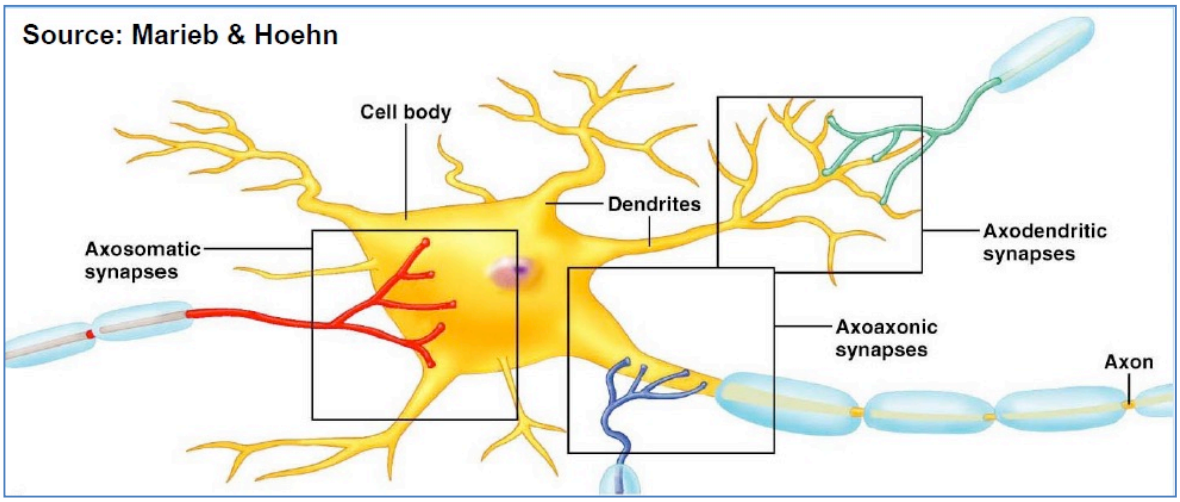
- Neuron → Neuron/Cel/Organ/Muscle/Etc. Communication
- Point of 'Communication' = The ***"Synapse"***

Terminology:

- **Pre-Synaptic Neuron:** The *'Sender'* Neuron
- **Synaptic Cleft:** The *'Gap'* Between cells
- **Post-Synaptic Cell:** The *'Receiver'* Cell
- **Synaptic Potential:** The *'Drive'* for Transmission (that mobilizes the synaptic vesicles to pre-synaptic membrane).

Neuron-Neuron Neurotransmission:

- **NB:** Neurons Synapse with Each Other in 3 Ways
- **3 Types of Synapses:**
  - **1. Axo-Somatic:** Axon → Cell Body (For ***Modulatory Effects***)
  - **2. Axo-Axonic:** Axon → Axon (For ***All/Nothing*** Signals)
  - **3. Axo-Dendritic:** Axon → Dendrite (For ***Multiple Inputs*** to a Neuron)



2 Types of Post-Synaptic Receptors:

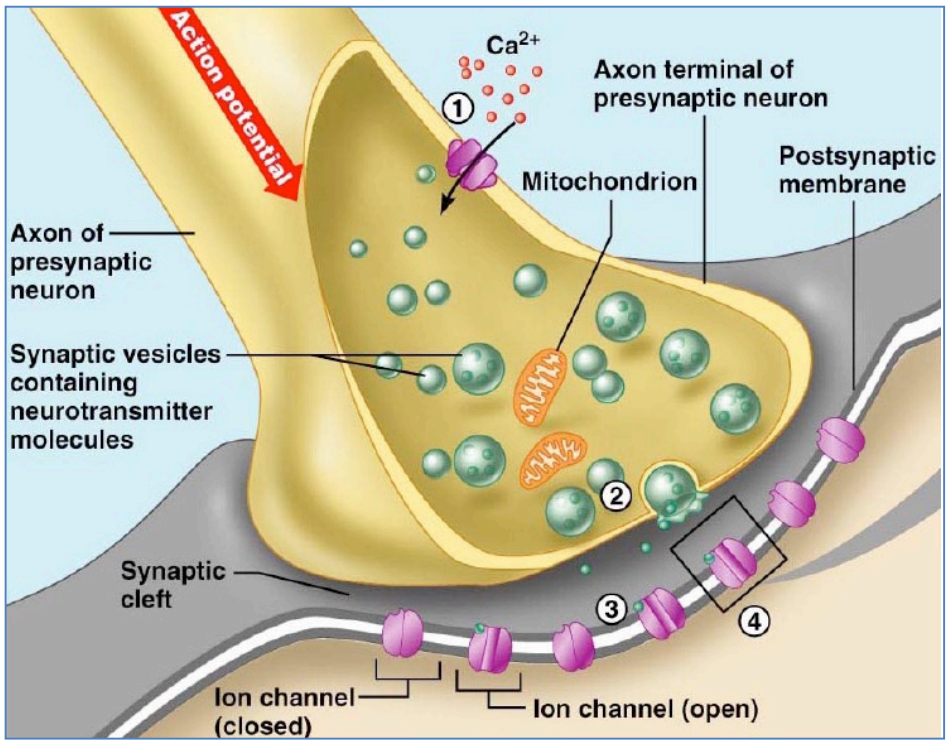
- **Ionotropic:** **(Ligand-Gated Ion Channels)**
  - **Mech:** Binding of Neurotransmitter → Opening of Ion Channel → Excitation/Inhibition of Cell.
    - **Excitatory: Na^+/Ca^+ Channel** – opening → Na^+/Ca^+ Influx → Depolarisation of Membrane → → *"Excitatory Post-Synaptic Potential" (EPSP)*
    - **Inhibitory: Cl^- Channel** – opening → Cl^- Influx → Hyperpolarisation of Membrane → **K^+ Channel** – opening → K^+ Efflux → Hyperpolarisation of Membrane → → *"Inhibitory Post-Synaptic Potential" (IPSP)*
- **Metabotropic:** **(G-Protein Linked Receptors)**
  - **Mech:** Binding of Neurotransmitter → Activates G-Protein → Activates 'Effector' Proteins → Activate secondary Messengers (Eg. cAMP) → Regulates Ion Channels/Activates Enzymes/Alters Metabolism.

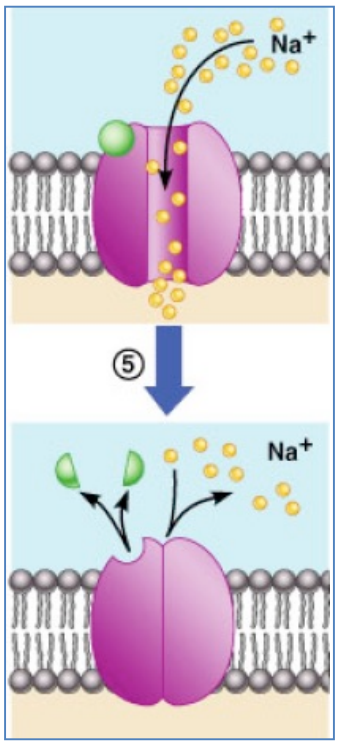
Actions of Neurotransmission:

- **Direct Physiological Action:**
  - Eg. Neuromuscular Junction → Muscle Contraction
  - Eg. Sympathetic Synapse @ SA-Node → ↑Heart Rate
- **Links in a Chain:**
  - Eg. Peripheral Sensory Neuron → Spinal Cord → Ascending Sensory Pathways → Thalamus → Cortex
- **Modulation:**
  - Ie. Exerting a +ve/-ve influence on transmission *by another neuron.*

Process of Neurotransmission:

1. **Action Potential** reaches axon terminal.
2. **Voltage Gated Ca^+ Channels** open in response to Action Potential → Ca^+ influx into Axon Terminal.
    a. **NB:** the amount of Ca^+ influx can be influenced by neuromodulators.
3. **Migration of Neurotransmitter-Filled Vesicles** due to Ca^+ influx → Vesicles fuse with Presynaptic Membrane.
    a. **NB:** The number of vesicles mobilised is Directly Proportional to the amount of Ca^+ Influx.
4. **Excytosis of Vesicles** → Neurotransmitter release into Synaptic Cleft
5. **Diffusion of Neurotransmitter Across Synapse** → to the Post-Synaptic Membrane.
6. **Binding of Neurotransmitter to Post-Synaptic Receptors:**
    a. **Receptors may be:**
        i. ***Ionotropic*** – Ligand Gated Ion Channels.
        ii. ***Or Metabotropic*** – G-Protein Linked Receptors.
    b. **Neurotransmitter may be:**
        i. **Excitatory** – Depolarise Post-Synaptic Membrane (By causing Na^+ Influx)
        ii. **Or Inhibitory** – Hyperpolarise Post-Synaptic Membrane (By causing Cl^- Influx)
7. **Termination of Signal** – Either by Neurotransmitter Destruction/Inactivation or Re-Uptake into the Neuron.



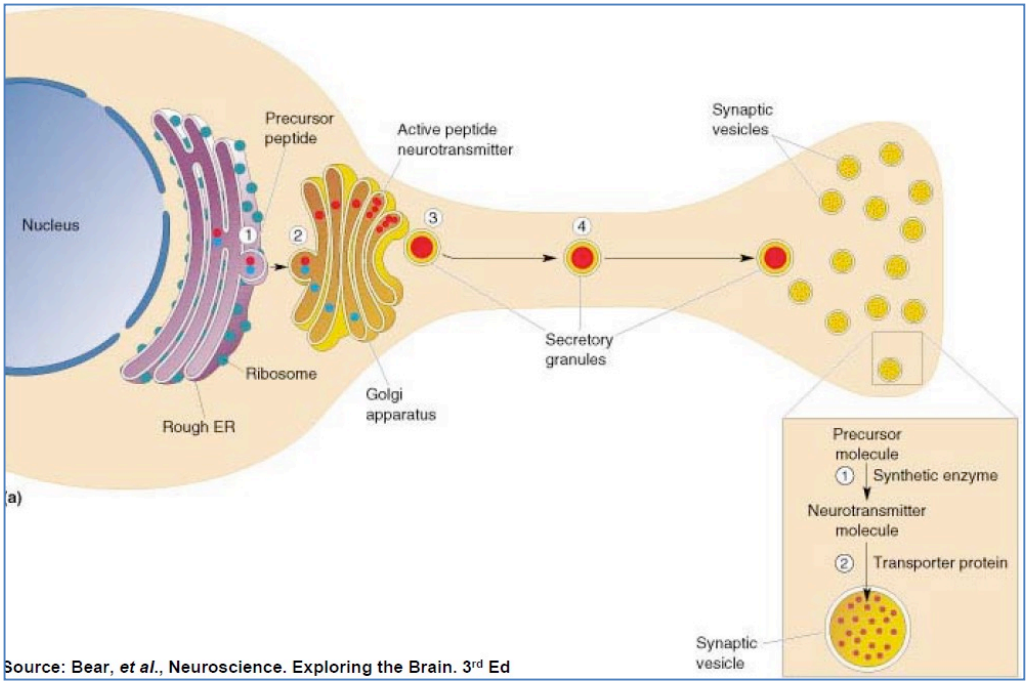


Key Ions Involved in Neurotransmission:

- **Na^+:** - Influx - To depolarise membrane to initiate/propagate an Action Potential
- **K^+:** - Efflux - To repolarise the membrane to resting potential once the Action Potential has passed.
- **Ca^+:** - Influx - To trigger the Exocytosis of Neurotransmitter into Synaptic Cleft.

For a Chemical to be a 'Neurotransmitter', it must have:

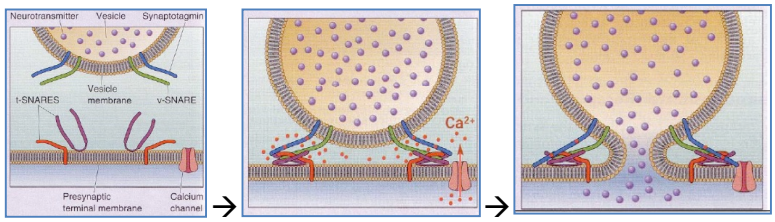
1. **Dedicated Synthesis**
   a. **NB:** Amine & Amino-Acid Neurotransmitters are synthesized in the Axon-Terminal, HOWEVER, Peptide Neurotransmitters are synthesized in the Cell Body & Transported to the Axon Terminal. (This is because Peptide Synthesis requires Gene Transcription & Translation which require a Nucleus & Rough Endoplasmic Reticulum.)
   b. **NB:** There is a ***Rate-Limiting Step*** for all Neurotransmitter Synthesis. (Eg. Activity/Amount of an Enzyme, Substrate Availability)
2. **Active Packaging**
   a. Amine & Amino-Acid NT's Actively Packaged Into Vesicles, Driven by H^+ Gradient within Vesicle. (Ie. H^+-Filled Vesicles exchange H^+ for Neurotransmitter)
   b. Peptide NT's Packaged by Golgi Apparatus & transported to Axon Terminal



Source: Bear, *et al.*, Neuroscience. Exploring the Brain. 3rd Ed

(Notice The Different Pathways of Synthesis of Peptide-NT's Vs. Amine/Amino-Acid -NT's.)

3. **Controlled Release**
   a. Various Proteins involved in Vesicle Mobilisation are activated by Ca^+ Influx. (NB: Many such proteins are destroyed by Botox, giving Botox recipients expressionless faces)
   b. Vesicle-Membrane fuses with Presynaptic-Membrane, Creating a *Release-Pore* → NT Diffuses across Synaptic-Cleft. Often some NT's end up in other neighbouring synapses.



4. **Receptive Post-Synaptic Cell**
   a. Neurotransmitter Activates either:
      i. Ionotropic Receptors: (Ligand-Gate Ion Channels)
      ii. Metabotropic Receptors: (G-Protein Linked Receptors → Secondary Messengers)
5. **Signal Termination Mechanism**
   a. <u>To Prevent Over-Release of NT</u>, ***Autoreceptors*** exist on Pre-Synaptic Membrane.
      i. Provide –ve feedback by inactivating Adenylate Cyclase → ↓cAMP → Closes Ca^+ Channels → Stops Vesicle Mobilisation & Release
   b. <u>To Prevent On-Going Stimulation</u>, a NT's signal is terminated by either:
      i. Synaptic Enzyme: (Destroys the NT in the Synapse)
      ii. Rapid Re-Uptake: (Transport of NT Back into Pre-Synaptic Cell)
      NB: For NT's taken back up, there are 2 fates:
      1. Recycling (Repackaged into Synaptic Vesicles)
      2. Enzymatic Degradation (NT is broken down into Metabolites)

Regulation of Receptor Response:

- **If NT is Over-Released and/or Not Terminated** → On-Going Stimulation → Receptor Activity is Altered:
  - **Desensitisation:** ↓Response to NT due to ↓Sensitivity of the Receptor.
  - **Down-Regulation:** ↓Response to NT due to ↓# of Receptors.

    NB: This functions to block out ***"Noise".***
- **If NT is Under-Released or if Antagonist is Administered for Too Long** → Receptor Activity is Altered:
  - **Supersensitisation:** ↑Response to NT due to ↑Sensitivity of the Receptor.
  - **Up-Regulation:** ↑Response to NT due to ↑# of Receptors.

Neuromodulation:

- **Ie.** The Fine-Tuning ("Volume Control") of a signal.
- A Neuromodulator can be conceptualized as a neurotransmitter that is not reabsorbed by the pre-synaptic neuron or broken down into a metabolite. Such neuromodulators end up spending a significant amount of time in the CSF (cerebrospinal fluid), influencing (or modulating) the overall activity level of the brain.
- Hence creates a Broad Signal across the brain → Synchronous activation of Separate Regions → Elicits markedly different level of responses from Synaptic Activity.
- Neuromodulators may either be released into a Synaptic Cleft, or Extracellular Fluid.
- **Types of Neuromodulators:**
  - **Metabolic Products** (Eg. Adenosine, ATP, H^+)
  - **Hormones** (Eg. Oestrogen)
  - **Gases** (Eg. Nitric Oxide, CO_2)
  - **Amines** (Eg. Dopamine, Serotonin, Histamine, Acetylcholine)
  - **Proteins**
  - **Prostaglandins**
  - **Etc.Etc. (ie. There are loads!)**

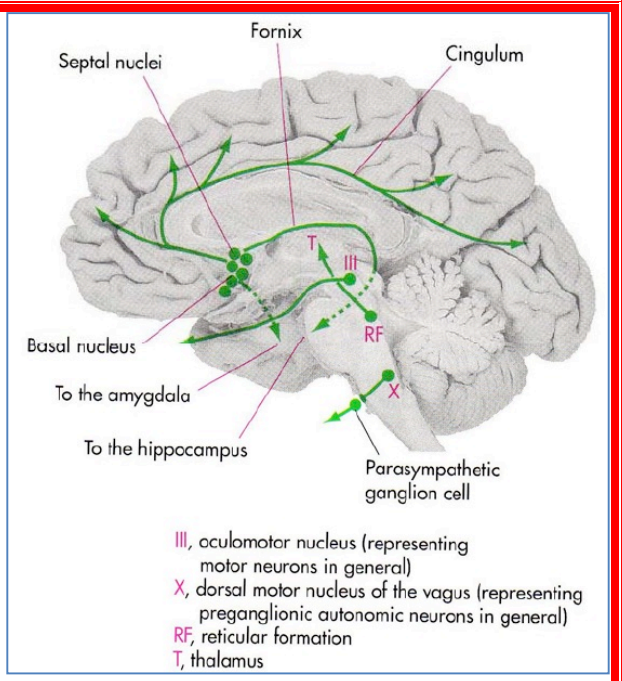
The Neurotransmitters

The Major Neurotransmitters (Classified by Structure):

- ****Amines ("Classical Neurotransmitters"):**
  - Acetylcholine (ACh)
  - Dopamine
  - Noradrenaline/Norepinephrine (NA/NE)
  - Epinephrine
    - (NB: NE is the Neurotransmitter, while Epinephrine is the Hormone)
  - Serotonin/5-Hydroxyl Tryptamine (5-HT)
  - Histamine
- **Amino Acids:**
  - Glutamate (#1 Excitatory Neurotransmitter of the Brain)
  - γ-Amino Butyric Acid (GABA) (#1 Inhibitory Neurotransmitter of the Brain)
  - Glycine
  - Aspartate
- **Peptides:**
  - Cholecystokinin
  - Enkephalins (Eg. Endorphins, Opioids) (Turn off Nociceptive/pain Pathways)
  - Neuropeptide Y (Regulates Food Intake/Hunger)
  - Somatostatin
  - TRH
  - Vasoactive Intestinal Peptide (VIP)

Acetylcholine/ACh (Cholinergic Nerves):

- **Roles:**
  - **Brain Functions:**
    - Voluntary Motor Control
    - Memory & Learning Pathways
    - Arousal
    - Sleep/Wake Cycles
  - **Peripheral Functions:**
    - Contraction of Skeletal Muscle
    - Parasympathetic Activity in the Heart/GI/Eye/Salivary Glands/Lacrimal (Tear) Glands



- **ACh Synthesis:**
  - ***Choline*** + ***Acetyl-CoA*** are combined by ***Choline-Acetyl-Transferase (CAT)*** to form ***Acetylcholine + CoA***
    - (Hence, Choline & the Acetate group from the Acetyl-CoA combine → ACh)
    - NB: This occurs *in the cytosol* of the Neuron at the Axon-Terminal.
- **ACh Packaging:**
  - ACh is concentrated into Vesicles by an ***ACh-Transporter***
- **ACh Release:**
  - Via Ca^{+} Mediated Vesicular Exocytosis
- **Cholinergic Receptors (2 Types):**
  - **1. Muscarinic:** - G-Protein Linked/Metabotropic Receptors (Parasympathetic NS)
  - **2. Nicotinic:** - Ligand-Gated Ion Channels/Ionotropic Receptors (Neuromuscular Junction/CNS/PNS)
- **ACh Signal-Termination:**
  - ***ACh*** is degraded within the synapse by ***Acetyl-Choline Esterase → Choline + Acetate***
  - The ***Choline*** released is Actively Transported back into the Pre-Synaptic Cell by a ***Choline Transporter***
- **Rate-Limiting Step:**
  - *The Reuptake of Choline*; Because the availability of Choline determines the amount of ACh synthesis

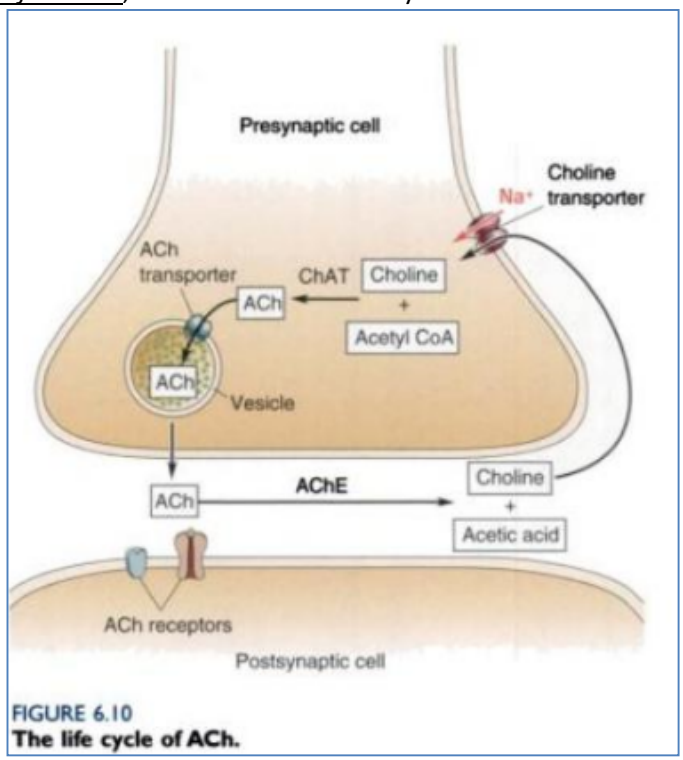
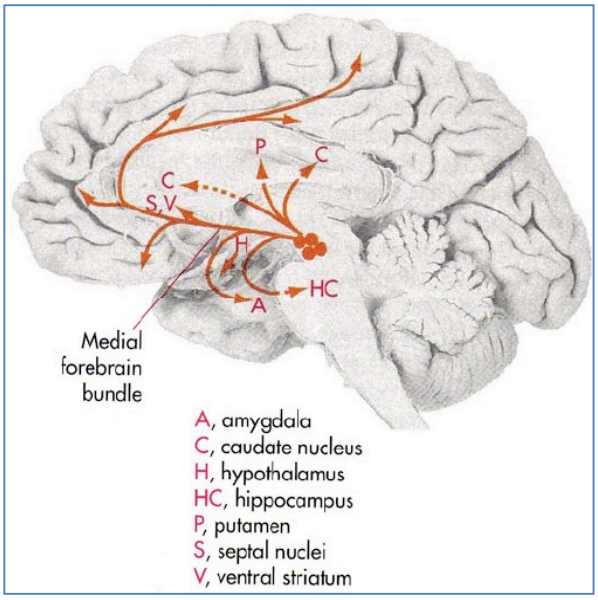


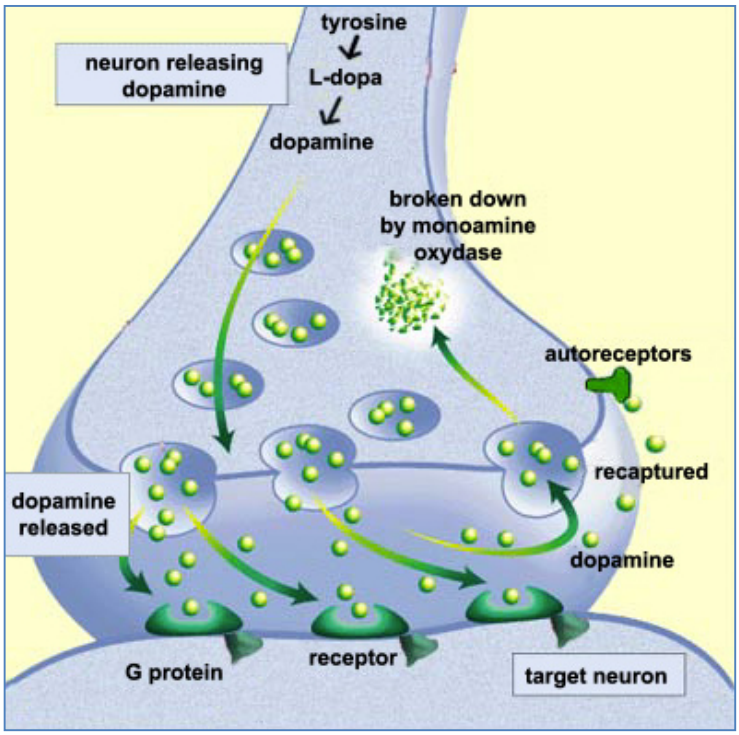
FIGURE 6.10
The life cycle of ACh.

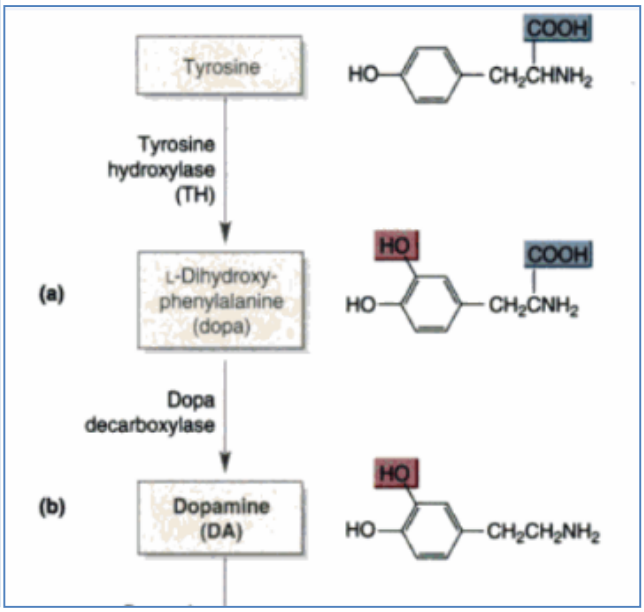
Catecholamines (Dopamine/Nor-Epinephrine(Nor-Adrenaline)/Epinephrine(Adrenaline):

- **Dopamine:**
  - **Roles:**
    - **Brain Functions:**
      - Voluntary Motor Control
      - Cognition
      - Reward Centre
      - Emotions & Behaviour
      - Vomiting
    - **Peripheral Functions:**
      - Cardiovascular Function (↑HR & Contraction)
      - Renal Vasodilation @ JG Apparatus (↑Filtration)

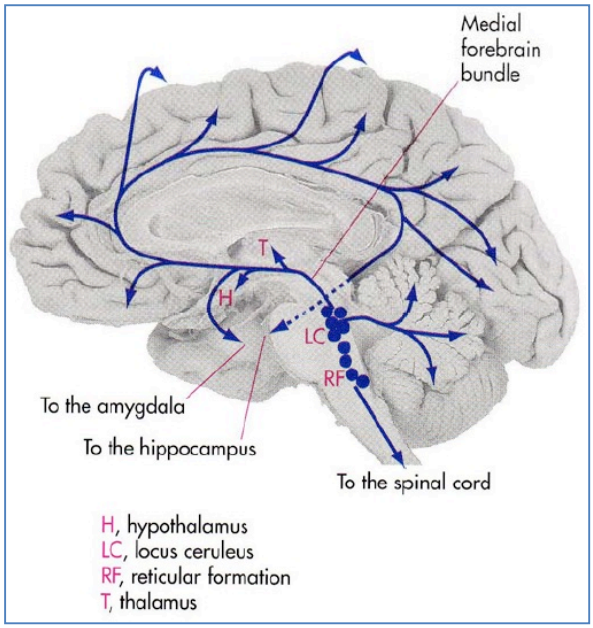


  - **Synthesis:**
    - Starts with ***Tyrosine*** (Amino Acid)
    - ***Tyrosine*** is converted to ***Dopa*** by ***Tyrosine-Hydroxylase***
    - ***Dopa*** is converted to ***Dopamine*** by ***Dopa-Decarboxylase***
  - **Packaging:**
    - Dopamine is packaged into vesicles in Axon Terminal.
  - **Release:**
    - Via Ca^{+} Mediated Vesicular Exocytosis
  - **Dopaminergic Receptors:**
    - - Are ***Metabotropic*** (G-Protein Linked Receptors)
      NB: All Catecholamine Receptors are Metabotropic.
  - **Dopamine Signal-Termination:**
    - Active Re-Uptake into the Axon via ***Na^{+}-Dependant Transporters*** → Repackaged/Destroyed.
      - NB: If Destroyed – Via enzymatic degradation by ***Mono-Amine Oxidase (MAO).***
  - **Rate-Limiting Step?:**
    - Conversion of *Tyrosine* → *Dopa* by ***Tyrosine-Hydroxylase***
    - Hence, the activity of ***Tyrosine-Hydroxylase*** is 'rate-limiting' for *All Catecholamine Synthesis*.

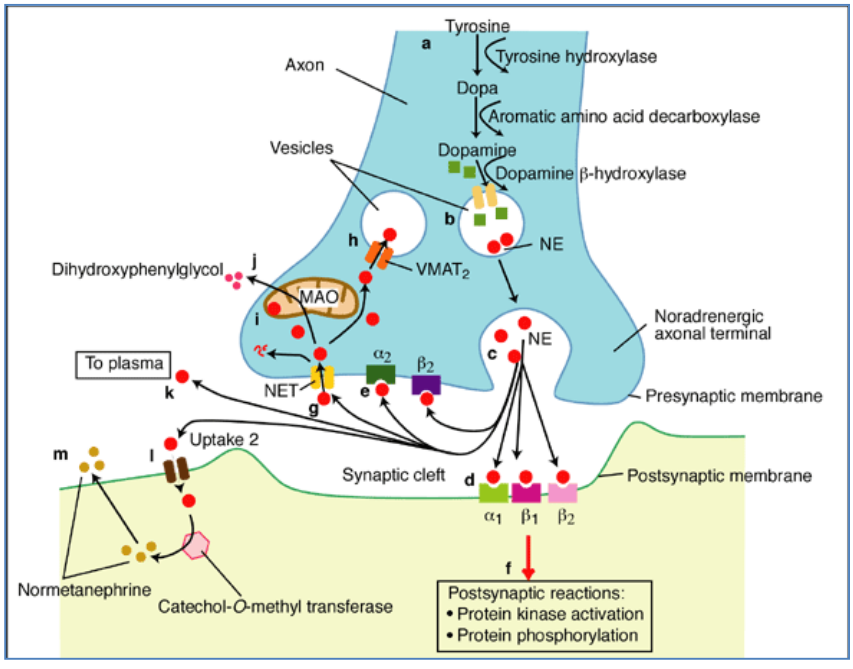




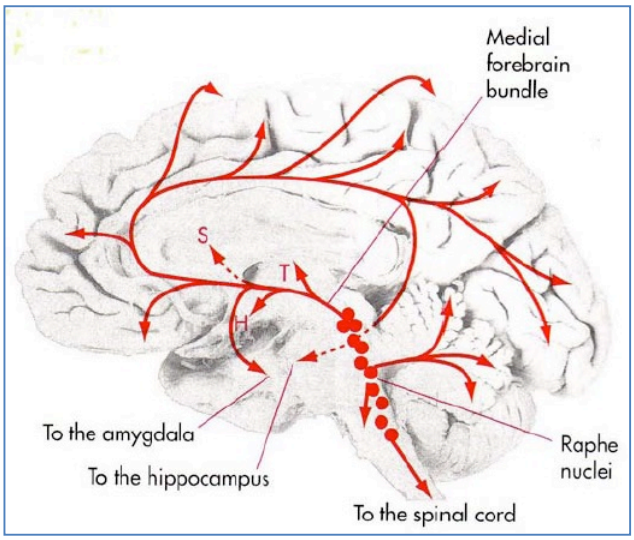
- **Nor-Epinephrine:**
  - **Roles:**
    - **Brain Functions:**
      - Attention/Arousal (Fight/Flight Response)
      - Sleep-Wake Cycle
      - Learning & Memory
      - Anxiety
      - Pain
      - Mood
    - **Peripheral Functions:**
      - Sympathetic Responses
      - ↑HR + BP
      - ↑Glycolysis + Gluconeogenesis + Fat Metabolism
      - ↑Blood flow to Muscles
      - ↑Blood Flow to Coronary Circulation



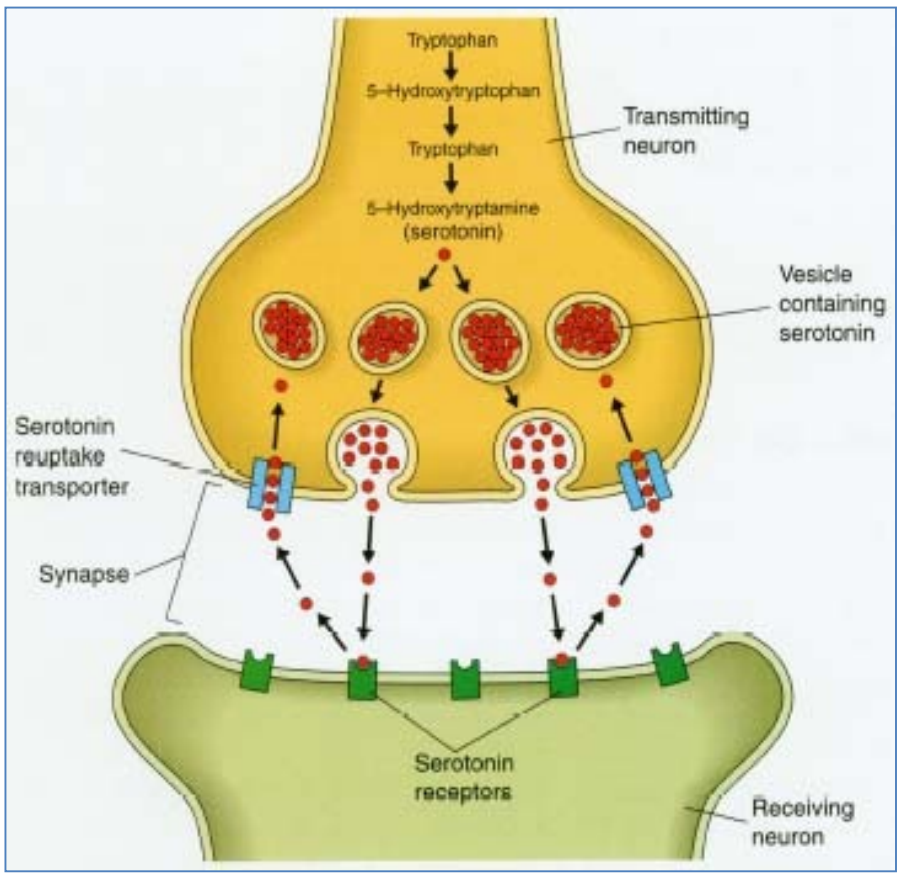
  - **Synthesis:**
    - Starts with ***Tyrosine*** (Amino Acid)
    - ***Tyrosine*** is converted to ***Dopa*** by ***Tyrosine-Hydroxylase***
    - ***Dopa*** is converted to ***Dopamine*** by ***Dopa-Decarboxylase***
    - Dopamine is packaged into vesicles in Axon Terminal.
    - ***Dopamine*** is converted to ***Nor-Epinephrine (Nor-Adrenaline)*** by ***Dopamine-Hydroxylase*** inside the Vesicles.
  - **Packaging:**
    - Dopamine is packaged into vesicles in Axon Terminal before conversion to Nor-Epinephrine.
  - **Release:**
    - Via Ca^{+} Mediated Vesicular Exocytosis
  - **Adrenergic Receptors:**
    - - Are ***Metabotropic*** (G-Protein Linked Receptors)
      NB: All Catecholamine Receptors are Metabotropic.
  - **Signal-Termination:**
    - Active Re-Uptake into the Axon via ***Na^{+}-Dependant Transporters*** → Repackaged/Destroyed.
      - NB: If Destroyed – Via enzymatic degradation by ***Mono-Amine Oxidase (MAO).***
  - **Rate-Limiting Step?:**
    - Conversion of *Tyrosine* → *Dopa* by ***Tyrosine-Hydroxylase***
    - Hence, the activity of ***Tyrosine-Hydroxylase*** is 'rate-limiting' for *All Catecholamine Synthesis*.



Serotonin:

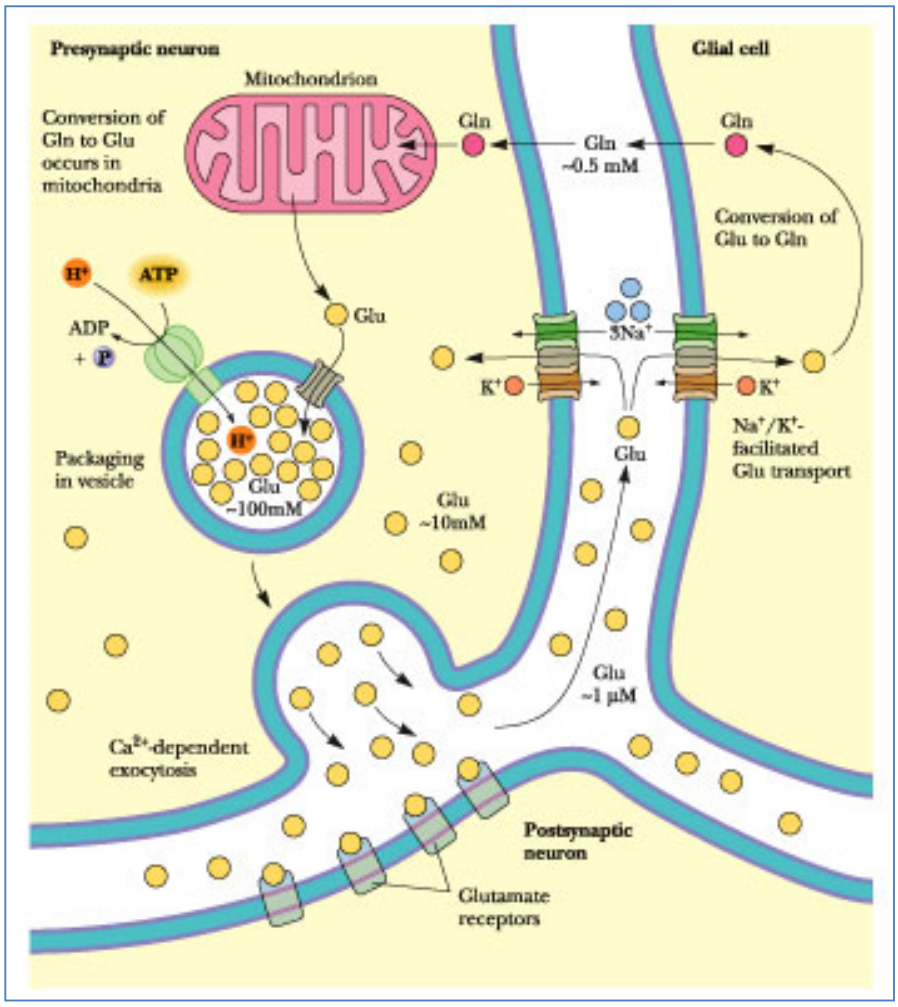


- **Roles:**
  - **Brain Functions:**
    - Pain
    - Wakefulness/Arousal
    - Sleep-Wake Cycle
    - Mood & Emotions
    - Vomiting
    - Circadian Rhythm (Indirectly by conversion to Melatonin)
  - **Peripheral Functions:**
    - GI Tract
    - Platelet Function
- **Synthesis:**
  - Starts with ***Tryptophan***
  - ***Tryptophan*** is converted to ***5-HTP*** by ***Tryptophan Hydroxylase***
  - ***5-HTP*** is converted to ***5-HT (Serotonin)*** by ***5-HTP-Decarboxylase.***
- **Packaging:**
  - Serotonin is packaged into vesicles in Axon Terminal.
- **Release:**
  - Via Ca^{+} Mediated Vesicular Exocytosis
- **Serotonergic (5-HT) Receptors:**
  - ***"5-HT"*** Receptors (Can have Ionotropic & Metabotropic Types)
- **Signal-Termination:**
  - Active Re-Uptake into the Axon via ***Na^{+}-Dependant Transporters*** → Repackaged/Destroyed.
    - NB: If Destroyed – Via enzymatic degradation by ***Mono-Amine Oxidase (MAO).***
- **Rate-Limiting Step?:**
  - Availability of Tryptophan in the Extracellular Fluid. (Tryptophan is an Essential Amino Acid)
  - Hence, a dietary deficiency of Tryptophan → Depletion of Serotonin in the brain.



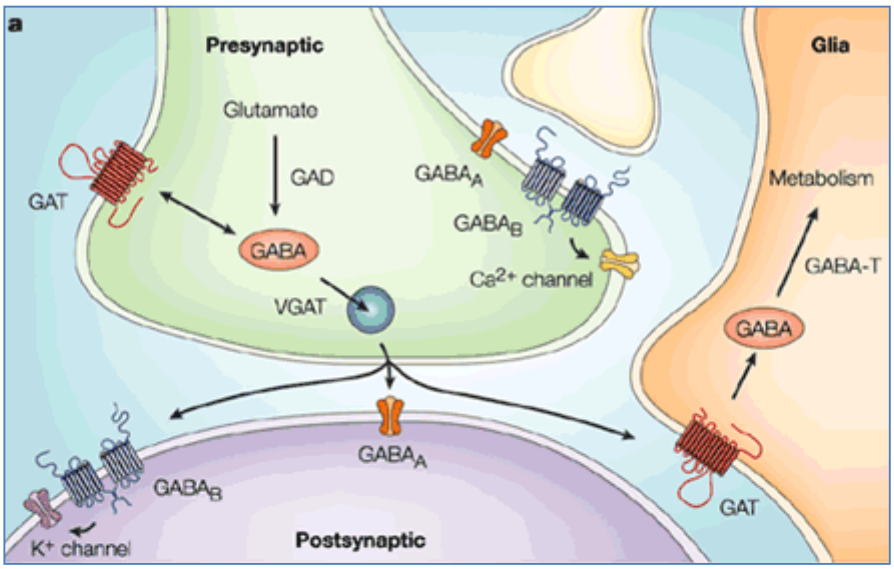
Amino Acid Neurotransmitters:

- **Glutamate:**
  - **Roles:**
    - Most common neurotransmitter in the brain.
  - **Synthesis:**
    - Begins with conversion of ***Glucose*** → ***α-KetoGlutarate*** Via Glycolysis & TCA-Cycle.
    - Then conversion of ***α-KetoGlutarate*** → ***Glutamate*** via a Transaminase Reaction.
  - **Packaging:**
    - Active Packaging in Vesicles
  - **Release:**
    - Ca^{+} Dependant Exocytosis
  - **Receptors:**
    - **Ionotropic:**
      - **NMDA Receptor**
      - **Kainate Receptor**
      - **AMPA Receptor**
    - **Metabotropic:**
      - **mGluR Receptor**
  - **Signal-Termination:**
    - K^{+} Dependant Re-Uptake into Pre-Synaptic Neuron → Repackaged into Vesicles.



?

- **GABA (Gamma Amino Butyric Acid):**
  - **Roles:**
    - Inhibitory Neurotransmitter in Brain
  - **Synthesis:**
    - Begins with conversion of ***Glucose*** → ***α-KetoGlutarate*** Via Glycolysis & TCA-Cycle.
    - Then conversion of ***α-KetoGlutarate*** → ***Glutamate*** via a Transaminase Reaction.
    - Then conversion of ***Glutamate*** → ***GABA*** by ***Glutamic-Acid-Decarboxylase*** (+ $VitB_6$)**.**
  - **Packaging:**
    - Packaged into vesicles by the ***Vesicular GABA Transporter (VGAT)***
  - **Release:**
    - Ca^+ Dependant Exocytosis
  - **Receptors:**
    - **$GABA_A$:** - Ligand Gated Cl^- Channels (Ionotropic)...Stimulation → Cl^- Influx → Hyperpolarises.
    - **$GABA_B$: -** G-Protein Linked (Metabotropic)...Stimulation → K^+ Efflux → Hyperpolarises.
  - **Signal-Termination:**
    - K^+ Dependant Re-Uptake into Pre-Synaptic Neuron → Destruction by ***GABA-Transaminase.***



- **Glycine:**
  - **Roles:**
    - Inhibitory Neurotransmitter in the Fore-Brain, Brain-Stem & Spinal Cord
      - Motor Functions
      - Sensory Functions
  - **Synthesis:**
    - Begins with Glucose → 3-Phospho Glycerate → Serine → Glycine
  - **Packaging:**
    - Vesicles
  - **Release:**
    - Ca^+ Dependant Release
  - **Receptors:**
    - Ionotropic Cl^- Receptors → Cl^- Influx → Hyperpolarisation.
  - **Signal-Termination:**
    - Re-Uptake of Glycine into Pre-Synaptic Neuron

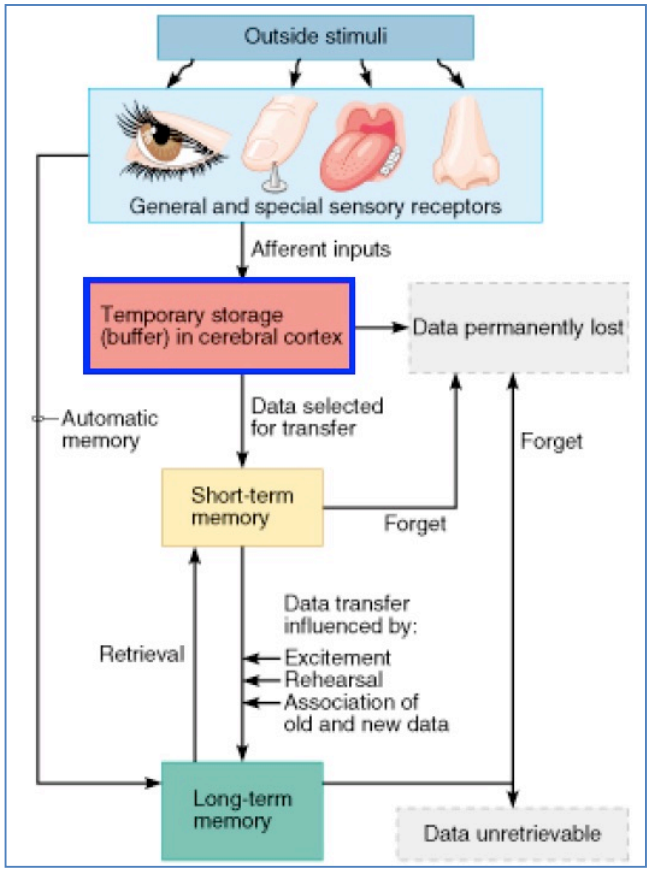
See SS Materials for Introductions to Myasthenia Gravis, Glaucoma & Parkinsons Disease.

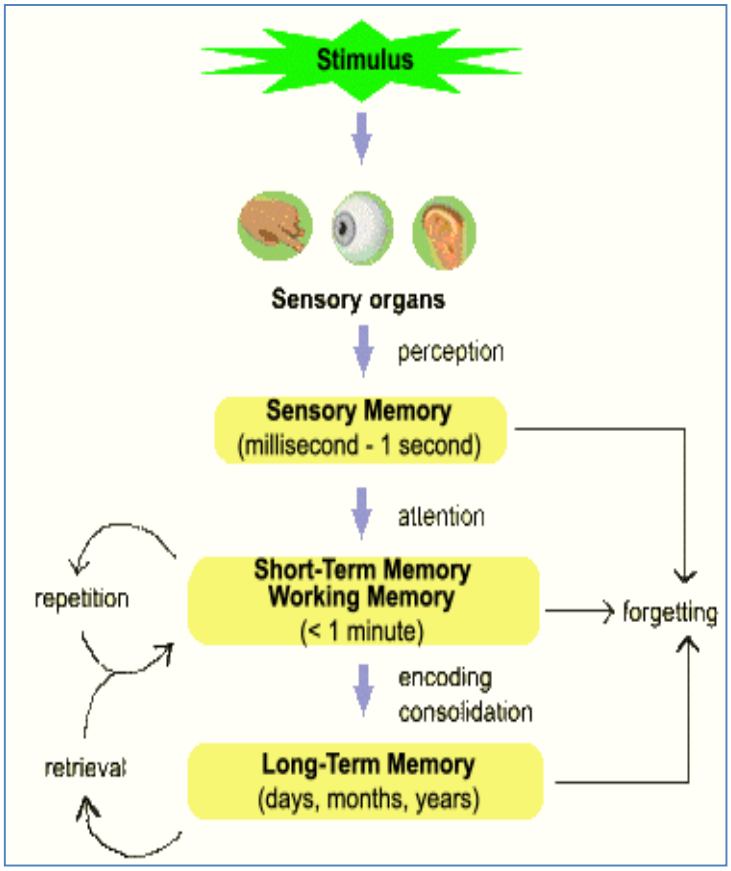
Neuroscience Notes
Memories

NB: We still don't know where exactly long-term memory is stored.
- **Believed that memory is stored throughout the brain.**

However: We DO know that in creating memories, cells of the brain *Change!!*
- **Eg. New Synapses:** An Architectural Change in the brain
- **Eg. Strengthening of Synapses:** Functional Changes (Ie. LTP)

Process of Memory Creation:
1. **External Stimuli:**
   a. Sensory input bombards the brain & is sent to Cerebral Cortex.
2. **Temporary Storage (Cerebral Cortex):**
   a. Sorts & Evaluates the Information.
   b. Depending which inputs you focus on, determines what info is sent to Short Term Memory.
      i. Input not focussed on is Forgotten.
3. **Short Term Memory:**
   a. In Medial Temporal Lobe (Hippocampus, Amygdala & Surrounding Cortical Areas).
   b. Excitement/Rehearsal/Association/Emotion → Transfer to Long Term Memory.
      i. Input not subjected to the above is Forgotten.
4. **Long Term Memory:**
   a. Requires: ACh – for Declarative; or Dopamine – for Non-Declarative.
      i. Declarative – Stored in ≈ Prefrontal Cortex
      ii. Non-Declarative – Stored in ≈ Premotor Cortex.

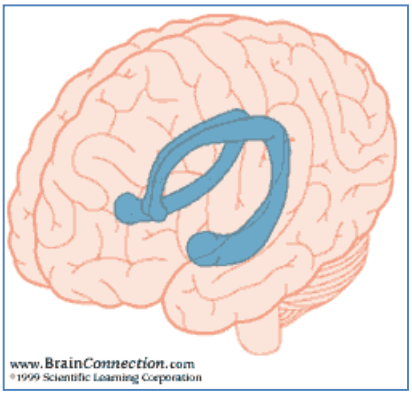


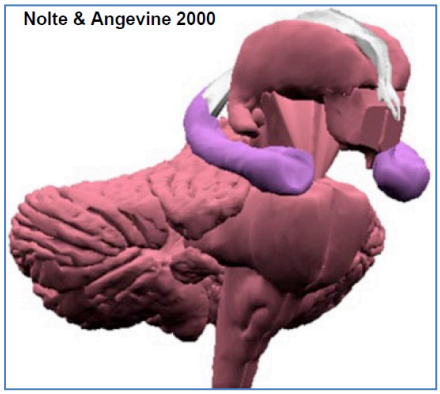


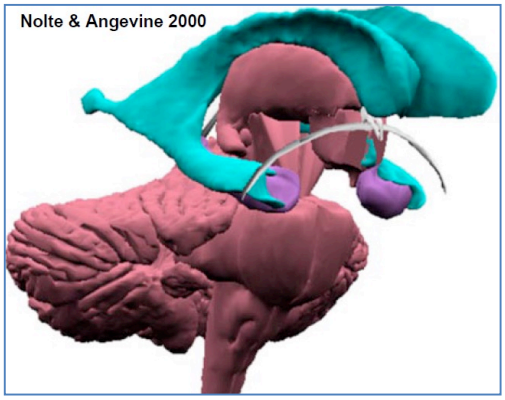
Short-Term Memory (STM):

- ***Based in Hippocampus***.
  - However, small links are established with Cortex (Visual/Auditory/Olfactory/Gustatory)
  - These Links are made by Changes to Neuron Signalling that don't require protein synthesis (Quicker)
- **Lasts Seconds → Several Hours MAX.** (AKA: "Crammers" Memory)
  - Ie. Changes to Neurons are ***Transient.*** (Temporary)
- **Limited to ≈7-8 "Chunks"** of Info.
- **Amnesia** ≈ Damage to Connection between STM & LTM.

NB: Hippocampus sits in the Medial walls of the 'Horns' of the Lateral Ventricle.







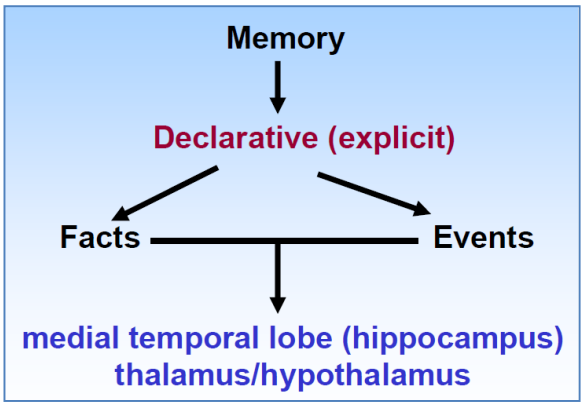
Working Memory:

- NB: Often Grouped with STM.
- **Temporary Retention, Integration** (*With other brain areas*) **& Manipulation of Sensory Info...**
  TO FACILITATE A RESPONSE.
  - Eg. Crossing the Road:
    - 1. Look Left – Remember position of cars
    - 2. Look Right
    - 3. Look Left Again – Compare position of cars to the initial look → Is it safe to cross??
- **Associated with Prefrontal Cortex:**
  - Closely tied to STM.
- **Neurotransmitter:**
  - *Dopamine*

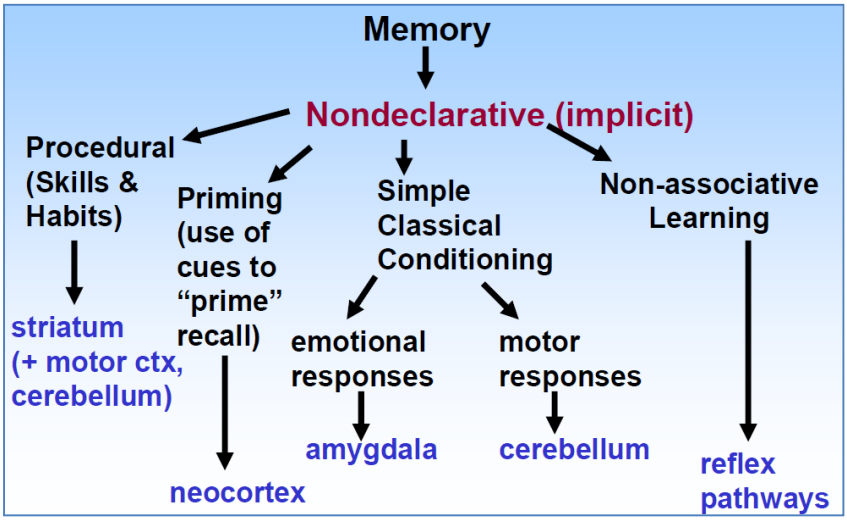
Long-Term Memory (LTM):

- **Limitless Capacity:**
  - The amount we can remember depends on ***Access*** rather than ***Capacity.***
- **Usually Requires STM Input:**
  - Generally LTM-Creation requires the info to pass through STM first.
  - However, some info can bypass STM by 'hijacking' existing LTM links
    - (Eg. Tying a fact to a Previously-Learned Fact)
- **LTM Creation - Influenced by 4 Factors:**
  - 1. Genetics
  - 2. Age
  - 3. Trauma
  - 4. Malnutrition
- **LTM Creation – Improved by:**
  - Positive/Powerful Emotional State
  - Rehearsal
  - Association of New data with Old Data.
  - The Belief that the Memory is Important
    - (Making memories is expensive & the brain must be convinced that it's worth the expense)

- **2 Types of Long-Term Memory:**
  - **1. Declarative (EXPLICIT):**
    - **Brain Regions:**
      - Hippocampus
      - Para-Hippocampal Regions (Medial Temporal Lobe)
      - Areas of Cerebral Cortex
      - Thalamus + Hypothalamus
    - **Learning "*WHAT*"**:
      - Facts/Words/Ideas/Concepts/Events

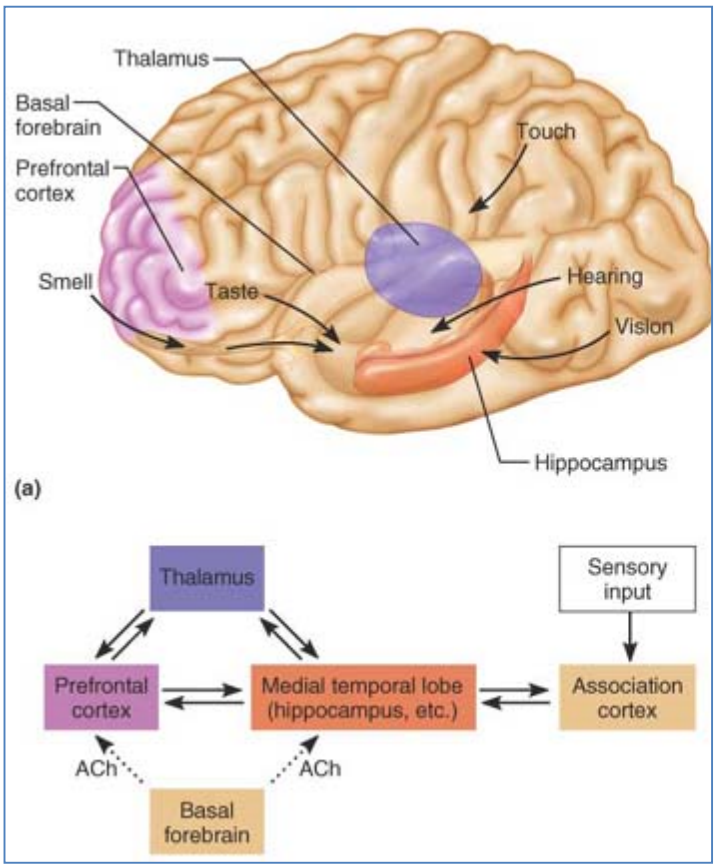


  - **2. Non-Declarative (IMPLICIT):**
    - Learning ***"HOW"***: - How to do things/How to recognise things.
      - **Procedural:**
        - Walking
        - Driving a car
        - Doing Algebra
        - How to get Home
      - **Priming (Anticipation):** - ie. The use of a trigger to pull out a memory.
        - Ache in gut if you get a letter from Tax Office – Due to Previous Association.
        - Reaction to seeing your Partner.
      - **Classically-Conditioned:**
        - **Emotional:**
          - Eg. Fear when seeing a Shark.
          - Eg. Ringing Bell → Dog Salivates
        - **Motor:**
          -
      - **Non-Associative:**
        - Isolated events not linked to anything



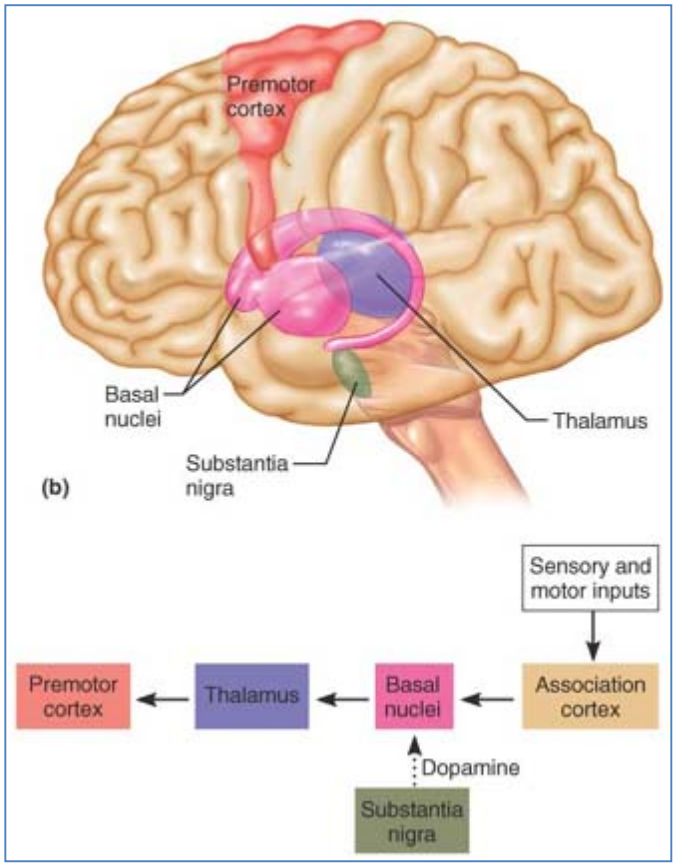
Circuit of Declarative Memory:

1. **Outside Stimuli:**
    a. Afferent Sensory Info → Sensory Nerves → Spinal Cord → Medulla → Brain (Somatosensory Cortex)
2. **Somato-Sensory Cortex:**
    a. Sensory Info is Sorted & Evaluated.
    b. Whatever is the main focus of your attention is Prioritised → Sent to Short-Term Memory In Medial Temporal Lobe (Hippocampus, Amygdala & Surrounding Cortical Areas).
3. **Medial Temporal Lobe Areas:**
    a. Role: Memory Consolidation & Retrieval Via Communication with Thalamus & **Prefrontal Cortex**.
    b. **Basal Forebrain:**
        i. Primes the Medial-Temporal Lobe & Prefrontal Cortex with ***Acetylcholine*** → **Triggers LTP in Hippocampus**
        ii. → Enables **Long-Term Memory Formation**.
        (NB: Loss of ACh input in Alzheimer's → ↓Memory Formation & Retrieval.)
4. **Feedback to Association Cortices:**
    a. Facilitates **Retrieval of Memories**.



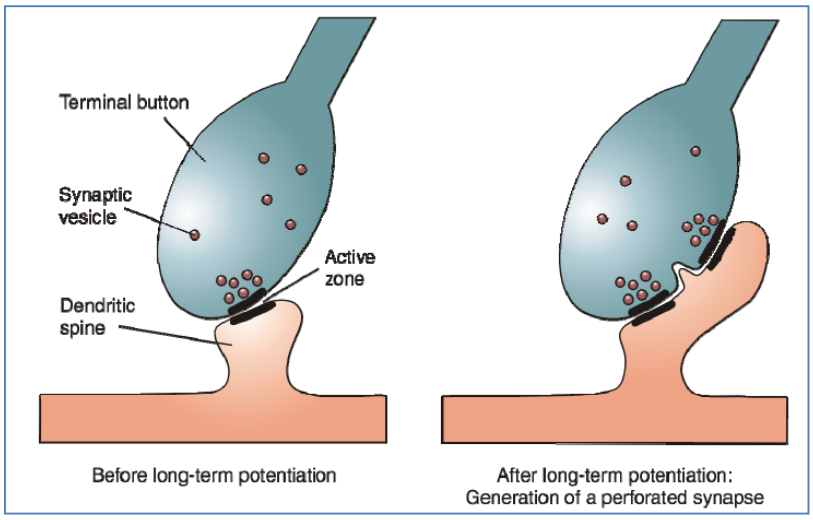
Circuit of Non-Declarative (Procedural) Memory:

1. **Sensory & Motor Input:**
    a. Afferent Sensori-Motor Info→ Spinal Cord → Medulla → Brain (Association Cortices)
2. **Association Cortices:**
    a. (Somatosensory/Visual/Auditory/etc)
    b. Relay Sensori-Motor Inputs to the Basal Nuclei.
3. **Basal Nuclei:**
    a. Relays Sensori-Motor Inputs through the Thalamus to the Premotor Cortex.
    b. **Substantia-Nigra:**
        i. Releases ***Dopamine*** onto Basal Nuclei → primes this circuit.
        (NB: Loss of Dopamine Input – Ie. Parkinson's – Interferes with Procedural Memory)
4. **Premotor Cortex:**
    a. Plans & Organises learned Actions.



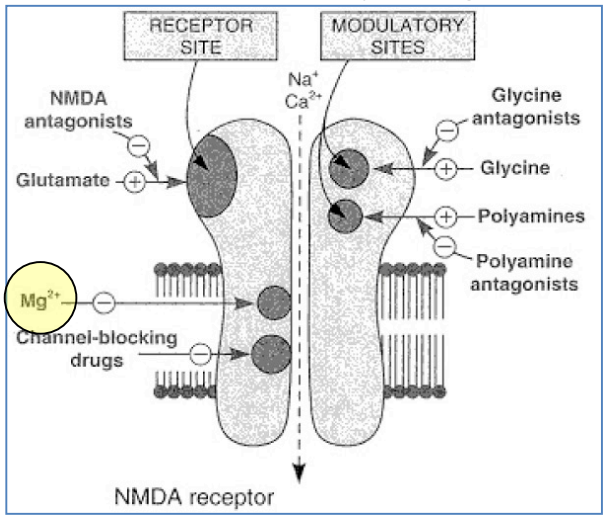
Long-Term Memory Formation @ the Cellular Level:

- **Simply – By Remodelling the Neuron** (Functionally/Structurally)
- More Specifically, **Synaptic Remodelling:**
    - Critical to many neurological changes



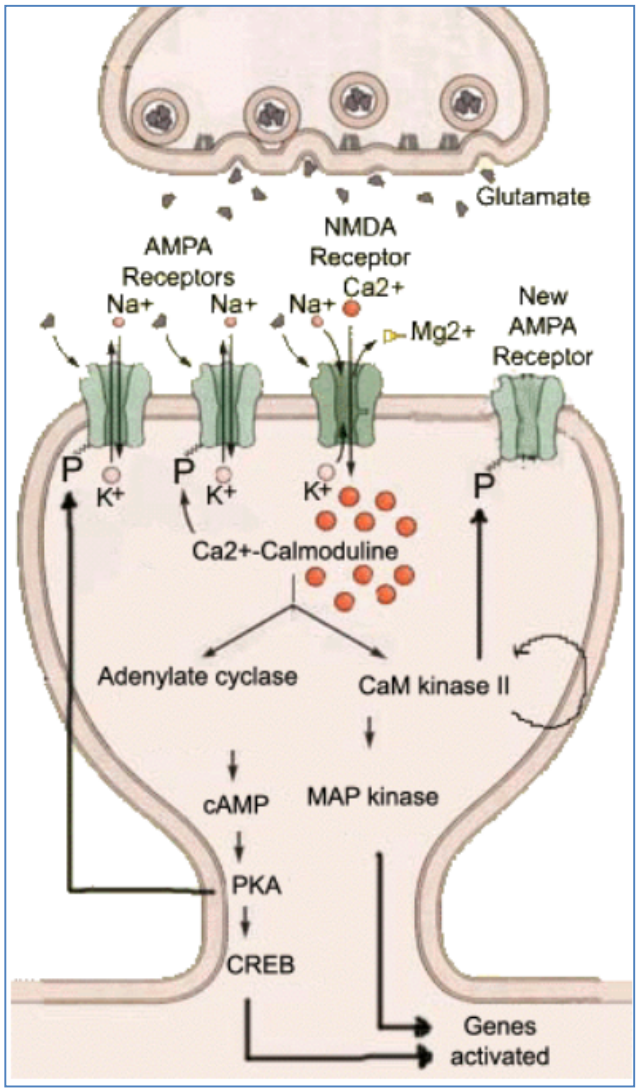
Synaptic Remodelling:

- **Long-Term Potentiation (LTP):**
    - **Definition:** "A Long-Lasting Post-Synaptic Depolarisation, induced through Repetitive Stimulation & Summation of Excitatory Post-Synaptic Potentials."
        - Simply – "A Persistent Increase in Synaptic Strength"
    - **Calcium, The #1 Mediator of LTP:**
        - NMDA-mediated Ca^+ Influx → Activation of ***Enzymes*** that cause:
            - ↑Neurotransmitter Release
            - Or Changes in Post-Synaptic Receptors
    - **The #1 Neurotransmitter:**
        - **Glutamate** → binds to ***NMDA*** and/or ***AMPA*** Receptors.
            - **NMDA Receptors:**
                - Act as ***Coincidence Detectors*** (Simultaneous Signals)
                - Ie. Detects coupling of occurrences.
                - Is essentially a Ligand(Glutamate)-Gated Ca^+ Channel
                - Has a Voltage-Dependant Mg^+-Block → Acts as a Voltage-Gate.
                - Therefore, NMDA Receptor is Ligand & Voltage-Gated.

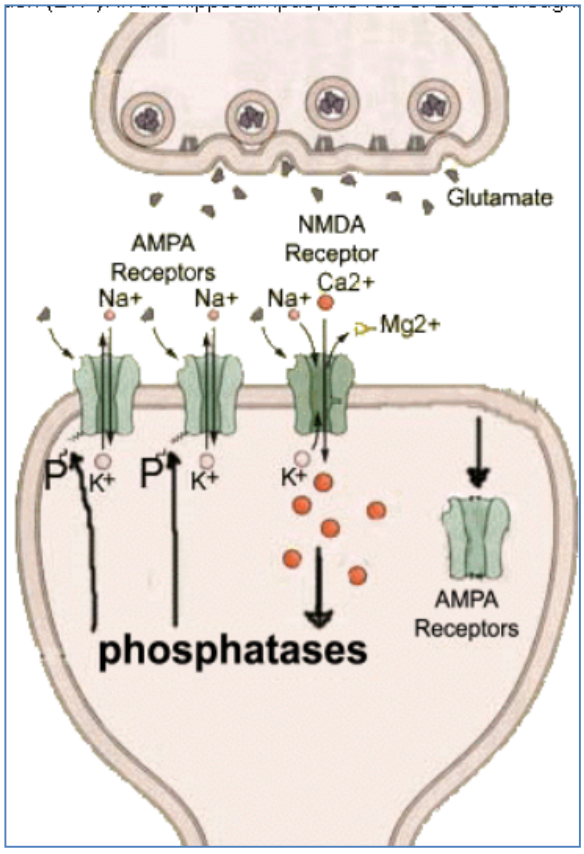


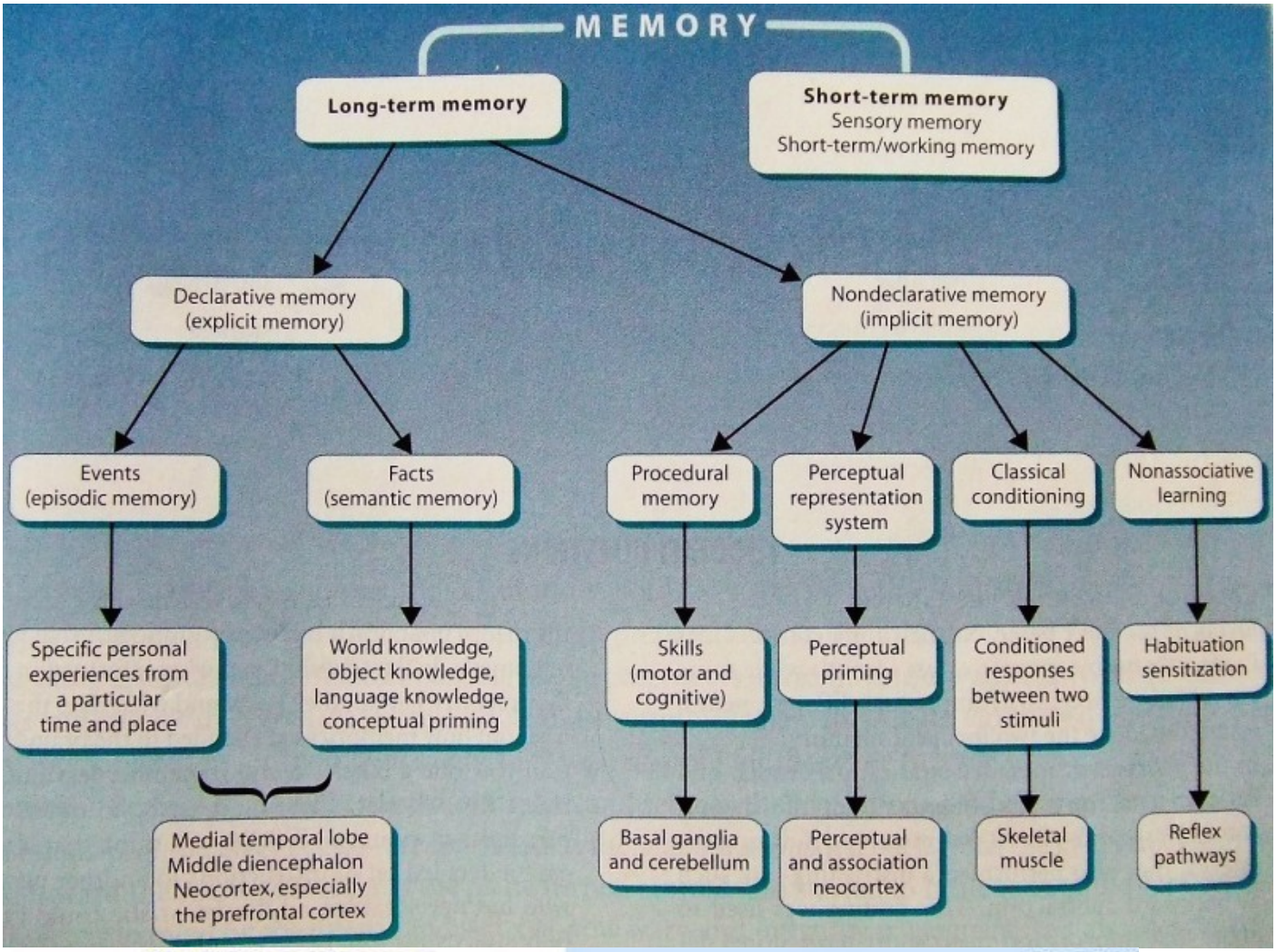
            - **AMPA Receptors:**
                - Is a Ligand-Gated Na^+ Channel.
                - When Glutamate Binds → Channel Opens → Depolarisation → AP.
                - Action Potential 'Kicks' out the Mg^+ Block on the NMDA Receptor.

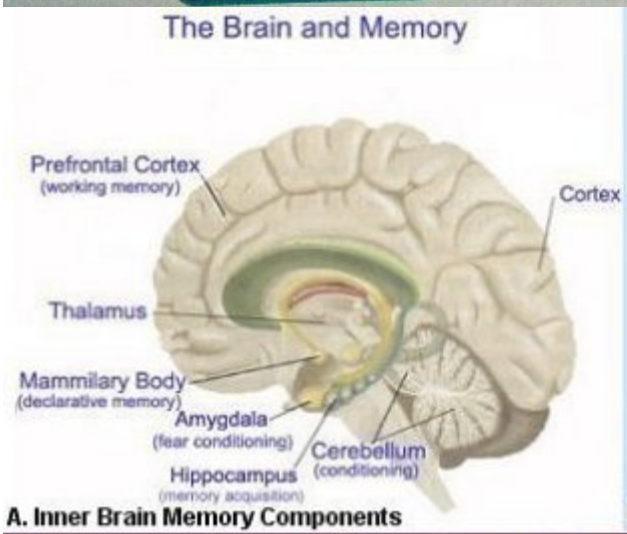
- **3 Phases of LTP:**
  - **1. Induction** - (Synaptic *Plasticity*)
    - ***Alleviating of the NMDA-Receptor's Mg^+ Block.***
      - This may be done by:
        - AMPA-Receptor mediated Action Potential.
        - Metabotropic-Receptor linked to Ion-Channel → AP
  - **2. Expression** - (Synaptic *Augmentation*)
    - ***NMDA-Mediated Ca^+ Influx*** → Activation of Enzymes that:
      - 1. Modify Proteins in Post-Synaptic Terminal or ↑in Pre-Synaptic Neurotransmitter Release → Strengthens response to subsequent Stimuli.
      - 2. Activation of Genes in Post-Synaptic Neuron's Nucleus → Synthesis of Synaptic Proteins → ↑Synaptic Strength
  - **3. Maintenance -** (Long Term Loss/Continuation of LTP)
    - ***Rise in mRNA Levels*** → Augmented Synthesis of Proteins linked to Memory.
      - This ↑in Protein Synthesis is regulated by a (+)Transcription Factor: "cAMP Response Element Binding" protein (CREB).
      - This perpetual ↑Protein-Synthesis → Long-Lasting ↑Synaptic Strength that is believed to underlie memory.



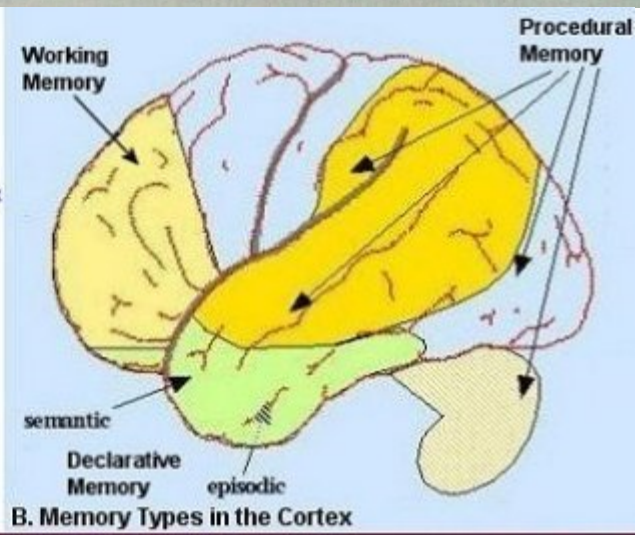
- **Long Term Depression (LTD):**
  - **Definition**: "The Weakening of a Neuronal Synapse that lasts from hours-days.
  - **Calcium, The #1 Mediator of LTP:**
    - NMDA-mediated Ca^{+} Influx → Activation of ***Phosphatases*** that cause:
      - De-phosphorylation of AMPA-Receptors.
        - → In Hippocampus → AMPA Dephosphorylation → ↓Amplitude of Post-Synaptic Potential to the Normal Level (Prior to LTP).
        - → Can also remove receptors from post-synaptic membrane & place them in reserve.
  - **Results From:**
    - Strong Synaptic Stimulation (Cerebellum)...Or
    - Persistent Weak Synaptic Stimulation (Hippocampus)
  - **Function in:**
    - **Overall:**
      - Plays a role in modulating impact of formed memories to prevent overload
    - **Hippocampus:**
      - Thought to return LTP'd synapses back to a normal level so they will be available to store new information.
    - **Cerebellum:**
      - Thought to promote Motor Learning.



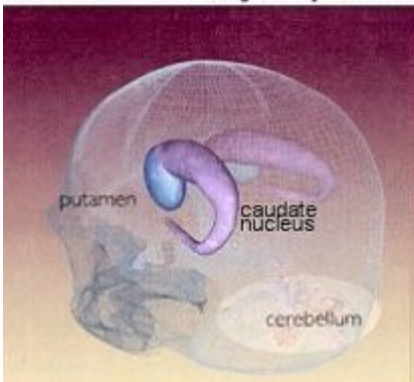




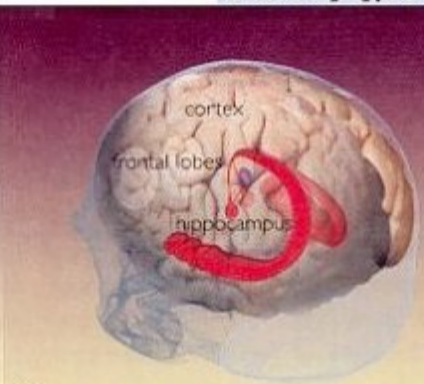
A. Inner Brain Memory Components



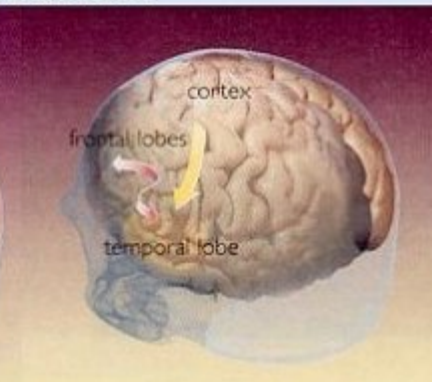
B. Memory Types in the Cortex



C. Procedural Memory Components



D. Episodic Memory Components



E. Semantic Memory Pathway

Common Memory Disorders:

- **Alzheimer's:**
  - **What?:**
    - Progressive memory loss ("Mild Cognitive Impairment"), Dementia & overwhelming Retrograde & Anterograde Amnesia.
    - No real diagnostic tests.
  - **Genetic Aetiology:** (Autosomal Dominant)
    - Amyloid Precursor-Protein Gene.
    - Presenilin 1 Gene
    - Presenilin 2 Gene
  - **Symptoms Due To:**
    - Loss of ACh Innervation onto Prefrontal Cortex & Medial-Temporal Lobe (hippocampus) by Basal Forebrain.
  - **Affects:**
    - Basal Forebrain Cholinergic System (Ie. Loss of ACh innervation)
    - Striatum (Caudate & Putamen) – Part of Basal Ganglia.
    - Thalamus
    - Cerebellum
  - **Inability to:**
    - Define simple words
    - Understand use of common items
    - Comprehend numbers
      - **Ie. A Loss in *Declarative Memory***.
  - **Emotional Disturbances:**
    - Confusion
    - Agitation
    - Delusion
    - Paranoia
- **Amnesia:**
  - Typically Declarative Memory Loss. (Therefore Hippocampal Damage)
  - Commonly caused by Temporal Lobe Damage (Hippocampus and/or Thalamus)
    - **NB: L-Hippocampus** = Language
      R-Hippocampus = Spatial Memory
  - **Anterograde:**
    - - Inability to form new memories from time of Injury/Damage ***Onwards.***
    - Non-Declarative Memory is Unaffected
  - **Retrograde:**
    - - Inability to recall memories from time of Injury/Damage ***Backwards.***
- **Korsakoff:**
  - Anterograde & Retrograde Amnesia
  - Caused by severe Thiamine Deficiency (Alcoholics & severe Malnutrition)
  - →Loss of connection between Temporal Lobes (Hippocampus) & Frontal Cortex.

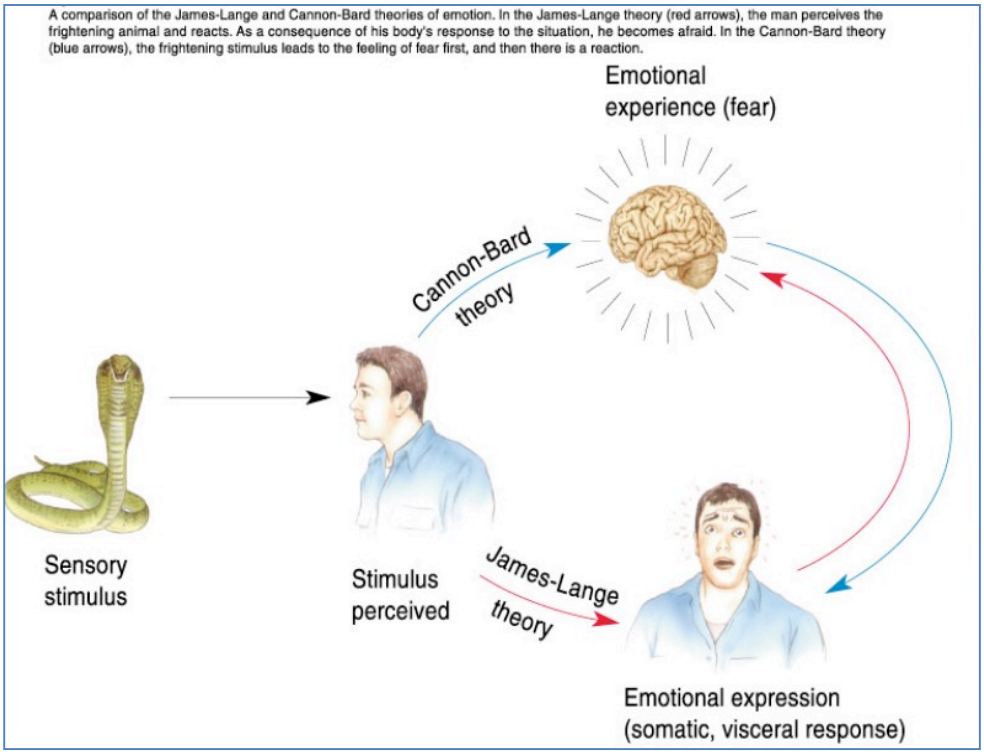
Neuroscience Notes
Neurobiology of Emotions

Definitions: (You will not be asked for definitions in the exam) – (Not by Anna Marie Babey anyway)

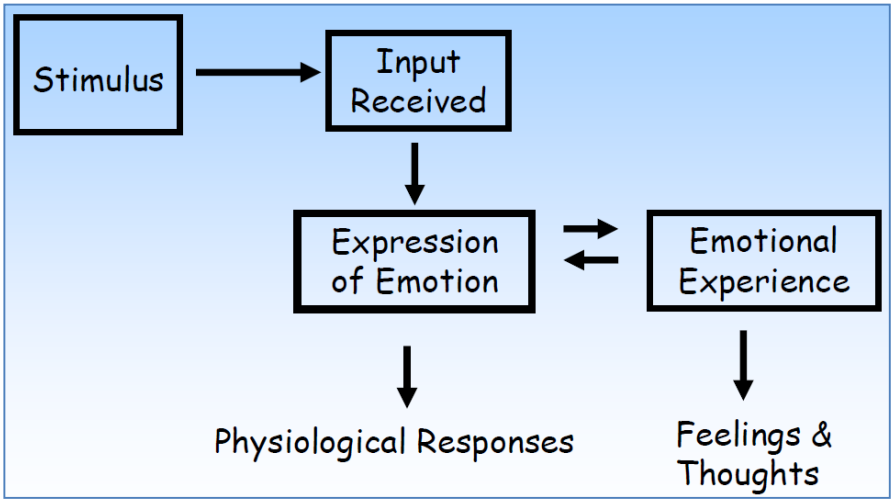
- **Affect:**
  - **"The Experience of a Feeling**/Emotion that's **NOT Related to Bodily Changes**."
- **Emotion:**
  - **"A Mental *And* Physiological reaction** to stimuli, experienced as **Affect *plus* Physiological Changes** in the Body."
- **Feelings:**
  - **"A partly mental, partly physical response** to a person, thing or situation, **marked by pleasure, pain, attraction or repulsion."**
- **Arousal:**
  - **"The Visceral (Body's) Response to stimuli**; Including Autonomic Nervous System & Neuro-Endocrine Activity."
- **Cognition:**
  - **"The process of knowing**, including both awareness & judgement."
- **Behaviour:**
  - **"The Active Response to Stimuli** (Posture, Facial Expression, Speed, Eye Movement, Vocalisation, etc)"

Emotion:

- **Why does it Exist?**
  - **Critical To Survival:**
    - Both the ability to Experience Emotion and to Recognise Other's Emotions
    - Gut Reactions
    - Recognising Danger, Friend/Foe
    - Vital to Decision Making
    - Important role in learning.
- **Theories of Emotion:**
  - A link exists between Physiological Responses to Stimuli & Affect of Emotion, *but which comes first?*
    - **Cannon-Bard Theory:**
      - Conscious Awareness of Emotion comes first, then the Visceral Reactions.
    - **James-Lange Theory:**
      - Visceral Reactions comes first, then the Conscious Emotional Experience follows.



- **Currently, the most Plausible Theory:**
  - Visceral Reaction (Physiological Responses) comes first, causing the Emotional Experience (Feelings & Thoughts)
  - However, the Emotional Experience can Influence and/or Perpetuate the Visceral Response.



- **3 Phases/Components/Types of Emotion:**
  1. **Primary Emotions:**
     - "What is Felt 1st" – The 1st Instantaneous Emotion - (Usually the Simplest/Primitive Emotions)
     - Generally independent of culture (Universal)
       - Joy
       - Sadness
       - Fear
       - Anger
       - Surprise
  2. **Secondary Emotions:**
     - "What is Felt 2nd" – What the Primary Emotion Leads to – (Slightly more Complex Emotion)
     - Generally a Combination of Primary Emotions + Context.
       - Affection/Love
       - Lust
       - Contentment
       - Disgust
       - Envy
       - Guilt
  3. **Tertiary Emotions:**
     - An Aggregate of Primary and/or Secondary Emotions – (The most Complex Emotions)
     - Generally the result of a Decision, taking into account Many Factors.
       - Satisfaction
       - Hope
       - Frustration
       - Gloom
       - Contempt

- **Physiological Context of Emotion:**
  - The physiological state of a person & body can influence resulting emotions & emotional reactivity.
    - Well-being
    - Depression
    - Calm
    - Tense
    - Fatigue

Consciousness & Emotion:

- Emotional Experience is thought to underpin Consciousness. (Ie. Ability to "feel" is being "truly alive")
- **Consciousness:**
    - **Core Consciousness:**
        - Sense of 'Here & Now'. "Feeling"
    - **Extended Consciousness:**
        - Ability to Recall Past Experiences, Learn & Plan for the Future.

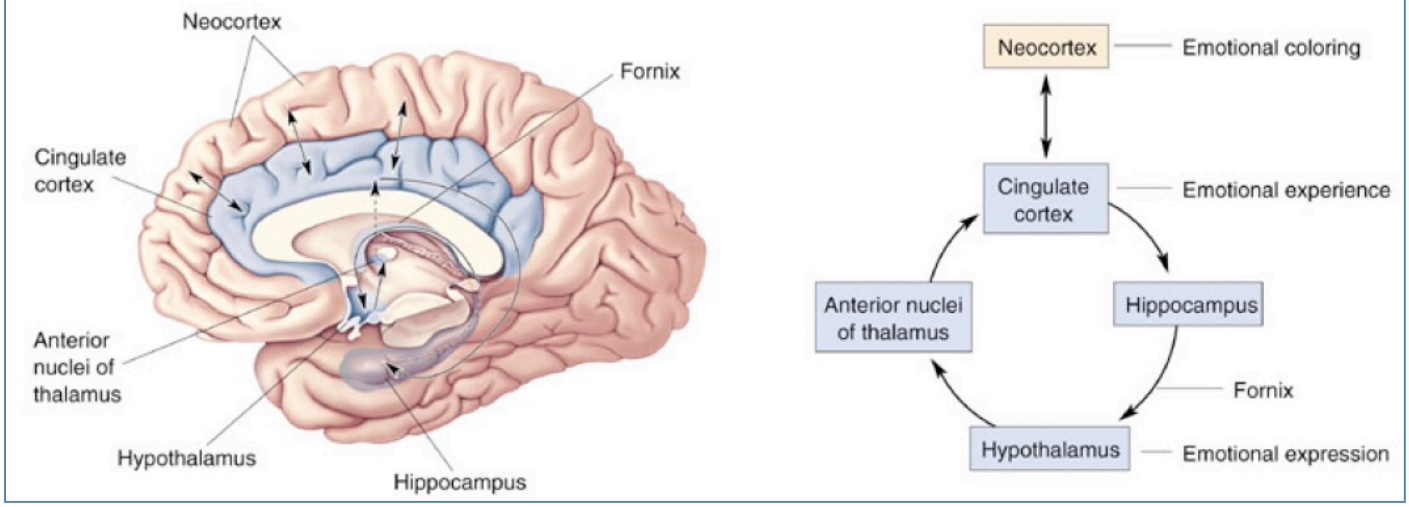
- **Emotions affect the way we respond to stimuli:**
    - People with 'Alexithymia' can't feel emotions. They experience:
        - Difficulty linking a Stimuli to an Experience
        - Serious Difficulty with Decision-Making
        - Difficulty Understanding Emotions
        - Difficulty Describing Emotions
        - Minimal Imagination
        - Feeling 'cold'/'alouf'

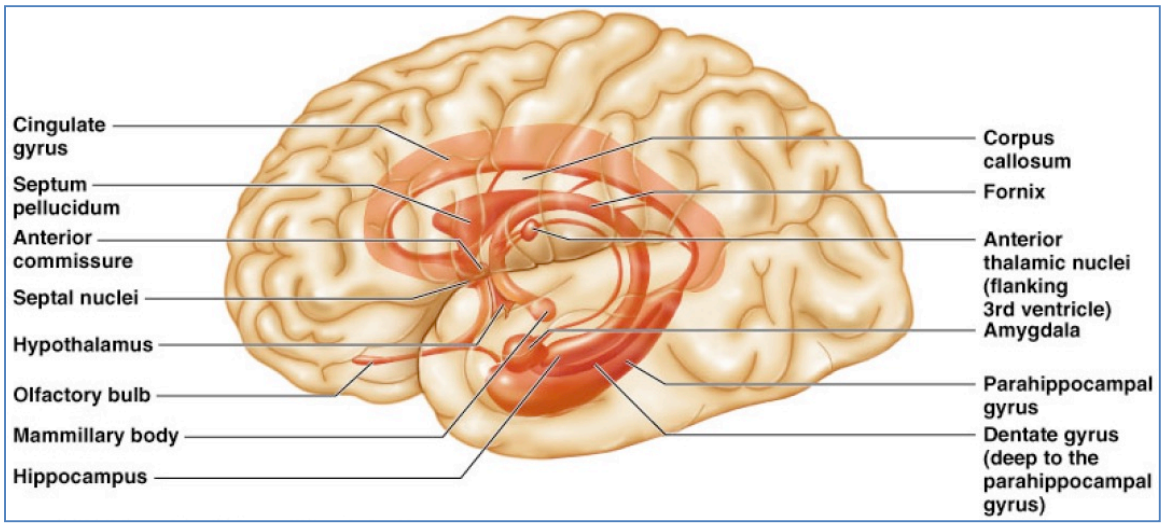
- **Rational Brain Vs. Emotional Brain:**
    - Higher Cognitive Processing & Decision-Making relies on Co-Operation of the "Rational Brain" & the "Emotional Brain".
    - Anatomically, the "Emotional Brain" is favoured. (Higher number & organisation of Synaptic Connections)
    - Relative Contributions of both "Rational" & "Emotional" Brains depend heavily on Context.
        - Eg. Triage – Letting someone die to save another's life.
            - Saving the one that can be saved is consistent with the "Rational Brain"
            - However, letting someone die goes against the "Emotional Brain".

Neuroanatomy of Emotion – The Limbic System:

- **The Papez Circuit:**
  - **1. Thalamus** relays Sensory Input to Cingulate Cortex.
  - **2. Cingulate Cortex** - gives you the Emotional Experience
    - also relays to the **Neocortex**, which gives Context/Colouring to the Emotion.
    - also relays to the **Hippocampus** →
  - **3. Hippocampus** Relays to the Hypothalamus – Causes the Emotional Expression (Visceral Response)

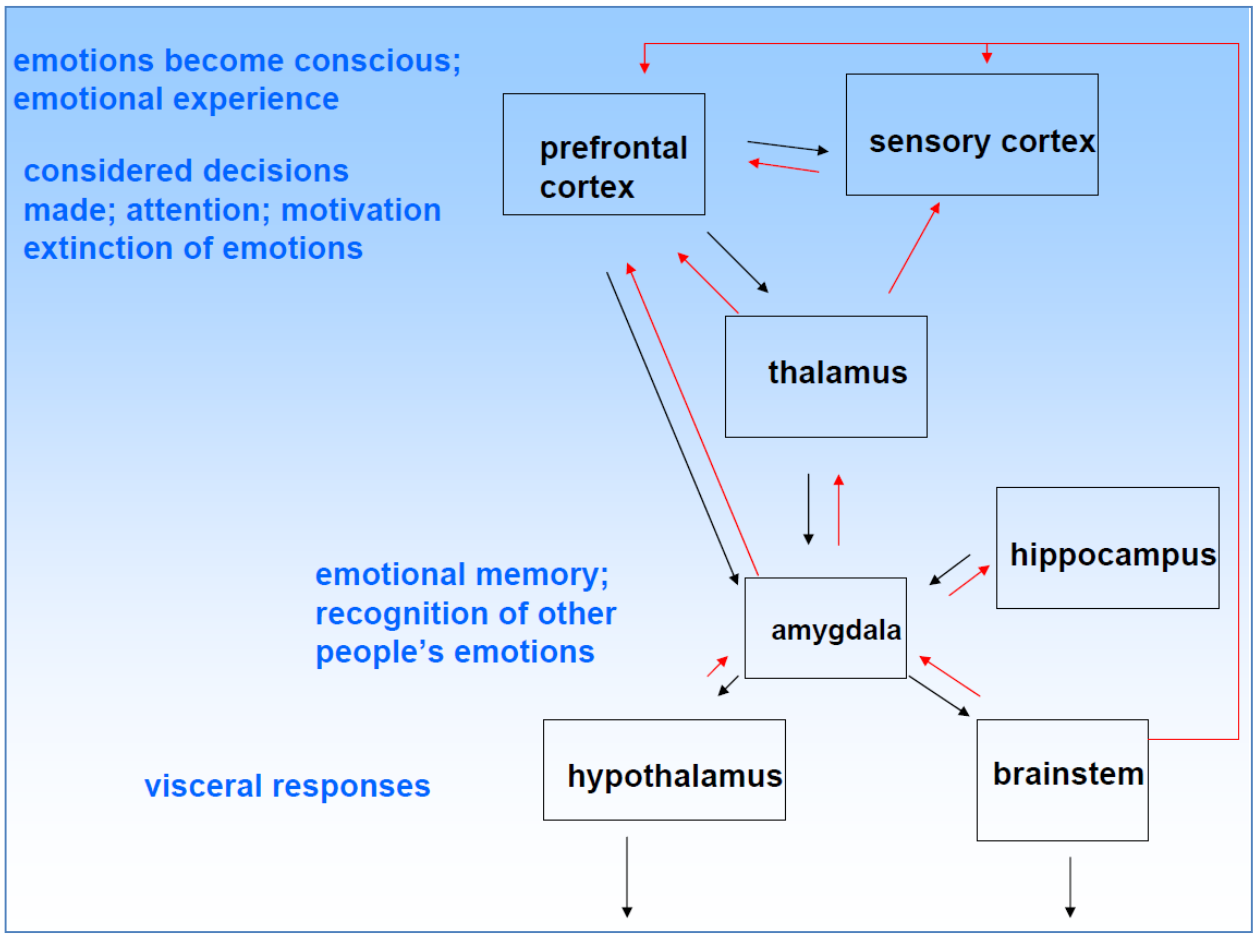
Figure 18.4
The Papez circuit. Papez believed that the experience of emotion was determined by activity in the cingulate cortex and, less directly, other cortical areas. Emotional expression was thought to be governed by the hypothalamus. The cingulate cortex projects to the hippocampus, and the hippocampus projects to the hypothalamus by way of the bundle of axons called the fornix. Hypothalamic effects reach the cortex via a relay in the anterior thalamic nuclei.





- **NB:** No single region of the brain is responsible for Emotions. Instead, most regions involved have multiple roles.

Brain Regions Involved in Recognition, Induction & Regulation of Emotions:



- **Thalamus:**
  - **Funnels Sensory info** to **Amygdala**, and the **Cerebral & Cingulate Cortices**.
  - Important in Fact-Based ***(Explicit) Memory.***

- **Cingulate Gyrus:**
  - Regulates **Attention**
  - Emotional **'Colouring'**

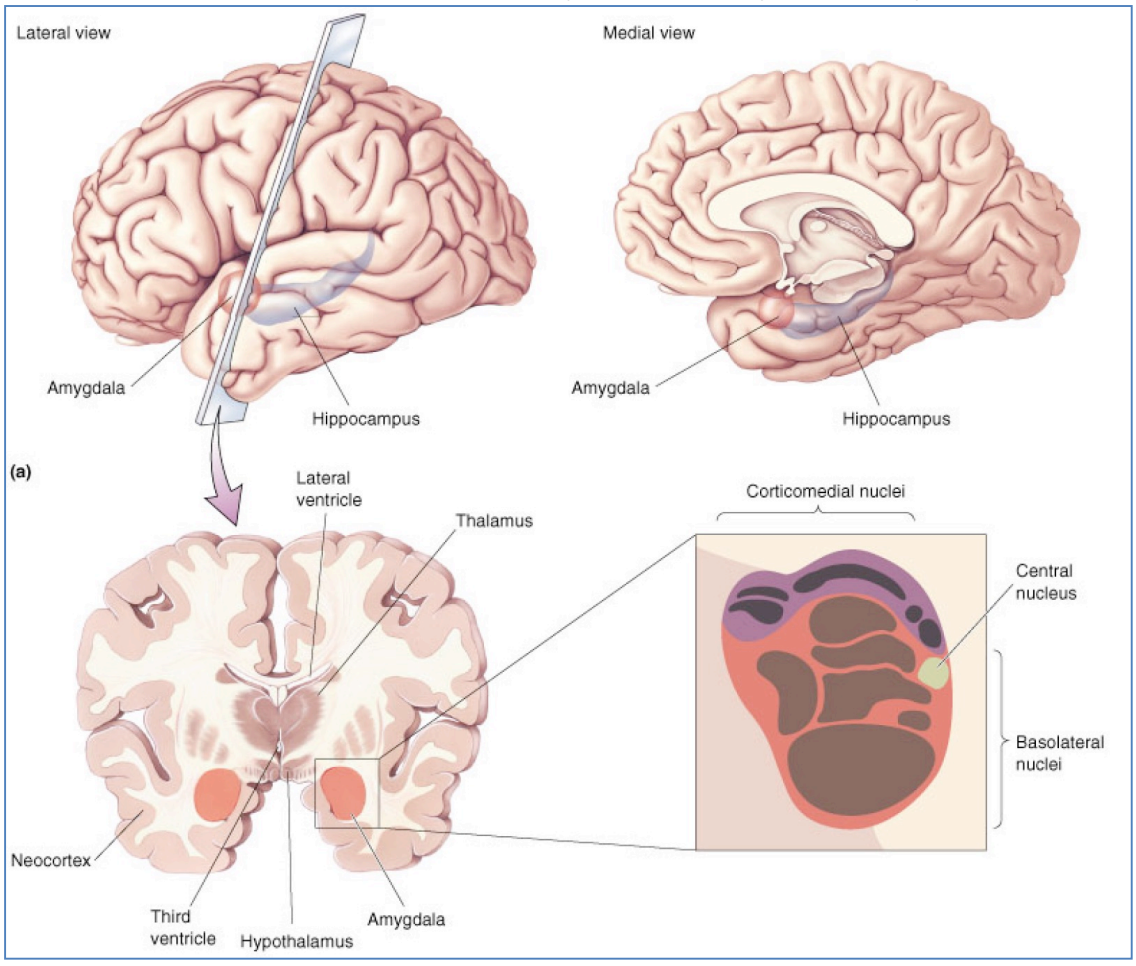
- **Ventromedial Prefrontal Cortex:**
  - Conscious ***Recognition of Emotions***

- **Cerebral Hemispheres:**
  - R-Brain → More Associated with Negative Emotions
  - L-Brain → More Associated with Positive Emotions

- **Sensory Cortices & Association Areas:**
  - Recognition of Stimuli.
  - Sensory Cortices: (Visual, Auditory, Olfactory, Gustatory, Tactile)
  - Sensory Association Areas: (Novel Vs. Familiar)

- **Insula:**
  - Involved with Recognition & Feeling of ***Disgust.***

- ***Amygdala***:**
    - #1 Structure involved in Emotion → The "Heart" of the Limbic System.
    - "The Fight/Flight Centre"
    - Linked to all but 8 areas of the Cortex → :. Thought to be #1 integrator of Cognitive & Emotional Info.
    - **Afferents (Receives Input From...):**
        - **Brainstem** – inputs associated with Physical States (BP/HR/etc)
        - **Hypothalamus** - inputs associated with Physical States (BP/HR/etc)
        - **Thalamus** – Sensory Info
        - **Hippocampus** – inputs associated with Explicit Memory
        - **Cortex** – Sensory Inputs & Decisions related to Perceived Threats
    - **Efferents (Sends Output to...):**
        - **Brainstem** – influences Visceral Fear-Driven, Fight/Flight Responses.
        - **Hypothalamus** – Influence on Memory & Aggression
        - **Thalamus** – Influences processing of new sensory info
        - **Hippocampus** – Fear is an important driver for learning & memory
        - **Pre-Frontal Cortex** – Fear is important in Decision Making & Cognition
    - **Regulates:**
        - Fear & Aggression
        - Vigilance & Attention
        - Recognition of Emotion (in Self & Others)
        - Emotional Contribution to Memory. (Emotional Implicit Memory)



- **Hypothalamus:**
    - ***Visceral Responses*** to Emotion
    - ***Aggression***
    - ***Sex Drive***

- **Brain Stem:**
    - ***Visceral Responses*** to Emotion

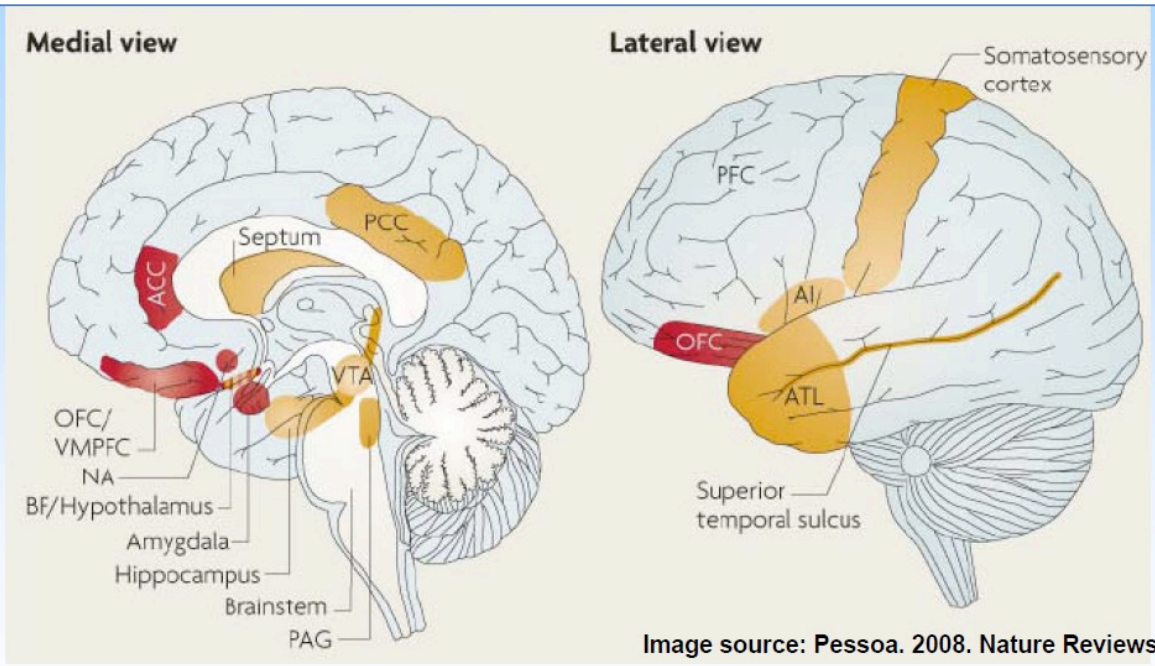


Image source: Pessoa. 2008. Nature Reviews Neuroscience

OFC = orbitofrontal cortex; VMPFC = ventromedial prefrontal cortex; NA = nucleus accumbens; BF = basal forebrain; ACC = anterior cingulate cortex; PCC = posterior cingulate cortex; VTA = ventral tegmental area; AI = anterior insula; ATL = anterior temporal lobe

Neurotransmitters & Emotion:

- ***Noradrenaline:**
  - **Activated By:**
    - Novel, Unexpected Stimuli
  - **Released By:**
    - ***Locus Coeruleus*** (A Nucleus In the Pons involved with physiological responses to stress & panic.)
  - **Regulates:**
    - Mood/Arousal
    - Anxiety
    - Pain
    - Sleep/Wake Cycles
    - Motor Activity

- ***Serotonin:**
  - **Activated By:**
    - General activity/arousal
  - **Released By:**
    - Raphe Nuclei (A group of Nuclei In the brainstem)
  - **Regulates:**
    - Mood
    - Emotions
    - Sleep/Wake Cycles
    - Dominance/Aggression
    - Anxiety

What we target in treating Depression.

- ***Dopamine:**
    - **Activated By:**
        - Pleasurable Activities
    - **Released By:**
        - Ventral Tegmental Area (VTA)
        - Substantia Nigra
    - **Regulates:**
        - *Somehow* plays a role in Regulation of Perception of Emotion
        - Involved in Reward Centre

- **Glutamate & GABA:**
    - Reduces Anxiety

- **Acetylcholine:**
    - **Released By:**
        - Basal & Septal Nuclei of Meynert
    - **Regulates:**
        - Cognitive Processing
        - Arousal & Attention

Panic Disorder:

- Overwhelming wave of Fear & Anxiety:
    - Not necessarily associated with apparent trigger (Can be spontaneous)
- NB: Direct administration of CCK (Cholecystokinin) to brain can cause Panic-Attack Symptoms

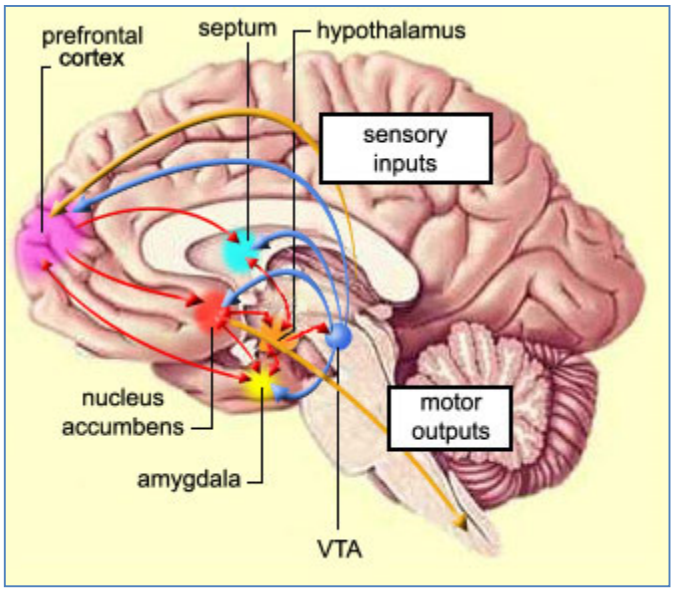
Aggression:

- **Affective Aggression Vs Predatory Aggression:**
    - Predatory aggression is related to feeding behaviour & isn't accompanied by sympathetic physiological response with which affective aggression is associated.
- **Associated Structures:**
    - Cerebral Cortex
    - ***Amygdala***
    - ***Hypothalamus***
    - Periaqueductal Grey-Matter (PAG)
    - Ventral Tegmental Area (VTA)

  IE. "Aggression is controlled by a neural pathway from the Amygdala through the Hypothalamus, PAG & VTA.
- **Neurotransmitter:**
    - Serotonin
- **Possible Hormonal Link:**
    - Adenosine.

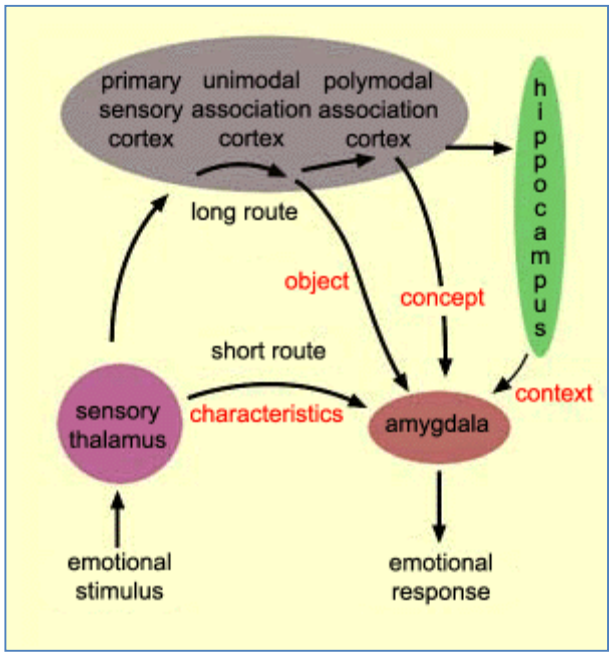
Pleasure & Reward: The 'Reward Circuit':

- **Brain Structures Involved:**
    - ****Ventral Tegmental Area (VTA)***
    - ****Nucleus Accumbens***
    - Amygdala
    - Pre-Frontal Cortex
    - Thalamus
- **Neurotransmitters Involved:**
    - ****Dopamine*** **-** VTA & Nucleus Accumbens



Fear:

- **Brain Structures Involved:**
  - Thalamus →
    - Amygdala
  - Thalamus →
    - Primary Sensory Cortex
    - Association Cortices
- **Long & Short Pathways:**
  - **Long:**
    - Info processed by higher brain centres & Hppocampus.
    - Results in a more complex response
  - **Short:**
    - Info sent straight to Amygdala
    - Results in a basic response (Recoil from stimulus/Freeze)
    - **Advantage =** *No cortical processing means quicker reaction times → ↑Survival.*
- **Process of Fear:**
  - 1.Sensory Info enters brain → Thalamus
  - 2.Thalamus Sends info to Amygdala (Via Long/Short Route)
  - 3.Amygdala activates Visceral Responses through Hypothalamus
  - 4.Amygdala Activates Ventromedial Pre-Frontal Cortex (Allows conscious recognition of the Emotion)
  - 5.Visual Cortex also inform Prefrontal Cortex about the Threat.



Neuroscience Notes
Somatosensory Processing

Sensation Types: **NB:** Sensations are initiated by *RECEPTOR ACTIVATION*.

- **Tactile:**
  - Touch
  - Vibration
  - Stretch
  - Pressure
  - Itches
- **Temperature:**
  - Hot/Cold
- **Pain:**
  - AKA: *'Nociception'*
- **Proprioception:**
  - Sensing the position of the body in space.
- **Visceral:**
  - Blood Pressure
  - pH
  - O_2
  - CO_2

Sensory Receptors:

What Are They?

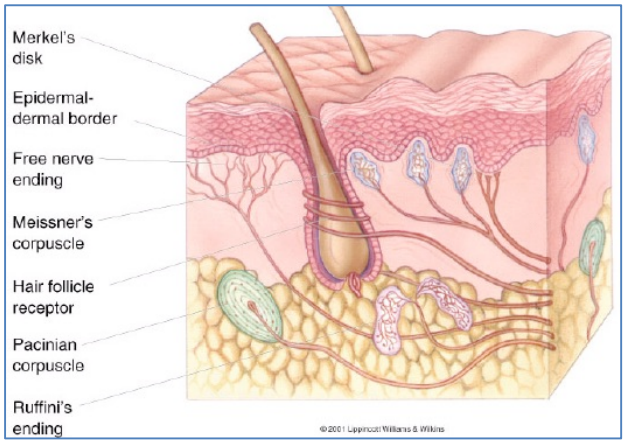
- Specialized Nerve Endings that monitor & respond to the Environment.

Classification – Based on 3 Things:

- **1. Physical Location:**
  - Exteroceptors - Located in Skin (Respond to *External Stimuli*)
  - Interoceptors - Located Viscerally (Respond to *Internal Stimuli*)
  - Proprioceptors - Located in Muscle/Bone/Tendon
- **2. Type of Stimulus:**
  - Mechanoreceptors - Respond to *Physical Forces*
  - Thermoreceptors - Respond to *Temperature*
  - Nociceptors - Respond to *Damaging Stimulus*
  - Chemoreceptors - Respond to *Chemicals* (Smell/Taste OR Blood $O_2/CO_2/H^+$)
  - Photoreceptors - Respond to *Light* (Eyes)
- **3. Receptor Structure**
  - Simple - *Naked ("Free") Nerve Endings* (Pain & Temperature)
  - Complex - *Structurally Elaborate Nerve Endings* (Pressure,Vibration, Stretch) (Enhances Specificity)

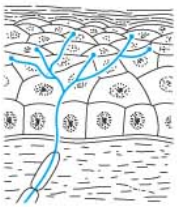
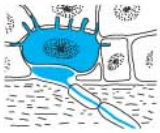
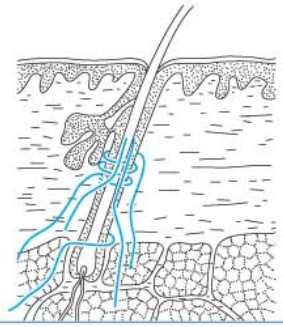
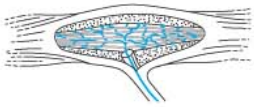
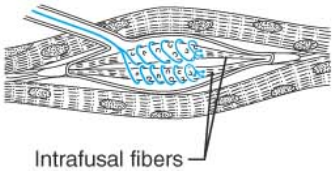
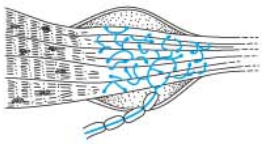
NB: Q – Why are *Pain Receptors* '*Simple*'?

A – Pain, a basic survival mechanism would have been first to evolve and its receptors have been sufficient since. Hence there has been no need for pain receptors to evolve further.



Receptor Types:

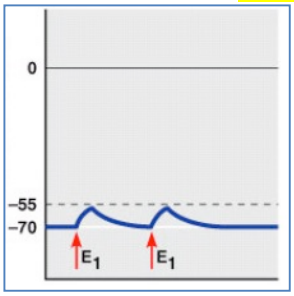
TABLE 13.1 General Sensory Receptors Classified by Structure and Function

STRUCTURAL CLASS	ILLUSTRATION	FUNCTIONAL CLASSES ACCORDING TO LOCATION (L) AND STIMULUS TYPE (S)	BODY LOCATION
UNENCAPSULATED			
Free nerve endings of sensory neurons		L: Exteroceptors, interoceptors, and proprioceptors S: Thermoreceptors (warm and cool), chemoreceptors (itch, pH, etc.), mechanoreceptors (pressure), nociceptors (pain, hot, cold, pinch, and chemicals)	Most body tissues; most dense in connective tissues (ligaments, tendons, dermis, joint capsules, periostea) and epithelia (epidermis, cornea, mucosae, and glands)
Modified free nerve endings: Merkel discs (tactile discs)		L: Exteroceptors S: Mechanoreceptors (light pressure); slowly adapting	Basal layer of epidermis of skin
Hair follicle receptors		L: Exteroceptors S: Mechanoreceptors (hair deflection); rapidly adapting	In and surrounding hair follicles
ENCAPSULATED			
Meissner's corpuscles (tactile corpuscles)		L: Exteroceptors S: Mechanoreceptors (light pressure, discriminative touch, vibration of low frequency); rapidly adapting	Dermal papillae of hairless skin, particularly nipples, external genitalia, fingertips, soles of feet, eyelids
Pacinian corpuscles (lamellated corpuscles)		L: Exteroceptors, interoceptors, and some proprioceptors S: Mechanoreceptors (deep pressure, stretch, vibration of high frequency); rapidly adapting	Dermis and hypodermis; periostea, mesentery, tendons, ligaments, joint capsules; most abundant on fingers, soles of feet, external genitalia, nipples
Ruffini endings		L: Exteroceptors and proprioceptors S: Mechanoreceptors (deep pressure and stretch); slowly or nonadapting	Deep in dermis, hypodermis, and joint capsules
Muscle spindles		L: Proprioceptors S: Mechanoreceptors (muscle stretch, length)	Skeletal muscles, particularly those of the extremities
Golgi tendon organs		L: Proprioceptors S: Mechanoreceptors (tendon stretch, tension)	Tendons
Joint kinesthetic receptors		L: Proprioceptors S: Mechanoreceptors and nociceptors	Joint capsules of synovial joints

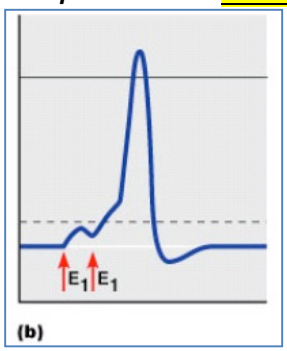
www.regentstudies.com

Receptor Transduction:

- ***Receptors respond to Stimuli*** by ***Transducing*** them into ***Electrical Signals***
- **These *'Electrical Signals'* =** Ion Movements across the Membrane → Changes Membrane Potential
    - These Changes in Membrane Potential are ***Graded*** – IE. Stimulatory or Inhibitory (Depol/Hyperpol)
    - These ***Graded Potentials*** at the ***Receptor Level = "Receptor Potentials"***



- ***"Receptor Potentials"*** may summate to *Threshold* → Initiating an ***Action Potential***
    - These ***Action Potentials*** at the ***Receptor Level = "Generator Potentials"***

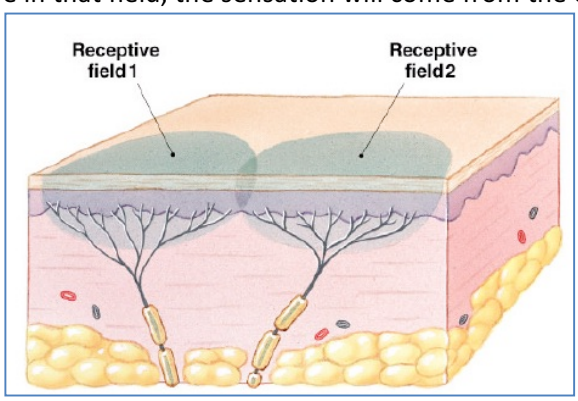


Receptors: Nature of Activity:

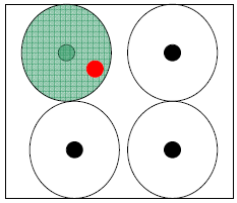
- **When Are They Active?**
    - **Tonic Receptors:**
        - Continually Firing
        - – Eg. Proprioceptors
    - **Phasic Receptors:**
        - Fire only with a ***Change*** in the Environment.
        - – Eg. Thermoreceptors
- **When Do They Inactivate? (How Quickly do they "Adapt"?):**
    - **NB: "Adaptation" =** ***Time Taken*** for receptor to ***Stop Firing*** during ***Sustained Stimulation***
        - **RARs – Rapidly Adapting Receptors:**
            - Receptor quickly stops firing under continuous stimulus
            - - Eg. Touch Receptors (Can't feel clothes after a while)
        - **SARs – Slowly Adapting Receptors:**
            - Receptor maintains firing under continuous stimulus
            - - Eg. Muscle Stretch Receptors (Proprioceptors)

Receptive Fields:

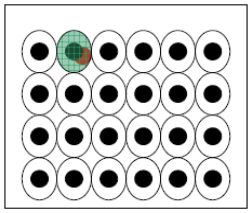
- **A Receptive Field:** The Area Monitored by 1x Receptor.
    - Ie. Touch anywhere in that field, the sensation will come from the entire receptive field.



- ***Large* Receptive Fields:**
  - Low Receptor Density
  - Poor Localisation
  - – Eg. Skin on your ***Back***

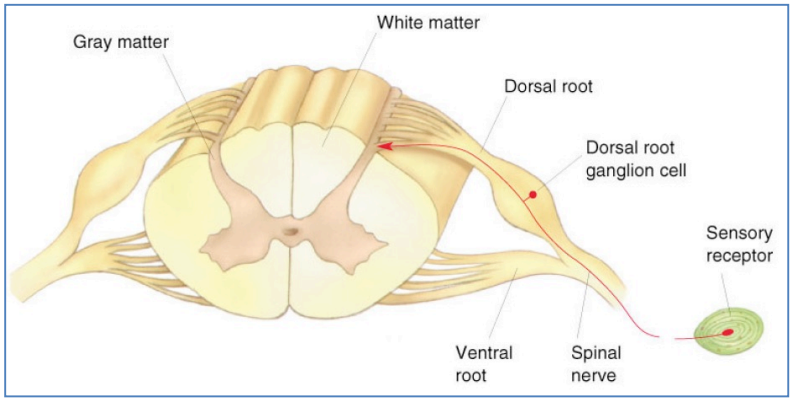


- ***Small* Receptive Fields:**
  - High Receptor Density
  - Good Localisation
  - – Eg. Skin on your ***Fingertips***
  - **NB: *2 Point Discrimination*** is best with Small, Dense Receptor Areas

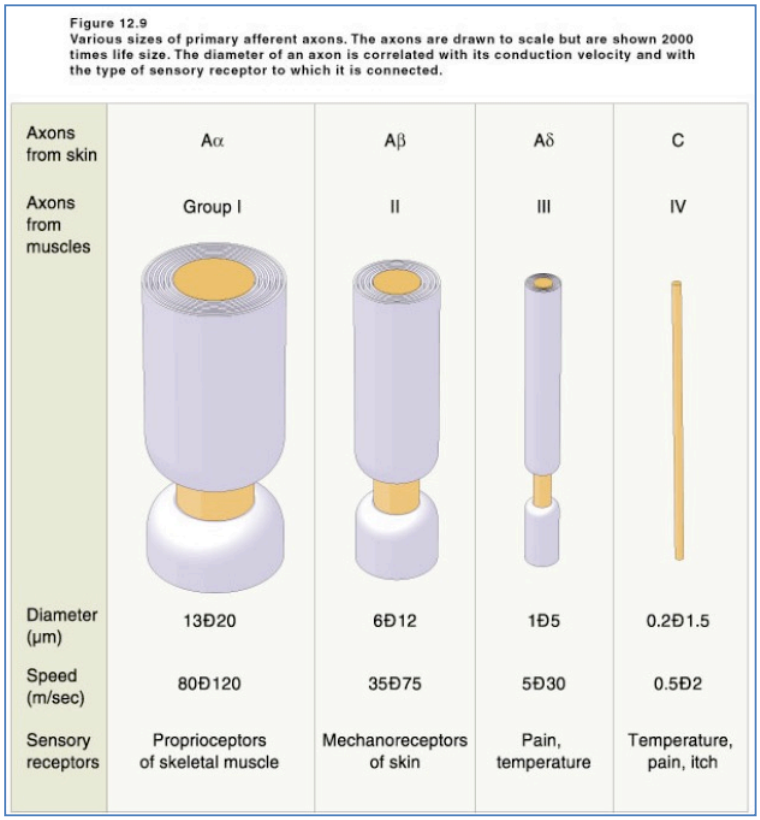


<u>Somatosensory Pathways:</u>

- **<u>First Order Neurons (Peripheral Afferent Nerves):</u>**
  - (Eg. Dorsal Root of Spinal Nerves & Sensory Cranial Nerves)
  - Sensory info is "*Frequency Coded*".
  - ***Enter Spinal Cord*** via Dorsal Nerve Root → Terminate in ***Dorsal Horn***.
  - ***NB: Cell-Bodies*** of the ***Pseudounipolar-Neuron Receptors*** culminate in the ***Dorsal Root Ganglion***



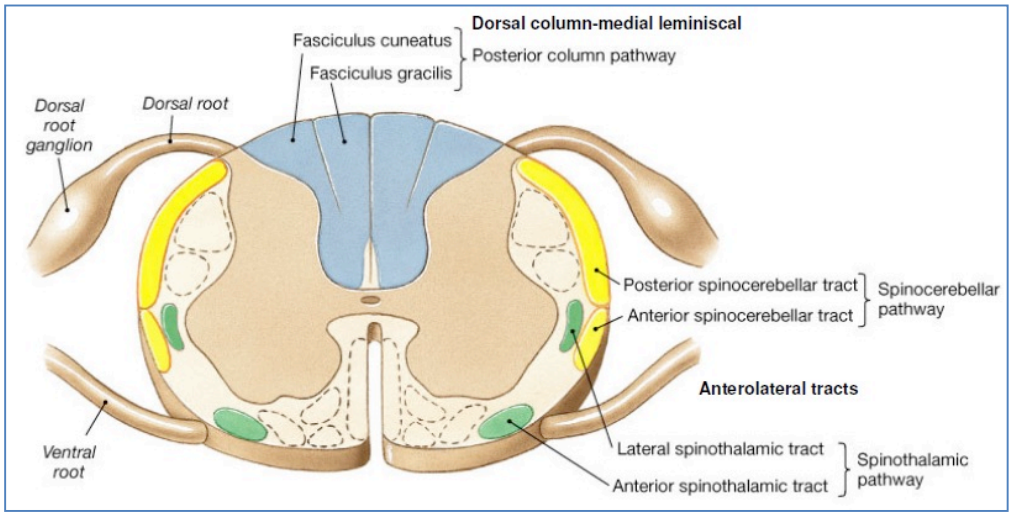
  - ***Vary by Diameter & Myelination*** – Affects Speeds of Conduction & Therefore type of Sensory Info:
    - Larger + Myelinated = Fastest
    - Smaller + Non-Myelinated = Slowest



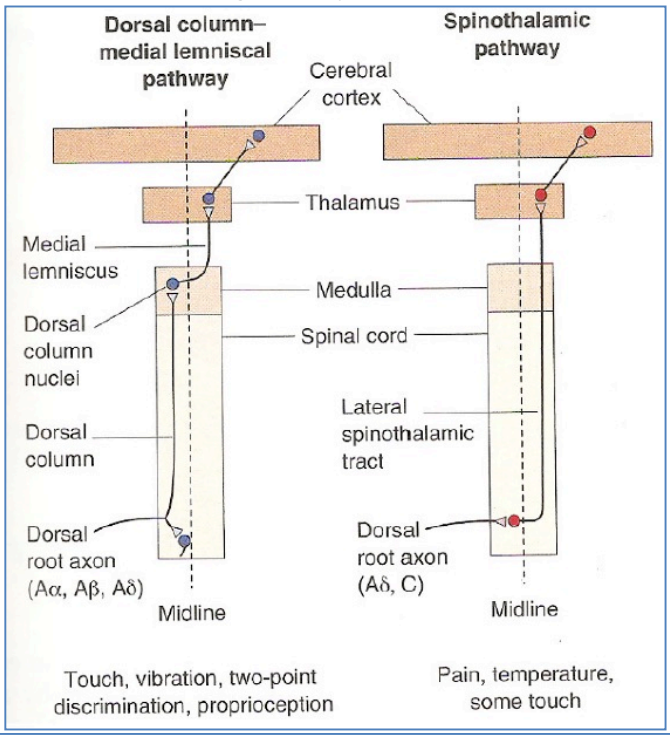
NB: Proprioceptors are *FAST* to Ensure FINE MOTOR CONTROL.

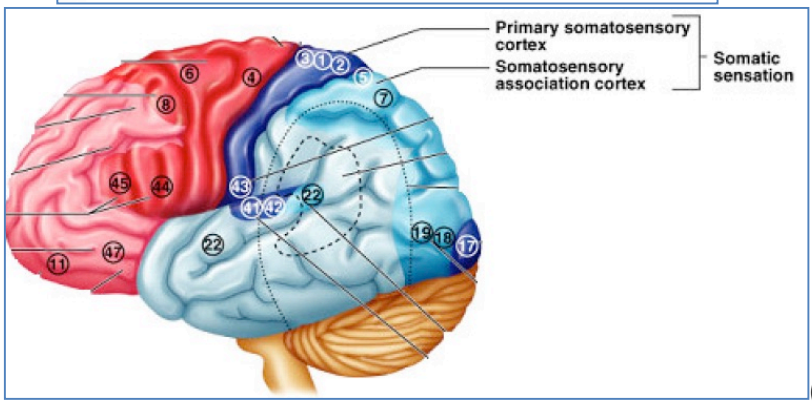
NB: There are 2 Types of Pain Receptors – The Fastest is responsible for the Initial (Sharp) Pain
– The Slowest is responsible for the Dull Ache that follows.

- **Second Order Neurons (Ascending Pathways of Spinal Cord):**
  - Once inside the Spinal Cord, ***1st-Order Neurons → Synapse with 2nd-Order Neurons***
  - ***2nd-Order Neurons*:**
    - Often responsible for ***Decussation*** (Crossing of Fibre-Tracts to the Other Side of the Body)
    - Different 1st-Order Neurons → Synapse with different 2nd-Order Neurons.....
      - Therefore, Different Sensory Info takes Different Ascending Pathways to the Brain.



- **Third Order Neurons:**
  - **NB:** 3rd-Order Neurons are only Relevant to the Posterior Column & The SpinoThalamic Pathways.
    - The SpinoCerebellar Pathway terminates in the Cerebellum with 2nd-Order Neurons.
  - Carry ***Sensory Info*** from ***Thalamus*** → to ***Primary Somatosensory Cortex*** in Parietal Lobe.
    - ***Thalamus –*** Sorts incoming Sensory Info → Sends it to Cortex.

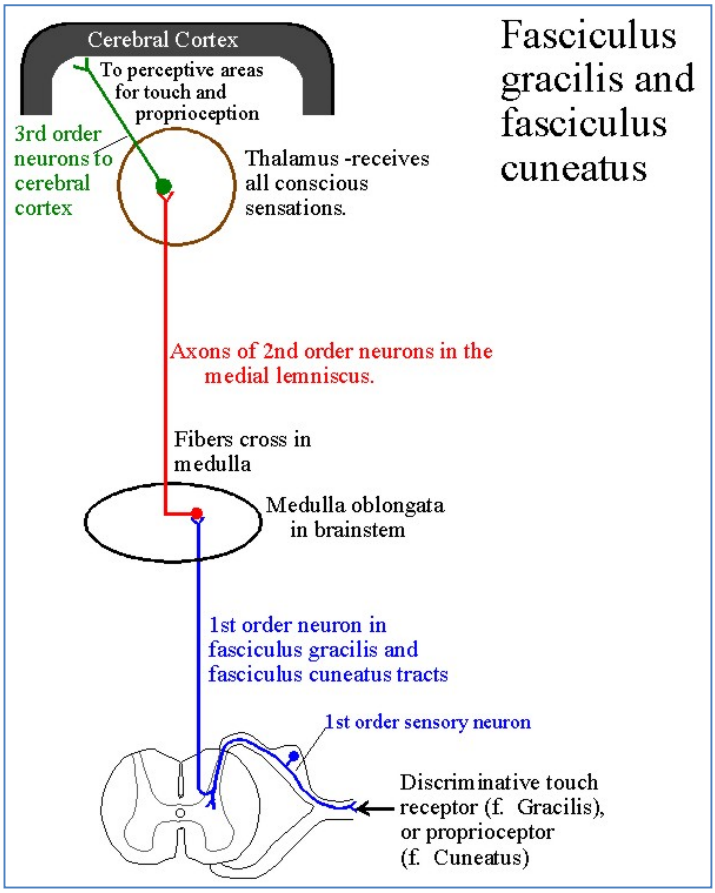




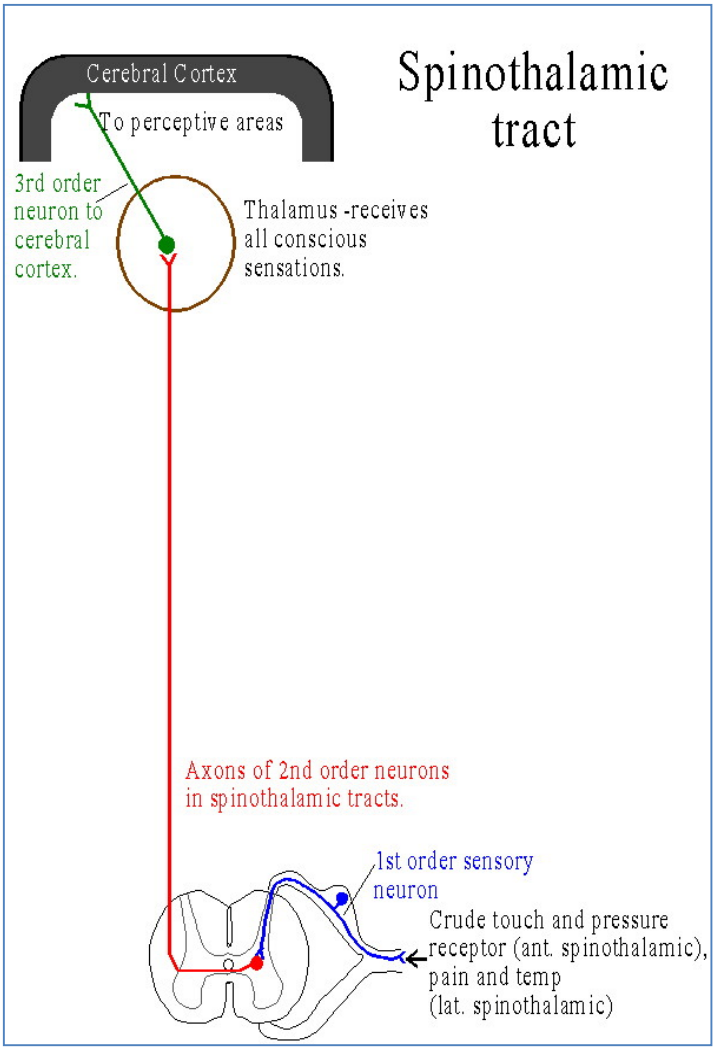
(The Dark Blue Area)

The 3 Ascending Pathways:

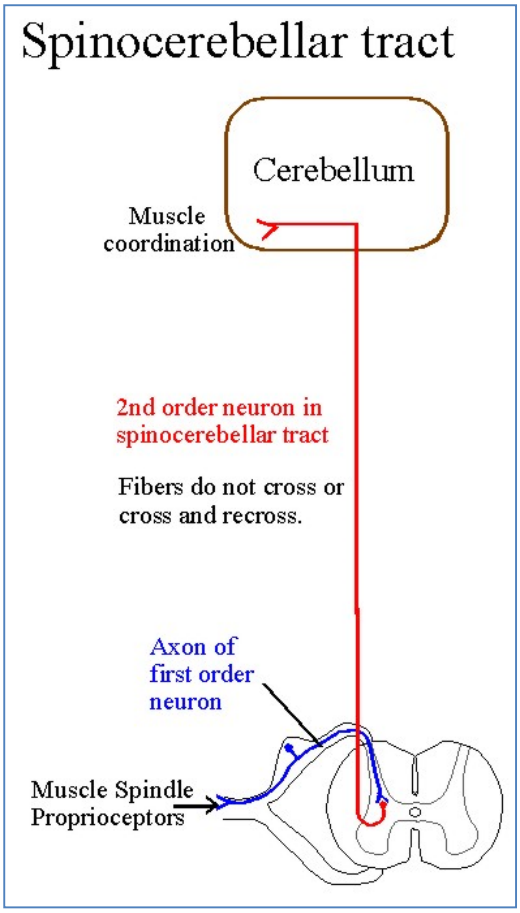
- **Posterior Column Pathway:**
  - ***Synapses*** with 2nd-Order Neurons ***in Medulla***
  - ***Decussate in the Medulla***
  - **Neurons Are:**
    - Large & Myelinated
    - Rapidly Adapting
  - **Sensory Info:**
    - Touch
    - Vibration
    - 2-Point Discrimination
    - Proprioception



- **SpinoThalamic Pathway:**
  - ***Synapses*** with 2nd-Order Neurons ***in Spinal Cord*** @ Level of Spinal Root
  - ***Decussate in Spinal Cord*** @ Level of Spinal Root.
  - **Neurons Are:**
    - Small & Myelinated
    - Slowly Adapting
  - **Sensory Info:**
    - Crude Touch & Pressure
    - Pain
    - Temperature

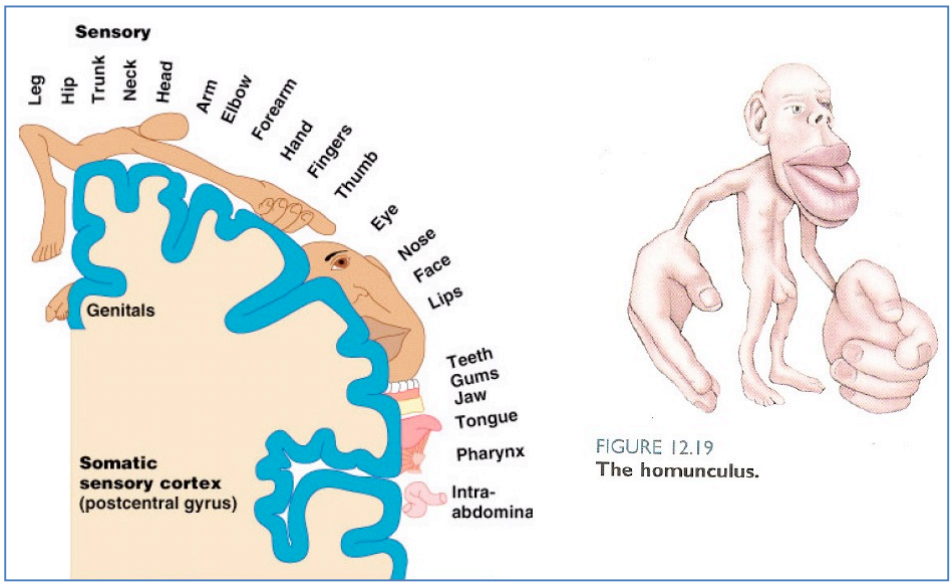


- **SpinoCerebellar Pathway:**
  - ***Synapse*** with 2nd-Order Neurons ***in Spinal Cord***
  - ***Doesn't Decussate*** – Remains ***Ipsilateral***
    - ("On the Same Side of the Body")
  - **Neurons Are:**
    - Large & Myelinated
    - Slowly Adapting
  - **Sensory Info:**
    - Proprioception from:
      - Muscle Spindles
      - Golgi Tendon Organs
      - Joint Capsules
    - → Coordinate Skeletal Muscle Activity



Somatosensory Processing:

- **Somatosensory Cortex:**
  - **Roles:**
    - Detection of Sensation & Conscious Awareness of Sensation
    - Feature/Quality Recognition (ie. Texture/Size/Shape)
  - Exhibits ***'Somatotopy'*** (Body Mapping)
    - – ie. Specific Cortical Areas responsible for Particular Body Regions
  - Receptor Density in a Body Region determines the Size of the respective Cortical Area. – See Below:

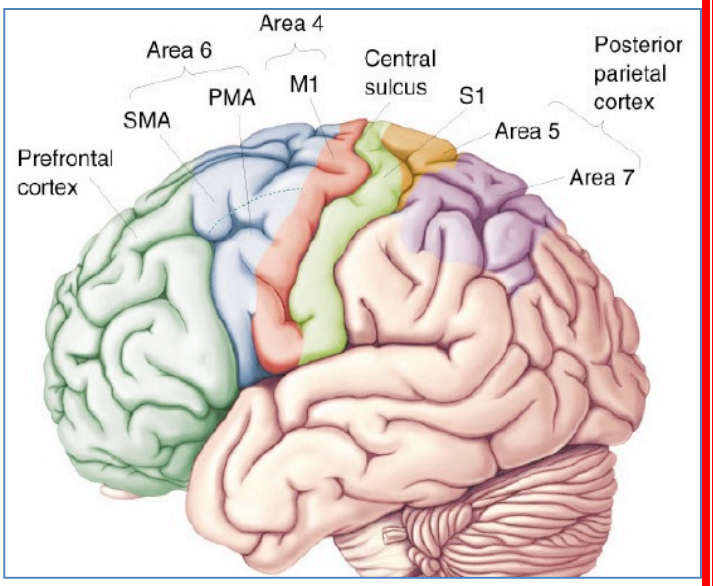


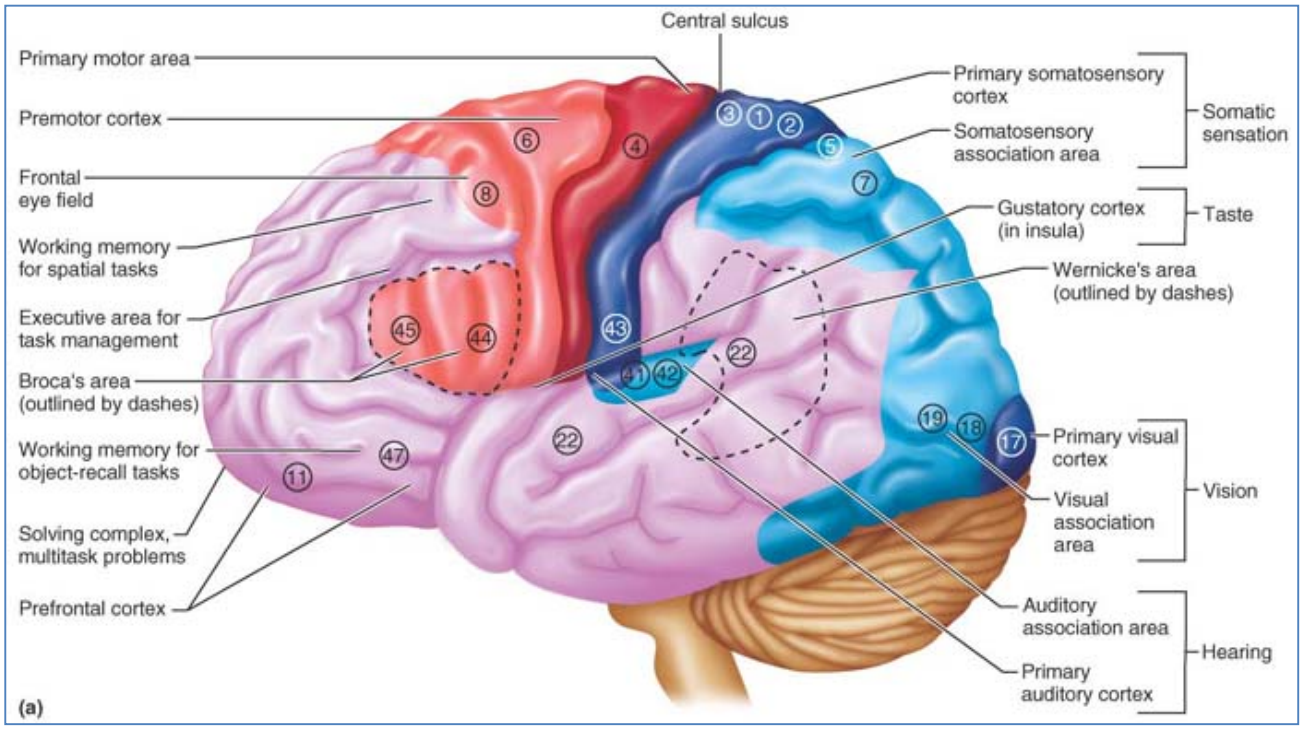
- **Somatosensory Association Area:**
  - The Somatosensory Cortex has Connections to the Somatosensory Association Areas
  - **Role:**
    - Compares Received Stimulus to Past Experiences.

Neuroscience Notes
Motor Processing

Motor Processing Hierarchy - The Levels of Motor Control:

- **1. Ready (*Strategy*) – Deciding 'What to do':**
  - Prefrontal Cortex
  - Somatosensory Association Cortex (5 & 7)
  - Basal Ganglia (NB: Basal Ganglia are the interface between 'Strategy' & 'Tactics'.)
- **2. Set (*Tactics*) – Deciding 'How to do it':**
  - Basal Ganglia
  - Pre-Motor Area (PMA)
  - Supplementary Motor Area (SMA)
- **3. Go (*Execution*) – 'Action':**
  - Primary Motor Cortex (M1)
  - Cerebellum
  - Brainstem
  - Descending Tracts
  - Spinal Nerves
  - Peripheral Motor Neurons



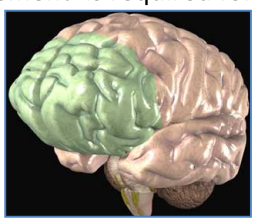


Brain Regions involved in Voluntary Motor Movement:

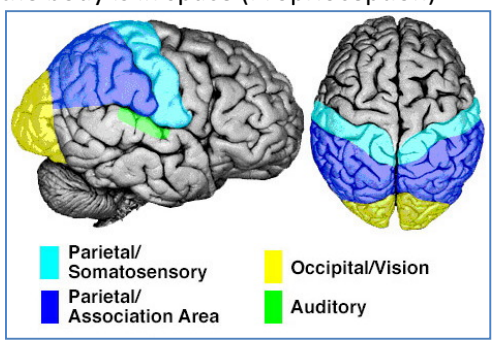
- **Cortical Regions:**
  - **Pre-Frontal Cortex** **(Frontal Lobe)**
  - **Somatosensory Association Areas** **(Parietal Lobe)**
  - **Pre-Motor Area** **(Frontal Lobe)**
  - **Supplementary-Motor Area** **(Frontal Lobe)**
  - **Primary Motor Cortex (M1)** **(Frontal Lobe)**
    - **Broca's Area** **(Frontal Lobe)**
- **Sub-Cortical Regions:**
  - **Basal Ganglia**
  - **Cerebellum**

Roles of these Brain Regions (In Motor Processing):

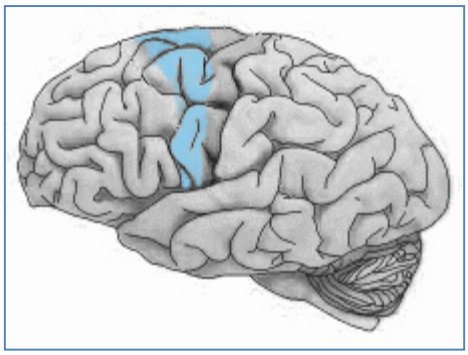
- **Pre-Frontal Cortex:**
  - Consciously Decides 'what movement' is required for the desired outcome. (Managerial Function)

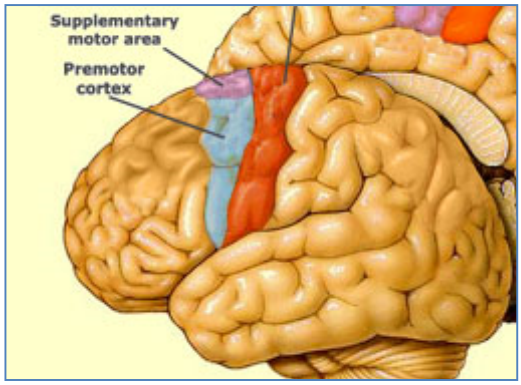


- **Somatosensory Association Areas:**
  - Tells the brain where the body is in space (Proprioception)

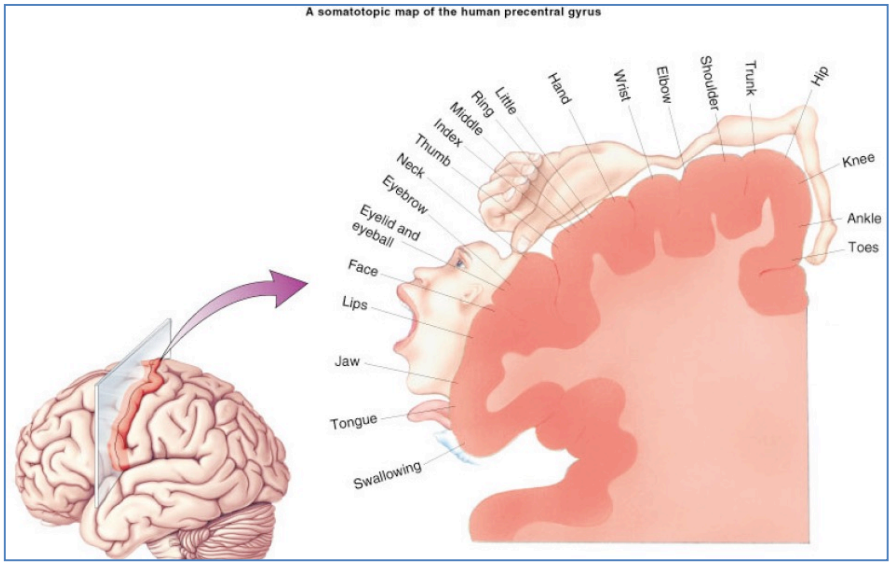


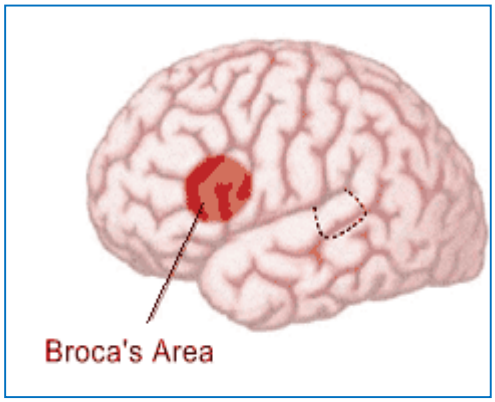
- **Pre-Motor Area & Supplementary-Motor Areas:**
  - Plans 'how to do the movement'.
  - Is also the *memory bank* of Complex, Patterned & Highly Skilled Learned Movements.



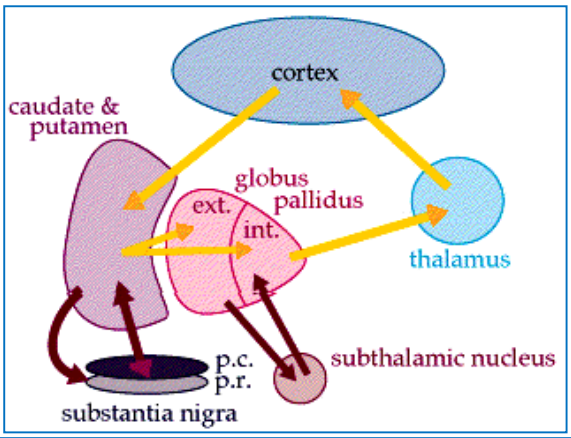


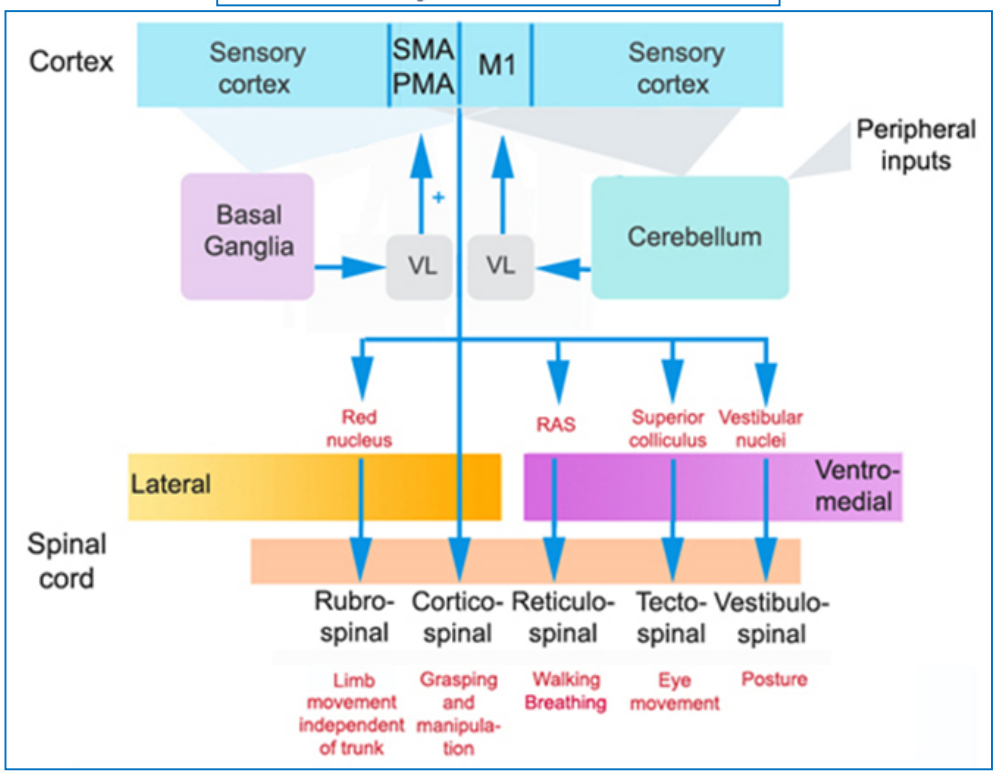
- **Primary Motor Cortex (M1):**
  - 'Initiates the movement' (Typically precise or skilled voluntary movement)
  - NB: M1 also exhibits ***Somatotopy*** – The Bigger the Cortical Area, The More Precise the Movements
  - **Receives Direct & Indirect Inputs:**
    - **Direct** – From: Prefrontal Cortex, SMA/PMA, Somatosensory Areas
    - **Indirect** – From: Cerebellum (Via Thalamus)
  - **Broca's Area –** Area of M1 that controls the Muscles responsible for speech (Tongue/Jaw/Lips/Face)





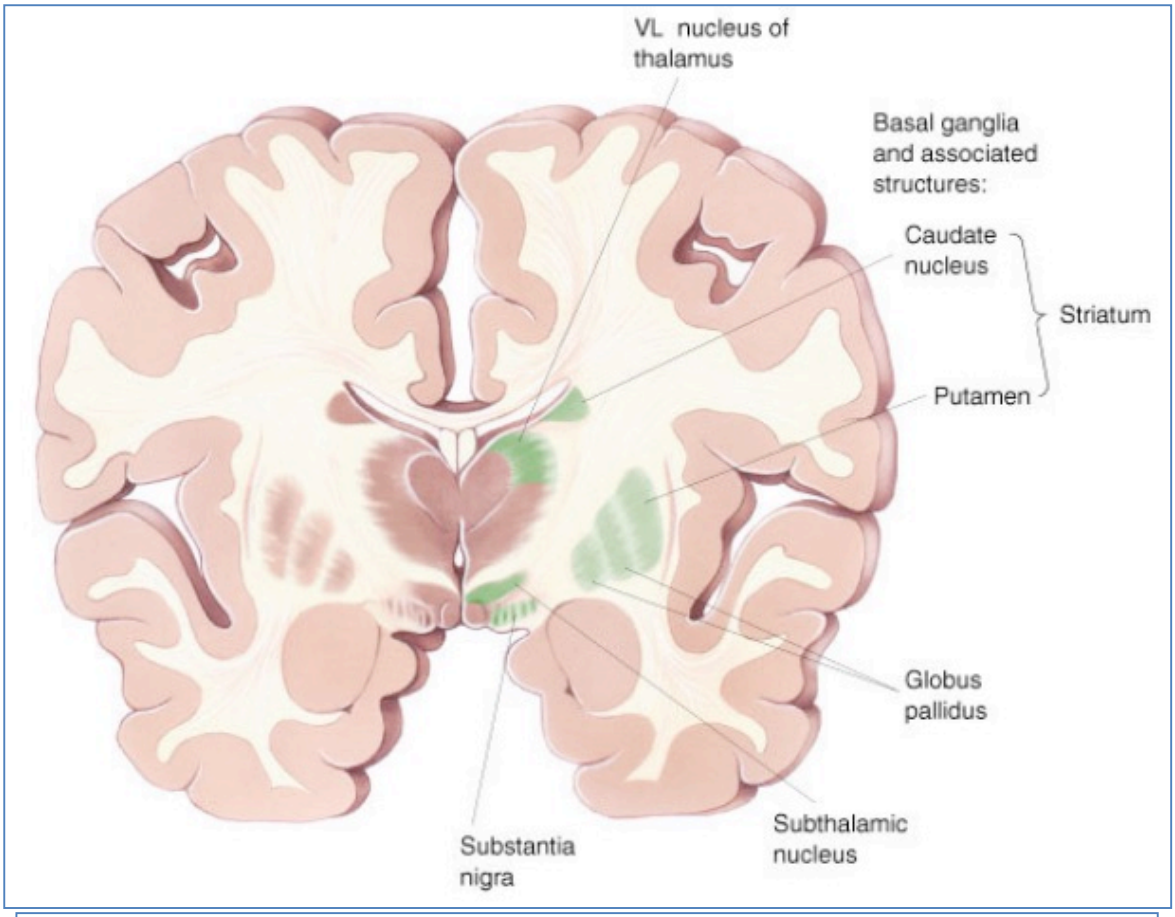
- **Basal Ganglia:**
  - **Involved in** Action-Selection & Initiation of Voluntary & Patterned Movements (Eg. Walking)
    - Motor Control & Motor Learning
      - NB: Also has a role in Cognition & Memory
  - **A Loop Exists** between the Cortex → **Basal Ganglia** → Thalamus → Pre-Motor Cortex → Cortex
    - Receives inputs from the Entire Cortex. (SMA/Prefrontal Cortex/Sensory Cortex/M1)
      - **Info travels through Basal Ganglia in This Order: Striatum→Globus Pallidus**.
    - Sends info to the PMA & ***SMA** via the (Ventro-Lateral Nucleus of the) Thalamus (VLo)

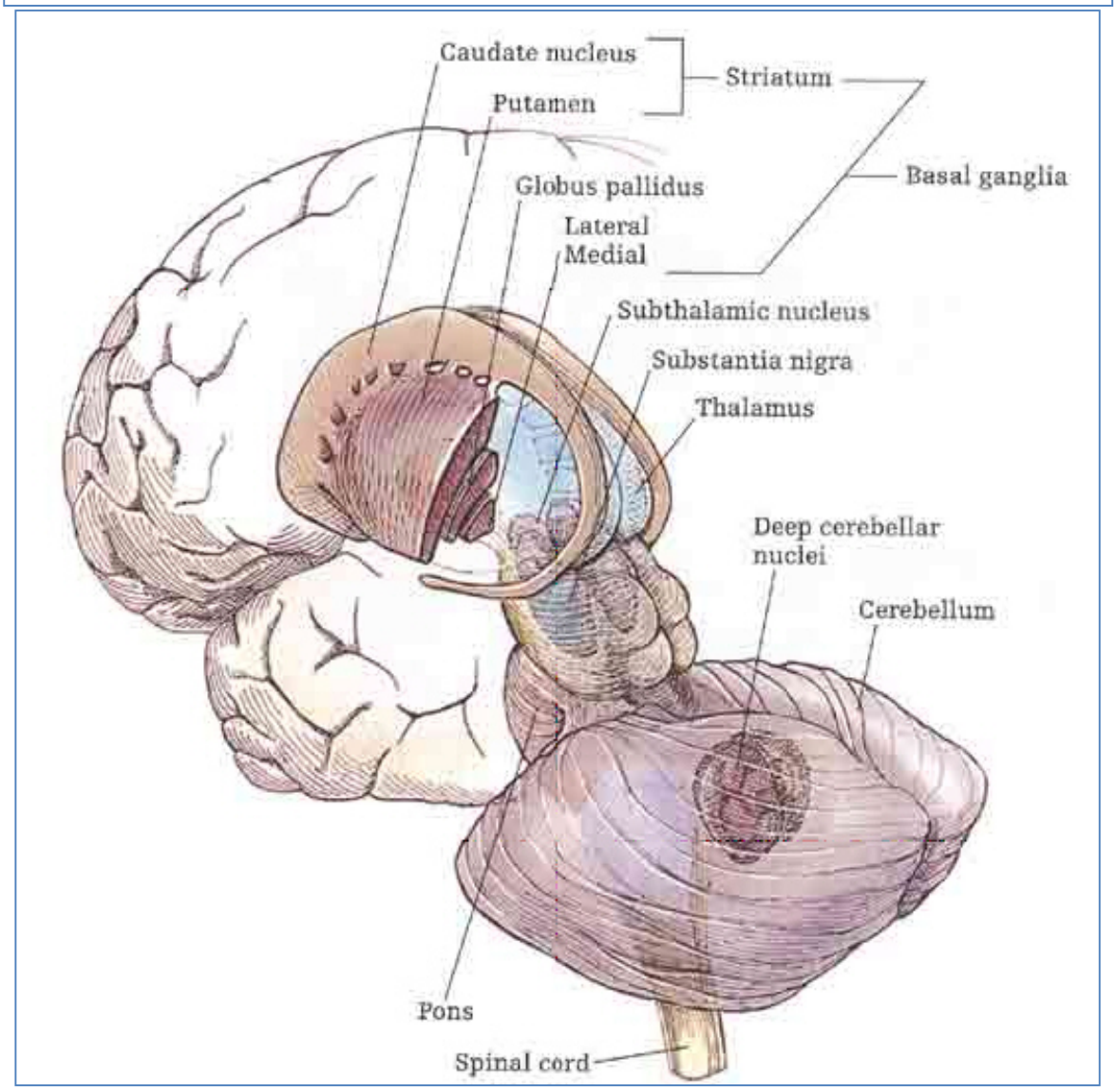




NB: The GLOBUS PALLIDUS is *Spontaneously Active*:
Globus Pallidus → Thalamus (Inhibits Thalamic-SMA Activity → Keeps the SMA 'Quiet')

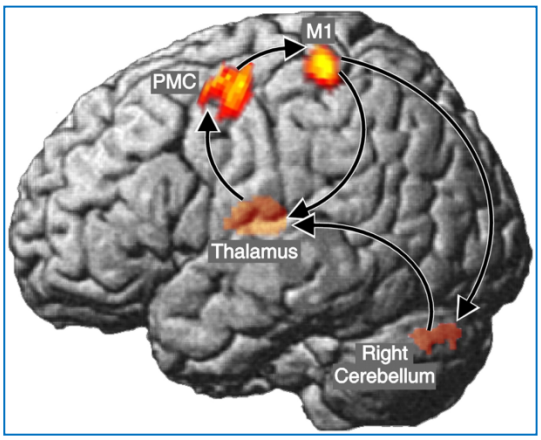
  - **Consists of:**
    - **Striatum:**
      - **Caudate Nucleus:** Cognition & Behaviour
      - **Putamen:** Motor (Automatic performance of previously learned movements.)
    - **Globus Pallidus**
  - **& Other Associated Structures:**
    - **Subthalamic Nuclei**
    - **Substantia Nigra:** Eye Movement, Motor Planning, (Reward Seeking, Learning, & Addiction)

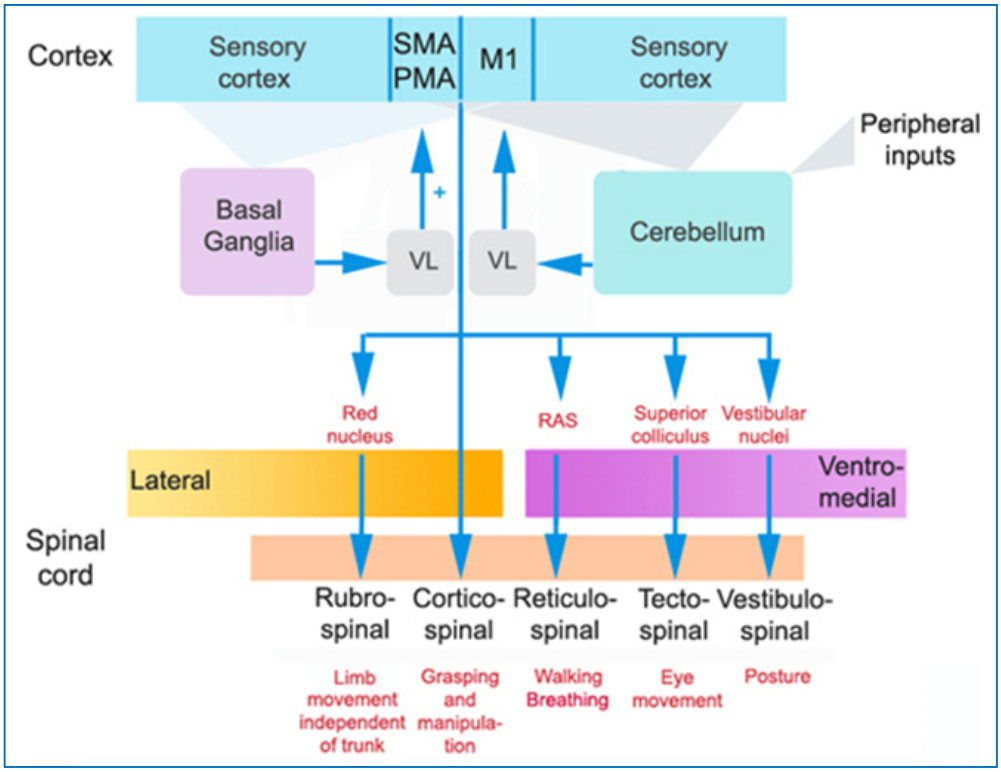




www.regentstudies.com

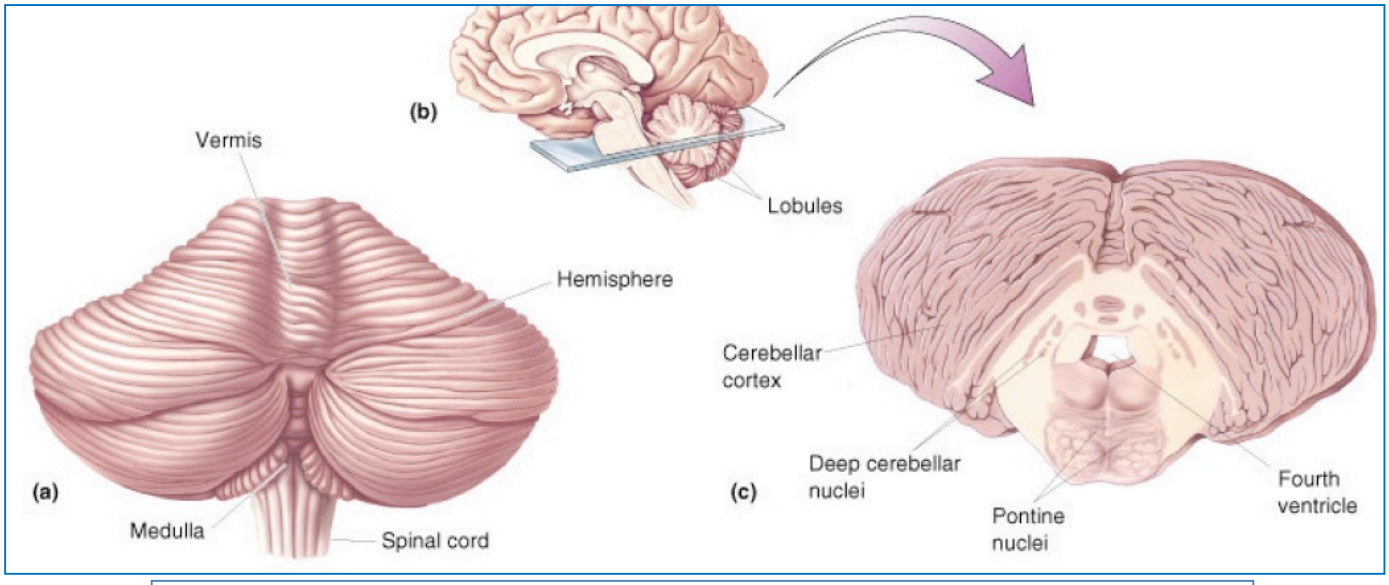
- **Cerebellum:**
  - **A Loop exists** between the Cortex → Pons → **Cerebellum** → Thalamus → M1 → Cortex.
    - Receives inputs from the Cerebral Cortex (M1, PMA, ***Somatosensory Areas**) via the Pons.
      - Also receives Proprioceptive Feedback
    - Sends info to the Primary Motor Cortex (M1) via the VentroLateral Nucleus of the Thalamus.
      - Informs Primary Motor Cortex (M1) about Direction, Force & Timing of Movements.

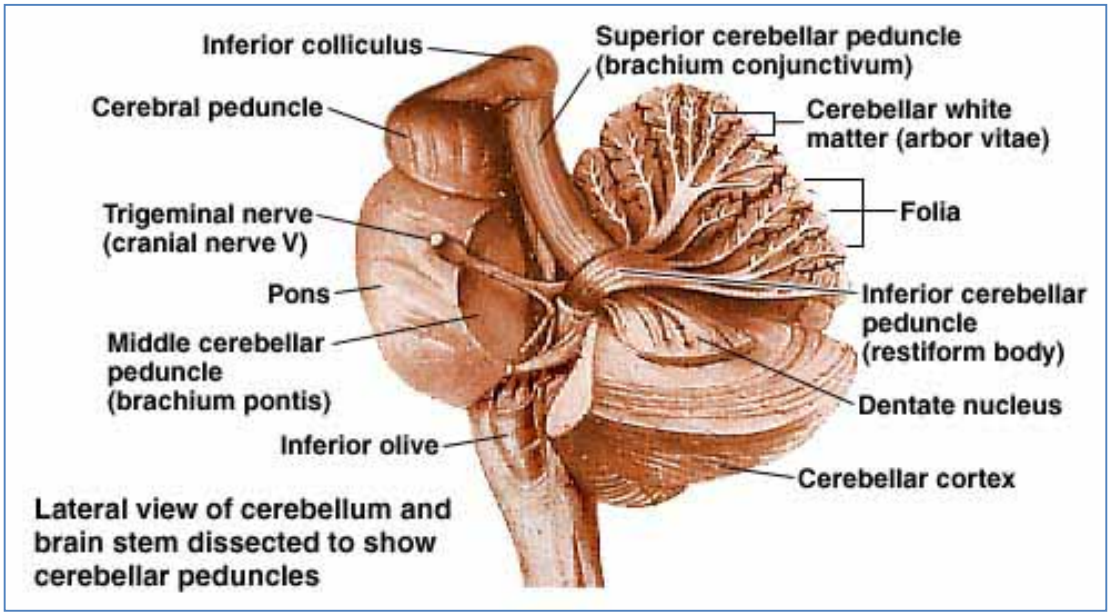




  - **Functions:**
    - *Precise Timing & Appropriate Patterns* of Skeletal Muscle Contraction – Required for Smooth, Coordinated movements & agility needed for daily living (Driving/Typing/Playing Music/etc)
    - Involved in the *Correct Sequencing & Coordination* of Muscle *Contractions.*
    - Involved in Motor Learning – Compares intention with result & corrects for next time.
    - Balance & Posture
  - **NB:** Cerebellar Activity is Subconscious (Ie. We have no awareness of its functioning.)
  - **Output into Descending Pathways:**
    - **Vermis** → Ventromedial Pathways
    - **Hemispheres** → Lateral Pathways

- **Cerebellar Processing:**
  - 1. Cortical Motor Areas Notify the Cerebellum (via 'relay nuclei' in the brainstem) of their ***intent*** to initiate voluntary muscle contractions.
  - 2. Constant Proprioceptive Input (Muscle/Tendon Tension, Joint Position, etc) enables the cerebellum to evaluate the body's position & momentum.
  - 3. Cerebellum calculates optimum Force, Direction & Extent of Muscle Contraction to ensure Smooth, Accurate & Coordinated Movements.
  - 4. Cerebellum sends its "Blueprint" for coordinating movement to the Cerebral Motor Cortex via the Superior Peduncles. It also sends info to Brainstem Nuclei → Influences Motor Neurons of the Spinal Cord.
- **Analogy:**
  - Just as an 'Autopilot' compares a plane's instruments with its planned course, the Cerebellum continually compares the higher brain's intention with the body's performance & makes appropriate corrections.



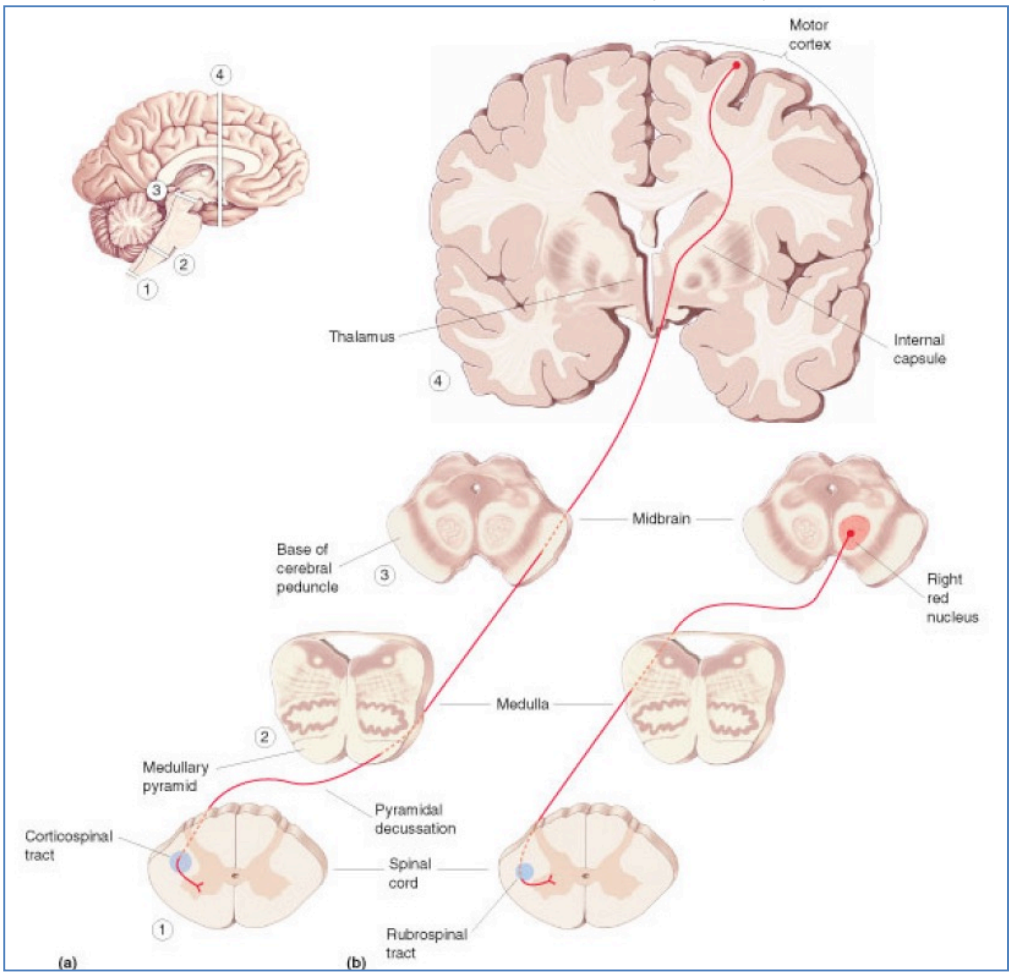


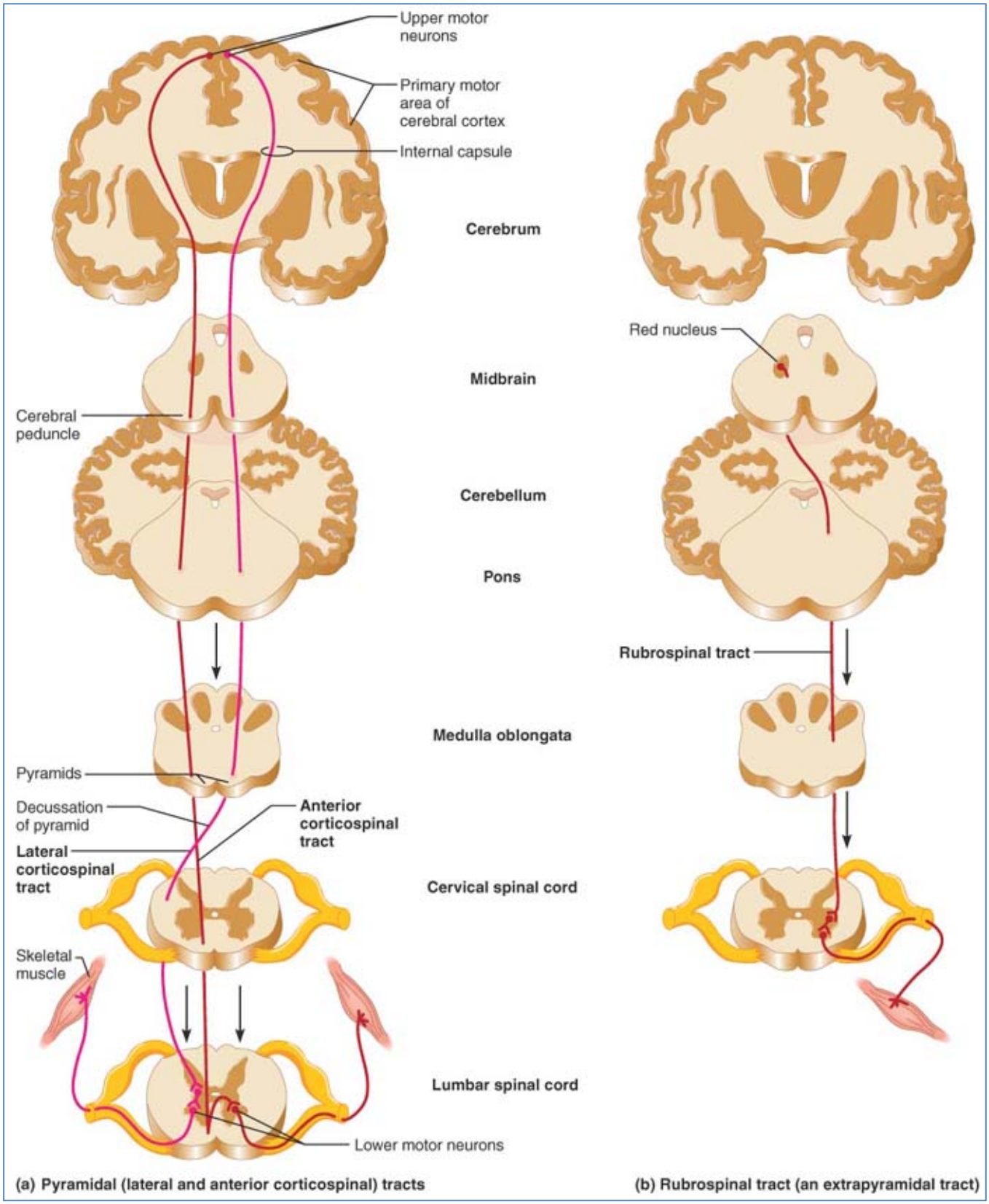
NB: The Cerebellar Peduncles

Descending Tracts Involved in Motor Function:

- **Descending Motor Pathways:**
  - **Lateral Pathways:**
    - **2 Divisions:**
      - #1 Corticospinal Tract:
      - Rubrospinal Tract:
    - **Roles:**
      - Both Tracts – Voluntary Movement of Distal Extremities (Particularly Hands & Feet)
    - **Corticospinal Tract Receives Input From:**
      - Primary Motor Cortex (M1) – The Main Origin
      - Pre-Motor Area
      - Supplementary Motor Area
      - Somatosensory Areas
    - **Rubrospinal Tract Receives Input From:**
      - Primary Motor Area (M1)
      - Pre-Motor Area
      - Supplementary Motor Area
      - Cerebellum
    - **Efferent Pathway of Upper Motor Neurons:**
      - **Corticospinal Tract:**
        - Originates in Primary Motor Cortex
        - Run through the ***Internal Capsule*** to the Brainstem.
        - Decussate in Medullary Pyramids (Medulla)
      - **Rubrospinal Tract:**
        - Originates in Red Nucleus of Midbrain.
        - Decussate immediately below Red Nucleus (In the Pons)

        →→
        - Continue down the spinal cord in the Lateral White Matter.
        - Terminate in Ventral Horn of Spinal Grey Matter





www.regentstudies.com

- **Ventromedial (Indirect/Extrapyramidal) Pathways:**
  - **4 Divisions:**
    - Tectospinal (AKA: Colliculospinal) Tract
    - Vestibulospinal Tract
    - Pontine Reticulospinal Tract
    - Medullary Reticulospinal Tract
  - **General Roles –** Reflexively Maintains**:**
    - Head & Eye Coordination ("Visual Tracking")
    - Balance
    - Muscle Tone } Ie. Proximal & Axial Muscle Groups (Trunk/Hip/Neck/Back/etc)
    - Body Posture
  - **Specific Functions:**
    - Tectospinal/Colliculospinal: Visual Tracking (Head/Eye Coordination)
    - Vestibulospinal: Maintain Balance During Standing & Moving
    - Pontine Reticulospinal: Maintains Muscle Tone & Visceral Motor Functions
    - Medullary Reticulospinal: Maintains Muscle Tone & Visceral Motor Functions
  - **Origins:**
    - Tectospinal/Colliculospinal: Superior Colliculus of Midbrain (in Brain Stem)
    - Vestibulospinal: Vestibular Nuclei in Medulla (in Brain Stem)
    - Pontine Reticulospinal: Pontine part of Reticular Formation of Brainstem
    - Medullary Reticulospinal: Medullary part of Reticular Formation of Brainstem
  - **All Divisions Receive Some Input From:**
    - The Corticospinal (Pyramidal) Pathways – Project into & Influence the Activity of these Brainstem Motor Nuclei (From which these tracts originate)

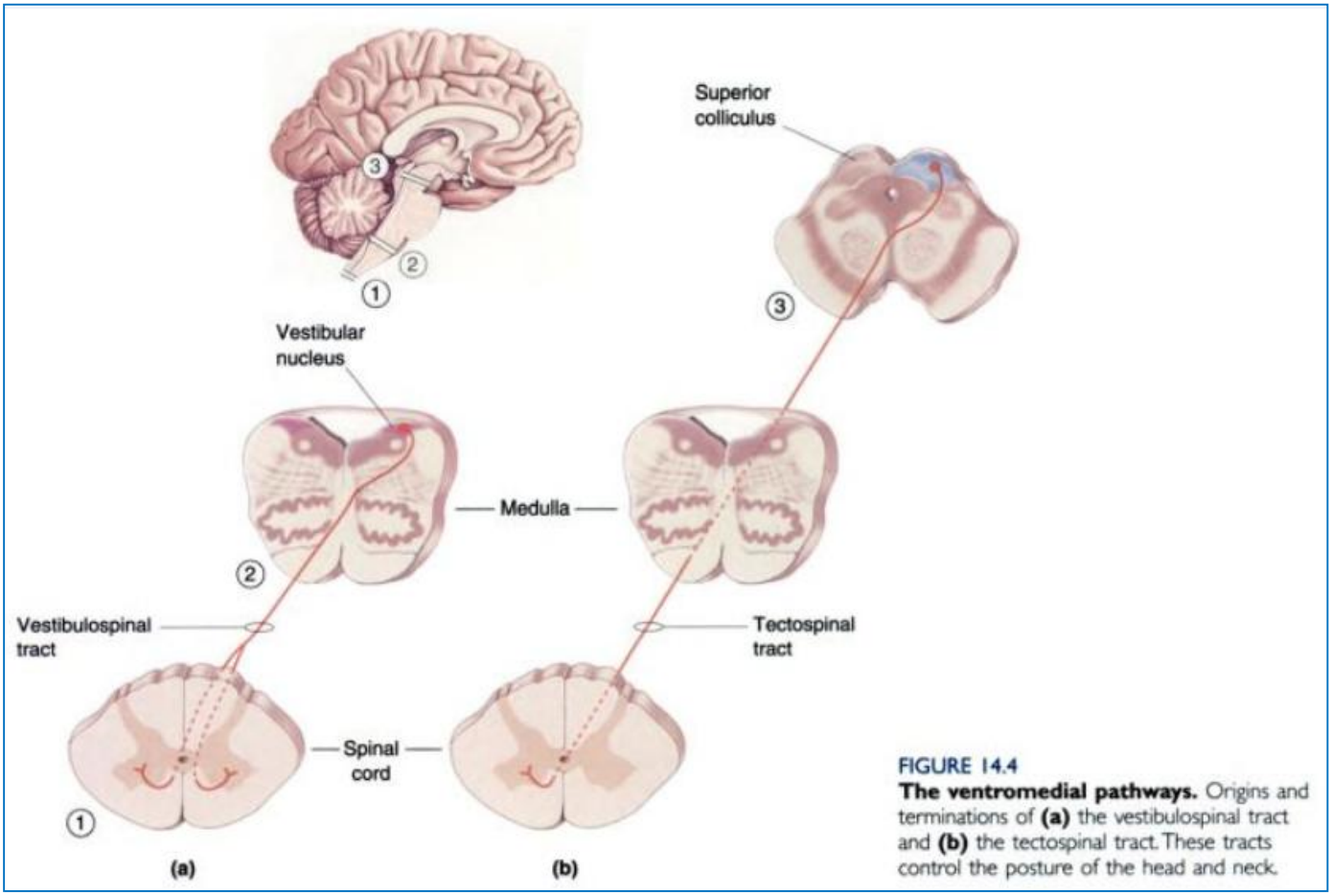


FIGURE 14.4
The ventromedial pathways. Origins and terminations of **(a)** the vestibulospinal tract and **(b)** the tectospinal tract. These tracts control the posture of the head and neck.

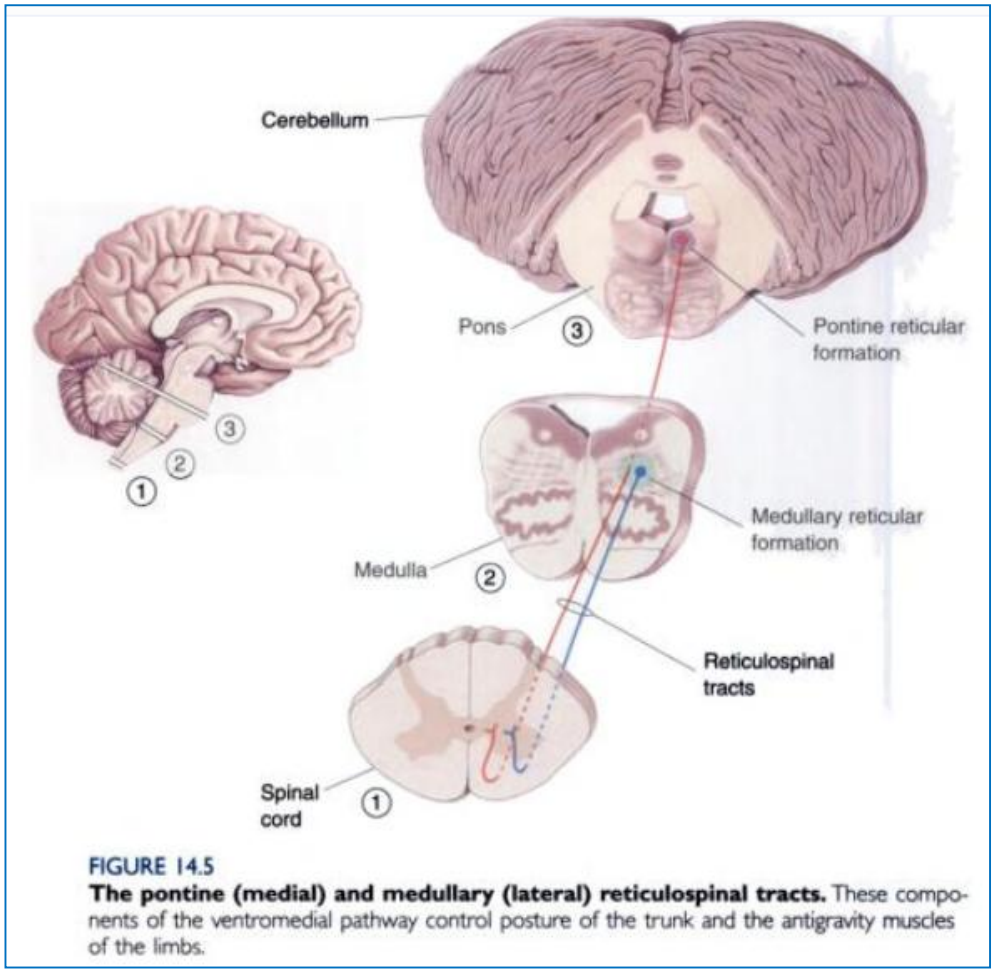
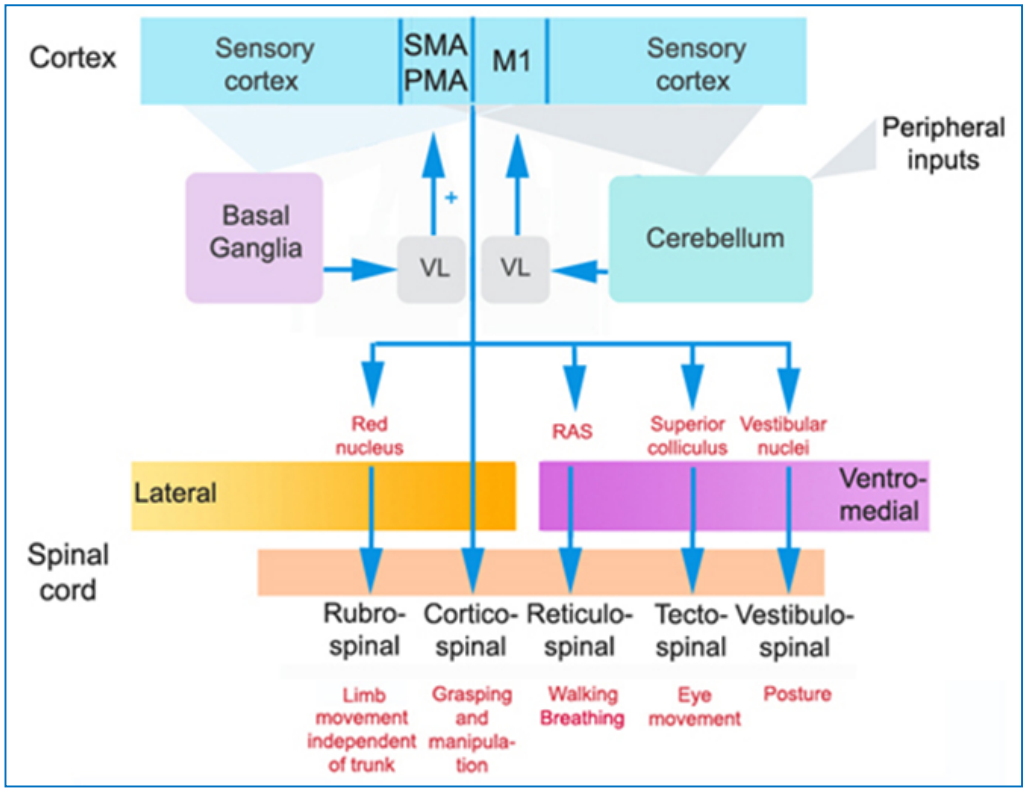
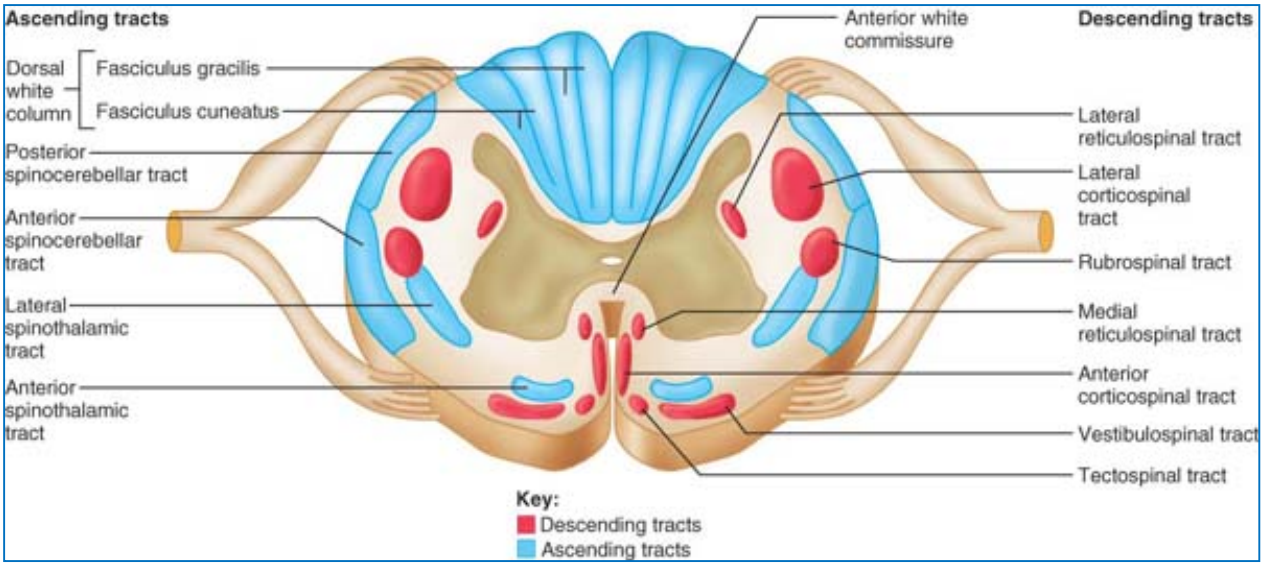


FIGURE 14.5
The pontine (medial) and medullary (lateral) reticulospinal tracts. These components of the ventromedial pathway control posture of the trunk and the antigravity muscles of the limbs.

- **NB: These Descending 'Upper Motor Neurons' Terminate in the Ventral Grey Horns of the Spinal Cord Grey Matter by Synapsing with either:**
  - **Spinal Interneurons – Enabling info to be sent to multiple outputs.**
    - Some Interneurons are '***Central Pattern Generators***' → generate timing for patterned movements (Eg. Walking)
  - **Or Lower Motor Neurons – That directly innervate skeletal muscle.**



Marieb's Version of Descending Motor Pathways & Spinal Cord Tracts:



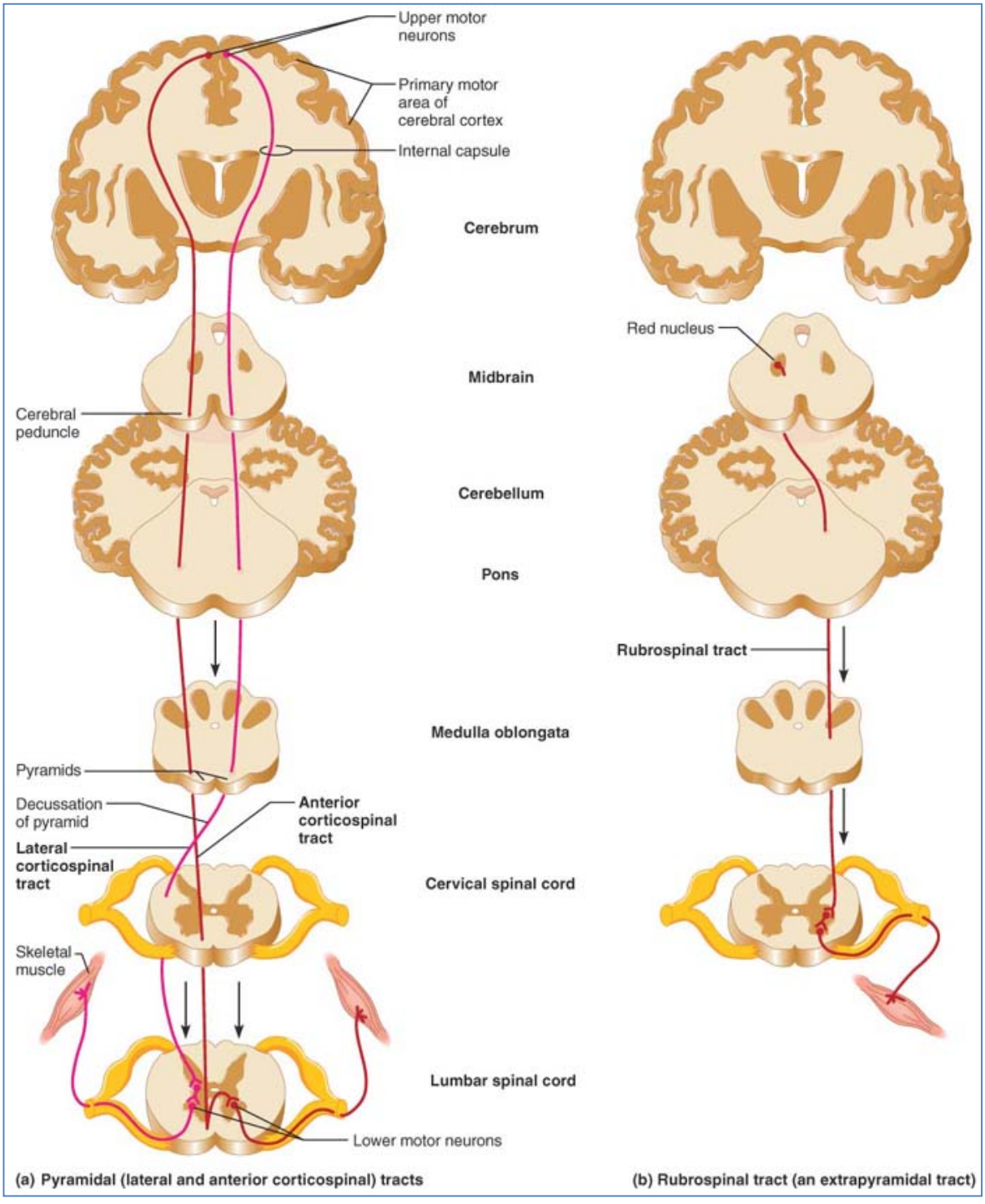
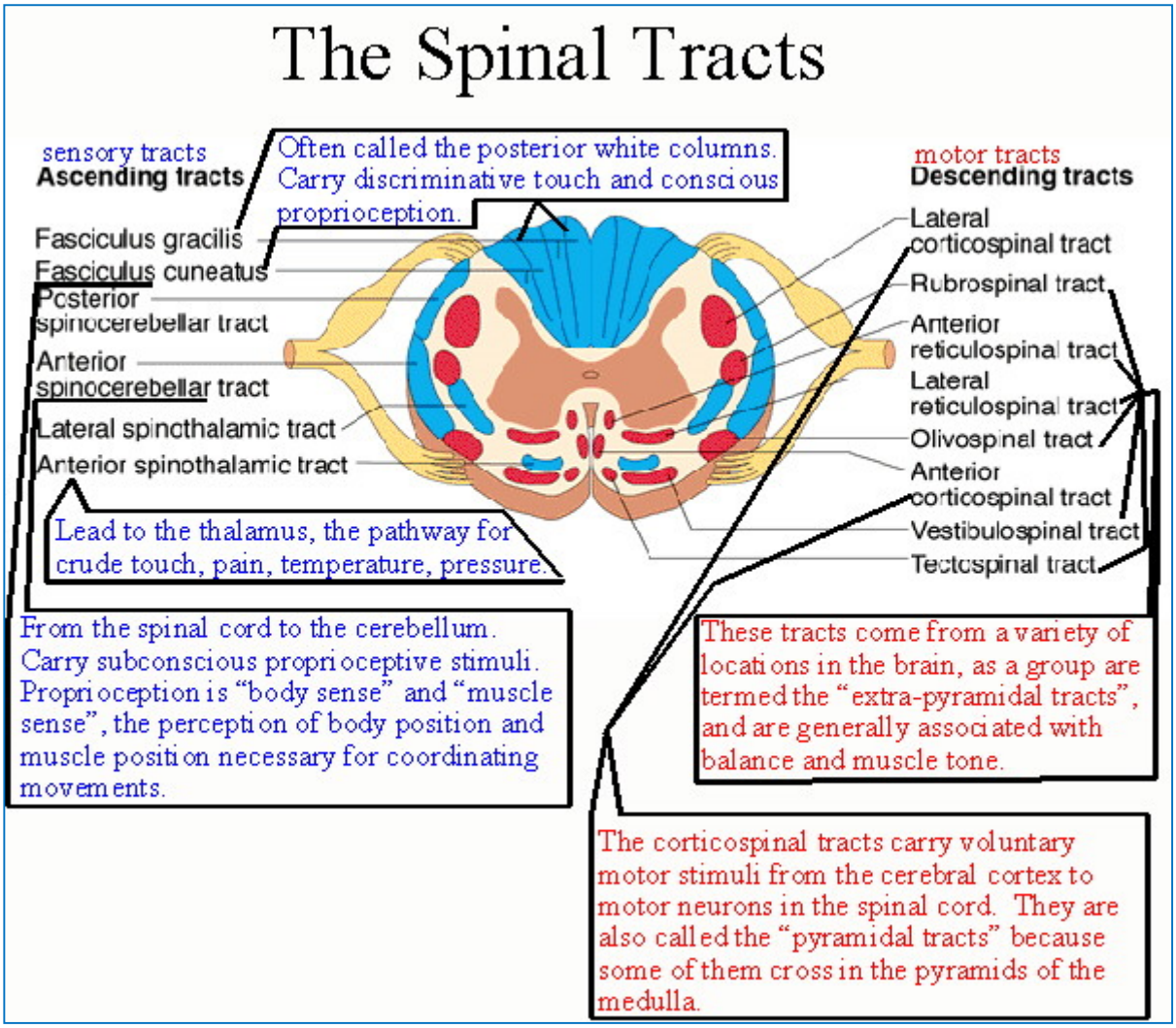


TABLE 12.3 Major Descending (Motor) Pathways and Spinal Cord Tracts

SPINAL CORD TRACT	LOCATION (FUNICULUS)	ORIGIN	TERMINATION	FUNCTION
DIRECT (PYRAMIDAL)				
Lateral corticospinal	Lateral	Pyramidal neurons of motor cortex of the cerebrum; decussate in pyramids of medulla	By synapse directly with ventral horn motor neurons and with ventral horn interneurons that influence motor neurons	Transmits motor impulses from cerebrum to spinal cord motor neurons (which activate skeletal muscles on opposite side of body); voluntary motor tract
Anterior corticospinal	Anterior	Pyramidal neurons of motor cortex; fibers cross over at the spinal cord level	Ventral horn (as above)	Same as lateral corticospinal tract
INDIRECT (EXTRAPYRAMIDAL) PATHWAYS				
Tectospinal	Anterior	Superior colliculus of midbrain of brain stem (fibers cross to opposite side of cord)	By synapse with ventral horn interneurons that influence motor neurons	Transmits motor impulses from midbrain that are important for coordinated movement of head and eyes toward visual targets
Vestibulospinal	Anterior	Vestibular nuclei in medulla of brain stem (fibers descend without crossing)	By synapse, directly with ventral horn motor neurons and with ventral horn interneurons that influence motor neurons	Transmits motor impulses that maintain muscle tone and activate ipsilateral limb and trunk extensor muscles and muscles that move head; in this way helps maintain balance during standing and moving
Rubrospinal	Lateral	Red nucleus of midbrain of brain stem (fibers cross to opposite side just inferior to the red nucleus)	Ventral horn (as above)	In experimental animals, transmits motor impulses concerned with muscle tone of distal limb muscles (mostly flexors) on opposite side of body; in humans, functions largely assumed by corticospinal tracts except for some upper limb movement
Reticulospinal (anterior, medial, and lateral)	Anterior and lateral	Reticular formation of brain stem (medial nuclear group of pons and medulla); both crossed and uncrossed fibers	Ventral horn (as above)	Transmits impulses concerned with muscle tone and many visceral motor functions; may control most unskilled movements

www.regentstudies.com

The Spinal Tracts

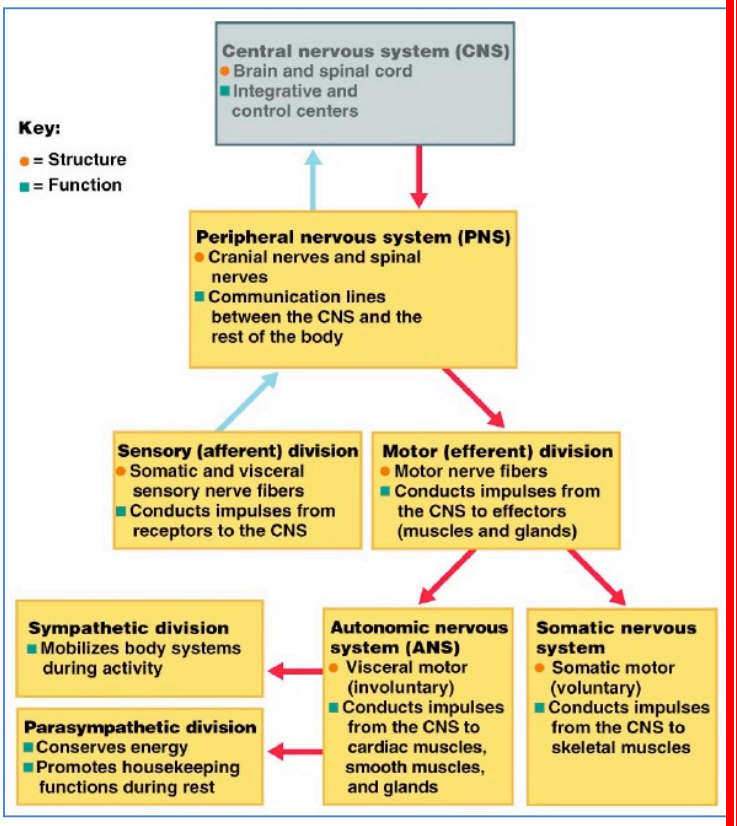


www.regentstudies.com

Neuroscience Notes
The Peripheral Nervous System

Composition of PNS:

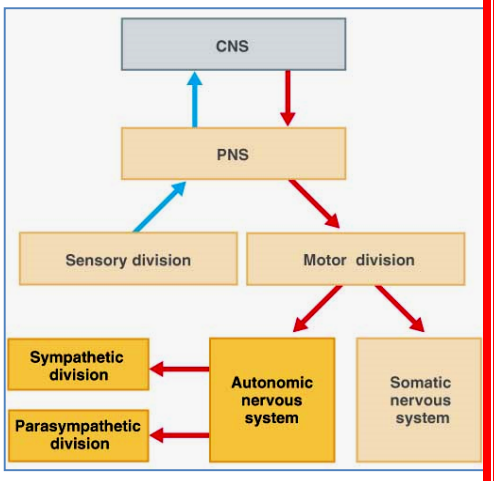
- **Spinal Nerves**
- **Cranial Nerves**
- **Peripheral Branch of Autonomic NS:**
  - **Sympathetic Trunks & Ganglia**
  - **Enteric Nervous System (Alimentary Tract)**



Functional Divisions of PNS:

- **Afferent (Sensory)**
- **Efferent (Motor):**
  - **Somatic/Voluntary (Skeletal Muscle)**
  - **Autonomic:**
    - **Sympathetic**
    - **Parasympathetic**

This Week's Focus = The Autonomic Nervous System:



- **Effectors:**
  - **Cardiac Muscle**
  - **Smooth Muscle**
  - **Glands**
  - (As opposed to the Somatic-NS & Skeletal Muscle)

- **Efferent Pathways & Ganglia:**
  - As opposed to the Somatic-NS which uses a mono-synaptic system (& Hence Lacks Ganglia), the Autonomic-NS uses a 2-Neuron-Chain system.

  - **1. The Pre-Ganglionic Neuron:**
    - The Cell-Body of the first neuron
    - Resides in the Brain or Spinal Cord
  - **2. The Pre-Ganglionic Axon:**
    - Synapses with a Ganglionic Neuron.
    - (Thin, Lightly Myelinated Fibres)
  - **3. The Ganglionic Neuron:**
    - Resides in an 'Autonomic Ganglion' outside the CNS.
  - **4. The Post-Ganglionic Axon:**
    - Extends from the Ganglion to the Effector Organ.
    - (Fibres are even Thinner & Totally Unmyelinated)

Divisions of the Autonomic NS:

- The 2 Divisions of the ANS (Sympathetic & Parasympathetic) serve the same visceral organs, but cause Opposite Effects. This ***Dual Innervation*** counterbalances each division's activities → Maintains Homeostasis.
- **Sympathetic:**
  - "Fight/Flight"
  - Mobilizes the body during activity
  - Effects are Widespread
- **Parasympathetic:**
  - "Rest/Digest"
  - Conserves Body Energy & Promotes Maintenance Functions.
  - Has relatively Short-Lived Effects (Due to short-acting nature of Acetylcholine)
  - Effects are relatively Localised

TABLE 14.5 Effects of the Parasympathetic and Sympathetic Divisions on Various Organs

TARGET ORGAN OR SYSTEM	PARASYMPATHETIC EFFECTS	SYMPATHETIC EFFECTS
Eye (iris)	Stimulates sphincter pupillae muscles; constricts pupils	Stimulates dilator pupillae muscles; dilates pupils
Eye (ciliary muscle)	Stimulates muscles, which results in bulging of the lens for close vision	Weakly inhibits muscles, which results in flattening of the lens for far vision
Glands (nasal, lacrimal, gastric, pancreas)	Stimulates secretory activity	Inhibits secretory activity; causes vasoconstriction of blood vessels supplying the glands
Salivary glands	Stimulates secretion of watery saliva	Stimulates secretion of thick, viscous saliva
Sweat glands	No effect (no innervation)	Stimulates copious sweating (cholinergic fibers)
Adrenal medulla	No effect (no innervation)	Stimulates medulla cells to secrete epinephrine and norepinephrine
Arrector pili muscles attached to hair follicles	No effect (no innervation)	Stimulates to contract (erects hairs and produces "goosebumps")
Heart muscle	Decreases rate; slows heart	Increases rate and force of heartbeat
Heart: coronary blood vessels	Weakly dilates coronary vessels	Causes vasodilation*
Bladder/urethra	Causes contraction of smooth muscle of bladder wall; relaxes urethral sphincter; promotes voiding	Causes relaxation of smooth muscle of bladder wall; constricts urethral sphincter; inhibits voiding
Lungs	Constricts bronchioles	Dilates bronchioles*
Digestive tract organs	Increases motility (peristalsis) and amount of secretion by digestive organs; relaxes sphincters to allow movement of foodstuffs along tract	Decreases activity of glands and muscles of digestive system and constricts sphincters (e.g., anal sphincter)
Liver	No effect (no innervation)	Stimulates release of glucose to blood*
Gallbladder	Excites (gallbladder contracts to expel bile)	Inhibits (gallbladder is relaxed)
Kidney	No effect (no innervation)	Causes vasoconstriction; decreases urine output; promotes renin release
Penis	Causes erection (vasodilation)	Causes ejaculation
Vagina/clitoris	Causes erection (vasodilation) of clitoris	Causes contraction of vagina; increases mucus secretion
Blood vessels	Little or no effect	Constricts most vessels and increases blood pressure; constricts vessels of abdominal viscera and skin to divert blood to muscles, brain, and heart when necessary; NE constricts most vessels when necessary; epinephrine dilates vessels of the skeletal muscles during exercise*
Blood coagulation	No effect (no innervation)	Increases coagulation*
Cellular metabolism	No effect (no innervation)	Increases metabolic rate*
Adipose tissue	No effect (no innervation)	Stimulates lipolysis (fat breakdown)*

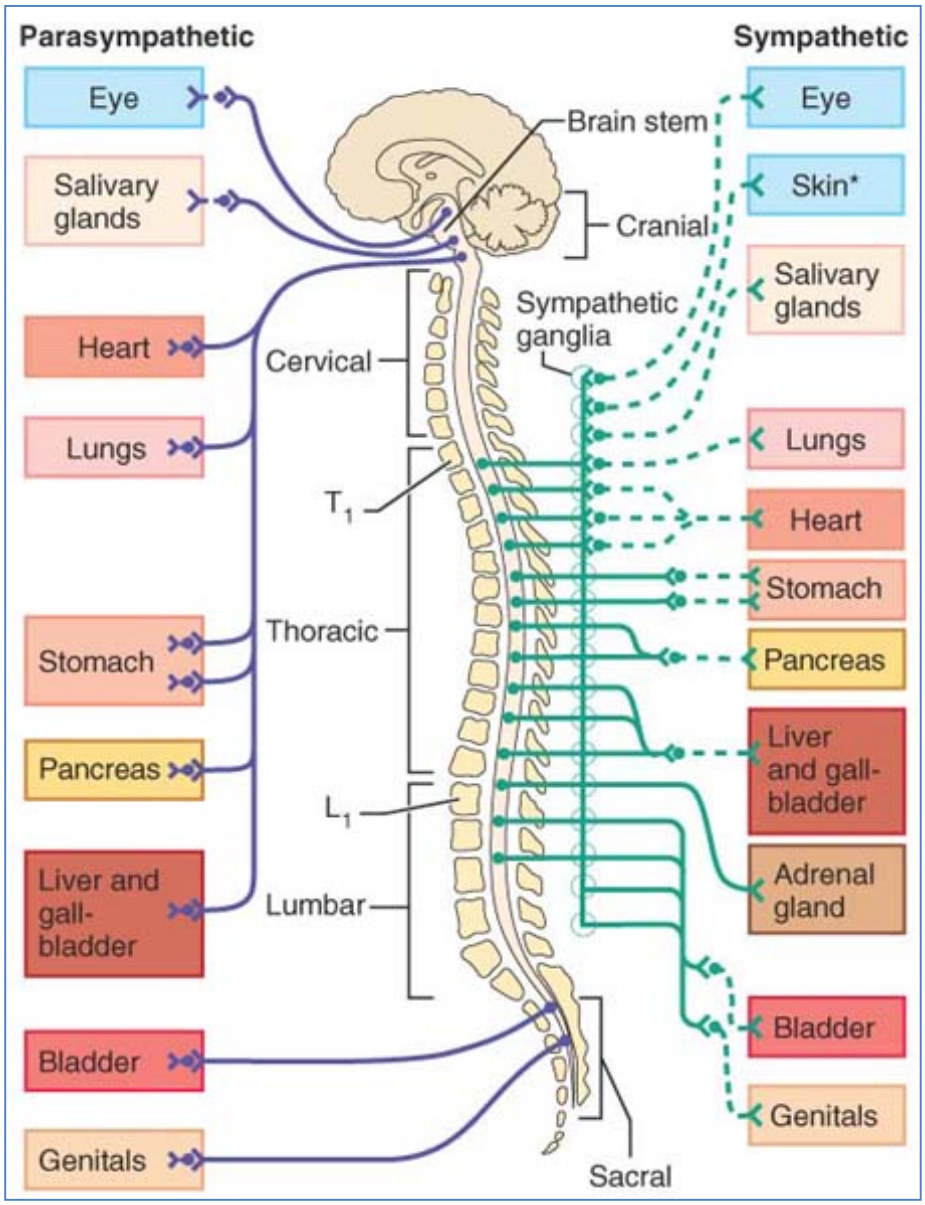
*Effects are mediated by epinephrine release into the bloodstream from the adrenal medulla.

Anatomy of the Autonomic NS:

Sympathetic & Parasympathetic Divisions Differ Anatomically in 3 Ways:

- 1. Site of Origin
- 2. Fibre Lengths
- 3. Location of Ganglia

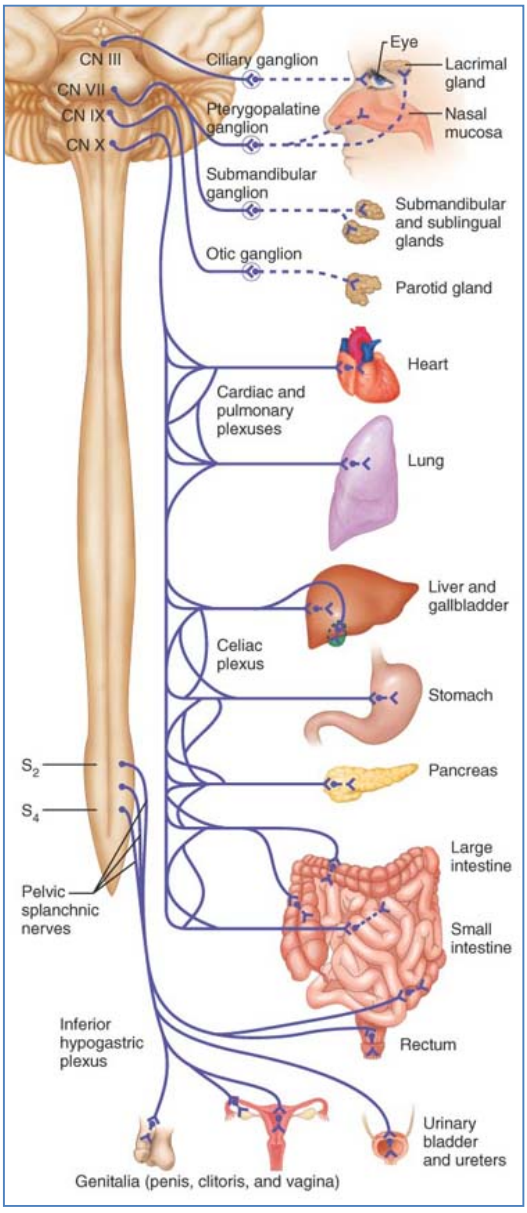
CHARACTERISTIC	PARASYMPATHETIC	SYMPATHETIC
Origin	Craniosacral outflow: brain stem nuclei of cranial nerves III, VII, IX, and X; spinal cord segments S_2–S_4	Thoracolumbar outflow: lateral horn of gray matter of spinal cord segments T_1–L_2
Location of ganglia	Ganglia in (intramural) or close to visceral organ served	Ganglia within a few centimeters of CNS: alongside vertebral column (sympathetic trunk, or chain, ganglia) and anterior to vertebral column (collateral, or prevertebral, ganglia)
Relative length of pre- and postganglionic fibers	Long preganglionic; short postganglionic	Short preganglionic; long postganglionic



Anatomy: The Parasympathetic (Craniosacral) Division:

- **Fibres originate from:**
  - Brain Stem
  - Sacral Region of Spinal Cord
- **Fibre Lengths:**
  - Preganglionic Fibres – Extend nearly all the way to the structures to be innervated.
  - Postganglionic Fibres – Very Short; Extend from the ***Terminal Ganglia*** & synapse with Effector Cells.
- **Ganglia Location:**
  - The ***'Terminal Ganglia'*** are located *Very Close To* or *Within* the Target Organs.

- **The Cranial Outflow:**
  - Fibres Originate From Cranial-Nerve Nuclei in the Brain Stem.
  - Fibres Extend to their Terminal Ganglia via 4 of the paired Cranial Nerves:
    - III – Oculomotor Nerves → Pupil Constriction & Lens Accommodation (close sight)
    - VII – Facial Nerves → Stimulate large Glands in the head (Nasal/Lacrimal/Submandibular & Sublingual Salivary)
    - IX – Glossopharyngeal Nerves → Stimulate Parotid Salivary Glands
    - X – Vagus Nerves → Serves virtually all organs of the thoracic & abdominal Cavities (Except Distal Large Intestine)
- **The Sacral Outflow:**
  - Fibres Originate from Neurons in the Lateral Gray Matter of Spinal Cord Segments S2-S4.
  - Fibres Extend to their Terminal Ganglia via ***Splanchnic Nerves*** of the ***Pelvic Plexus***.
  - Serve Distal Large Intestine & the Pelvic Organs (Bladder, Ureters, Repro. Organs)



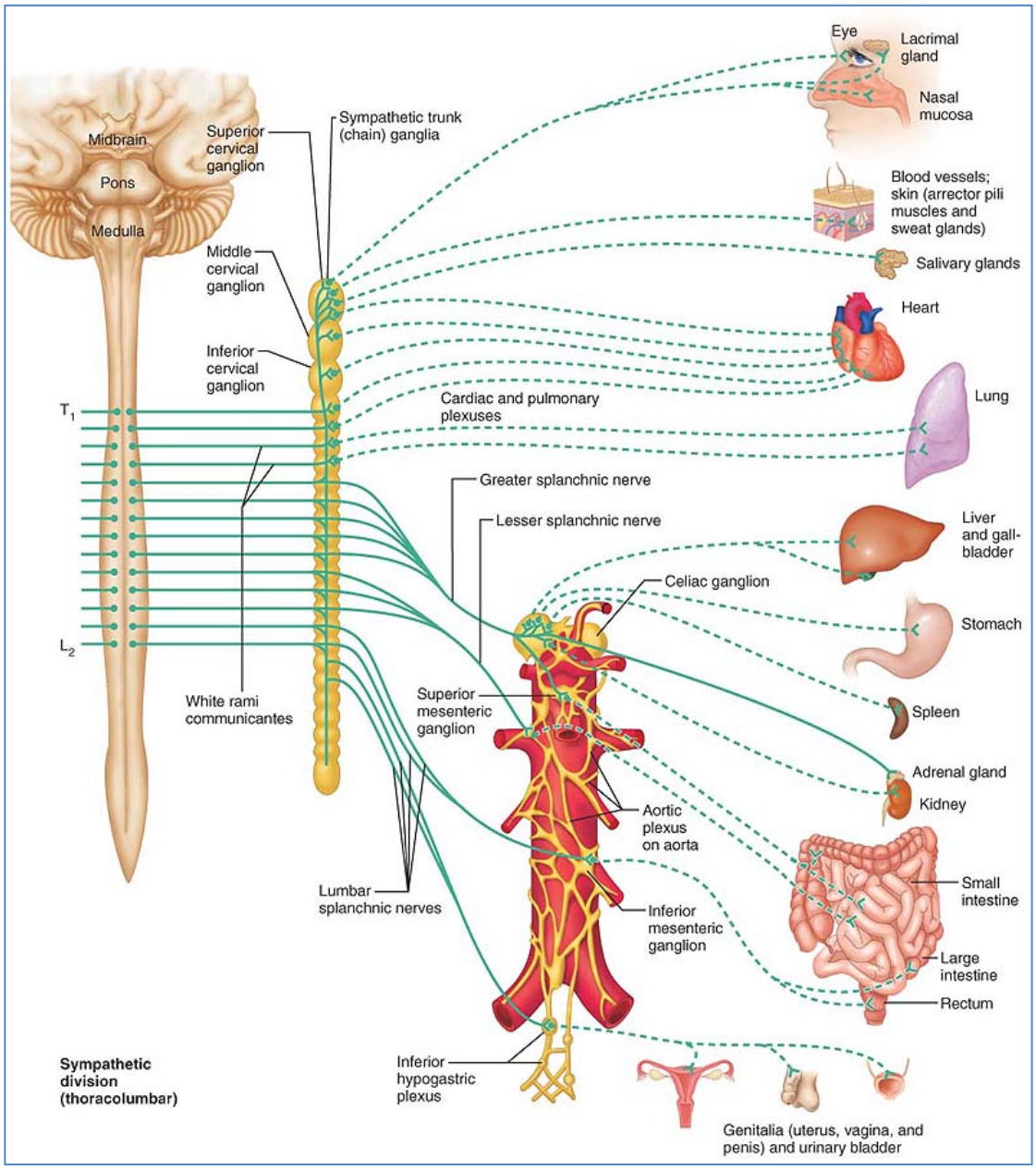
Anatomy: The Sympathetic (Thoraco-Lumbar) Division:

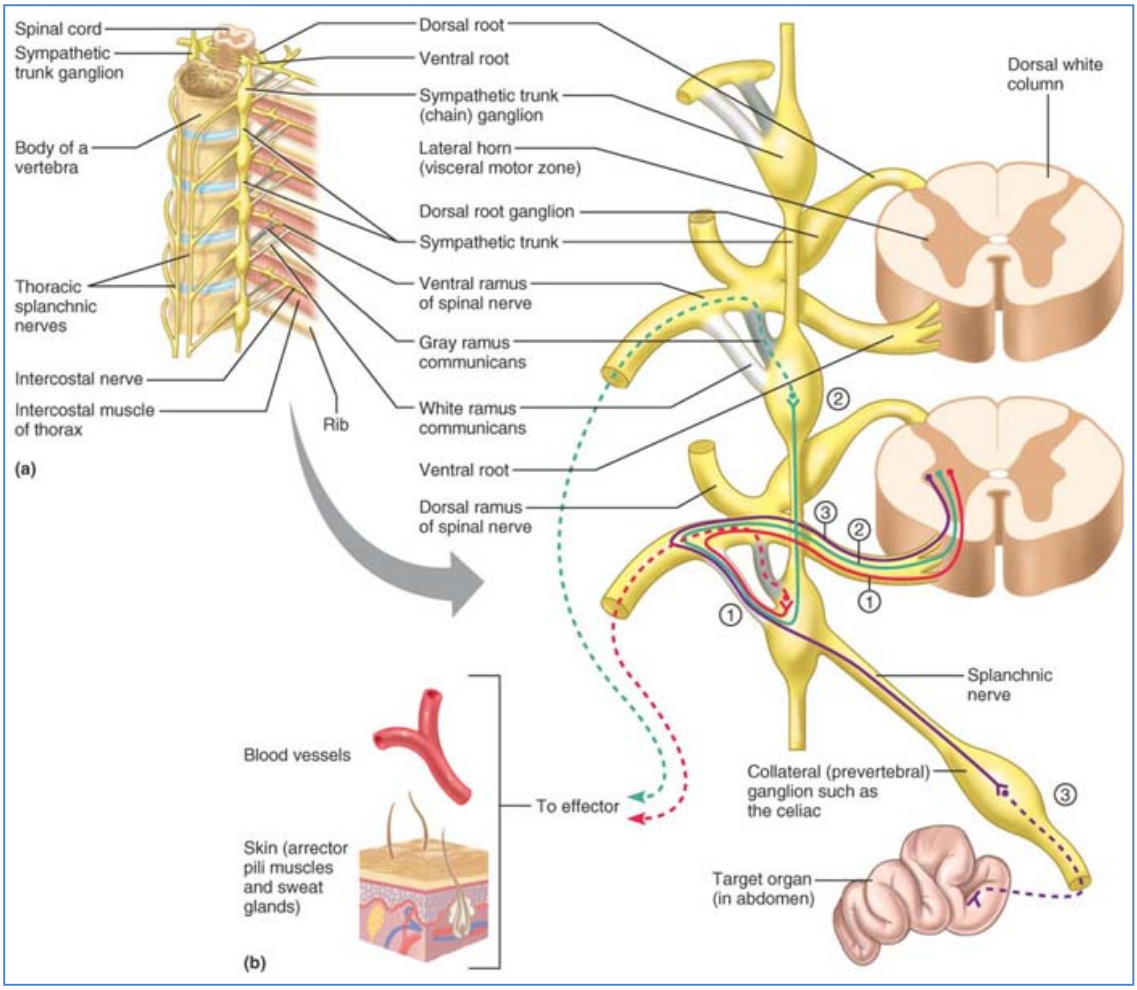
- NB: Sympathetic-NS innervates more organs than the Parasympathetic, and its effects are longer-lasting.
- **Fibres originate from:**
  - Cell bodies of Preganglionic Neurons in the ***Lateral Horns Spinal Cord Segments T1 → L2***.
- **Fibre Lengths:**
  - Preganglionic Fibres – Exit the Spinal Cord via the ***Ventral Root*** → Then pass through a ***White Ramus Communicans*** → Synapse adjoining ***Sympathetic Trunk (Chain) Ganglion***. (NB: These fibres are short)
  - Postganglionic Fibres – Exit the Sympathetic Ganglion at/below/above their spinal level via a ***Gray Ramus Communicans*** → Then enters the Ventral Spinal Nerve at that level → Effector Organs.

  NB: The Colour of the Rami Communicans reveals whether or not their fibres are myelinated.
  Preganglionic Fibres = Myelinated Postganglionic Fibres = Unmyelinated

- **Ganglia Location:**
  - Sympathetic Trunks (Chains of Ganglia) Flank each side of the Vertebral Column from the Neck to Pelvis.

  NB: Although the Sympathetic *Trunks* exist along the length of the spinal cord, the *Fibres* arise only from Thoracic & Lumbar cord segments.

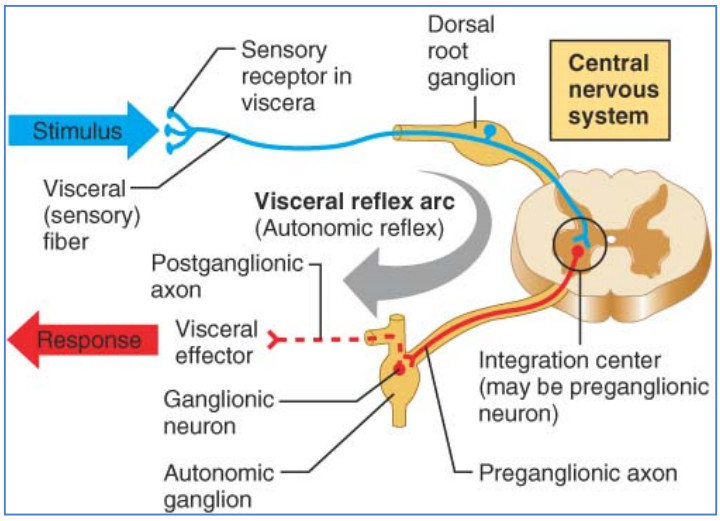


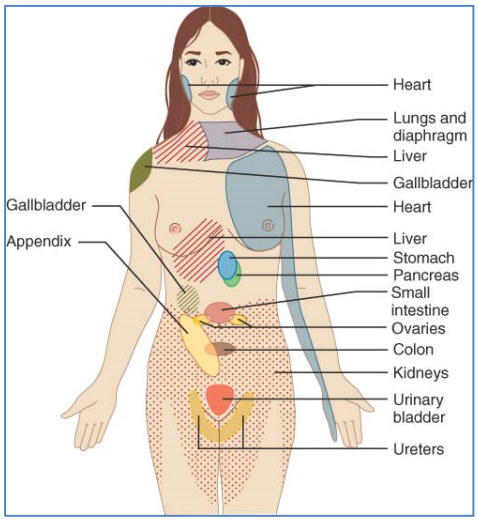


Visceral Reflexes:

- Similar to the Somatic-NS, the ANS also has reflex arcs;
- **Visceral Reflex Arcs Components:**
    - Visceral Sensory Neurons (Chemical Changes/Stretch/Irritation of Viscera)
      Neurons originate in Sensory Ganglia of Cranial Nerves or Dorsal Root Ganglia.
    - Integration Centre
    - Motor Neuron
    - Effector

- **This Explains the Phenomenon of '*Referred Pain*':**
    - Visceral pain afferents enter the spinal cord via the Dorsal Root Ganglion, the same pathway as somatic pain fibres. Hence pain stimuli arising in the Viscera can be confused as Somatic in origin.

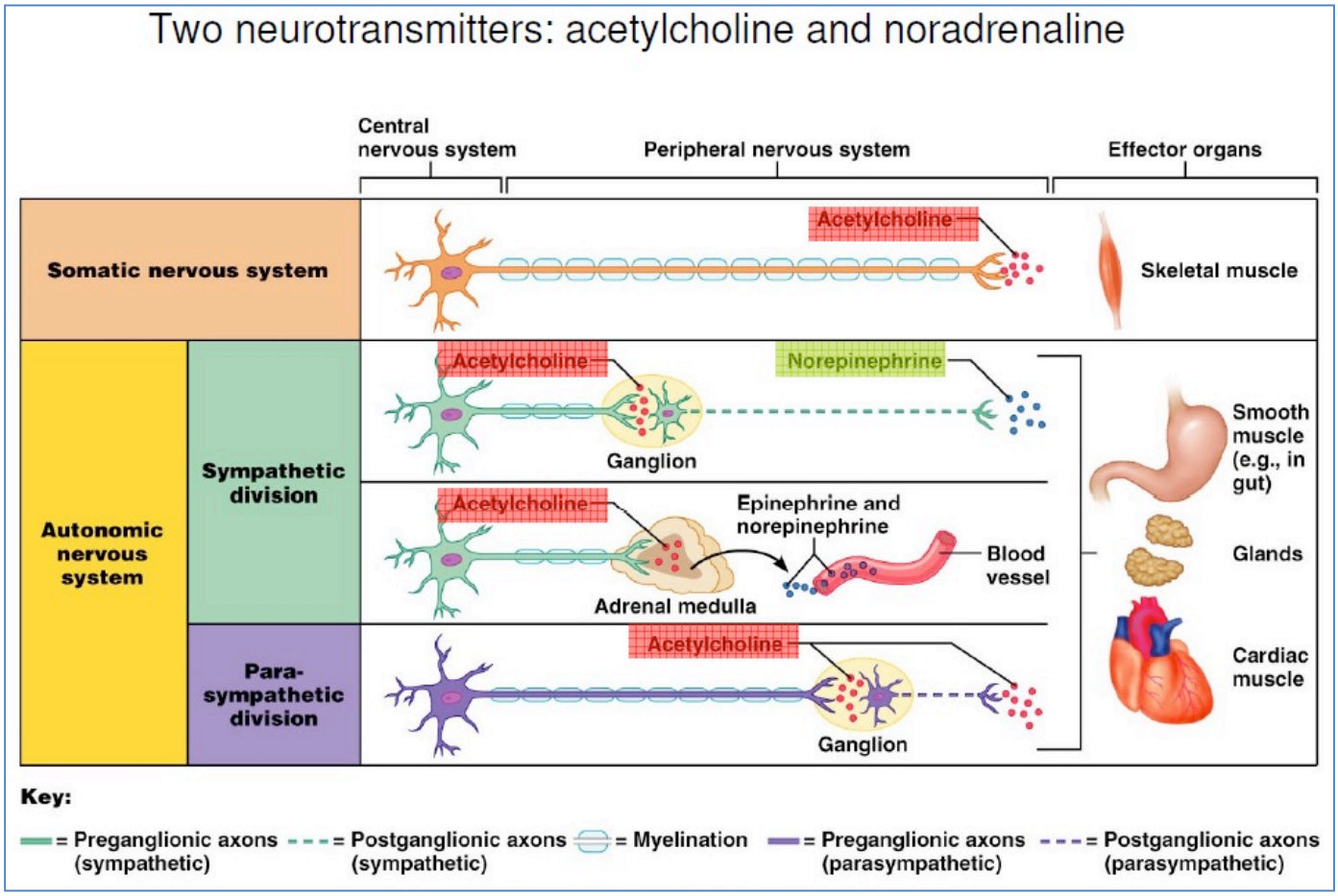




Physiology of the Autonomic NS:

Neurotransmitters of the PNS:

- **Afferent (Sensory):** *Glutamate*/Calcitonin-Gene-Related Peptide/Substance P
- **Efferent (Motor):**
  - **Somatic/Voluntary (Skeletal Muscle):** Acetylcholine (ACh)
  - **Autonomic:**
    - **Sympathetic:**
      - **Preganglionic:** Acetylcholine (ACh) →Stimulates Ganglia & Adrenal Medulla
      - **Postganglionic:** Norepinephrine
      - **→Adrenal Medulla:** Stim. by Acetylcholine (ACh) to release Epinephrine & NE into Blood.
    - **Parasympathetic:**
      - **Preganglionic:** Acetylcholine (ACh)
      - **Postganglionic:** Acetylcholine (ACh)



Somatic Division: *Axons extend from CNS to their Effectors (Skeletal Muscle). They are typically Thick & Heavily Myelinated and have a High Conduction Speed.*
Their Neurotransmitter is Acetylcholine, and its effect is always Stimulatory.

Autonomic Division: *Pre-Ganglionic Axons extend from CNS & synapse with either: (1) Peripheral Autonomic Ganglia, or (2) Cells of the Adrenal Medulla; and release Acetylcholine.*

(1) Post-Ganglionic Axons *extend from Ganglia to Effectors & Release Either:*
ACh *(Parasympathetic)*
or ***NE*** *(Sympathetic)*

(2) Adrenal Medullary Cells *Release* ***NE*** *&* ***Epinephrine*** *into the Blood.*

(NB: Pre-Ganglionic Fibres are Thin & Lightly Myelinated & Post-Ganglionic Fibres are Thinner & Unmyelinated. Hence Conduction Speed within the Autonomic Neurons is Slow – Much slower than Somatic NS)

Receptors of the ANS:

- **Parasympathetic - Cholinergic (ACh) Receptors:**
  - **Nicotinic:**
    - **Found on:**
      - (Motor End-Plates of Skeletal Muscle - Somatic)
      - Receptive Regions of All **Ganglionic Neurons** (Both Sympathetic & Parasympathetic)
      - Hormone-Producing Cells of the **Adrenal Medulla**
    - **Action:**
      - Binding of ACh → Directly Opens Ion Channels (:.Ionotropic) → Depolarises the Postsynaptic Cell → ***Stimulatory***.
  - **Muscarinic:**
    - **Found on:**
      - All ***Effector Cells*** stimulated by Postganglionic Cholinergic Fibres (Ie. ***All Parasympathetic target*** organs & ***some Sympathetic Targets*** [eccrine sweat glands & some skeletal-muscle blood vessels])
    - **Action:**
      - Binding of ACh → Activates the receptor's G-Protein, which detaches from the receptor → Causes an intra-cellular signalling cascade (:.Metabotropic).
        → May be ***Stimulatory OR Inhibitory*** Depending on the Subclass of Muscarinic Receptor on the target organ.
    - **Tissue-Specific Receptor Subtypes:**
      - **M_1 –** Brain
      - **M_2 –** Heart
      - **M_3 –** Smooth Muscle & Glands
- **Sympathetic - Adrenergic Receptors:**
  - – Receptors that respond to Norepinephrine/Epinephrine.
  - – May be ***Excitatory OR Inhibitory*** depending on which Subclass of receptor *Predominates* in that organ. (Organs responsive to NE/Epi often have more than one receptor subclass)
  - **Alpha:**
    - **$\alpha_{1/2}$**
  - **Beta:**
    - **$\beta_{1/2/3}$**

TABLE 14.3 Cholinergic and Adrenergic Receptors

NEUROTRANSMITTER	RECEPTOR TYPE	MAJOR LOCATIONS*	EFFECT OF BINDING
Acetylcholine	**Cholinergic**		
	Nicotinic	All ganglionic neurons; adrenal medullary cells (also neuromuscular junctions of skeletal muscle)	Excitation
	Muscarinic	All parasympathetic target organs	Excitation in most cases; inhibition of cardiac muscle
		Limited sympathetic targets:	
		■ Eccrine sweat glands	Activation
		■ Blood vessels in skeletal muscles	Vasodilation (may not occur in humans)
Norepinephrine (and epinephrine released by adrenal medulla)	**Adrenergic**		
	β_1	Heart predominantly, but also kidneys and adipose tissue	Increases heart rate and strength; stimulates renin release by kidneys
	β_2	Lungs and most other sympathetic target organs; abundant on blood vessels serving the heart, liver and skeletal muscle	Effects mostly inhibitory; dilates blood vessels and bronchioles; relaxes smooth muscle walls of digestive and urinary visceral organs; relaxes uterus
	β_3	Adipose tissue	Stimulates lipolysis by fat cells
	α_1	Most importantly blood vessels serving the skin, mucosae, abdominal viscera, kidneys, and salivary glands; also, virtually all sympathetic target organs except heart	Constricts blood vessels and visceral organ sphincters; dilates pupils of the eyes
	α_2	Membrane of adrenergic axon terminals; pancreas; blood platelets	Inhibits NE release from adrenergic terminals; inhibits insulin secretion by pancreas; promotes blood clotting

Clinical Manipulation of the Peripheral NS:

- PNS is easy to manipulate
- **Aim:** To *Use* the Nervous System to regulate Organ Function.
- **Drugs:** Mimic/Enhance/Block messages sent along the nerves.
- **Problem: *Side Effects* –** Because the PNS only uses 2 Neurotransmitters, Side effects can be widespread.
    - **Eg. Some Elicit Drugs** have ***Sympathomimetic*** side effects:
        - **Cocaine & Amphetamines** → ↑↑Cardiovascular Stimulation (Tachycardia & Hypertension)
- **Can Reduce Side Effects by:**
    - Topical Application
    - Targeting specific receptor subtypes with more specific drugs.
    - Targeting *Tissue-Specific Differences in Receptor Subtypes*.
- **Examples of PNS Manipulation:**
    - **Somatic NS:**
        - Acetylcholinesterase Inhibitors (→↓Deactivation of ACh in Synapse → ↑ACh Action)
        - Neuromuscular Blockers (Eg. Nicotinic Antagonists)
    - **Autonomic NS:**
        - **Sympathetic:**
            - Agents that affect Release/Reuptake of Catecholamines (NE, Epi & Dopamine)
            - Adrenergic Agonists
            - Adrenergic Antagonists
        - **Parasympathetic:**
            - Acetylcholinesterase Inhibitors (→↓Deactivation of ACh in Synapse→ ↑ACh Action)
            - Muscarinic Agonists
            - Muscarinic Antagonists
- **Ganglionic Blockers:**
    - Drugs which block chemical transmission at autonomic ganglia – Essentially Denervates the entire Autonomic Nervous System. (Main effect – Vasodilation [Loss of vasomotor tone]
    - Effects vary from tissue to tissue, depending on whether Sympathetic/Parasympathetic nerves are usually dominant in that tissue:
        - If Sympathetic usually dominates, Ganglionic Blockers mimic Parasympathetic Stimulation.
        - If Parasympathetic usually dominates, Ganglionic Blockers mimic Sympathetic Stimulation.

TABLE 14.4 Selected Drug Classes That Influence the Activity of the Autonomic Nervous System

DRUG CLASS	RECEPTOR BOUND	EFFECTS	EXAMPLE	CLINICAL USE
Nicotinic agents (little therapeutic value, but important because of presence of nicotine in tobacco)	Nicotinic ACh receptors on all ganglionic neurons and in CNS	Typically stimulation of sympathetic effects; heart rhythm becomes less regular; blood pressure increases	Nicotine	Used in smoking cessation products
Parasympathomimetic agents (muscarinic agents)	Muscarinic ACh receptors	Mimics effects of ACh, enhances PNS effects	Pilocarpine	Glaucoma (opens aqueous humor drainage pores)
			Bethanechol	Difficulty urinating (increases bladder contraction)
Acetylcholinesterase inhibitors	None; binds to the enzyme (AChE) that degrades ACh	Indirect effect at all ACh receptors; prolongs the effect of ACh	Neostigmine	Myasthenia gravis, (increases availability of ACh)
			Sarin	Used as chemical warfare agent (similar to widely used insecticides)
Sympathomimetic agents	Adrenergic receptors	Enhances sympathetic activity by increasing NE release or binding to adrenergic receptors	Albuterol (Ventolin)	Asthma (dilates bronchioles by binding to β_2 receptors)
			Phenylephrine	Colds (nasal decongestant, binds to α_1 receptors)
Sympatholytic agents	Adrenergic receptors	Decreases sympathetic activity by blocking adrenergic receptors or inhibiting NE release	Propranolol	Hypertension (member of a class of drugs called *β blockers* that decrease heart rate and blood pressure)

Table 6.1 The main effects of the autonomic nervous system

Organ	Sympathetic	Adrenergic receptor type	Parasympathetic	Cholinergic receptor type
Heart				
SA node	Rate ↑	β_1	Rate ↓	M_2
Atrial muscle	Force ↑	β_1	Force ↓	M_2
AV node	Automaticity ↑	β_1	Cond. vel. ↓	M_2
			AV block	M_2
Ventricular muscle	Automaticity ↑ Force ↑	β_1	No effect	
Blood vessels				
Arterioles				
Coronary	Constriction	α		
Muscle	Dilatation	β_2	No effect	
Viscera, Skin, Brain	Constriction	α	No effect	
Erectile tissue, Salivary gland	Constriction	α α	Dilatation	? M_3
Veins	Constriction Dilatation	α β_2	No effect	
Viscera				
Bronchi				
Smooth muscle	No sympathetic innervation, but dilated by circulating adrenaline	β_2	Constriction	M_3
Glands	No effect		Secretion	M_3
GI tract				
Smooth muscle	Motility ↓	α_1, α_2, β_2	Motility ↑	M_3
Sphincters	Constriction	α_2, β_2	Dilatation	M_3
Glands	No effect		Secretion	M_3
			Gastric acid secretion	M_1
Uterus				
Pregnant	Contraction	α	Variable	
Non-pregnant	Relaxation	β_2		
Male sex organs	Ejaculation	α	Erection	? M_3
Eye				
Pupil	Dilatation	α	Constriction	M_3
Ciliary muscle	Relaxation (slight)	β	Contraction	M_3
Skin				
Sweat glands	Secretion (mainly cholinergic)	α	No effect	
Pilomotor	Piloerection	α	No effect	
Salivary glands	Secretion	α, β	Secretion	M_3
Lacrimal glands	No effect		Secretion	M_3
Kidney	Renin secretion	β_2	No effect	
Liver	Glycogenolysis Gluconeogenesis	α, β_2	No effect	

www.regentstudies.com

Sympathetic & Parasympathetic Tone:

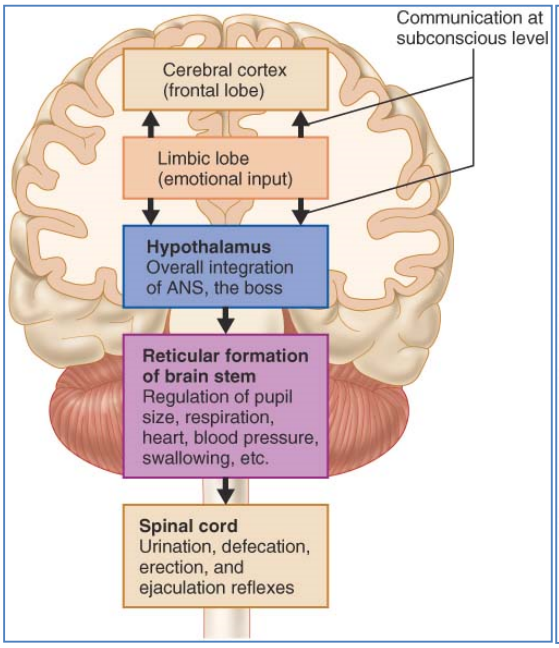
- **Sympathetic (Vasomotor) Tone:**
  - The continual state of Partial Constriction of the Vascular System that Maintains BP (even @ rest)
  - During Activity, a Higher BP is needed → the ***Vasomotor Fibres*** fire more rapidly → Vasoconstriction.
  - **NB:** Alpha-Blockers dull the effects of the Sympathetic/Vasomotor Tone → Control Hypertension.
- **Parasympathetic Tone:**
  - Slows the heart, sets the *Normal* activity levels of the Digestive & Urinary Systems, & Stimulates Glandular Secretion (Except Adrenal Glands & Skin Glands)
  - NB: The Sympathetic division an override this during times of stress.
  - **NB:** Drugs that block Parasympathetic Responses → ↑HR, Faecal/Urinary Retention & ↓Glandular Secretion.

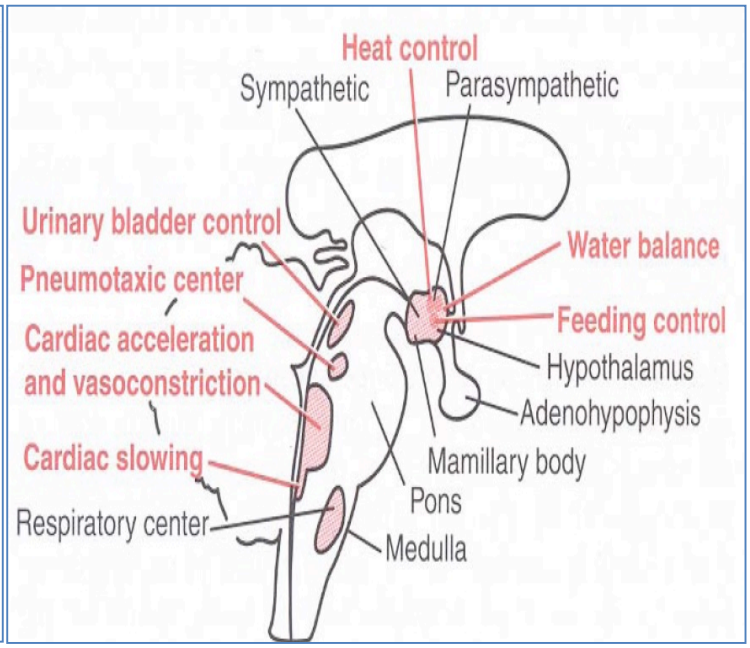
Unique Roles of the Sympathetic NS:

- **NB:** The Sympathetic Division is more Wide-Spread than the Parasympathetic Division – Because it innervates more organs.
  - **Eg.** Adrenal Medulla, Sweat Glands, Hair-Follicle Muscles of the Skin, the Kidneys & Most Blood Vessels *Only Receive Sympathetic Fibres.*
- **There are other Uniquely Sympathetic Functions:**
  - **Thermoregulatory Response to Heat:**
    - Cutaneous vasodilation.
    - Activation of sweat glands.
  - **Thermoregulatory Response to Cold:**
    - Cutaneous vasoconstriction.
  - **Release of Renin from the Kidneys:**
    - Sympathetic impulses Stimulate Renin Release → Promotes ↑BP
  - **Metabolic Effects:**
    - Sympathetic Stimulation → Release of Adrenal Medullary Hormones →
      - ↑metabolic Rate of body cells
      - ↑Blood Glucose Levels
      - Mobilises fats for use as fuels.
      - Puts skeletal muscle on 'red alert' – Contract more strongly & quickly.

Central Control of the Autonomic NS:

- **ANS Activity is regulated by a hierarchy of CNS controls:**
  - Hypothalamus
  - Brain Stem
  - Spinal Cord
- **NB:** Subconscious Cerebral inputs via Limbic Lobe influences Hypothalamic Functioning.





Disorders of the Peripheral Nervous System:

- **Categories:**
  - Inflammation (Eg. Guillain Barre Syndrome – Immune mediated demyelinating neuropathy)
    (Eg. Myasthenia Gravis – Antibody attack on Nicotinic ACh Receptor in NMJ)
  - Trauma (Eg. Spinal Injuries)
  - Metabolic (Eg. Diabetic Neuropathies – Macro/Micro-vascular)
    (Eg. Vitamin Deficiencies – B_{12}, B_6 & E)
  - Toxicity (Eg. Urea/Alcohol/etc.)
  - Genetics
  - Infection (Eg. Shingles / Diphtheria / Leprosy)

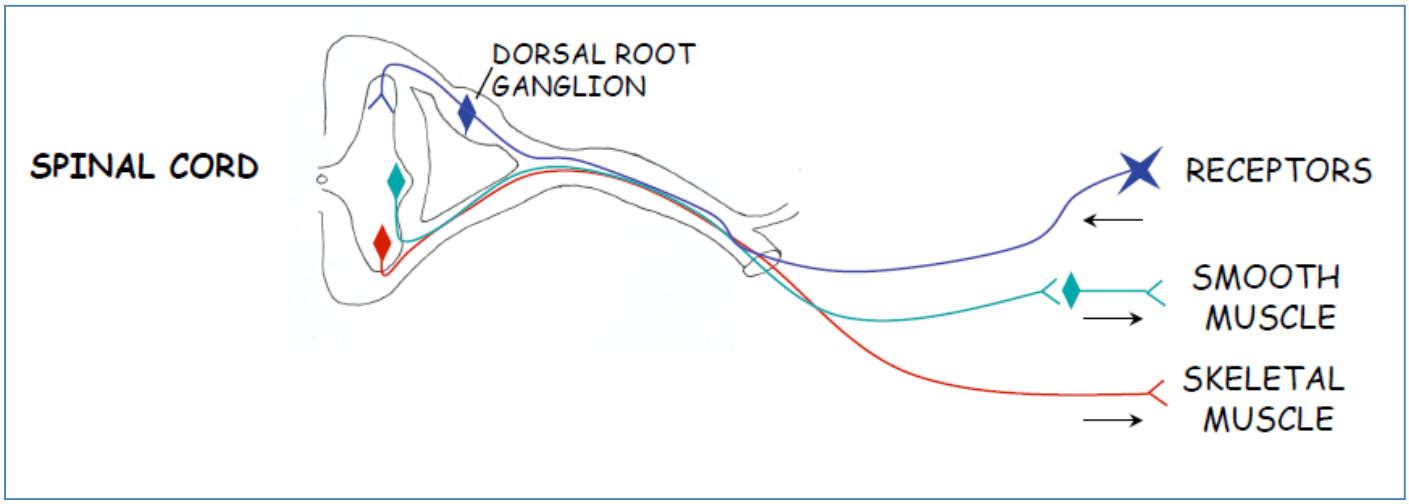
Examples of Homeostatic Imbalances of The ANS:

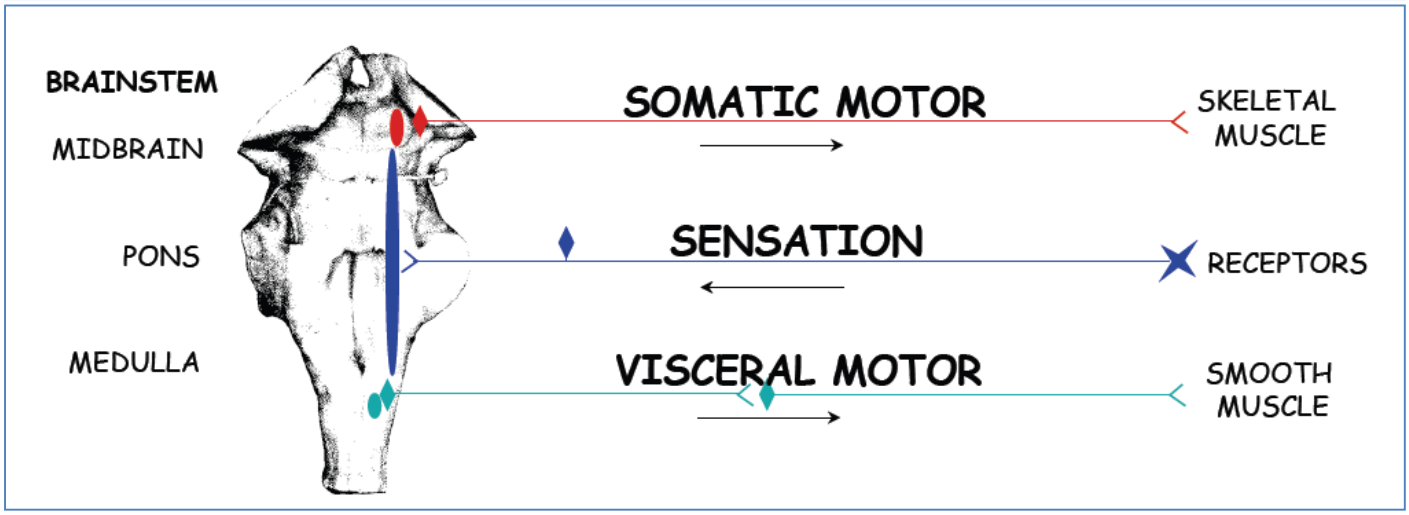
- **Hypertension –** Results from overactive sympathetic vasoconstriction promoted by chronic stress.
  Can be treated with β-Blockers / other Adrenergic Antagonist.
- **Raynaud's Disease –** Characterised by intermittent attacks of peripheral cyanosis, provoked by exposure to cold or emotional stress. It is an exaggerated vasoconstriction response.
- **Autonomic Dysreflexia** – Uncontrolled activation of Autonomic Neurons (Mechanism Unclear) in patients with quadriplegia → ↑Arterial BP, Headache, Flushed Face, Sweating.
  - Is Life Threatening.

Neuroscience Notes
The Cranial Nerves & Their Pathways

Similarities Between Spinal Nerves & Cranial Nerves:

- **Cranial Nerves develop similar to Spinal Nerves, & hence have a similar structural Organisation:**
  - **Sensory:**
    - Similar to Afferent Spinal Nerves – Sensory Cranial Nerves' Dendrites are associated with peripheral sensory receptors & their Cell Bodies are located in a *Sensory Ganglia* (Similar to the Dorsal Root Ganglion in the spinal cord). Their axons then terminate in the Sensory Nuclei of the Brainstem (Similar to Dorsal Horn of Spinal Cord), and synapse with one of the Ascending Pathways (Depending on the type of stimulus):
      - Touch → Posterior Pathway
      - Pain → Spinothalamic
      - Proprioception → Spinocerebellar
  - **Somatic Motor:**
    - Similar to Efferent Spinal Nerves – Motor Cranial Nerves (Both Somatic & Branchial) have their Cell Bodies in grey-matter Motor Nuclei in the Brainstem (Similar to Ventral Horn of Spinal Cord). Their axons leave the brainstem & *directly* innervate the Skeletal Muscles.
  - **Visceral Motor:**
    - Similar to Autonomic Spinal Nerves – Visceral-Motor Cranial Nerves have their cell bodies in the Grey-Matter Visceral Nuclei in the Brainstem (Similar to Lateral Horn of Spinal Cord). Their axons then synapse with a 2nd-Order Neuron in an Autonomic Ganglion, where the 2nd neuron innervates the smooth muscle.



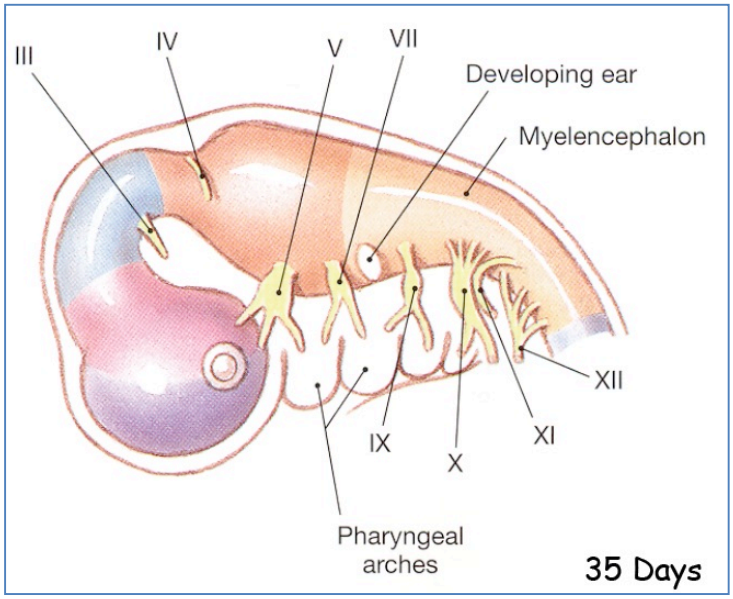


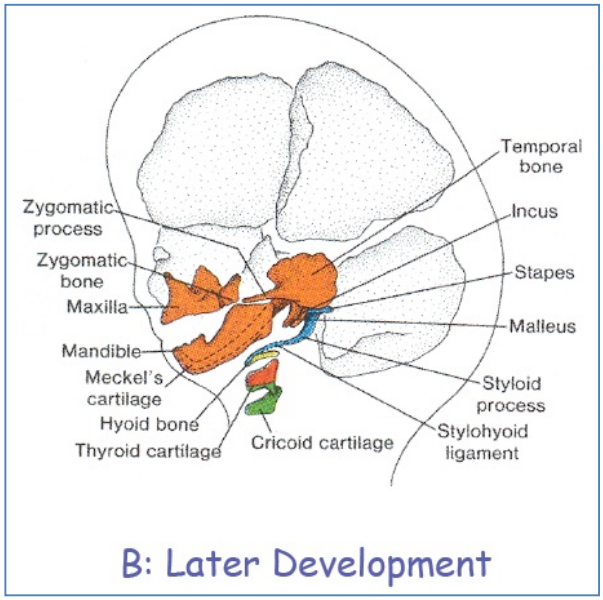
  - Eg. Just as spinal nerves grow in association with their *Somites*, some Cranial Nerves grow in association with **The 6 *Pharyngeal Arches*: (See Next Page)**

The Pharyngeal (Branchial) Arches:

- NB: There are 6 pharyngeal arches, but the 5th only exists transiently during embryonic growth
- (No structures result from the 5th arch)
- Appear ≈4-5 weeks of development

Pharyngeal Arch	Nerve	Muscular Contributions
1st – "Mandibular"	Trigeminal (V)	Muscles of Mastication: - Ant. Digastric - Mylohyoid - Tensor Tympani - Tensor Veli Palatini
2nd – "Hyoid Arch"	Facial (VII)	- Muscles of Facial Expression - Post. Digastric - Stylohyoid - Buccinator
3rd	Glossopharyngeal (IX)	- Stylopharyngeus
4th	Vagus (X)	- Cricothyroid Muscle - Soft Palate Muscles
6th	Vagus (X)	- Intrinsic Laryngeal Muscles





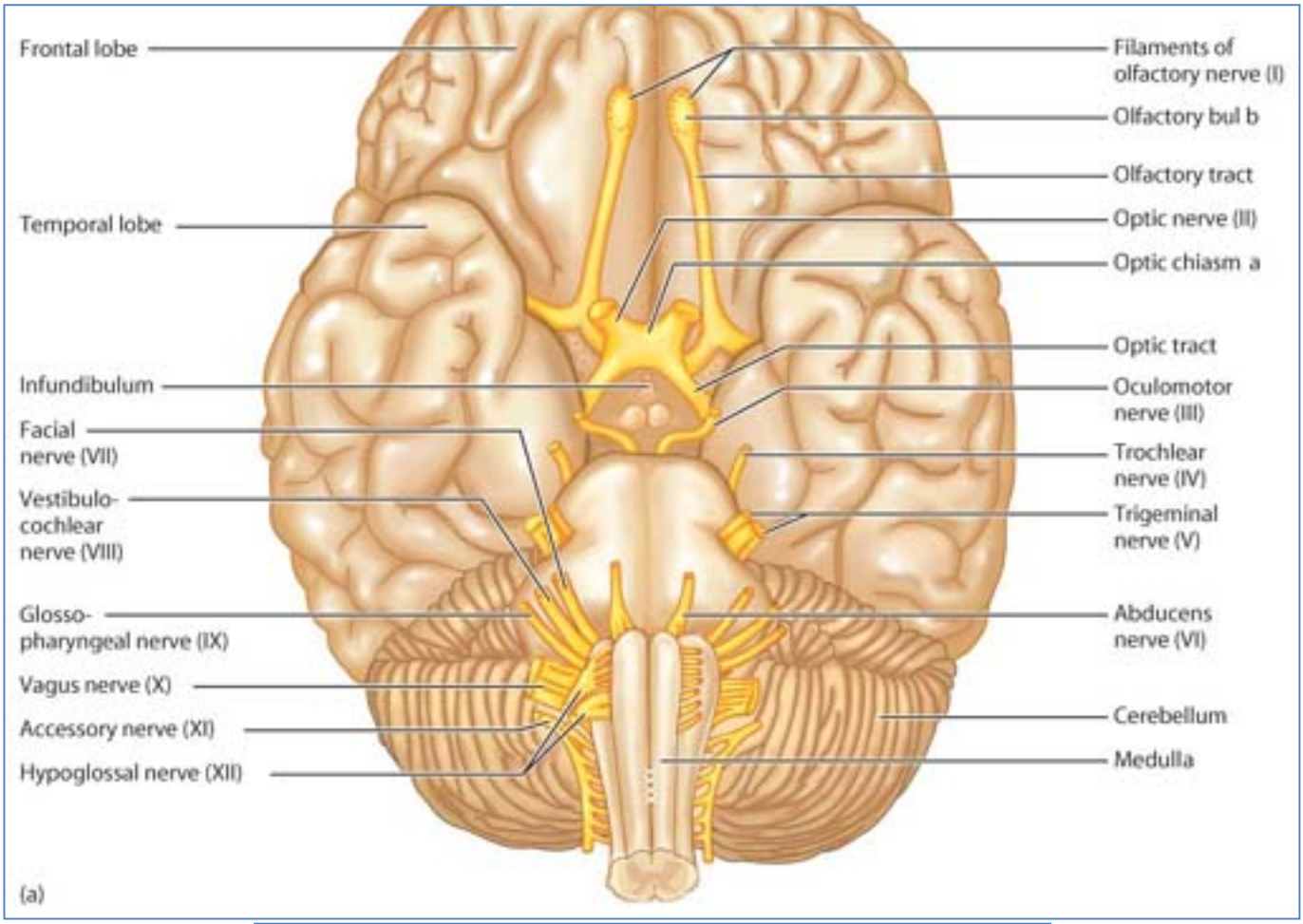
The 12 Cranial Nerves & Respective Branches:

Nerve	Branches	Functional Components
I Olfactory nerve		Special Sensory
II Optic nerve		Special Sensory
III Oculomotor nerve		Somatic Motor
		Visceral Motor (parasympathetic)
IV Trochlear nerve		Somatic Motor
V Trigeminal nerve	- V1 Ophthalmic Division	General Sensory
	- V2 Maxillary Division	
	- V3 Mandibular Division	
		Branchial Motor
VI Abducent nerve		Somatic Motor
VII Facial nerve		Branchial Motor
		Special Sensory
		Visceral Motor (Parasympathetic)
VIII Vestibulocochlear	- Vestibular Division	Special Sensory
	- Cochlear Division	Special Sensory
IX Glossopharyngeal		Branchial Motor
		Visceral Motor
		Visceral Sensory
		Special Sensory
		General Sensory
X Vagus		Branchial Motor
		Visceral Motor
		Visceral Sensory
		Special Sensory
		General Sensory
XI Spinal Accessory		Somatic Motor
XII Hypoglossal		Somatic Motor

- **NB:** Cranial Nerves are Numbered Systematically according to their attachment to the brain. (Rostral-Caudal)
- **NB:** Cranial Nerves are Named based on their *Distribution* or *Function*.
- **NB:** Other than the Vagus (Which extends to the abdomen), Cranial Nerves serve ***Only*** **the Head & Neck.**

Mnemonics:

- Oh Oh Oh, Try Try Again, Four Very Good Virgins Are Hot.
- Oh Oh Oh, To Touch And Feel Virgin Girl's Vaginas And Hymens



(a)

Cranial nerves I – VI	Sensory function	Motor function	PS* fibers
I Olfactory	Yes (smell)	No	No
II Optic	Yes (vision)	No	No
III Oculomotor	No	Yes	Yes
IV Trochlear	No	Yes	No
V Trigeminal	Yes (general sensation)	Yes	No
VI Abducens	No	Yes	No
VII Facial	Yes (taste)	Yes	Yes
VIII Vestibulocochlear	Yes (hearing and balance)	Some	No
IX Glossopharyngeal	Yes (taste)	Yes	Yes
X Vagus	Yes (taste)	Yes	Yes
XI Accessory	No	Yes	No
XII Hypoglossal	No	Yes	No

(b) *PS = parasympatheti c

www.regentstudies.com

Cranial Nerve Nuclei:

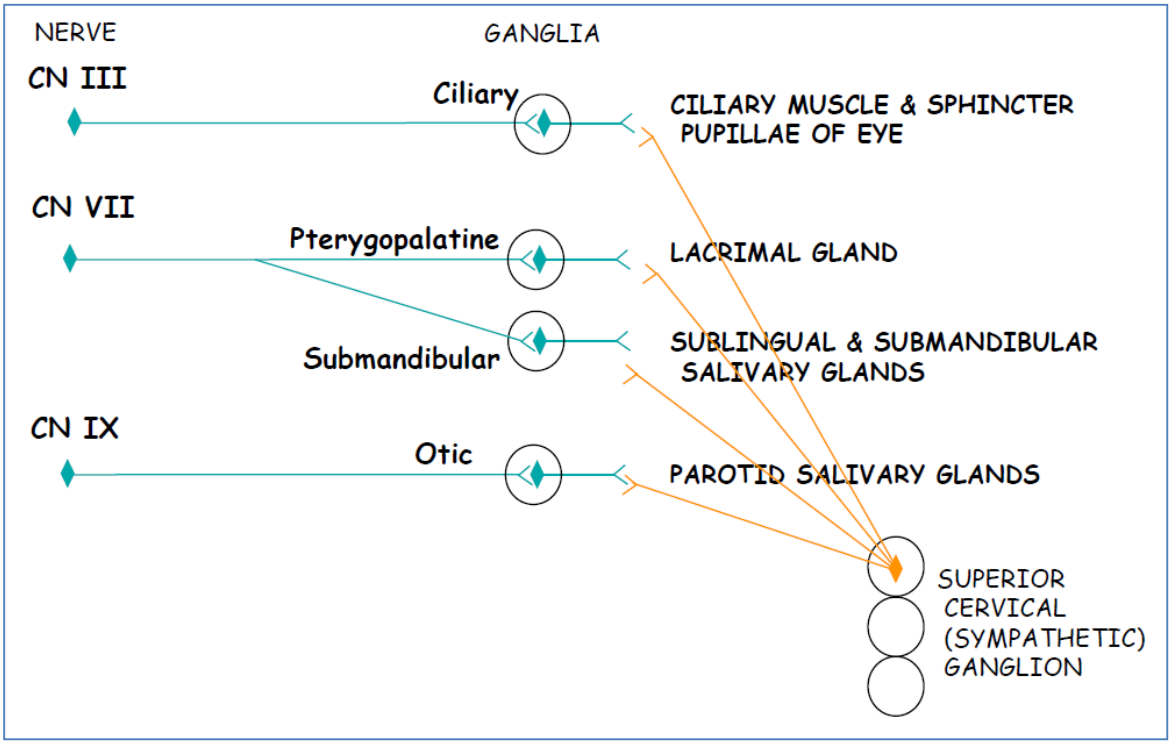
- **Location:**
  - **CN I (Olfactory) & II (Optic)** = Are both extensions of the Forebrain.
  - **CN III – XII (All others)** = They originate from Nuclei located in the Brainstem.
- **Organisation:**
  - Nuclei of similar Functional Components (Ie. General Somatic/Visceral Motor or General Somatic/Visceral Sensory) are generally aligned into functional columns in the brainstem.

***Sensory Ganglia* of Cranial Nerves:**

Cranial Nerve:	Receptor Types:	Sensory Ganglia:
Olfactory	Olfactory (Smell)	Olfactory Epithelium
Optic	Retinal (Vision)	Retina of the Eye
Trigeminal	Somatosensory	Trigeminal Ganglion
Facial	Somatosensory	Geniculate Ganglion
Vestibulocochlear	Equilibrium & Hearing	Vestibular Ganglion & Spiral Ganglion
Glossopharyngeal	Somatosensory, Visceral & Taste	Inferior Ganglion
Vagus	Somatosensory, Visceral & Taste	Superior & Inferior Ganglion

***Parasympathetic Ganglia* of Cranial Nerves:**

Cranial Nerve	Ganglion	Location	Main Distribution
Oculomotor	**Ciliary**	Between the Optic Nerve & the Lateral Rectus Muscle of Eye	Ciliary Muscle & Pupillary Sphincter of Eyes
Facial	**Pterygopalatine**	In Pterygopalatine Fossa; Just anterior to the opening of the Pterygopalatine Canal.	Lacrimal (Tear) Gland
	Submandibular	Just inferior to Submandibular Salivary Duct	Sublingual & Submandibular Salivary Glands
Glossopharyngeal	**Otic**	Between Tensor Veli Palatini & Mandibular Nerve (Just anterior to Foramen Ovale of Sphenoid Bone)	Parotid Salivary Gland.



NB: Sympathetic Input is important for the Dual Innervation setup of the Autonomic NS. The Sympathetic Fibres ascending from the Superior Cervical Sympathetic Ganglion hitch a ride with the Parasympathetic Cranial Nerves and follow them to their targets.

Functional Components of Cranial Nerves:

- **Cranial Nerves carry one/more of the following 5 Functional Components:**
  - **Efferent:**
    1. **Voluntary (Somatic) Motor:**
       - **a. Somatic Motor: *"General Somatic Efferents" (GSE)***
         - **i.** Innervate striated skeletal muscle derived from embryonic somites, not pharyngeal arches. (Incl. Ocular Muscles, Tongue, External Neck Muscles – Sternocleidomastoid & Trapezius)
       - **b. Branchial Motor: *"Special Visceral Efferents" (SVE)***
         - **i.** Innervate striated skeletal muscle derived from embryonic pharyngeal arches. (Incl. Muscles of the Face, Palate, Pharynx, Larynx & Mastication)

       (Oculomotor, Trochlear, Trigeminal, Abducens, Facial, Glossopharyngeal, Vagus, Accessory & Hypoglossal)

    2. **Involuntary (Visceral) Motor: *"General Visceral Efferents" (GVE)***
       - i. Innervate Smooth Muscle in vessels/glands/etc. Via a 2-neuron approach; (Presynaptic fibres emerge from the brain as cranial nerves, which then synapse in a parasympathetic ganglion. The postsynaptic neurons then innervate the smooth muscles & glands etc.)
       - ii. Constitute the ***Cranial Outflow*** of the ***Parasympathetic Nervous System***.

       (Oculomotor, Facial, Glossopharyngeal, Vagus)
  - **Afferent:**
    3. **Somatic Sensation: *"General Somatic Afferents" (GSA)***
       - i. (Touch, Pressure, Heat, Cold, etc)

       (Trigeminal, Facial, Glossopharyngeal & Vagus)

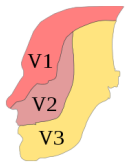
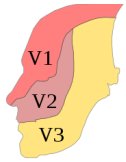
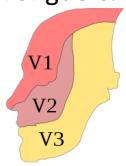
    4. **Visceral Sensation: *"General Visceral Afferents" (GVA)***
       - i. (Blood Pressure & Blood-O_2/CO_2 from Carotid Sinus & Body, plus Visceral Sensation from Pharynx, Larynx Trachea, Bronchi, Lungs, Heart & GI Tract.)

       (Oculomotor, Trigeminal, Facial, Glossopharyngeal, Vagus)

    5. **Special Sensation: *"Special Somatic/Visceral Afferents" (SSA/SVA)***
       - i. (Vision, Taste, Smell, Hearing & Balance)

       (Olfactory, Optic, Facial, Vestibulocochlear, Vagus)

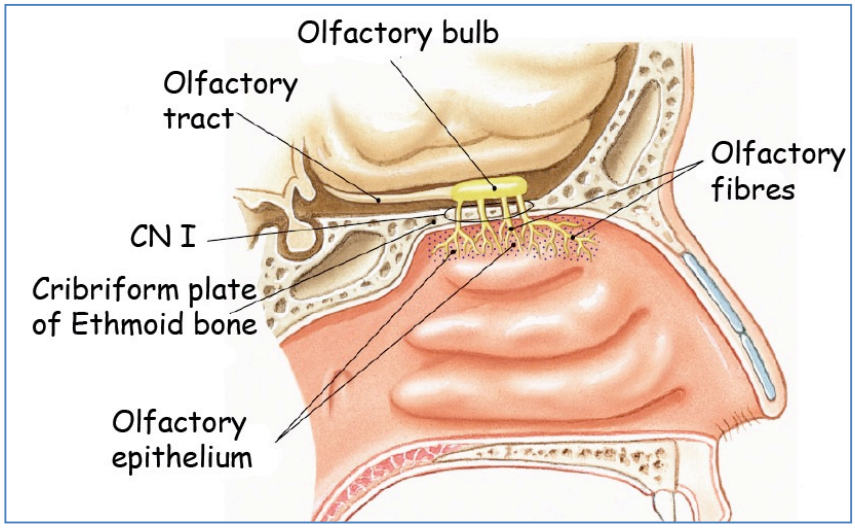
- **NB: YOU NEED TO KNOW WHICH NERVES CARRY EACH TYPE OF INFORMATION – See Table Overleaf:**

Nerve	Functional Components	Location of Nerve Cell Bodies	Cranial Exit Point	Functions (major)
I Olfactory nerve	Special Sensory	Olfactory Epithelium	Cribriform Plate of The Ethmoid Bone	Smell
II Optic nerve	Special Sensory	Retinal Ganglion	Optic Canal	Vision and associated reflexes
III Oculomotor nerve	Somatic Motor	Midbrain	Superior Orbital Fissure	Movements of eyes (Superiorly, Inferiorly & Medially)
	Visceral Motor (parasympathetic)	**Presynaptic:** Midbrain **Postsynaptic:** *Ciliary* Ganglion		Pupillary constriction and lens accommodation (parasympathetic)
IV Trochlear nerve	Somatic Motor	Midbrain	Superior Orbital Fissure	Movements of eyes (Inferolaterally)
V Trigeminal nerve				
- V1 Opthalmic Division	General Sensory	Trigeminal Ganglion	Superior Orbital Fissure	Sensation from Cornea, & V_1 Dermatome 
- V2 Maxillary Division			Foramen Rotundum	Sensation from Maxillary Teeth, Nasal Mucosa, Maxillary Sinuses, Palate, & V_2 Dermatome 
- V3 Mandibular Division			Foramen Ovale	Sensation from Mandibular Teeth, Mucosa of Mouth, Tongue & V_3 Dermatome 
	Branchial Motor	Pons		Muscles of Mastication & Swallowing
VI Abducent nerve	Somatic Motor	Pons	Superior Orbital Fissure	Lateral Rectus Muscle - Abduction (Lateral Rotation) of the Eye
VII Facial nerve	Branchial Motor	Pons	Internal Acoustic Meatus; Facial Canal; Stylomastoid Foramen	Facial Muscles + Some Muscles of Mastication
	Special Sensory	Geniculate Ganglion		Taste (Anterior 2/3 of Tongue)
	Visceral Motor (Parasympathetic)	**Presynaptic:** Pons **Postsynaptic:** Pterygopalatine Ganglion; Submandibular Ganglion		Stimulation of Submandibular & Sublingual Salivary Glands, & Lacrimal Glands.

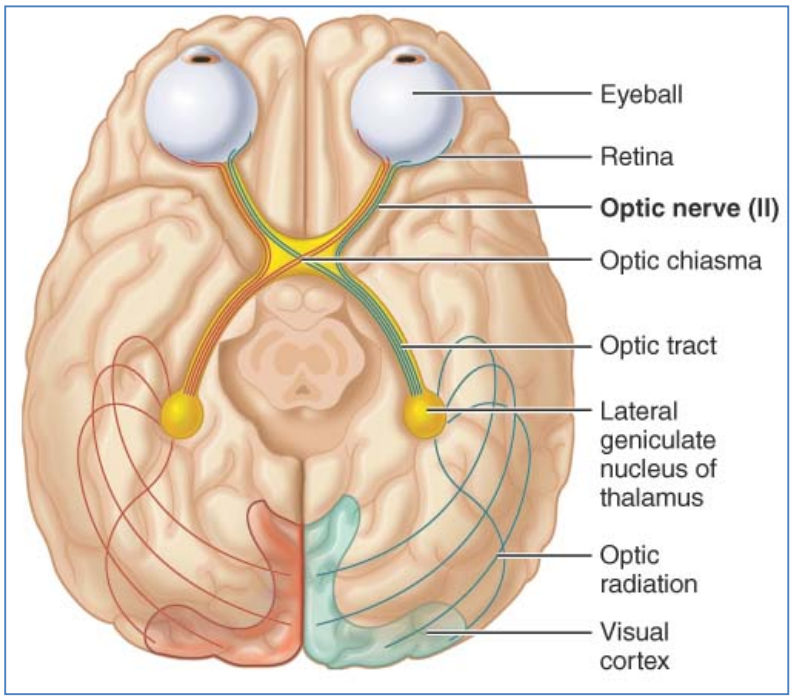
VIII Vestibulocochlear				
- Vestibular Division	Special Sensory	Vestibular Ganglion	Internal Acoustic Meatus	Position of the Head & Balance (The body's Gyro)
- Cochlear Division	Special Sensory	Spiral Ganglion		Hearing (Via Spiral Organ)
IX Glossopharyngeal	Branchial Motor	Medulla	Jugular Foramen	Stylopharyngeus Muscle (Assists with swallowing)
	Visceral Motor	**Presynaptic:** Medulla **Postsynaptic:** *Otic* Ganglion		Stimulates Parotid Salivary Gland
	Visceral Sensory	Superior Ganglion		Visceral Sensation from Parotid Gland, Carotid Sinus, Pharynx & Middle Ear
	Special Sensory	Inferior Ganglion		Taste(Posterior 1/3 of Tongue)
	General Sensory	Inferior Ganglion		Cutaneous Sensation of External Ear
X Vagus	Branchial Motor	Medulla	Jugular Foramen	Constrictor Muscles of Pharynx, Muscles of Larynx, Palate & Upper 2/3 Esophagus
	Visceral Motor	**Presynaptic:** Medulla **Postsynaptic:** Viscera		Maintains Smooth Muscle Tone in Trachea & Bronchi, Peristalsis in GIT & ↓HR.
	Visceral Sensory	Superior Ganglion		Visceral Sensation from Base of Tongue, Pharynx, Larynx Trachea, Bronchi, Heart, Esophagus, Stomach & Intestine → L-Colic Flexure.
	Special Sensory	Inferior Ganglion		Taste (Epiglottis & Palate)
	General Sensory	Superior Ganglion		Sensation from the External Ear.
XI Spinal Accessory	Somatic Motor	Spinal Cord	Jugular Foramen	Sternocleidomastoid & Trapezius Muscles
XII Hypoglossal	Somatic Motor	Medulla	Hypoglossal Canal	Intrinsic & Extrinsic Muscles of the Tongue.

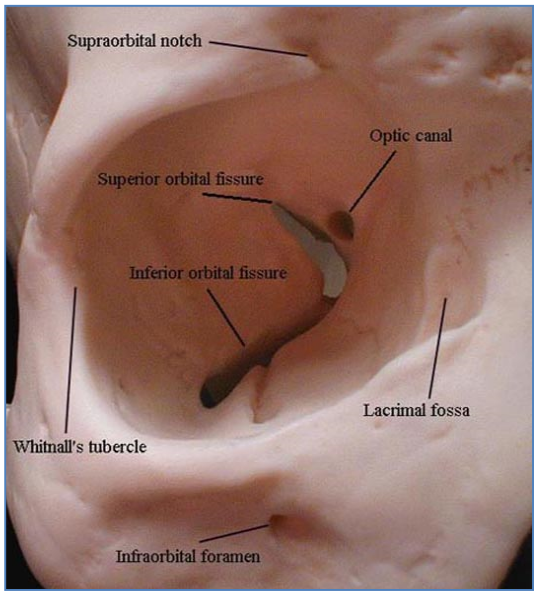
More Detail: NB: YOU WILL NEED TO KNOW WHERE EACH CN. ENTERS/EXITS THE CRANIUM

I. **Olfactory:**
   a. **Function:**
      i. Purely Special Sensory; Carry Afferent Impulses of ***Smell*** (Olfaction)
   b. **Origin & Course:**
      i. Olfactory Nerves arise from Olfactory Receptors in the Olfactory Epithelium. They pass up through the ***Cribriform Plate of the Ethmoid Bone*** & synapse with the Olfactory Bulb.
      ii. Olfactory Bulb Neurons run posteriorly as the ***Olfactory Tract*** & terminates in Primary Olfactory Cortex.



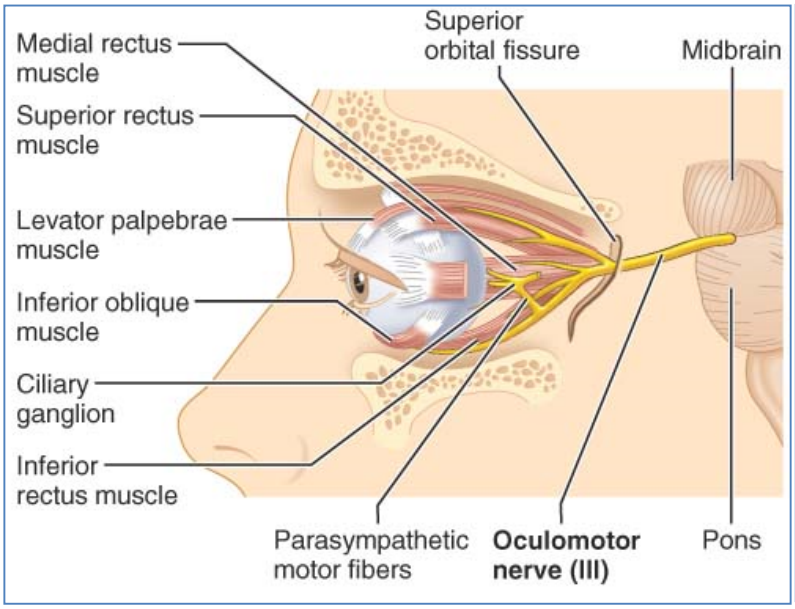
II. **Optic:**
   a. **Function:**
      i. Purely Special Sensory; Carry Afferent Impulses of ***Vision***
   b. **Origin & Course:**
      i. Fibres arise from the ***Retina*** and form the ***Optic Nerve***.
      ii. The Optic Nerve passes through the ***Optic Canal*** of the Orbit.
      iii. The Optic Nerves converge to form the ***Optic Chiasma*** where half of each nerve's fibres cross over & continue on as ***Optic Tracts***.
      iv. The Optic Tracts synapse in the ***Thalamus***, & Thalamic fibres extend to the ***Visual Cortex.***

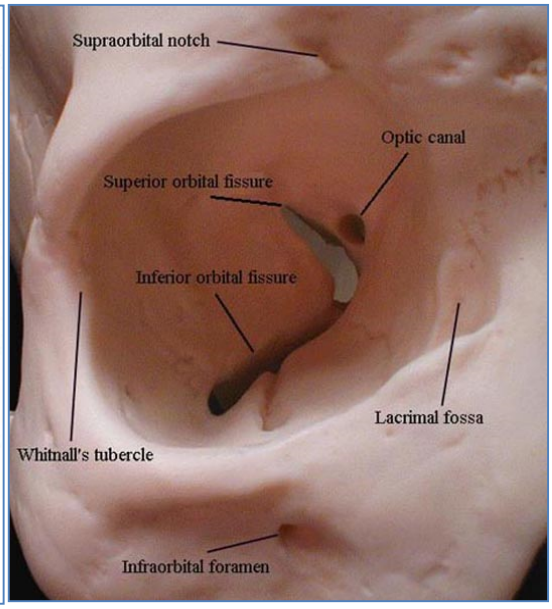




III. Oculomotor:

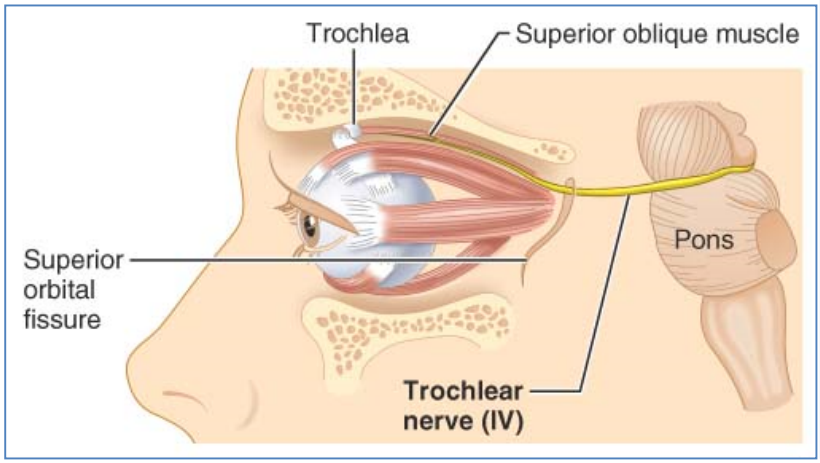
- **a. Function:**
  - **i.** Somatic Motor– Voluntary Movement of 4 of the 6 of the Extrinsic Eye Muscles (Inf. Oblique, Sup. Rectus, Inf. Rectus, Med. Rectus & Upper-Eyelid Muscle)
    NB: Proprioceptive Afferents exist for each muscle.
  - **ii.** Visceral Motor – Parasympathetic control of Pupillary Sphincter (Constriction) & Ciliary Muscle (Lens Accommodation)
- **b. Origin & Course:**
  - **i.** Fibres arise from the ***Midbrain*** and pass through the ***Superior Orbital Fissure*** to the eye.

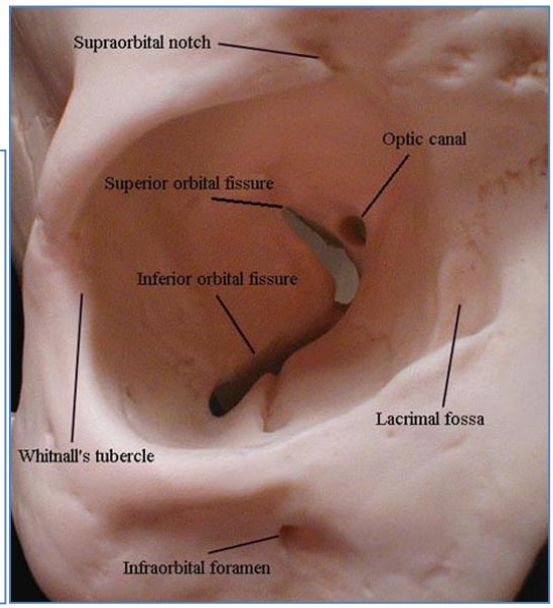




IV. Trochlear:

- **a. Function:**
  - **i.** Purely Somatic Motor – Voluntary Movement of 1 of the 6 Extrinsic Eye Muscles (The Superior Oblique)
- **b. Origin & Course:**
  - **i.** Fibres arise from the ***Midbrain*** and pass through the ***Superior Orbital Fissure*** to the Eye.





V. Trigeminal:

NB: Has 3 Divisions (Ophthalmic, Maxillary & Mandibular), each with different specific functions & courses through the skull.

a. Function:

i. Mostly Somatosensory (From Face)

ii. Some Branchial Motor

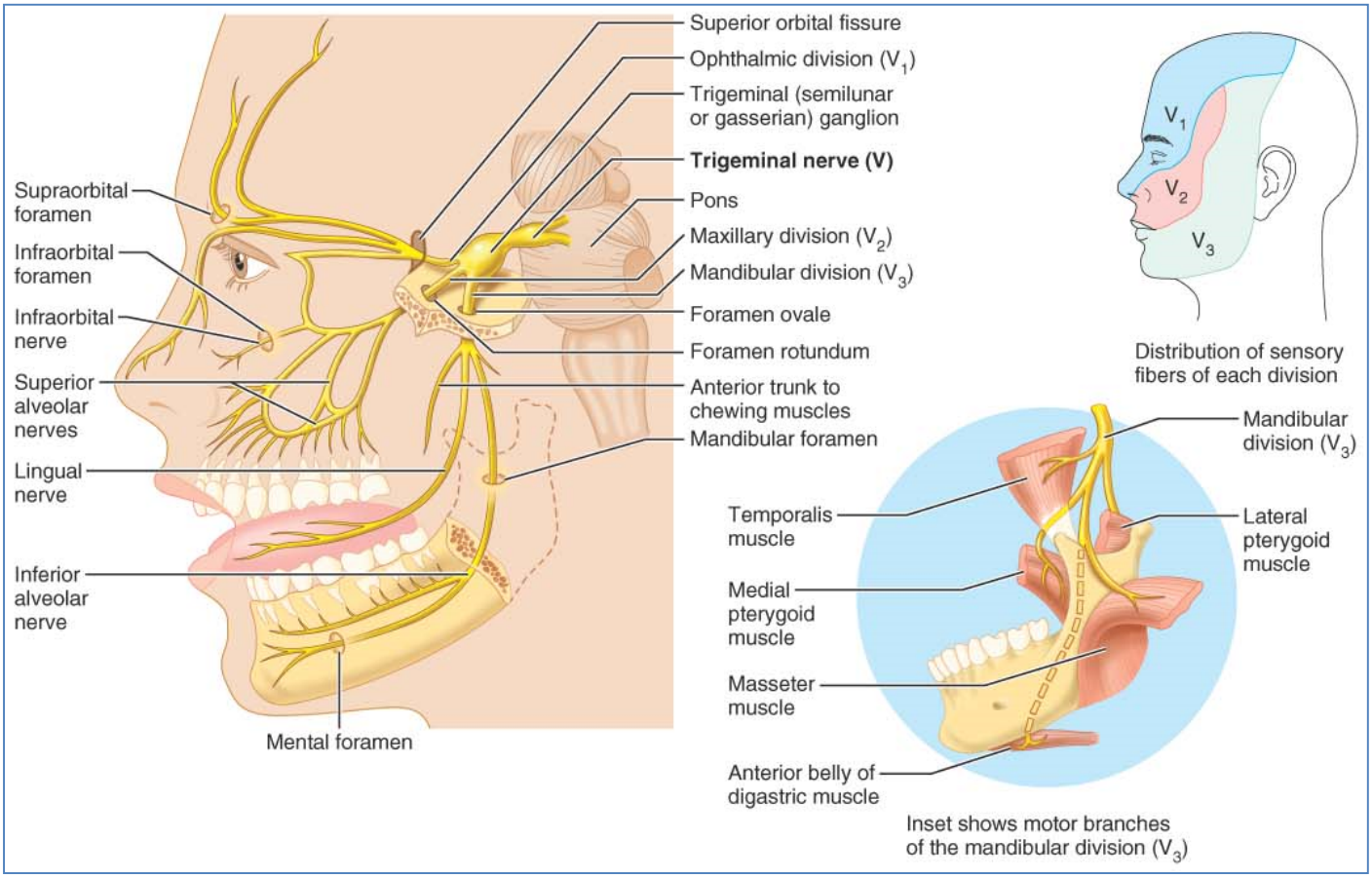
b. Origin & Course:

i. **Ophthalmic –** Fibres run from Face → Through ***Superior Orbital Fissure*** → Pons.

ii. **Maxillary –** Fibres run from face → Through the ***Foramen Rotundum*** → Pons.

iii. **Mandibular –** Fibres pass through the ***Foramen Ovale***

	Ophthalmic division (V_1)	Maxillary division (V_2)	Mandibular division (V_3)
Origin and course	Fibers run from face to pons via superior orbital fissure	Fibers run from face to pons via foramen rotundum	Fibers pass through skull via foramen ovale
Function	Conveys sensory impulses from skin of anterior scalp, upper eyelid, and nose, and from nasal cavity mucosa, cornea, and lacrimal gland	Conveys sensory impulses from nasal cavity mucosa, palate, upper teeth, skin of cheek, upper lip, lower eyelid	Conveys sensory impulses from anterior tongue (except taste buds), lower teeth, skin of chin, temporal region of scalp; supplies motor fibers to, and carries proprioceptor fibers from, muscles of mastication



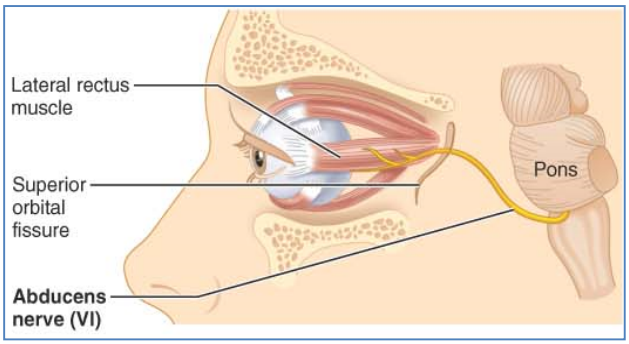
VI. Abducents:

a. **Function:**

i. Purely Somatic Motor – Voluntary Movement of the ***Lateral Rectus Muscle*** of the Eye. (Abducts the eye – hence the name)
NB: Proprioceptive Afferents exist as well.

b. **Origin & Course:**

i. Fibres arise from the ***Pons*** and pass through the ***Superior Orbital Fissure*** to the Eye.



VII. Facial:

a. **Function:**

i. Branchial Motor – Voluntary Movement of Muscles of Facial Expression

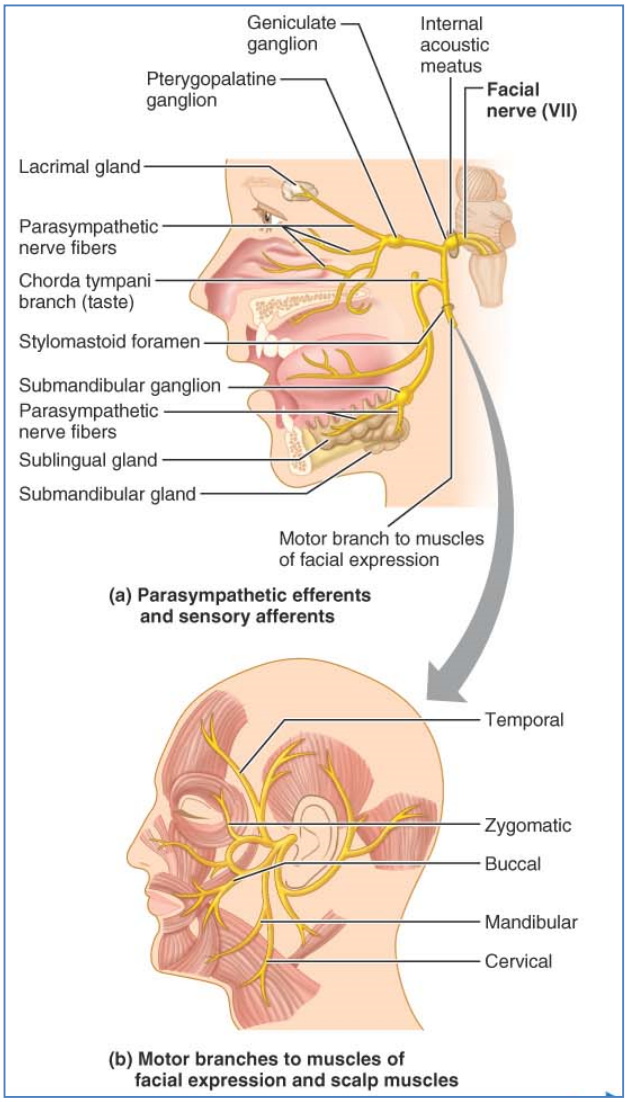
1. ***Has 5 Branches (See Picture) – KNOW THESE & Their Myotomes.***

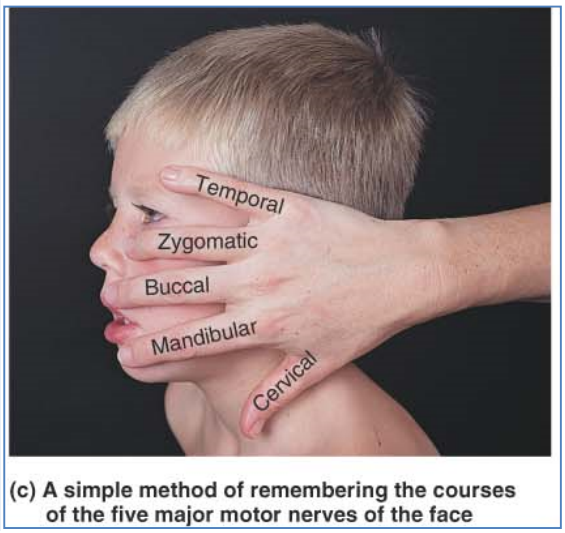
ii. Special Sensory – Taste Buds of Anterior 2/3 of Tongue

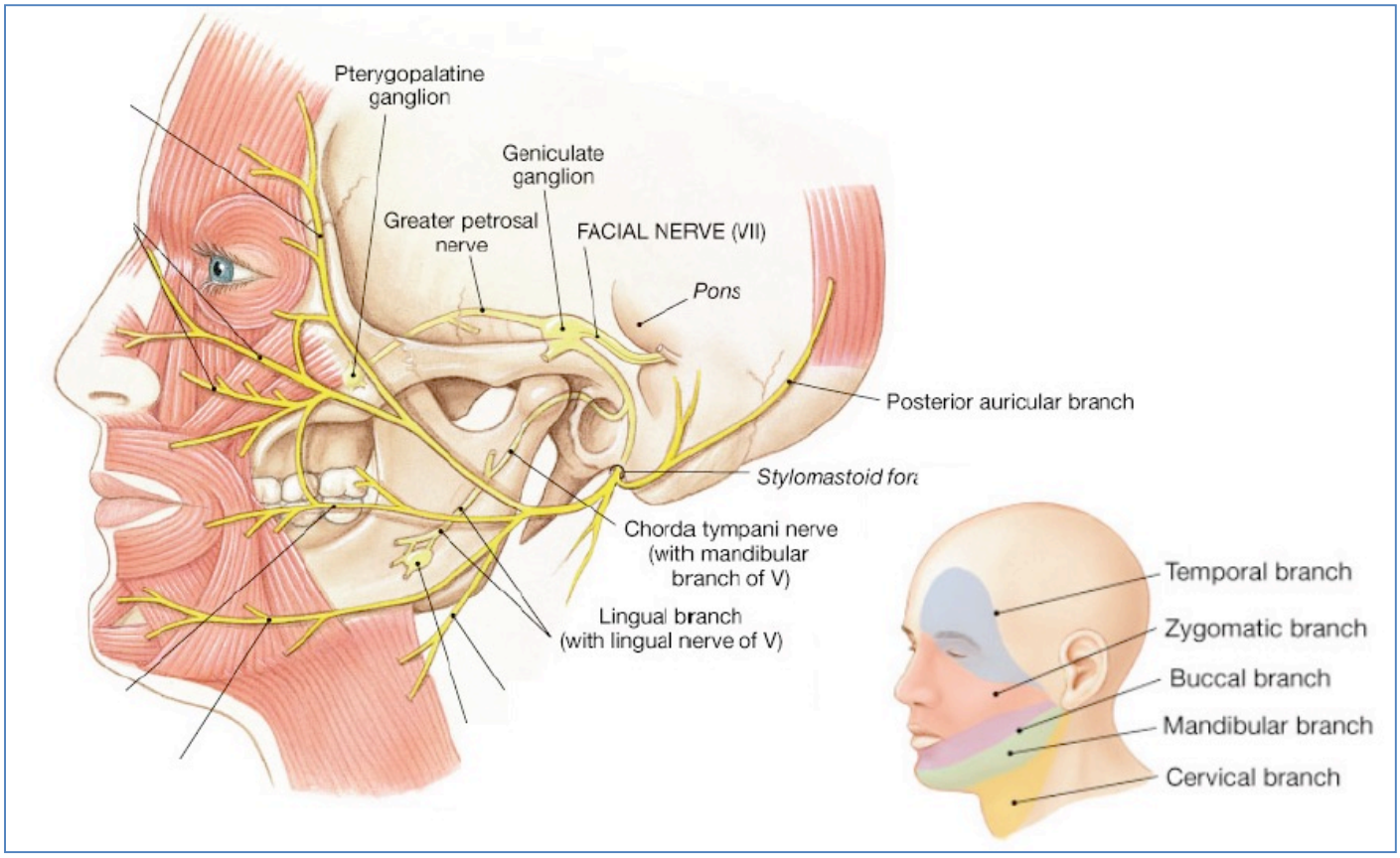
iii. Visceral Motor – Parasympathetic control of Lacrimal (Tear) Glands, Nasal & Palatine Glands, & Submandibular & Sublngual Salivary Glands.

b. **Origin & Course:**

i. Fibres arise from the ***Pons*** & enter the Temporal Bone via the ***Internal Acoustic Meatus*** and emerge through the ***Stylomastoid Foramen*** to run through lateral face.

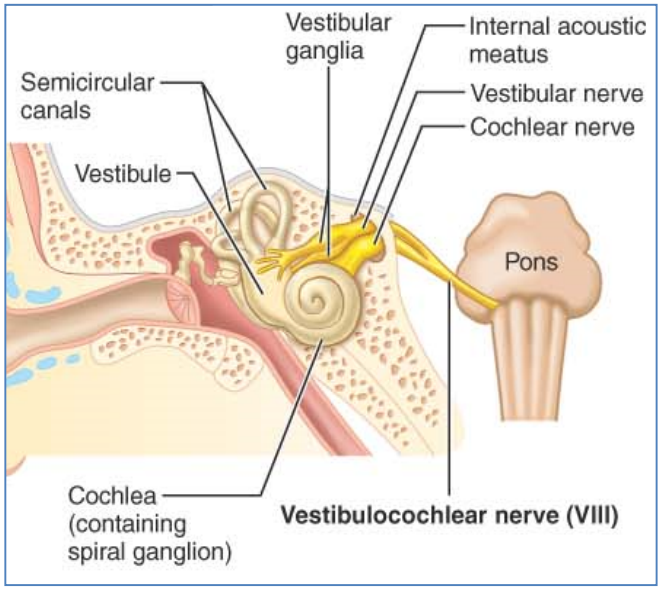


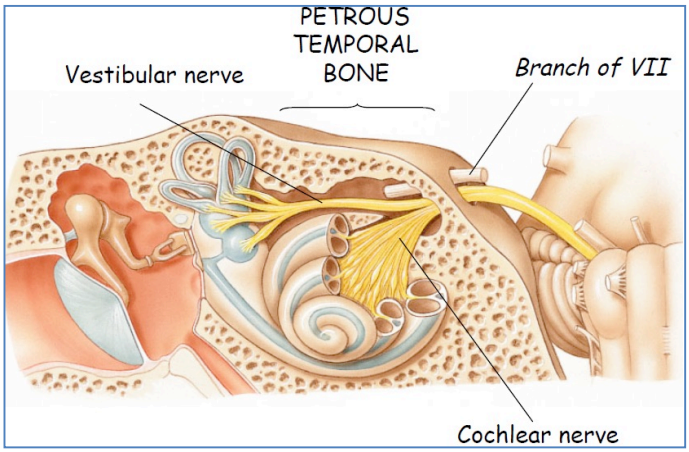




VIII. <u>Vestibulocochlear:</u>

- **a. Function:**
  - **i.** Special Sensory:
    1. Vestibular Branch – Sense of Equilibrium/Balance.
    2. Cochlear Branch – Sense of Hearing.
- **b. Origin & Course:**
  - **i.** Fibres arise from the Vestibule & the Cochlear of the Inner Ear of the Temporal Bone & pass through the ***Internal Acoustic Meatus*** and enter the brainstem @ the Pons-Medulla Border.





IX. Glossopharyngeal:

a. Function:

i. Somatic Motor – Voluntary Movement of the ***Stylopharyngeus*** (Elevates the Pharynx in Swallowing)

ii. Visceral Motor – Parasympathetic control of Parotid Salivary Glands (Nerve Cell Bodies locate in the ***Otic Ganglion***)

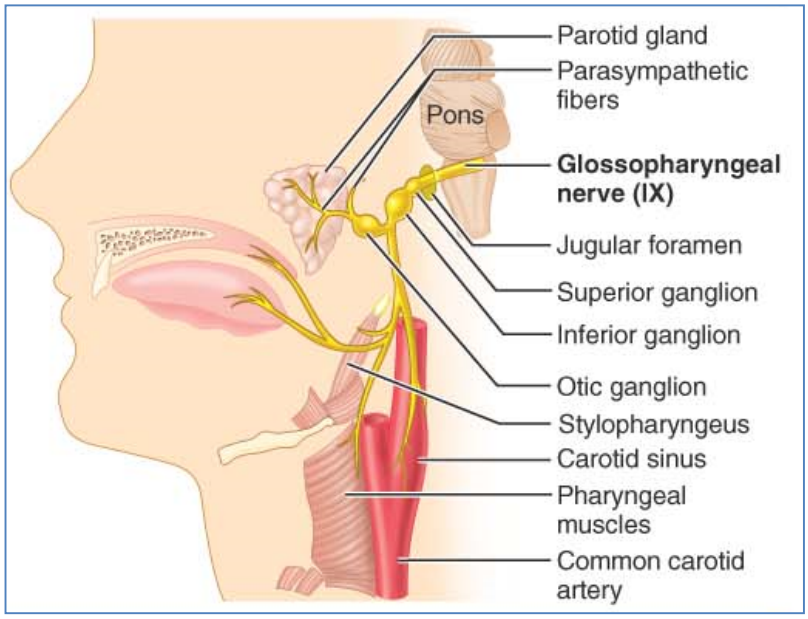
iii. Special Sensory – Taste Buds of Posterior 1/3 of Tongue

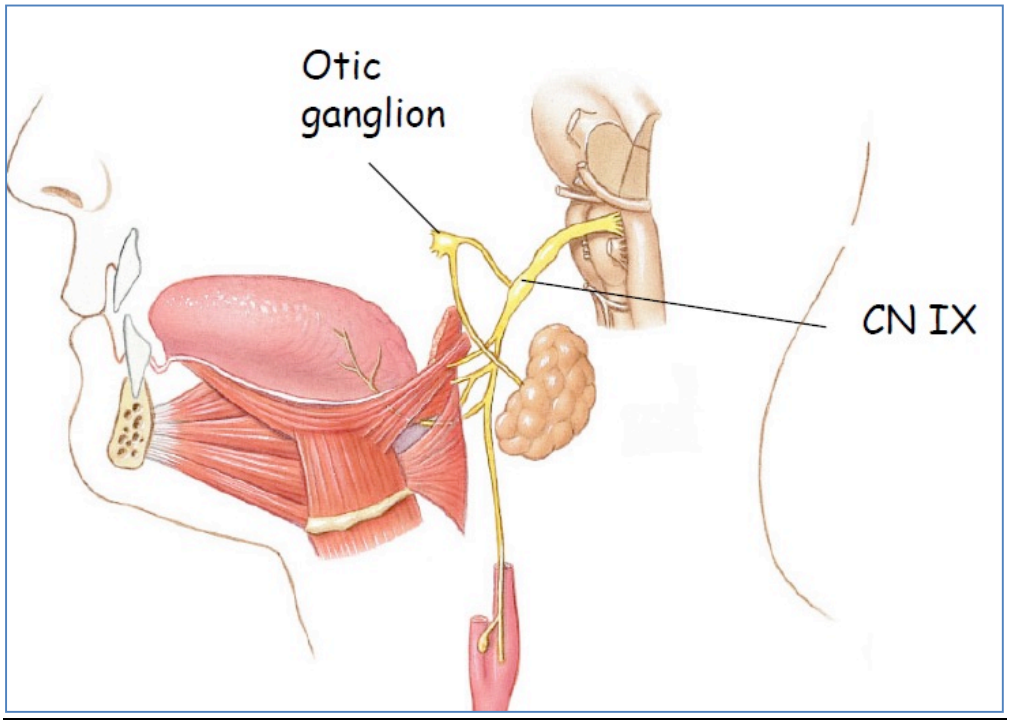
iv. SomatoSensory – Touch/Pressure/Pain from Pharynx, Posterior Tongue & External Ear

v. Visceral Sensory – Chemoreceptors in Carotid Body (Blood O_2 / CO_2) & Baroreceptors in Carotid Sinus (BP)

b. Origin & Course:

i. Fibres arise from Medulla, leave skull via the ***Jugular Foramen*** & run to the Throat.





X. Vagus:

a. Function:

i. Visceral Motor – Parasympathetic Control of:

1. Heart (HR)
2. Lungs (Breathing)
3. Abdominal Organs (GI Activity)

ii. Visceral Sensory – Visceral Sensation from:

1. Thoracic Viscera
2. Abdominal Viscera
3. Aortic Arch Baroreceptors (BP)
4. Carotid & Aortic Bodies (Chemoreceptors)

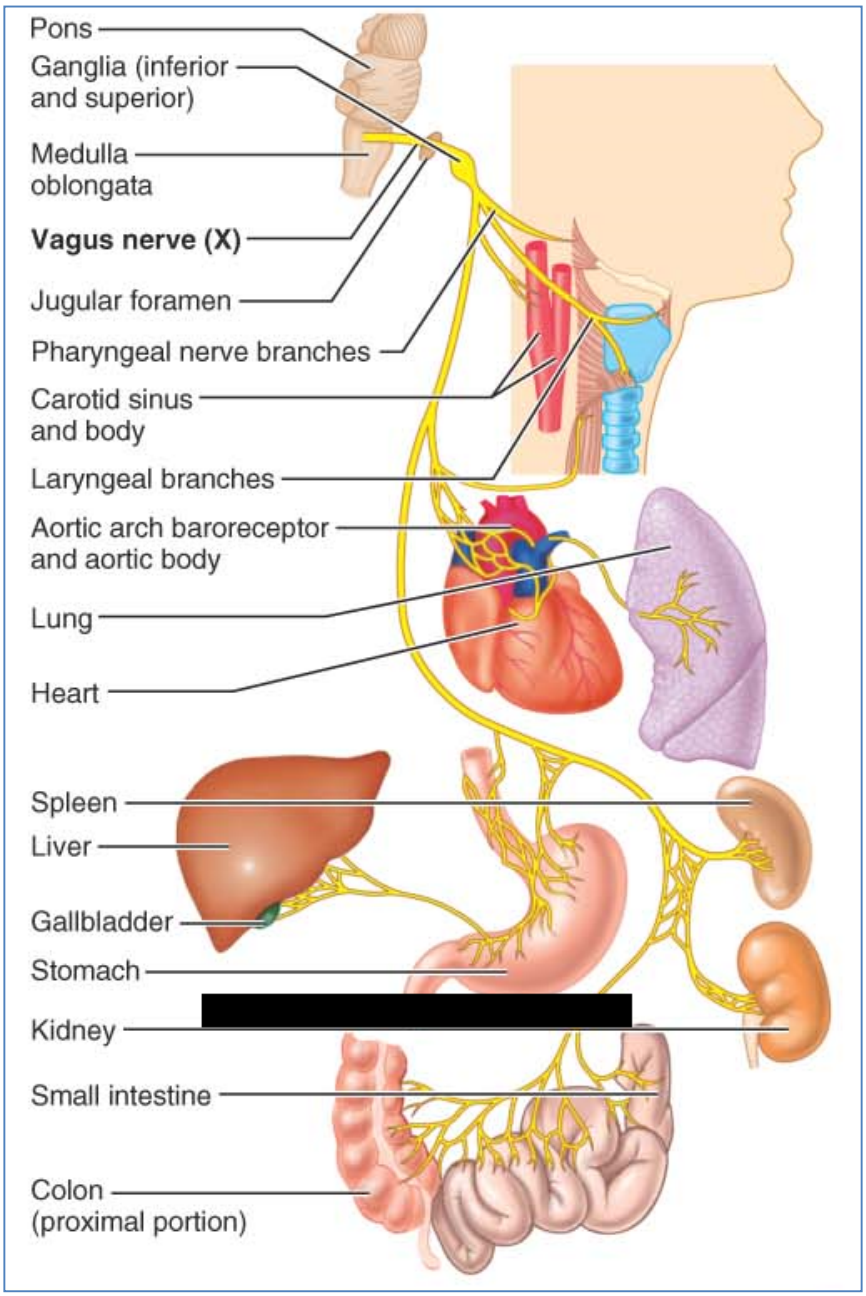
iii. Special Sensory – Taste Buds from Posterior Tongue

iv. Somatic Motor – Voluntary control of Muscles of Pharynx & Larynx involved in swallowing.

b. Origin & Course:

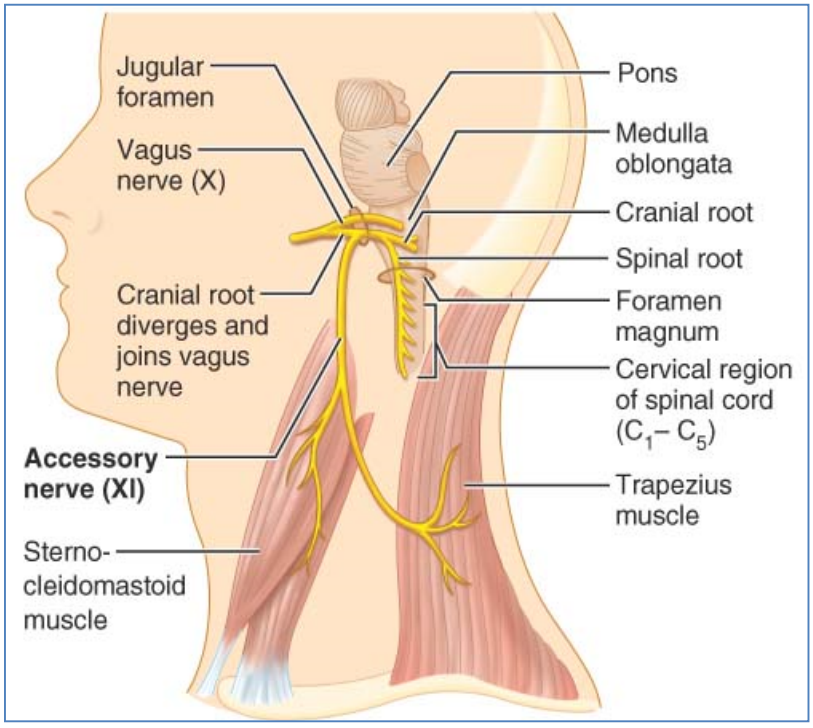
NB: Vagus – the only cranial nerve to extend beyond the head & neck.

i. Fibres arise from Medulla, pass through the skull via the ***Jugular Foramen*** & descend through the Neck into the Thorax & Abdomen.



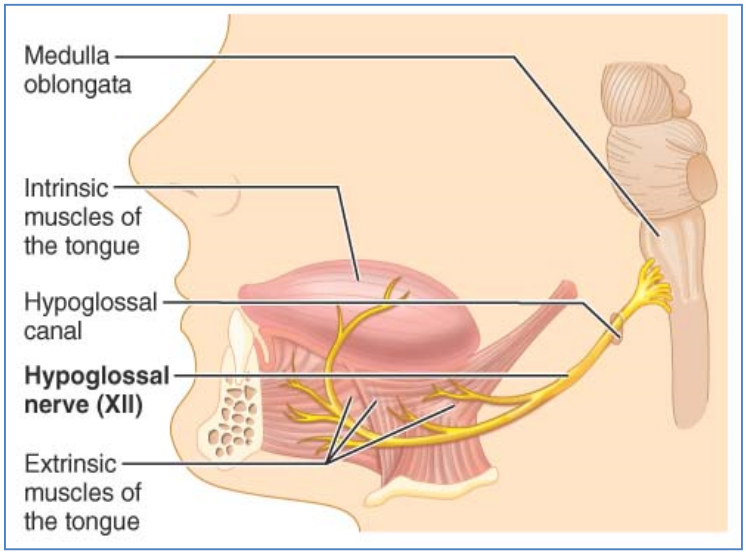
XI. **Accessory:**

- **a. Function:**
  - **i.** Somatic Motor – Voluntary Movement of Sternocleidomastoid & Trapezius Muscles
- **b. Origin & Course:**
  - **i.** Unique in that it is formed by union of a *Cranial Root* & a *Spinal Root*.
    - **1.** Cranial Root – Arises from Medulla of Brainstem
    - **2.** Spinal Root – Arises from Cervical Region of Spinal Cord (C1-C5) & Enters the Skull via the ***Foramen Magnum*** where it joins with the Cranial Root.
  - **ii.** The Resulting Accessory Nerve exits the skull through the ***Jugular Foramen***, where it bifurcates to either 1) Join the Vagus Nerve; or 2) Run down to the Neck Muscles.



XII. **Hypoglossal:**

- **a. Function:**
  - **i.** Somatic Motor – Voluntary Movement of the Tongue (Food Mixing/Manipulation, Speech & Swallowing)
- **b. Origin & Course:**
  - **i.** Fibres arise from the Medulla & exit the skull via the ***Hypoglossal Canal*** to travel to the underside of the Tongue.



Cranial Foramina That Carry Cranial Nerves:

Cranial Foramina	Cranial Nerves
Cribriform Foramina in Cribriform Plate	Olfactory Nerves
Optic Canals	Optic Nerves
Superior Orbital Fissure	Oculomotor Trochlear Abducens Trigeminal (Ophthalmic Division)
Foramen Rotundum ("Round Foramen")	Trigeminal (Maxillary Division)
Foramen Ovale ("Oval Foramen")	Trigeminal (Mandibular Division)
Groove of the Greater Petrosal Nerve	Petrosal Nerve (Branch of the Facial Nerve)
Internal Acoustic Meatus	Facial (And exits the skull via the Stylomastoid Foramen) Vestibulocochlear
Jugular Foramen	Glossopharyngeal Vagus Accessory (Both Roots Exit the Skull Here)
Hypoglossal Canal	Hypoglossal
Foramen Magnum	Accessory (Spinal Root Enters the Skull Here)

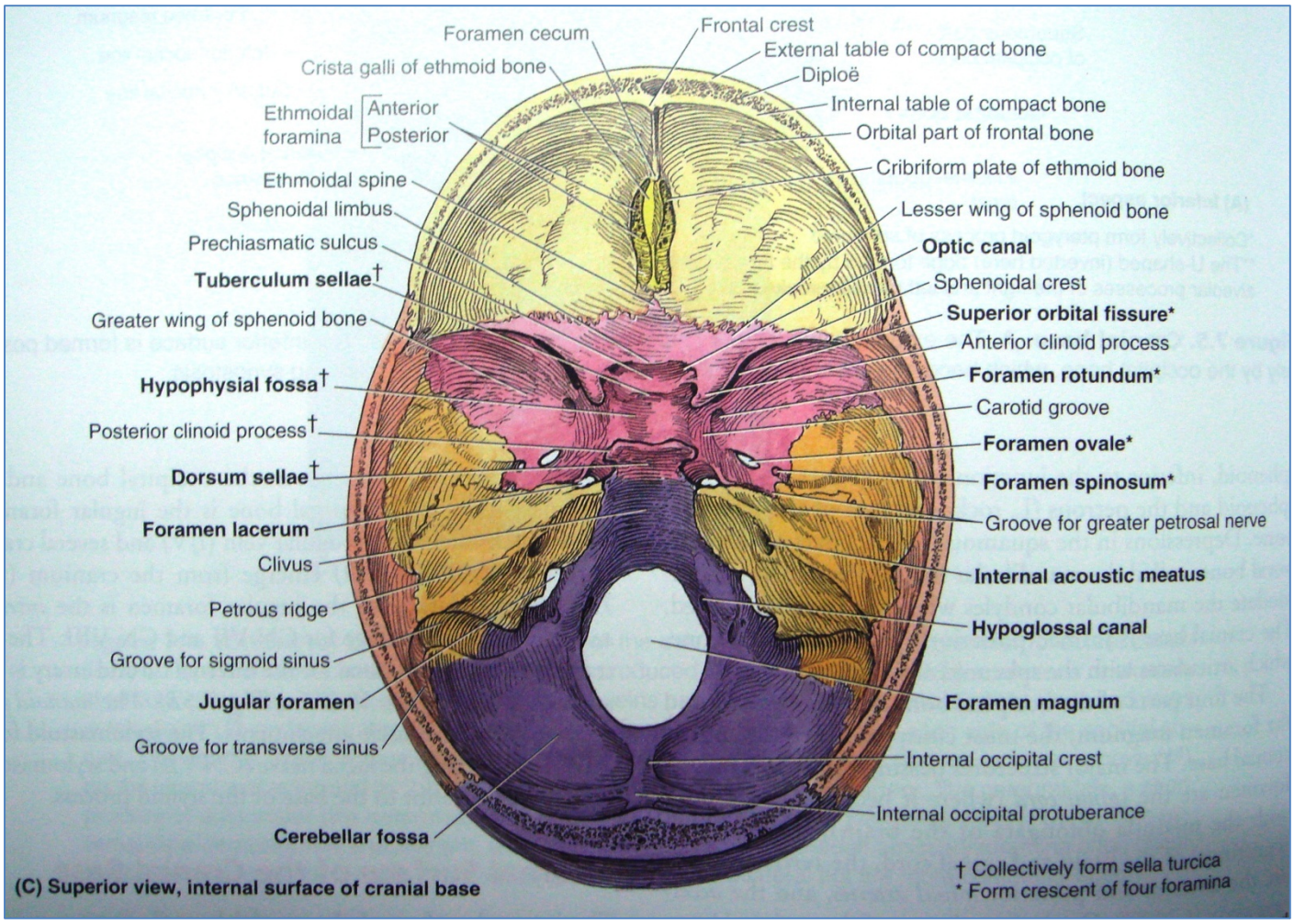
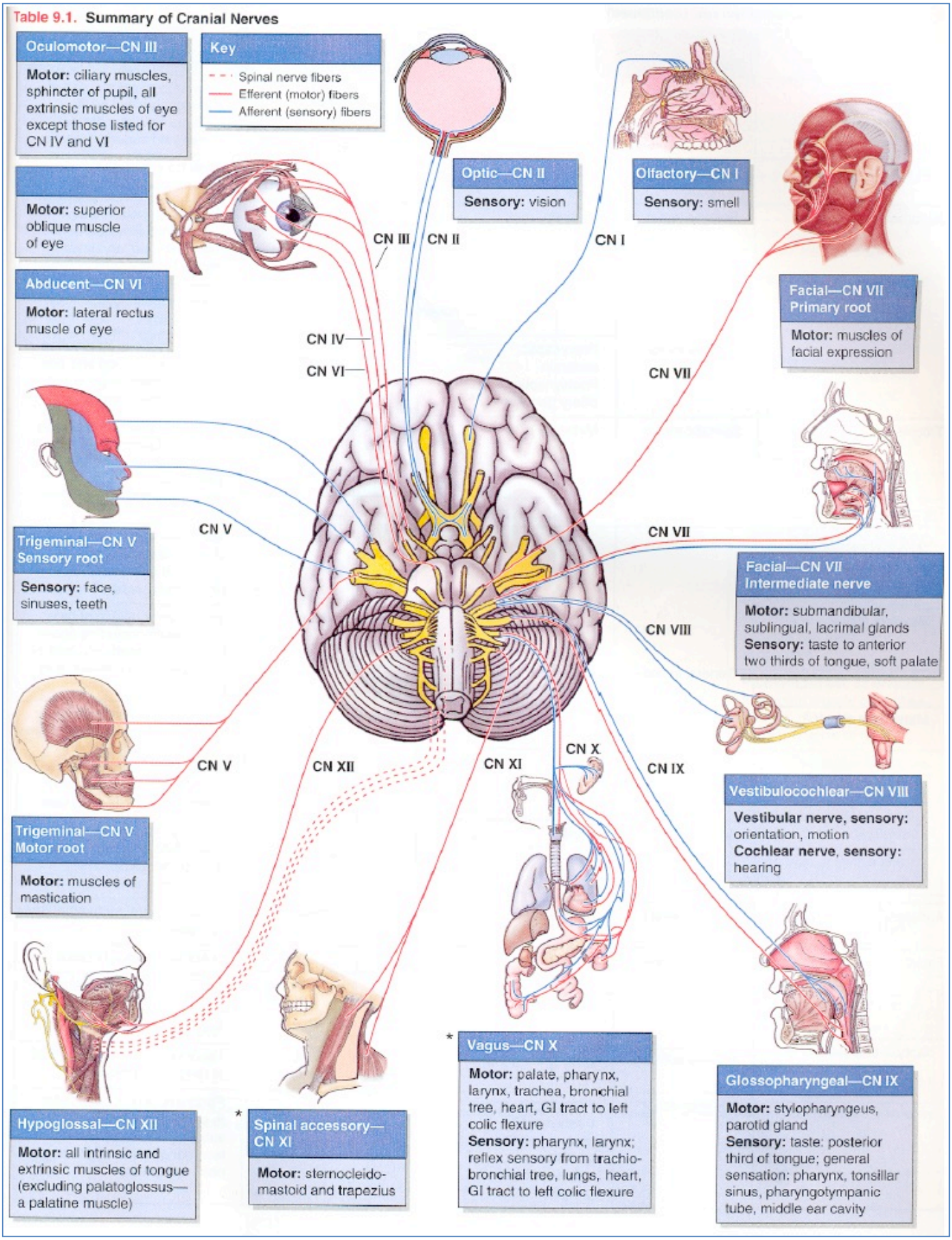
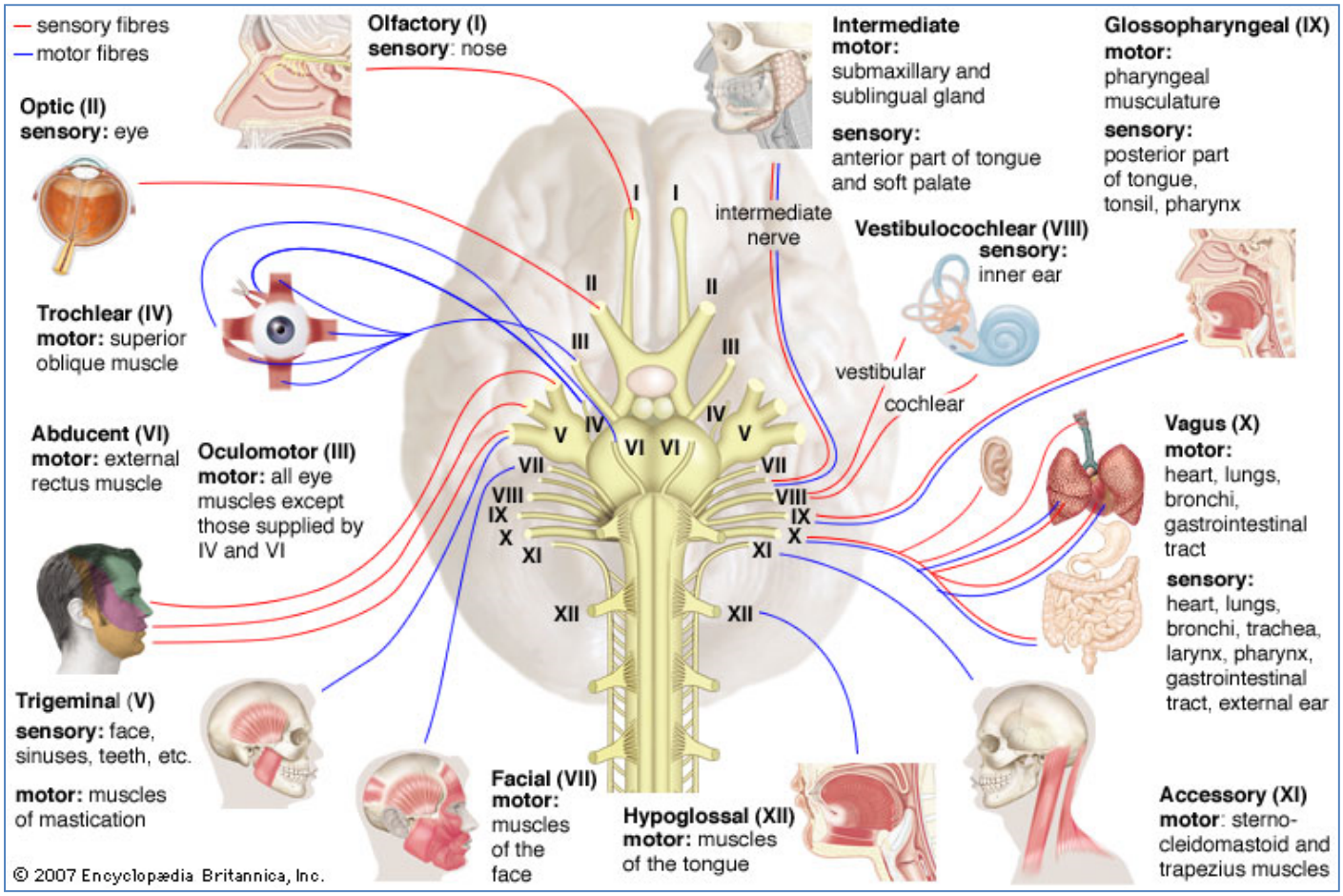


Table 9.1. Summary of Cranial Nerves



www.regentstudies.com



PRACTICE EMQ

a. Olfactory nerve (CN I)
b. Optic nerve (CN II)
c. Oculomotor nerve (CN III)
d. Trochlear nerve (CN IV)
e. Opthalmic branch of V (CN V_1)
f. Maxillary branch of V (CN V_2)
g. Mandibular branch of V (CN V_3)
h. Trigeminal nerve (CN V)
i. Facial nerve (CN VII)
j. Vestibulocochlear nerve (CN VIII)
k. Glossopharyngeal nerve (CN IX)
l. Vagus nerve (CN X)
m. Accessory nerve (CN XI)
n. Hypoglossal nerve (CN XII)

FIBRES FROM THIS NERVE PERFORATE THE CRIBRIFORM PLATE.

Ie. Know which cranial nerves exit through which foramina.

a. Olfactory nerve (CN I)
b. Optic nerve (CN II)
c. Oculomotor nerve (CN III)
d. Trochlear nerve (CN IV)
e. Opthalmic branch of V (CN V_1)
f. Maxillary branch of V (CN V_2)
g. Mandibular branch of V (CN V_3)
h. Trigeminal nerve (CN V)
i. Facial nerve (CN VII)
j. Vestibulocochlear nerve (CN VIII)
k. Glossopharyngeal nerve (CN IX)
l. Vagus nerve (CN X)
m. Accessory nerve (CN XI)
n. Hypoglossal nerve (CN XII)

THE NERVE OF THE 2ND PHARYNGEAL ARCH.

Ie. Know which nerves are associated with each pharyngeal arch.

a. Olfactory nerve (CN I)
b. Optic nerve (CN II)
c. Oculomotor nerve (CN III)
d. Trochlear nerve (CN IV)
e. Opthalmic branch of V (CN V_1)
f. Maxillary branch of V (CN V_2)
g. Mandibular branch of V (CN V_3)
h. Trigeminal nerve (CN V)
i. Facial nerve (CN VII)
j. Vestibulocochlear nerve (CN VIII)
k. Glossopharyngeal nerve (CN IX)
l. Vagus nerve (CN X)
m. Accessory nerve (CN XI)
n. Hypoglossal nerve (CN XII)

THIS NERVE GIVES RISE TO THE GREATER PETROSAL NERVE.

Ie. Know the major branches of each cranial nerve.

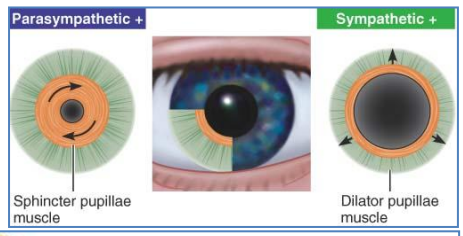
BASIC ANATOMY & PHYSIOLOGY
Special Senses

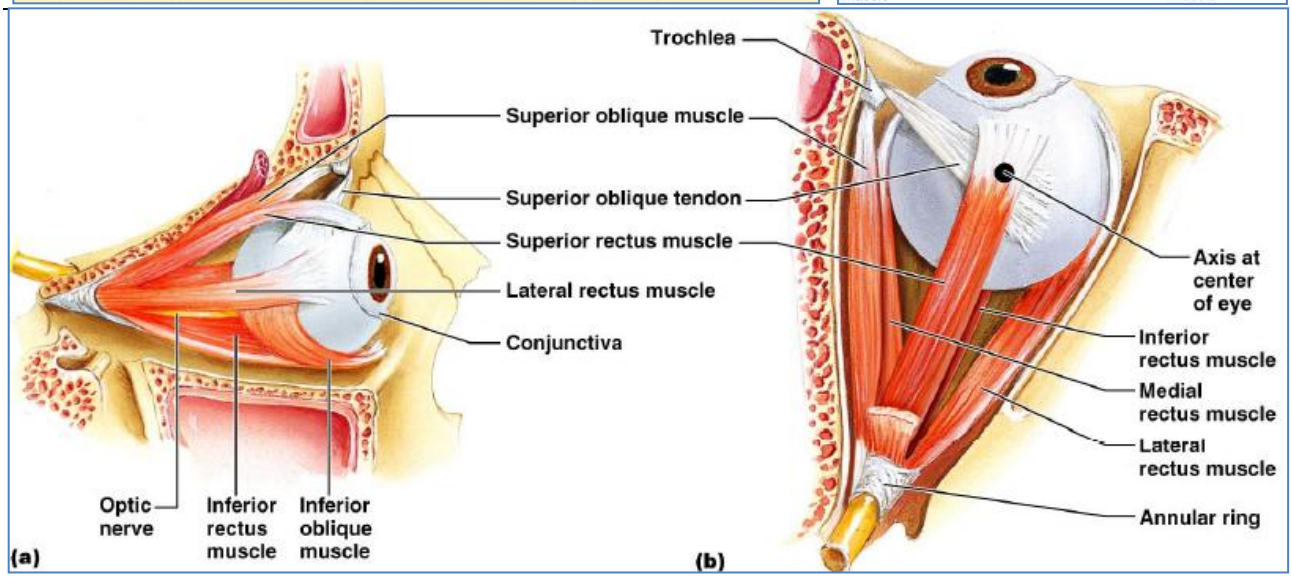
Vision:

Accessory Structures of the Eye:

- **Eyebrows:**
  - Shade the eyes from sunlight
- **Eyelids ('Palpebrae'):**
  - Protect the eye when threatened by foreign objects
- **Conjunctiva ("Joined Together"):**
  - Transparent mucus membrane lining the eyelids ('Palpebral Conjunctiva') & the anterior eyeball surface ('Bulbar Conjunctiva').
- **Lacrimal Apparatus:**
  - **Consists of:**
    - **Lacrimal Gland (Tear Gland):**
      - Located in the orbit above the eye.
    - **Lacrimal Canaliculi:**
      - 2 openings on medial margin of each eyelid.
- **Eyelid Muscles:**
  - **Levator Palpebrae Superioris Muscle:**
    - Elevates & Retracts Upper Eyelid (Opens Eye)
  - **Orbicularis Oculi Muscle:**
    - (A Sphincter Muscle) - Closes Eye
- **Extrinsic Eye Muscles:**
  - Eyeball movement is controlled by 6 muscles
  - **The 4x Rectus Muscles** originate from a common tendinous ring (**Annular Ring**) at the back of the eye.
  - **The 2x Oblique Muscles** take different paths through the orbit. They are required to cancel the medial pull of the superior & inferior recti to allow purely vertical eye movement.

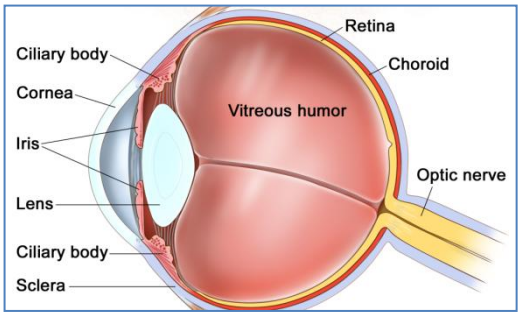
Name	Action	Controlling cranial nerve
Lateral rectus	Moves eye laterally	VI (abducens)
Medial rectus	Moves eye medially	III (oculomotor)
Superior rectus	Elevates eye and turns it medially	III (oculomotor)
Inferior rectus	Depresses eye and turns it medially	III (oculomotor)
Inferior oblique	Elevates eye and turns it laterally	III (oculomotor)
Superior oblique	Depresses eye and turns it laterally	IV (trochlear)

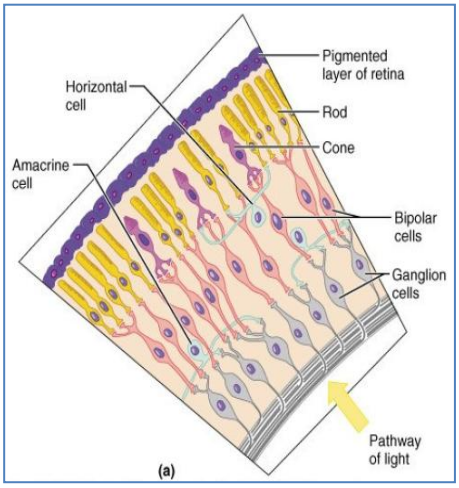




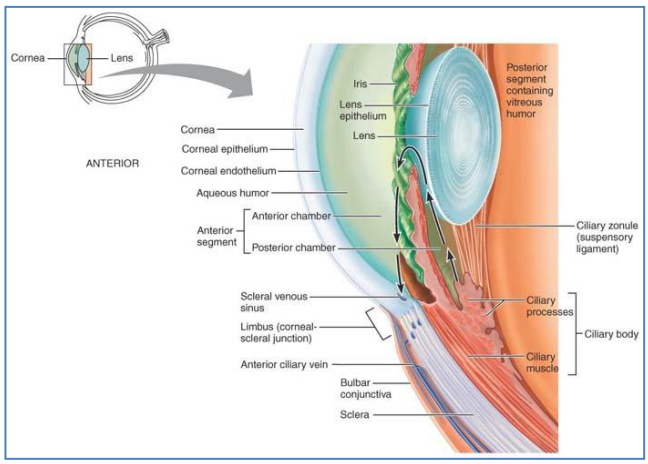
Eye Anatomy:

- **3-Layered Wall (Tunics):**
  - **1. Fibrous Layer:**
    - **2 Regions:**
      - **Cornea:**
        - The Clear, Anterior part of the eye that lets light in.
      - **Sclera:**
        - The white/opaque, Posterior part of the eye.
  - **2. Vascular Layer:**
    - Middle Layer
    - **2 Parts:**
      - **Choroid:**
        - Highly vascular, dark membrane (Posterior 5/6 of eye).
          - Supplies nutrition to all eye layers
          - Absorbs light, preventing it from scattering/reflecting within the eye.
      - **Iris ("Rainbow"):**
        - The Anterior, coloured portion of the Vascular Layer
        - Lies between the Cornea & the Lens.
  - **3. Retinal Layer:**
    - Innermost Layer
    - **2 Sub-Layers:**
      - **Pigmented Layer:**
        - Outer Retinal Layer
        - Dark, Single-cell-thick lining adjacent to the Choroid.
      - **Neural Layer:**
        - Inner Retinal Layer
        - Transparent layer of Photoreceptors/Neurons/ & Glia
        - **Composed of 3 Types of Neurons:**
          - **Photoreceptors:**
            - **2 Types:**
              - **Rods –** Light Detectors (Dim & Fuzzy)
              - **Cones** – Colour Detectors (Bright & Sharp)
          - **Bipolar Neurons:**
            - Connect Photoreceptors to Ganglion Cells
          - **Ganglion Cells:**
            - Generate & Conduct the Action Potentials → Brain

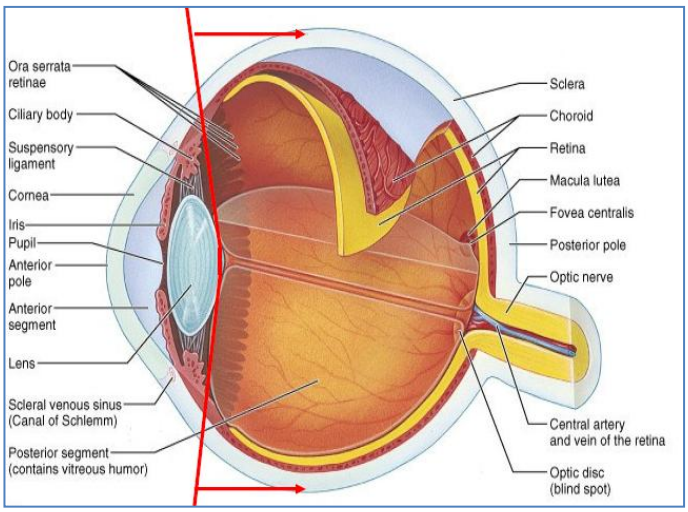




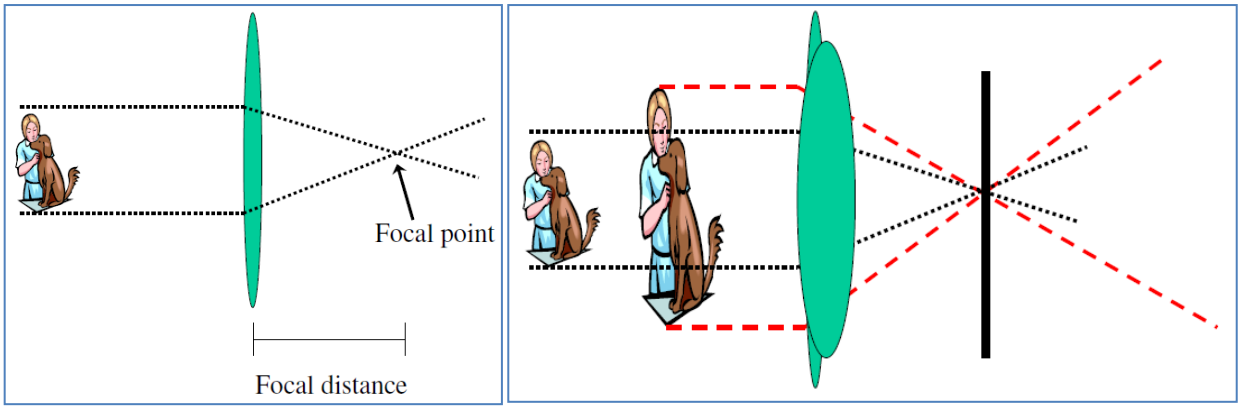
- **The Eye's 2x Segments & Fluids:**
  - The Lens & Suspensory Ligaments (Ciliary Zonule) Divide the eye into 2 segments. (Ant/Post).
  - **1. Anterior Segment (In front of the lens):**
    - **Filled with 'Aqueous Humour':**
      - Clear, plasma-like substance
      - Has the same refractive index as the Cornea
      - Continually formed by capillaries of the **Ciliary Processes** (in the Posterior Chamber).
        - Flows from the Posterior Chamber to the Anterior Chamber
        - Drains from Ant. Chamber through the **Scleral Venous Sinus (Canal of Schlemm)** which encircles the Limbus.
      - **Functions:**
        - Its pressure supports the eyeball internally.
        - Supplies Nutrients & Oxygen to the Lens & Cornea
    - **Subdivided by the Iris into 2 Chambers:**
      - **Anterior Chamber:**
        - Between the Cornea & the Iris
      - **Posterior Chamber:**
        - Between the Iris & the Lens.



  - **2. Posterior Segment (Behind the lens):**
    - **Filled with 'Vitreous Humour'** ("Glassy Fluid"):
      - A clear Gel
      - Has the same refractive index as the cornea
      - Formed in the Embryo & Lasts a Lifetime
      - **Functions:**
        - Supports the posterior surface of the lens
        - Holds the Neural Retina firmly against the Pigmented Layer
        - Contributes to Intraocular Pressure



- **The Eye's Lens:**
  - **Features:**
    - Responsible for 1/3 of the *'Power'* of the Eye. (Cornea is other 2/3)
    - Biconvex
    - Held in place by the Ciliary Zonule (Suspensory Ligaments)
  - **Lens Physics:**
    - A lens of a certain 'power' has a certain **Focal Point**. The distance between the lens & the focal point is the **Focal Distance**.
    - NB: The eye has a **fixed Focal Distance**, therefore the Lens **'Power' must be variable**.
  - **Function:**
    - Focuses light rays onto the retina.
    - **Accommodation:** Changes shape (& hence, lens 'Power') to maintain Focal Distance.



- **3 Prerequesites to *'Near-Vision'*:**
  - **1. Accommodation of the Lenses:**
    - Achieved by contraction of the ciliary muscles → Thickens lens → More power.
  - **2. Constriction of The Pupils:**
    - Achieved by contraction of the Constrictor Muscles of the Iris.
    - Allows increased clarity
  - **3. Convergence of The Eyeballs:**
    - Keeps the object being looked at focussed on the Retinal Fovea

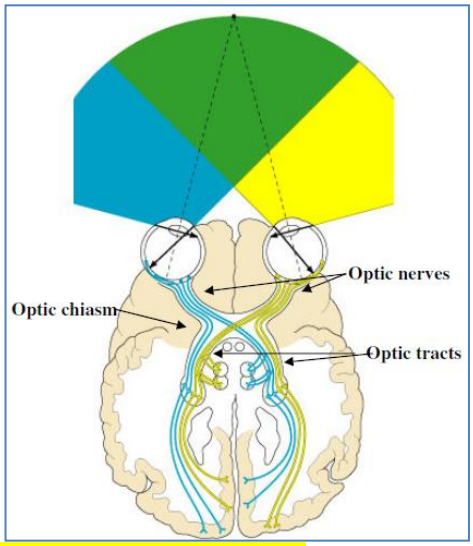
- **Photoreceptors:**
  - The cells that transduce light. (Rods & Cones)
  - Contain an array of **Visual Pigments (Photopigments)** that change shape as they absorb light:
  - **Differences (Rods Vs. Cones):**
    - Have different *thresholds* for activation.
    - Contain different visual pigments - absorb different wavelengths of light.
    - Are "wired" differently.
  - **Rods:**
    - High Sensitivity (Respond well to dim light)
    - Contain only 1 type of Photopigment (Therefore only send a 'monochrome' signal)
  - **Cones:**
    - Low Sensitivity (Requires bright light for activation)
    - Have 1 of 3 different pigments that respond to different colours. (Allow you to see colour)

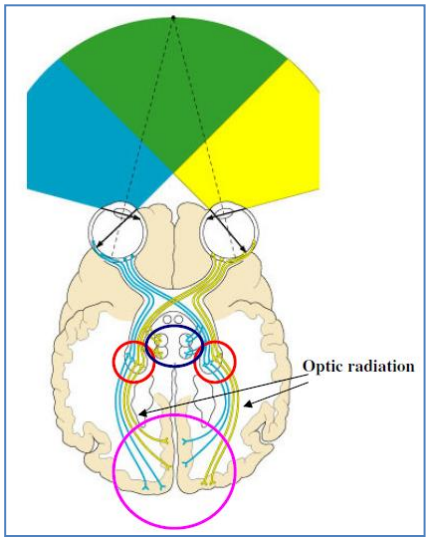
- **Phototransduction:**
  - The light-absorbing molecule is called '**Retinal**'. (A derivative of Vitamin-A)
  - **Retinal** combines with proteins called '**Opsins**', to form 4-types of **Photopigments.**

- **Light/Dark Adaptation:**
  - **Light Adaptation:**
    - Occurs when we move from Darkness into Bright Light.
    - To Compensate, the Rod system quickly desensitises and essentially turns off. The Cone system rapidly adapts, and takes over. Hence, overall the retina Desensitises.
  - **Dark Adaptation:**

- Occurs when we move from Brightness to Darkness. Initially we see nothing but black because:
  - 1. Cones stop functioning in low light. &
  - 2. Because Rods have been 'bleached' out by the bright light & are still turned off.
- Once rhodopsin accumulates in the Rods, their function slowly increases.

- **Pathways to the Brain:**
  - Ganglion Cell axons become the Optic Nerve.
  - Some of the Optic Nerve Fibres cross @ the **Optic Chiasm**.
  - After the Optic Chiasm, Optic Nerves become the **'Optic Tracts'**.
  - **Optic Tract fibres synapse in the:**
    - **Superior Colliculi** of the Midbrain (Blue Circles):
      - - Visual Reflex Centres controlling Extrinsic Eye Muscles
    - **Lateral Geniculate Nucleus of the Thalamus** (Red Circle):
      - - Sorts/Relays info Via the **Optic Radiation** to the **Primary Visual Cortex**. (Pink Circle)
    - **Primary Visual Cortex** (Pink Circle):
      - Topographical map of the Retina (Similar to Homunculus)
        - **Sends Info to Visual Association Areas** – regarding Form, Colour & Motion.



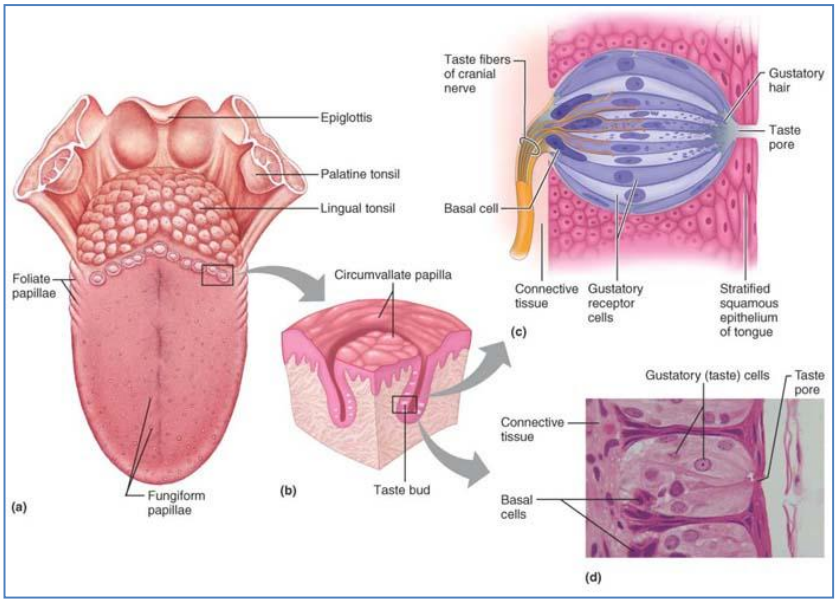


  - **Information Route/Pathway:** Photoreceptor → Bipolar Cell → Ganglion Cell → Optic Nerve → Optic Chiasm → Optic Tract → Superior Colliculus / Lateral Geniculate Nucleus of the Thalamus → Primary Visual Cortex → Visual Association Area → Perception.

Taste/Smell:

Gustation (Taste):

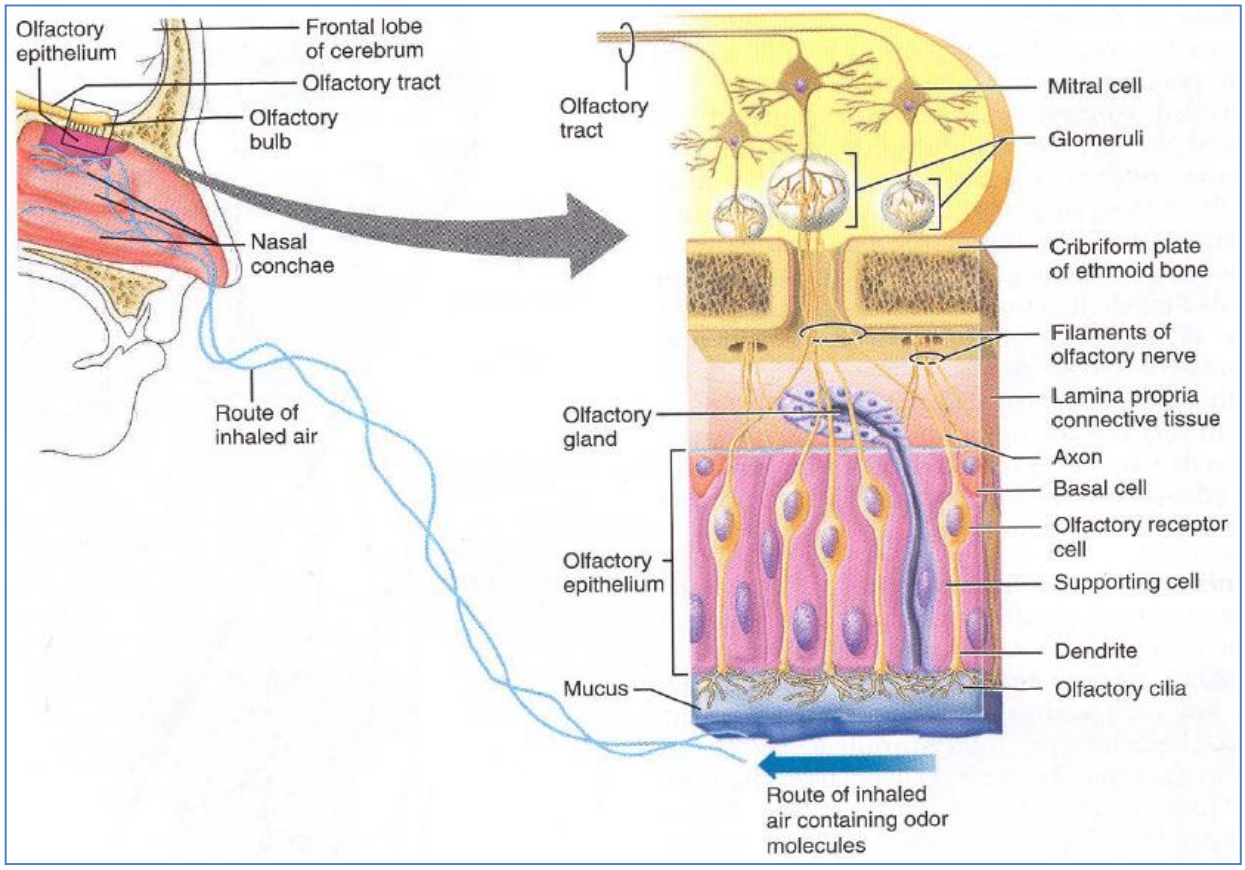
- **Structure of Taste Buds:**
  - *Each* taste bud consists of 50-100 epithelial cells. (3 Types of associated epithelial cells):
    - **Supporting Cells**:
      - Form the bulk of the taste bud.
    - **Receptor Cells:**
      - Have Long Microvilli that project from their tips, through a taste pore to the surface.
      - These Long Microvilli (Gustatory Hairs) are the sensitive portions of these cells.
      - Taste fibres of the Facial/Glossopharyngeal/Vagus Cranial Nerves coil around the Receptor Cells.



- **Basic Taste Sensations:**
  - **Sweet** - Sugars, some Amino Acids, Lead Salts
  - **Sour** - Acids
  - **Salt** - Metal Ions (Particularly Sodium)
  - **Bitter** - Alkaloids (Quinine, Caffeine, and Nicotine) – NB: Dislike for bitter is Protective.
  - **Umami** - "Delicious" - Glutamate (Steak, Cheese) & MSG.
- **Physiology of Taste:**
  - Tasting requires a chemical to dissolve in the saliva, then diffuse through a **Taste Pore**, and contact **Gustatory Hairs**.
  - Binding of chemical induces a depolarising potential → Release of Neurotransmitter.
  - Neurotransmitter → Triggers dendrites of sensory nerves → Action Potentials.
- **Taste Transduction:**
  - **Basic Overview:**
    - Stimulation of Gustatory Cell → leads to an ↑in intracellular [Ca^+] → Causes NT Release → Stimulates sensory nerves.
  - **Each taste-quality has its own way of stimulating the receptor cells:**
    - Salty – due to Na^+ influx → directly depolarises the Gustatory Cell.
    - Sour – due to H^+ either: 1) Entering the cell, 2) Opening Ion Channels, or 3) Blocking K^+ Channels.
    - Bitter, Sweet & Umami – G-Protein Linked Receptors that produce depolarisation.
- **Gustatory Pathway:**
  - Afferent fibres from taste buds run in 3 Cranial Nerves:
    - **Facial** (first 2/3 of tongue)
    - **Glossopharyngeal** (last 1/3 of tongue)
    - **Vagus** (Epiglottis & Lower Pharynx)
  - Afferent Fibres synapse in the Solitary Nucleus of the Medulla → Thalamus → Gustatory Cortex in Parietal Lobes.

Olfaction (Smell):

- **Location of Olfactory Receptors:**
  - Located in the 'Olfactory Epithelium' – a 5cm^2 patch of Pseudostratified Columnar Epithelium in the roof of the Nasal Cavity.
- **Structure of Olfactory Receptor Cells:**
  - They are Modified **Bipolar** Neurons
  - Have a thin apical dendrite, terminating in the olfactory mucus as **Olfactory Cilia.** (↑Surface Area)
  - Have thin, Unmyelinated Axons that collect to form the **Olfactory Nerve** (CN-I)
    - Filaments of the Olfactory Nerves project superiorly through the **Cribriform Plate**.
    - Axons Synapse in the **Olfactory Bulbs**.

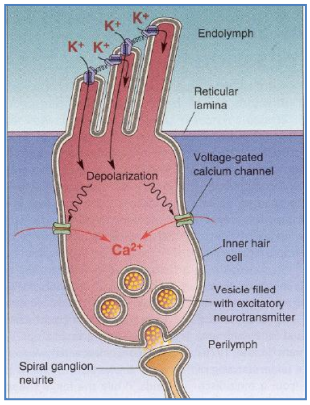


- **Physiology of Olfactory Receptors:**
  - For an odorant to be smelt, it must dissolve in the olfactory mucus.
  - Once dissolved, odorants:
    - Stimulate the olfactory receptors by binding to Odorant Binding Proteins in the membranes of the Olfactory Cilia
    - Depolarisation → Action potential → Stimulates the Olfactory Bulb.
- **The Olfactory Pathway:**
  - Olfactory Receptors → Mitral Cells (in 'Glomeruli' – Each glomerulus receives only 1 type of odour) → Mitral Cell Axons (Olfactory Tracts) → Either:
    - 1) The Thalamus → Olfactory Cortex & Frontal Lobe (conscious interpretation/identification).
    - 2) The Hypothalamus, Amygdala & other Limbic System regions – Elicit emotional responses to odours.

Special Senses II: Hearing & Equilibrium

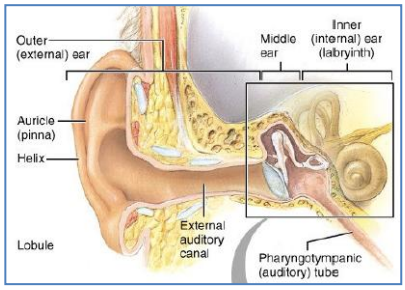
Functional Overview of the Ear:

- **Ear is Responsible for 2 Special Senses:**
  - **Hearing** – Associated with Outer, Middle & Inner Ear (Cochlear) Structures.
  - **Equilibrium** - Associated with *just* the Inner Ear (Vestibular Apparatus)
- **NB: Receptors for both = "*Hair Cells*":** (NB: their functional differences are due to specialised anatomy)
  - **How they Work:**
    - Hair Cells have '*Cilia'* projecting from their apical surface into gelatinous masses:
    - These 'Cilia' are distorted by movements in the gelatinous masses → Change in Membrane Potential (:. Hair Cells are Mechanoreceptors)
  - **How Distortion of Cilia causes the Change in Membrane Potential:**
    - At the top of each cilia, there are Mechano-Gated **K^+ Channels**, joined together by '***Tip Links***'
    - **At Rest:** Half of the K^+ Channels are open, maintaining RMP.
    - **If Distorted & *Tip Links* are *Stretched*:** All K^+ Channels open → Depolarisation
    - **If Distorted & *Tip Links* are *Compressed*:** All K^+ Channels are closed → Repolarisation

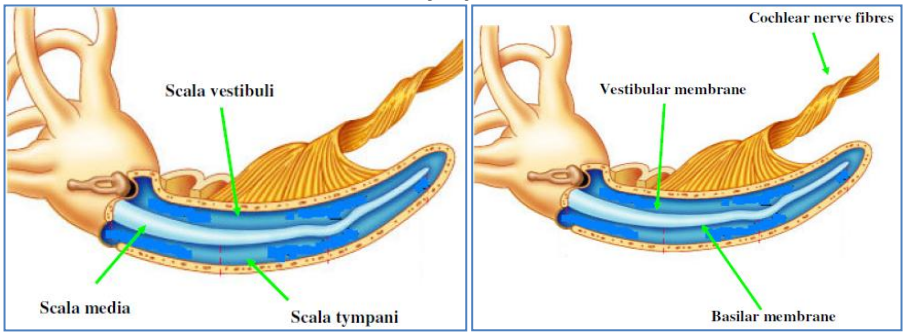


Ear Anatomy:

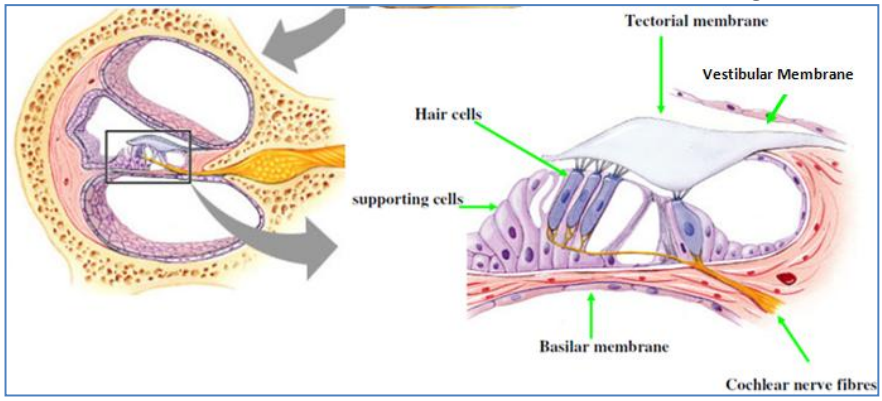
- **Outer Ear:**
  - **Pinna (Auricle):**
    - The Outermost part of the ear
  - **External Auditory Canal:**
    - The canal that conducts the soundwaves waves into the Tympanic Membrane (Eardrum)
- **Middle Ear:**
  - **Tympanic Membrane (Eardrum):**
    - Thin, translucent, connective Tissue Membrane (Skin on outside, mucosa on inside)
    - Connect to the 3 Auditory Ossicles
  - **The 3 Auditory Ossicles:**
    - Malleus("Hammer"/"Mallet")
    - Incus ("Anvil")
    - Stapes ("Stirrup")
    - NB: 2 Skeletal Muscles (Tensor Tympani & Stapedius) Reflexively contract when ears are assaulted by loud sounds – Reduces Sound Conduction.
  - **Oval Window of the Cochlea:**
    - Transfers Vibration of the Stapes → Into the Cochlea.
  - **Eustachian (Pharyngotympanic) Tube:**
    - Equalizes pressure between the Outer & Middle Ear



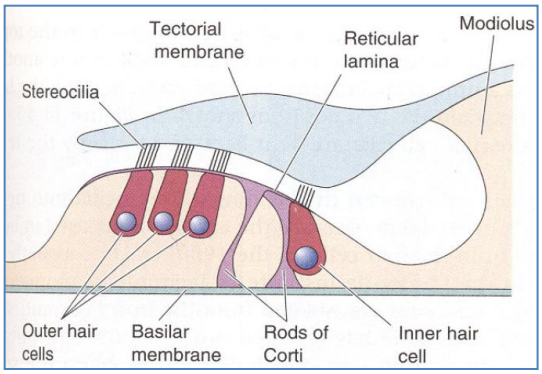
- **Inner Ear – (Cochlea & Vestibular Apparatus):**
  - **Cochlea - HEARING:**
    - The Spiral-Shaped Organ
    - **Begins @ the *Oval Window*:**
      - The *Entry Point* of the Cochlea.
    - **Ends @ the Round Window:**
      - The Exit-Point of the Cochlea
    - **Consists of 3 Coiled Ducts – Separated by 2 Membranes:**
      - **Scala Vestibuli (Vestibular Duct):**
        - Begins @ the Oval Window
        - Ends @ the apex of the Cochlea
        - Filled with ***Perilymph***.
        - Separated from the Scala Media by the ***Vestibular Membrane***.
      - **Scala Media (Cochlear Duct):**
        - Runs through the middle of the Cochlea.
        - Separates the Vestibular Duct & Tympanic Duct.
        - Filled with ***Endolymph***.
        - Separated from the Scala Tympani by the ***Basilar Membrane***.
        - Contains the ***Spiral Organ of Corti*: (See Next Page)**
      - **Scala Tympani (Tympanic Duct):**
        - Begins @ the apex of the Cochlea
        - Ends @ the Round Window
        - Filled with ***Perilymph***.

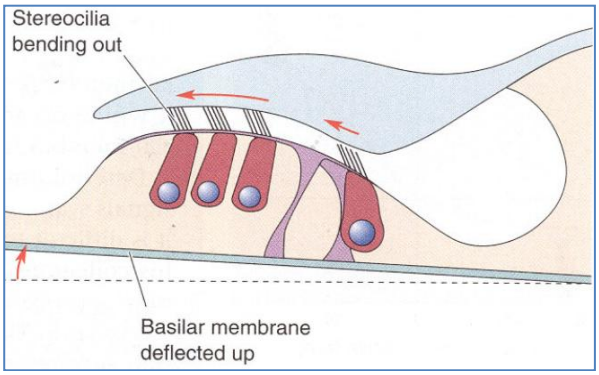


- ***The Spiral Organ of Corti*:**
  - Sits inside the Scala Media & runs along the Basilar Membrane.
  - **Composed of:**
    - **The Tectorial Membrane** (Overlying the Hair Cells)
    - **Hair Cells** (Receptors for hearing) – Associated with cochlear nerve fibres:
      - **1x Row of Inner Hair Cells** – Has several inputs to the Spiral Ganglion
      - **3x Rows of Outer Hair Cells** – Has Only 1 input to the Spiral Ganglion
    - **Supporting Cells**
    - **The Basilar Membrane**
  - Cochlear Branch of the Vestibulocochlear Nerve Originates Here.

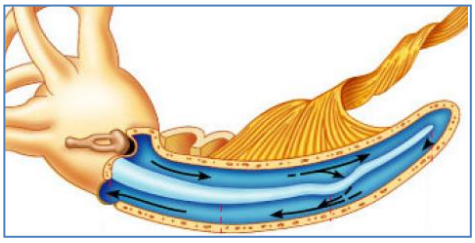


- **Audiotransduction:**
  - → Waves exit the Scala Media by Penetrating the Basilar Membrane & enter the Scala Tympani:
    - The waves penetrating the Basilar Membrane cause it to Vibrate.
    - Vibration of the Basilar Membrane pushes the Hair Cells in the Organ of Corti up into the Tectorial Membrane, Distorting the Cilia & Initiating Graded Potentials in the Cochlear Nerve.





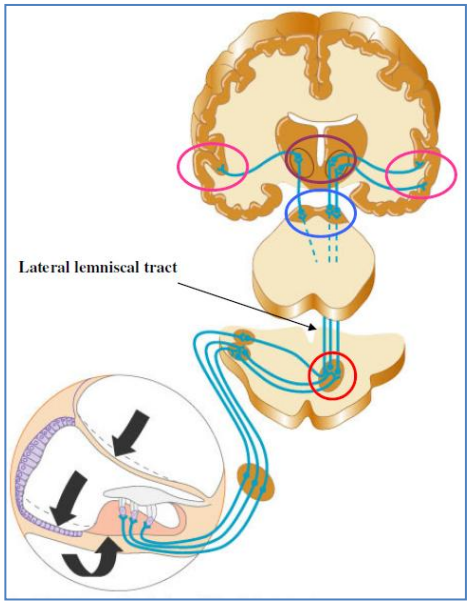
  - → Waves continue down the Scala Tympani & leave the Cochlea via the Round Window – This prevents echoing of the sound waves within the Cochlea.



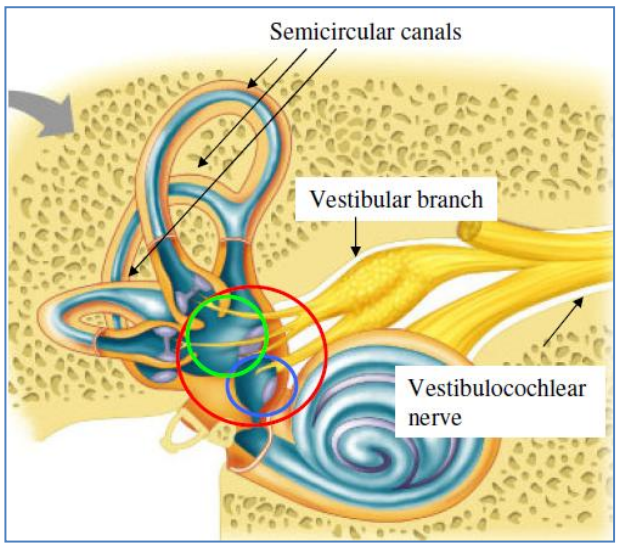
- **Pitch & Volume:**
  - **Pitch** – is coded in the ***point along the basilar membrane*** which is distorted by the wave.
  - **Volume** – is coded by the ***degree of distortion of the hair cells*** by the wave.

Pathway From the Cochlea to the Brain:

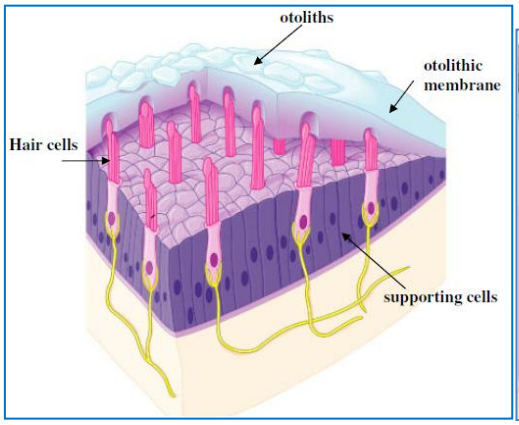
- Hair Cells → Cochlear Branch of the Vestibulocochlear Nerve → Cochlear Nuclei of the Medulla → Superior Olivary Nucleus → Lateral Lemniscal Tract → Inferior Colliculus → Medial Geniculate Nucleus of the Thalamus →
  - Primary Auditory Cortex – (Conscious Sound)
  - Superior Colliculus – (Auditory Reflexes – Startle, Turning Head, etc.)

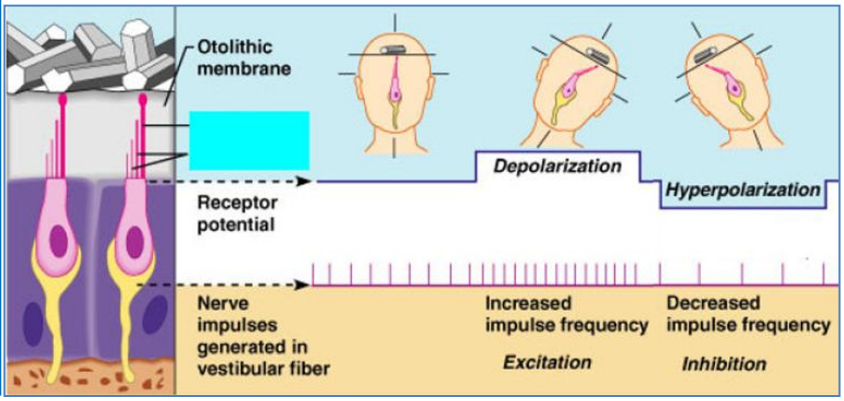


- **<u>Vestibular Apparatus - EQUILIBRIUM:</u>**
  - Vestibular Branch of the Vestibulocochlear Nerve Originates Here.
  - **Consists of:**
    - **A Vestibule, Containing:**
      - **1x Utricle:**
      - **1x Saccule:**
    - **& 3 Semicircular Canals.**

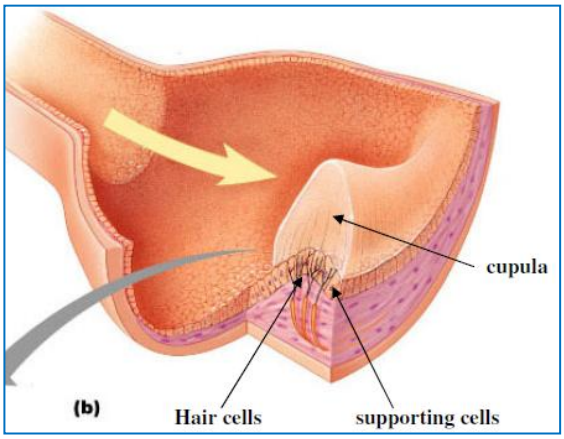


  - **<u>The Vestibule:</u> NB: Both the Utricle & Saccule have a Maculae:**
    - **Maculae =** Receptor Organs for Linear Acceleration (Static Equilibrium)
      - Provides Info about Orientation of the Head with respect to Gravity, Linear Acceleration & Angular Acceleration.
    - **Composed of:**
      - **Hair Cells** (Cilia Project into the Otolithic Membrane)
      - **Supporting Cells**
      - **Otolithic Membrane** - (Gelatinous Mass with 'Otoliths' – "Ear Stones" – of Calcium Carbonate Crystals resting on top. These 'Otoliths' provide the inertia required to move the Otolithic Membrane during head movement)

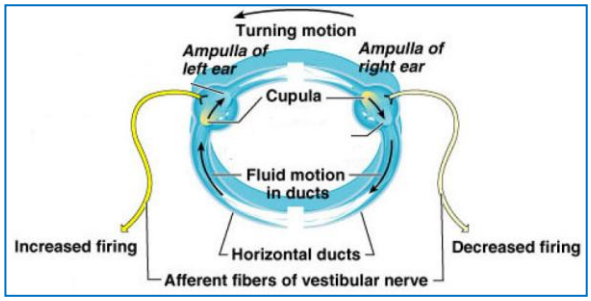




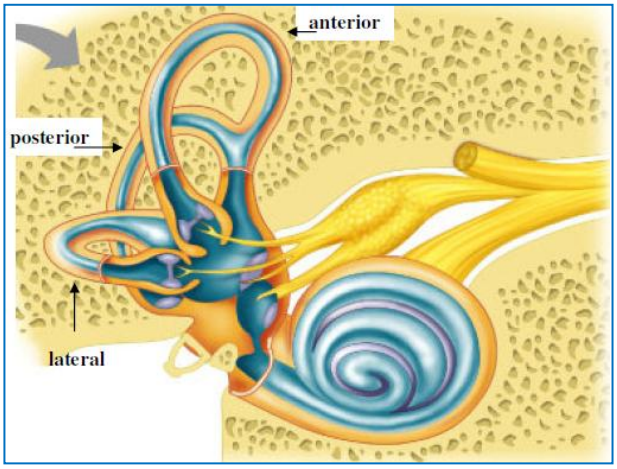
  - **<u>The 3 Semicircular Canals:</u> NB: At the end of each Canal is a Swelling = "*Crista Ampularis*":**
    - **Crista Ampularis** = Receptors for Rotation (Dynamic Equilibrium).
    - **Composed of:**
      - **Hair Cells** (Cilia Project into the Cupula)
      - **Supporting Cells**
      - **Cupula** – (Gelatinous Mass encircling the entryway of each Crista Ampularis. Rotation of the head in the plane of the canal causes fluid movement over the Cupula, distorting the Hair Cells)



- **NB: There are 2 Semi-Circular Canals for each *'Plane'* of Movement:**
  - One on each side of the head
  - This allows you to determine the ***Direction*** of head motion.



- **NB: Each Semi-Circular Canal is Responsible for a different *Plane*:**
  - **Anterior –** ('Ear-to-Shoulder' Motion)
  - **Posterior-** ('Nodding' Motion)
  - **Lateral** - ('Shaking' ('no') Motion)



<u>Equilibrium Pathways To the Brain:</u>

- Equilibrium is Subconscious
- Info goes straight to the reflex centres in the **Brainstem** & **Cerebellum**:
  - **Vestibular Nuclei:**
    - Integrates Balance + Receive some Visual & Somatic Inputs
    - Sends commands to Brainstem Motor Centres controlling Eyes & Neck/Limb/Trunk Reflexes.

Neuroscience Notes
Special Senses I: Vision, Taste/Smell

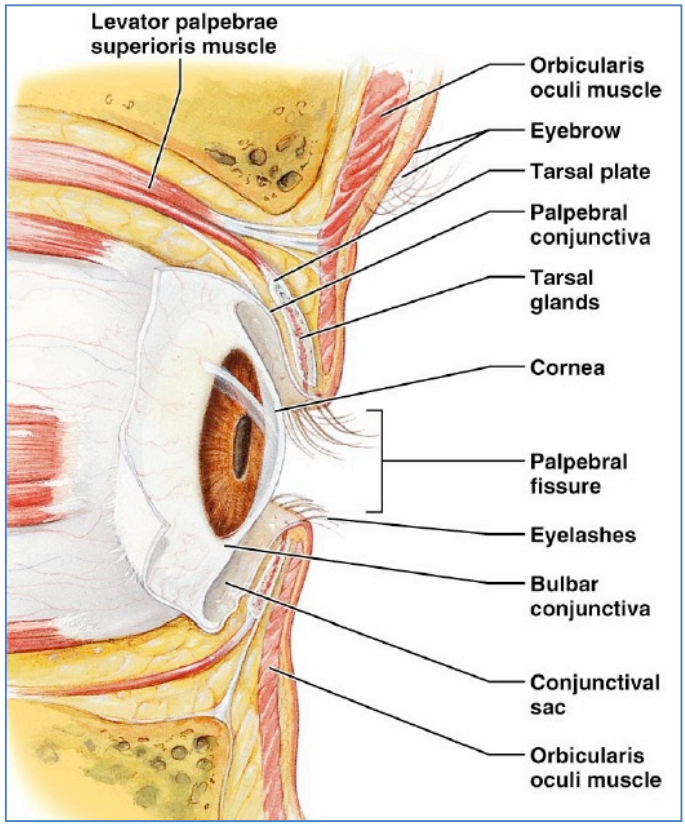
The Special Senses:

- **There are 5 Special Senses:**
  - Vision
  - Taste
  - Smell
  - Hearing
  - Equilibrium
- **They allow us to respond to:**
  - Photons (Light)
  - Chemicals
  - Vapours
  - Air-Waves
  - Gravity & Body Movement
- **ALL Sensory *Receptor Cells* are confined to the Head Region.**
  - NB: In contrast to general receptors (which are just modified nerve-endings), sensory receptors of the special senses are distinct ***Receptor Cells***, & are housed in complex sensory organs. (eg. Eye)
  - **NB: All *Receptor Cells* are *CILIATED***.

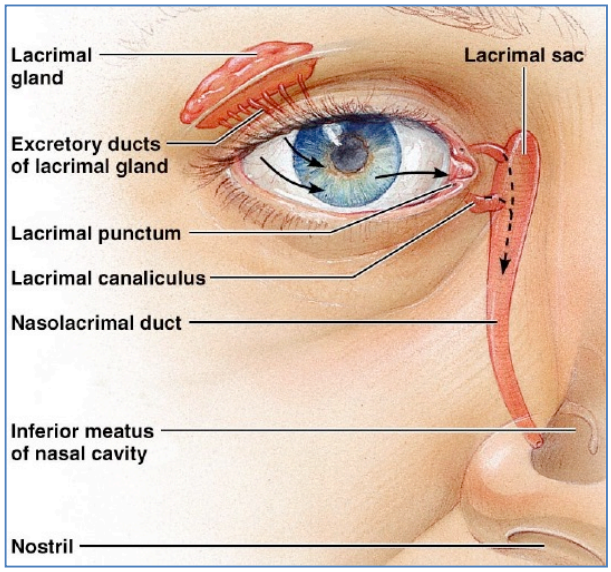
Vision:

Accessory Structures of the Eye:

- **Eyebrows:**
  - Shade the eyes from sunlight
  - Prevent water/perspiration trickling down the forehead into the eyes.
- **Eyelids ('Palpebrae'):**
  - Protect the eye when threatened by foreign objects
  - Blinking prevents drying of the eyes
- **Conjunctiva ("Joined Together"):**
  - Transparent mucus membrane lining the eyelids ('Palpebral Conjunctiva') & the anterior eyeball surface ('Bulbar Conjunctiva').
  - Produces lubricating mucus – Prevents drying out.

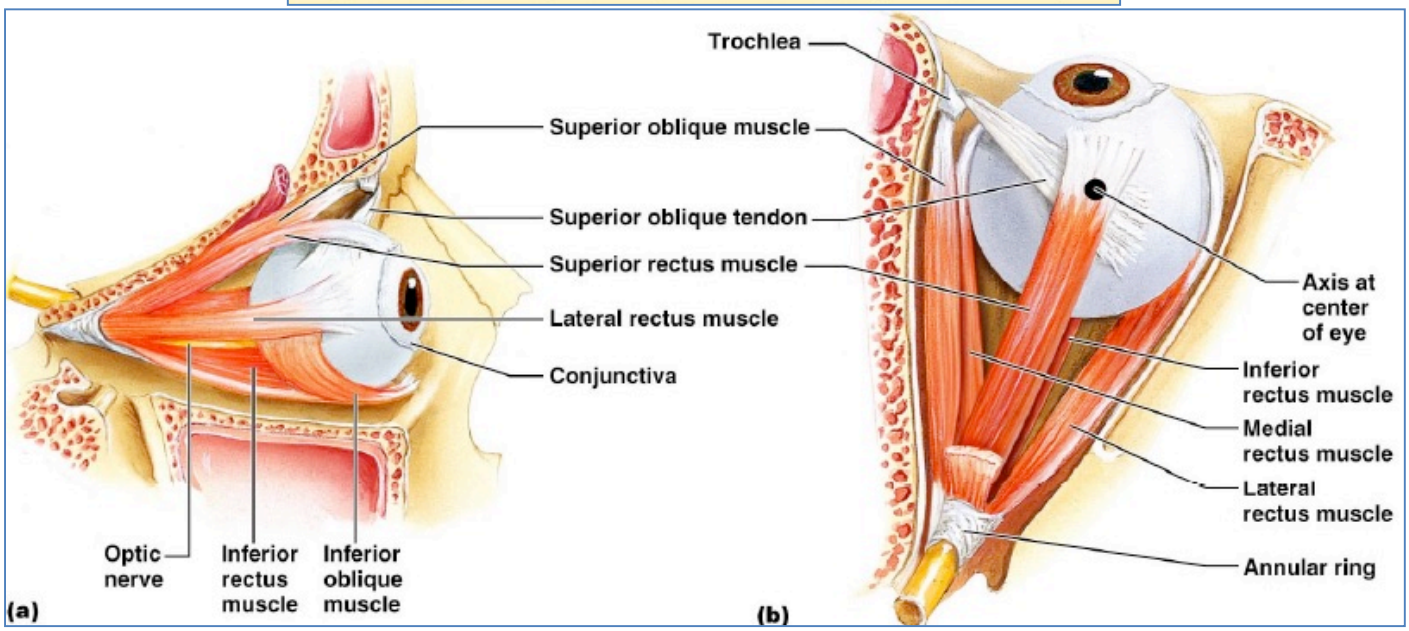


- **Lacrimal Apparatus:**
  - **Consists of:**
    - **Lacrimal Gland (Tear Gland):**
      - Located in the orbit above the eye.
      - - Secretes dilute saline (Lacrimal secretion/tears)
    - **Lacrimal Canaliculi:**
      - 2 openings on medial margin of each eyelid.
      - - Drains tears into the Lacrimal Sac → Nasolacrimal Duct → Nose.
  - NB: Lacrimal fluid contains *Mucus, Antibodies &* ***Lysozyme*** (an antibacterial)



- **Extrinsic Eye Muscles:**
  - Eyeball movement is controlled by 6 muscles
  - **The 4x Rectus Muscles** originate from a common tendinous ring (**Annular Ring**) at the back of the eye.
  - **The 2x Oblique Muscles** take different paths through the orbit. They are required to cancel the medial pull of the superior & inferior recti to allow purely vertical eye movement.

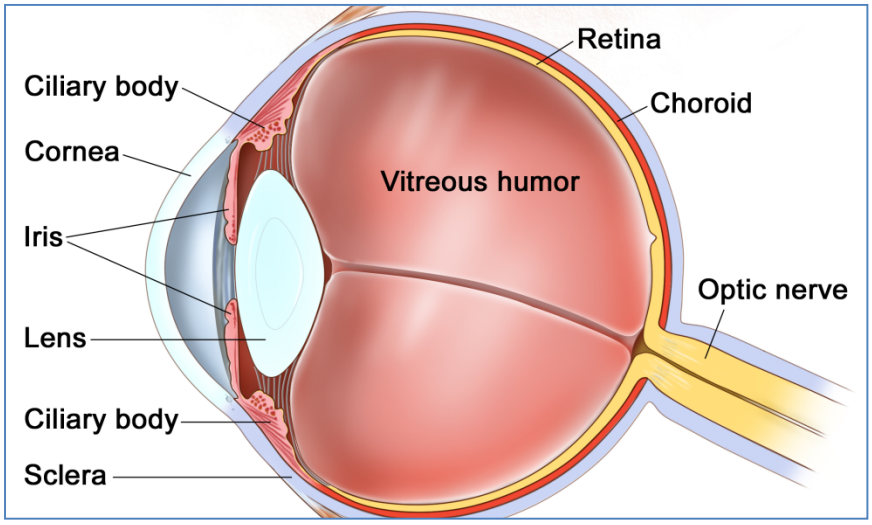
Name	Action	Controlling cranial nerve
Lateral rectus	Moves eye laterally	VI (abducens)
Medial rectus	Moves eye medially	III (oculomotor)
Superior rectus	Elevates eye and turns it medially	III (oculomotor)
Inferior rectus	Depresses eye and turns it medially	III (oculomotor)
Inferior oblique	Elevates eye and turns it laterally	III (oculomotor)
Superior oblique	Depresses eye and turns it laterally	IV (trochlear)



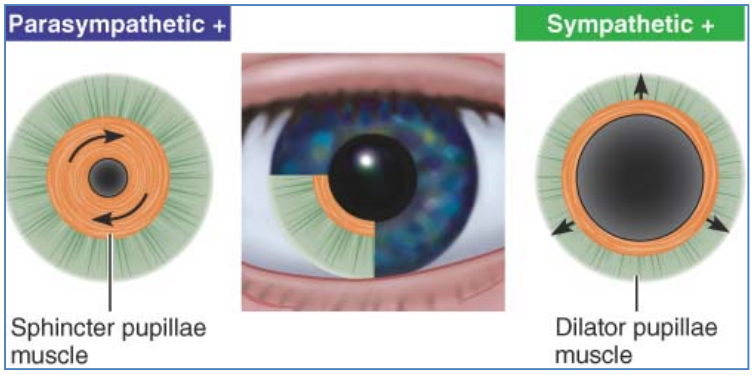
Lateral View of R-Eye **Superior View of R-Eye**

Eye Anatomy:

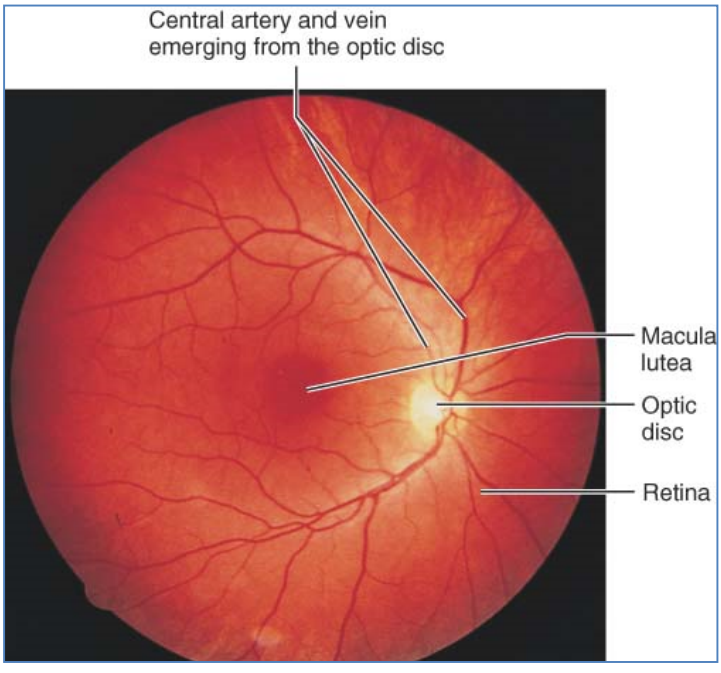
- **3-Layered Wall (Tunics):**

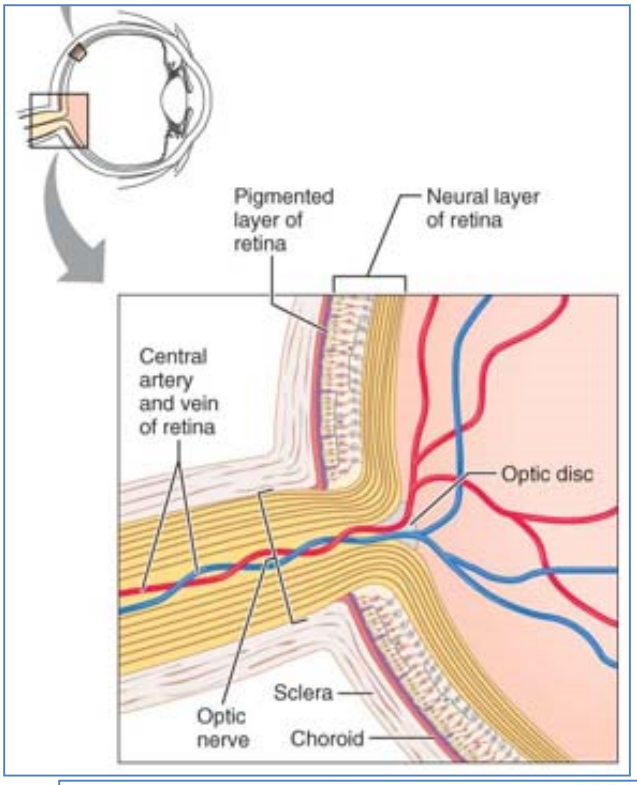


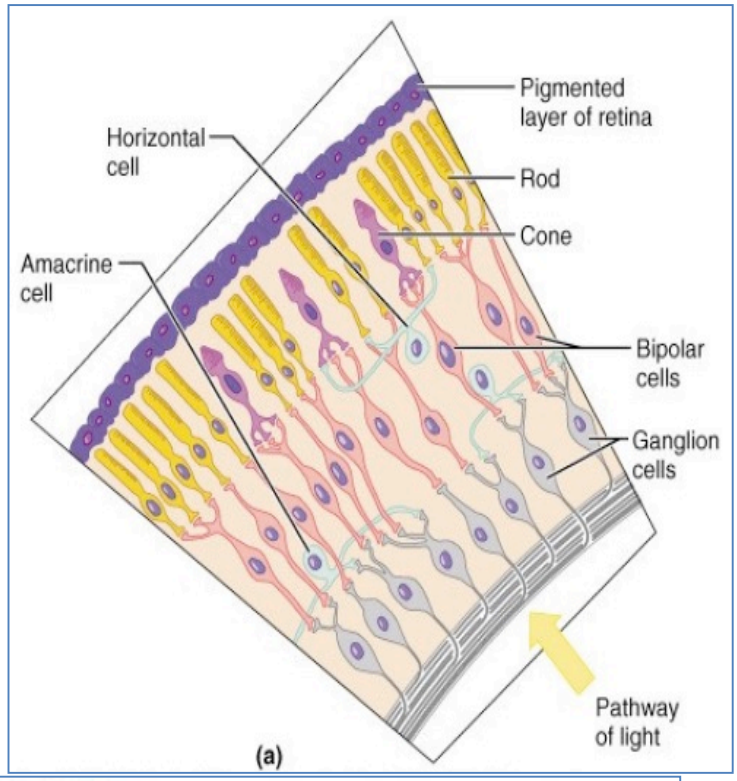
  - **1. Fibrous Layer:**
    - Outermost layer
    - Made of Dense Connective Tissue
    - **2 Regions:**
      - **Cornea:**
        - The Clear, Anterior part of the eye that lets light in.
        - Major role in the refractive apparatus of the eye.
      - **Sclera:**
        - The white/opaque, Posterior part of the eye.
        - Protects & shapes the eyeball.
        - It is continuous with the Dura Mater of the brain via the optic nerve sheath.
  - **2. Vascular Layer:**
    - Middle Layer
    - **2 Parts:**
      - **Choroid:**
        - Highly vascular, dark membrane (Posterior 5/6 of eye).
          - Supplies nutrition to all eye layers
          - Absorbs light, preventing it from scattering/reflecting within the eye.
        - Anteriorly, it becomes the **Ciliary Body:**
          - A thickened ring of smooth muscle around the lens.
          - These **Ciliary Muscles** control lens shape.
          - **The Ciliary Zonule** (Suspensory ligaments) connects the Ciliary Muscles to the lens.
      - **Iris ("Rainbow"):**
        - The Anterior, coloured portion of the Vascular Layer
        - Lies between the Cornea & the Lens.
        - Its round, central opening (**The Pupil**) allows light in.
        - Consists of **2 Smooth Muscle Layers:**
          - **Sphincter Pupillae** (Circular) → Pupil Constriction
          - **Dilator Pupillae** (Radial) → Pupil Dilation

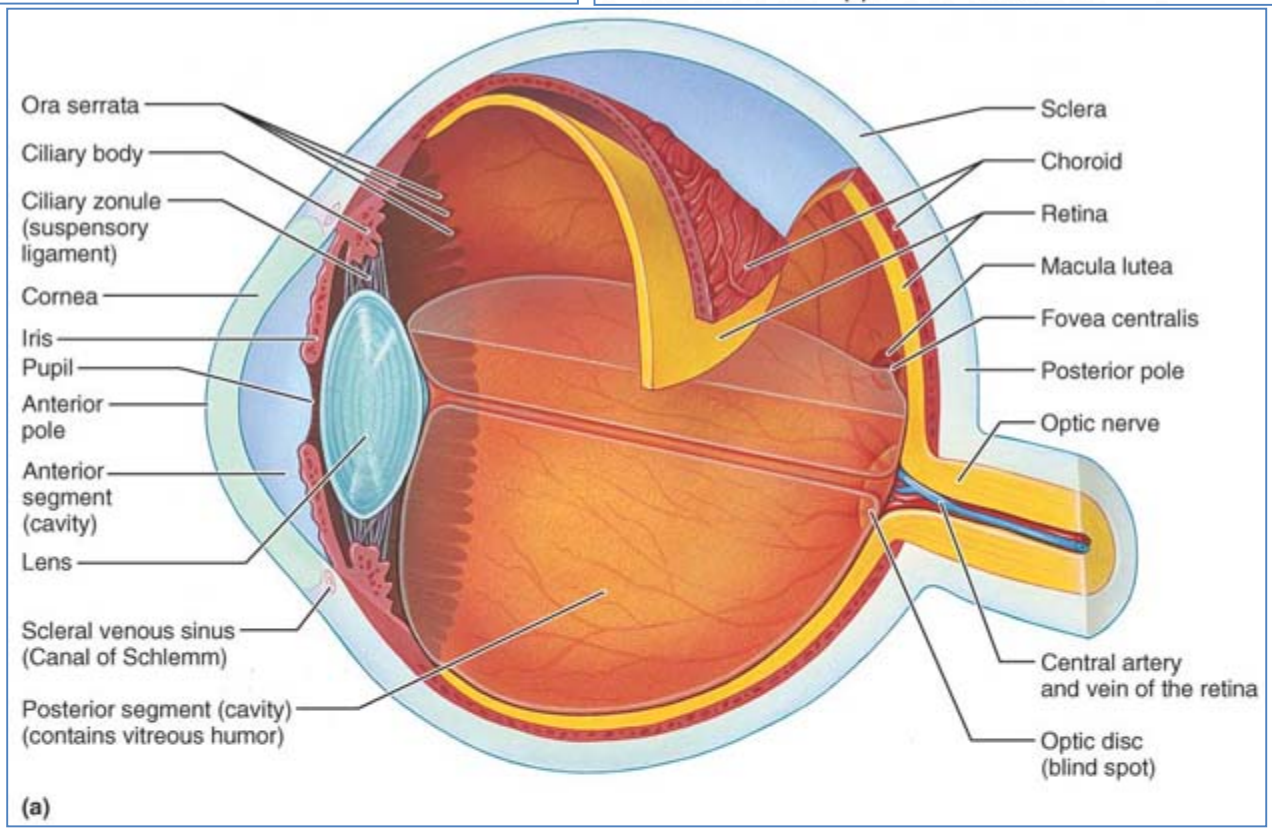


- **3. Retinal Layer:**
  - Innermost Layer
  - **2 Sub-Layers:**
    - **Pigmented Layer:**
      - Outer Retinal Layer
      - Dark, Single-cell-thick lining adjacent to the Choroid.
      - Absorbs light, prevents scattering/reflection within the eye.
      - Also function as phagocytes, removing dead/damaged photoreceptor cells.
      - Store Vitamin-A (needed by photoreceptor cells)
    - **Neural Layer:**
      - Inner Retinal Layer
      - Transparent layer of Photoreceptors/Neurons/ & Glia
      - Direct Role in Vision (Light Transduction)
      - **Composed of 3 Types of Neurons:**
        - **Photoreceptors:**
          - Light Transduction
          - Blood Supply = The Choroid
          - **2 Types:**
            - **Rods –** Light Detectors (Dim & Fuzzy)
            - **Cones** – Colour Detectors (Bright & Sharp)
        - **Bipolar Neurons:**
          - Connect Photoreceptors to Ganglion Cells
          - Blood Supply = The Central Artery/Vein of the Retina.
        - **Ganglion Cells:**
          - Generate & Conduct the Action Potentials → Brain
          - Blood Supply = The Central Artery/Vein of the Retina.
      - **NB:** Also contains other types of neurons (**Amacrine Cells & Horizontal Cells**) which play a role in visual processing.
      - **The Optic Disc -** Where the Ganglion Cells' Axons exit the eye to form the optic nerve. (Aka: Blind Spot)
      - **The Macula Lutea ("Yellow Spot"):**
        - Oval region directly at the eye's Posterior Pole.
        - Contains mostly **Cones**
        - **The Fovea Centralis –** a tiny pit in the centre of the Macula Lutea – Contains ONLY **Cones.**
      - **NB: Cone density** decreases toward the retinal periphery.
      - **NB: Rod density** increases toward the retinal periphery.



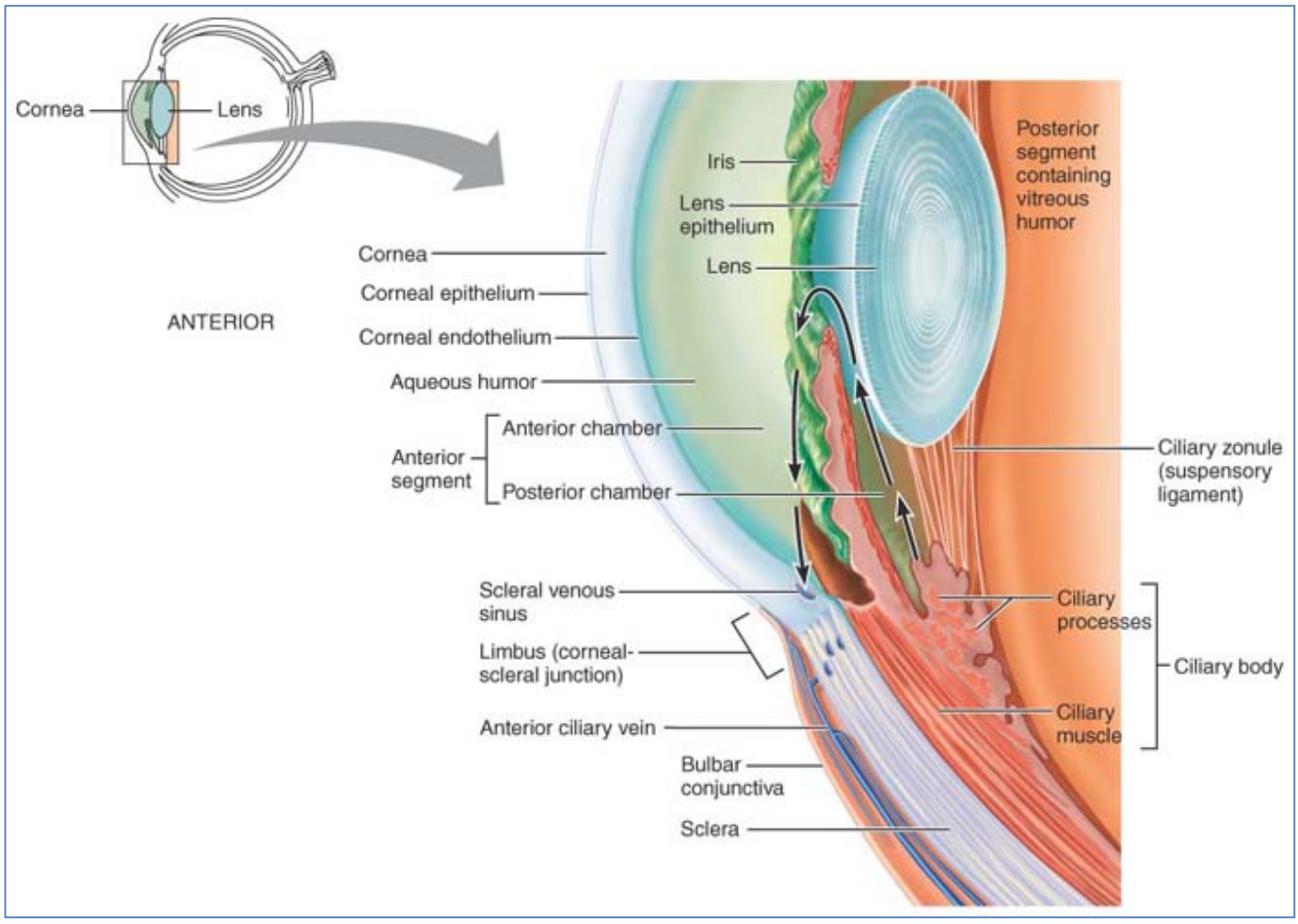




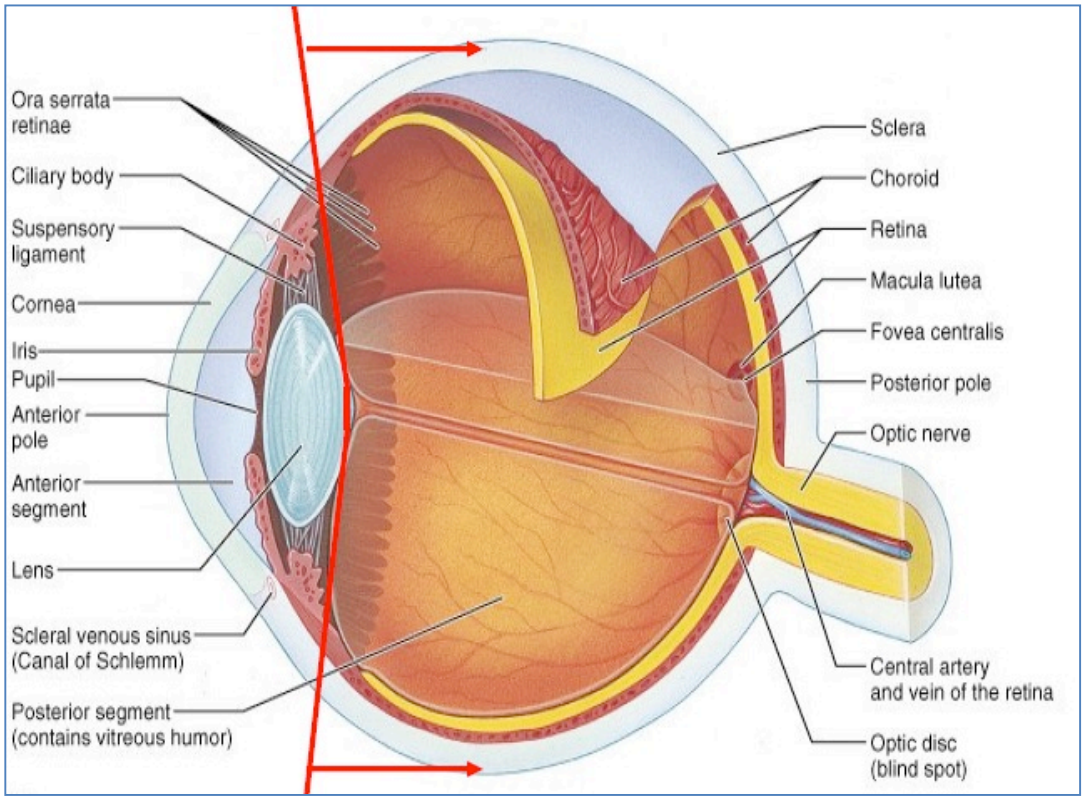


www.regentstudies.com

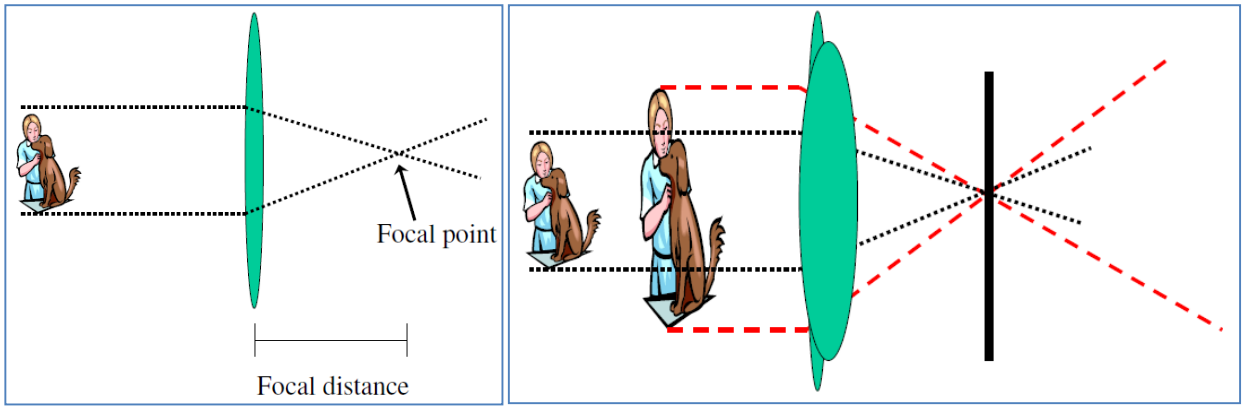
- **The Eye's 2 Segments & Fluids:**
  - The Lens & its Ciliary Zonule (Suspensory Ligaments) Divide the eye into 2 segments:
  - **1. Anterior Segment:**
    - In front of the lens.
    - **Filled with 'Aqueous Humour'** – a clear, plasma-like substance:
      - **Features:**
        - Continually formed by capillaries of the **Ciliary Processes** in the posterior chamber.
        - Flows from the Posterior Chamber to the Anterior Chamber
        - Drains from Ant. Chamber into venous blood via the **Scleral Venous Sinus** (Canal of Schlemm) which encircles the Sclera-Cornea Junction
        - Has the same refractive index as the Cornea
      - **Functions:**
        - Its pressure supports the eyeball internally.
        - Supplies Nutrients & Oxygen to the Lens & Cornea
    - **Subdivided by the Iris into 2 Chambers:**
      - **Anterior Chamber:**
        - Between the Cornea & the Iris
      - **Posterior Chamber:**
        - Between the Iris & the Lens.
    - **Contains:**
      - Cornea
      - Iris
      - Lens
      - Ciliary Muscles (Lens accommodation)
      - Ciliary Processes (Aqueous humour production)
      - Aqueous Humour
      - Ciliary Zonule (Suspensory Ligaments)
      - Scleral Venous Sinuses (Canal Of Schlemm)



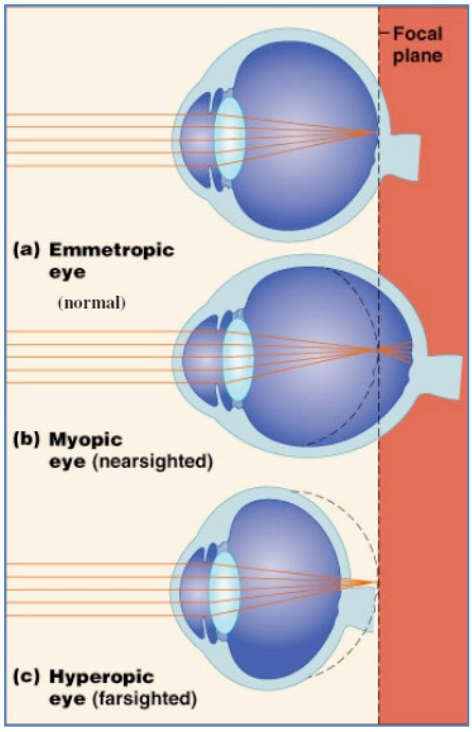
- **2. Posterior Segment:**
  - Behind the lens.
  - **Filled with a clear gel called 'Vitreous Humour'** ("Glassy Fluid"):
    - **Features:**
      - Formed in the Embryo & Lasts a Lifetime
      - Has the same refractive index as the cornea
    - **Functions:**
      - Transmits light
      - Supports the posterior surface of the lens
      - Holds the Neural Retina firmly against the Pigmented Layer
      - Contributes to Intraocular Pressure
  - **Contains:**
    - Vitreous Humour
    - Retina
    - Choroid
    - Sclera
    - Macula Lutea & Fovea Centralis
    - Optic Disc
    - Optic Nerve



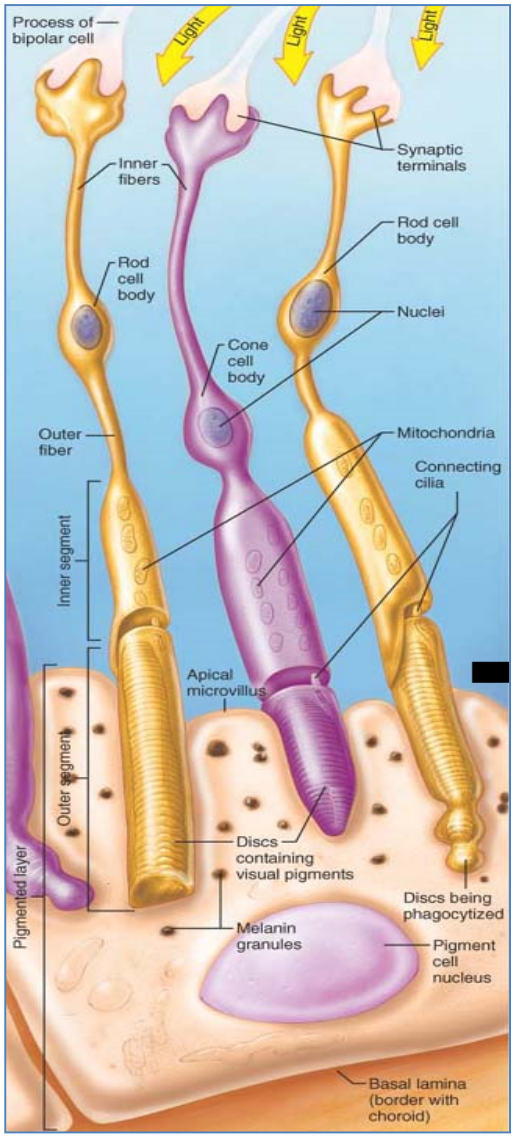
- **The Eye's Lens:**
  - **Features:**
    - Biconvex
    - Transparent
    - Flexible
    - Enclosed in a thin, elastic capsule
    - Held in place by the Ciliary Zonule (Suspensory Ligaments)
    - **2 Parts:**
      - **Lens Epithelium:**
        - On the Anterior Lens Surface
        - Cuboidal Cells
      - **Lens Fibres:**
        - Form the bulk of the lens
        - Arranged in layers (like an onion)
  - **Lens Physics:**
    - A lens of a certain 'power' has a certain **Focal Point**. The distance between the lens & the focal point is the **Focal Distance**.
    - NB: The eye has a **fixed Focal Distance**, therefore the Lens **'Power' must be variable**.
  - **Function:**
    - Focuses light rays onto the retina.
    - **Accommodation:** Changes shape (& hence, lens 'Power') to maintain Focal Distance.

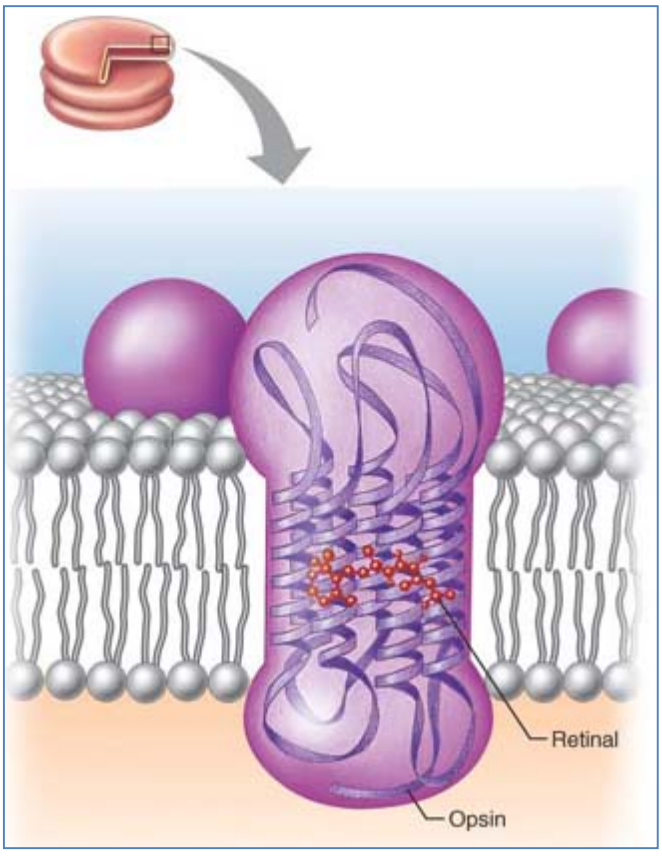


  - **Focal Disorders:**
    - **Emmetropia** (Normal Vision)
    - **Myopia** (Short Sighted) – Eye is too long
    - **Hyperopia** (Far Sighted) – Eye is too short

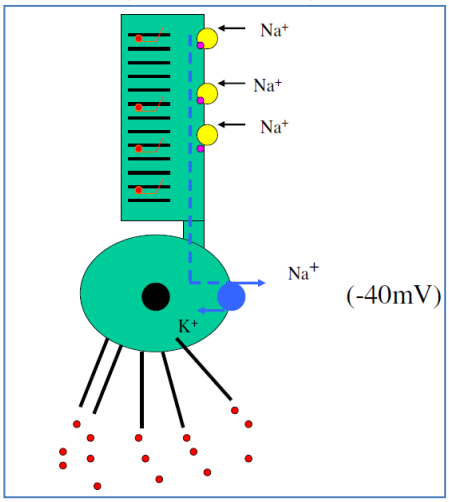


- **Photoreceptors:**
  - The cells that transduce light. (Rods & Cones)
  - Contain an array of **Visual Pigments (Photopigments)** that change shape as they absorb light:
  - These Photopigments are imbedded in areas of the Photoreceptor Membranes that form discs.
    - NB: Folding the PM into discs magnifies the surface area available for trapping light.
  - **Photoreceptor Anatomy:**
    - **Outer Segment:**
      - Contains the Membranous Discs embedded with Photopigments
    - **Connecting Cilia:**
      - Joins the Outer & Inner Segments
    - **Inner Segment:**
      - Contains the Photoreceptor Cell Bodies
  - **Differences (Rods Vs. Cones):**
    - Have different *thresholds* for activation.
    - Contain different visual pigments - absorb different wavelengths of light.
    - Are "wired" differently.
  - **Rods:**
    - High Sensitivity (Respond well to dim light)
    - Contain only 1 type of Photopigment (Therefore only send a 'monochrome' signal)
      - Hence why things have no 'colour' in very dim light.
    - As many as 100 Rods may feed into a single Ganglion Cell → Fuzzy, indistinct vision.
  - **Cones:**
    - Low Sensitivity (Requires bright light for activation)
    - Have 1 of 3 different pigments that respond to different colours. (Allow you to see colour)
    - Each Cone has its OWN Private Ganglion Cell → Detailed, High-Res vision.

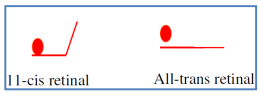




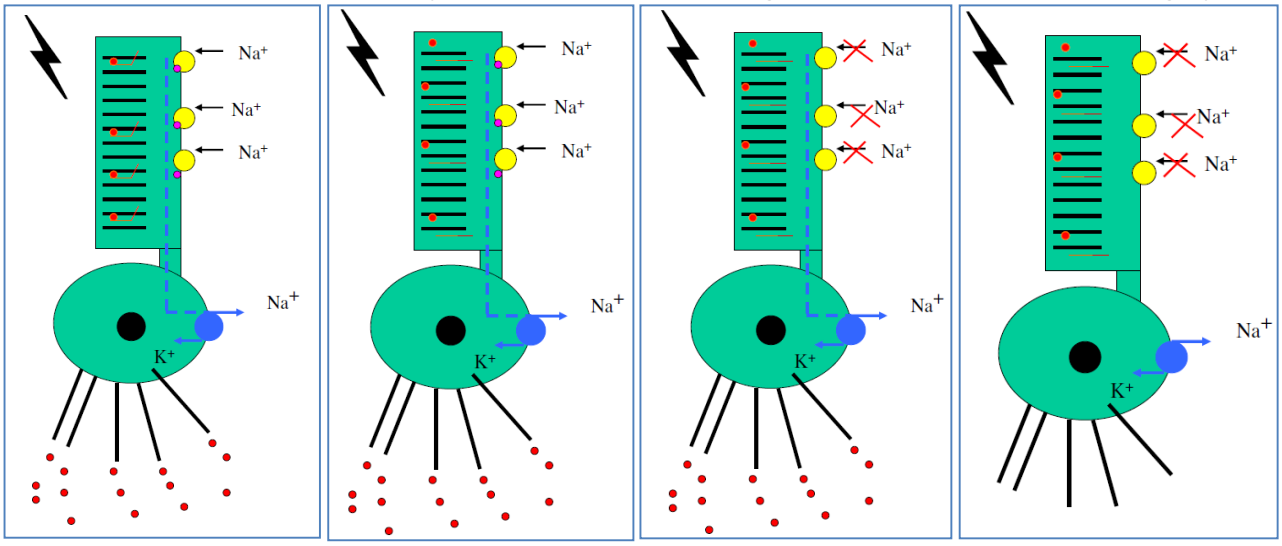
- **Phototransduction:**
  - Transforming light waves into electrical impulses.
  - The light-absorbing molecule is called '**Retinal**'. (A derivative of Vitamin-A)
  - **Retinal** combines with proteins called '**Opsins**', to form 4-types of **Photopigments.**
  - The wavelengths absorbed by the different Photopigments depend on the Type of Opsin contained.
  - **The Underlying Process:**
    - **In the Dark:**
      - **Cyclic-GMP** holds Na^+ Channels open in the Outer-Segment Membrane (Na Influx)
      - **Na^+ Flows** from the Outer-Segment, through the Connecting Cilia, and **into the cell body**. Na/K-ATPases pump Na^+ out of the cell body. (This constant flow of current is around **-40mV**, and is termed **"Dark Current"**)
      - -40mV is a **Depolarisation** Potential (RMP ≈ -70mV) → **Cell is Active**
      - Active Photoreceptors constantly release **Glutamate**.
      - **Glutamate** Directly Inhibits the Bipolar Neurons → Indirectly inhibit Ganglion Cells.



    - **When Light Strikes:**
      - Light strikes the inactive isomer of Retinal ("11-cis"), converting it to its *active isomer*.

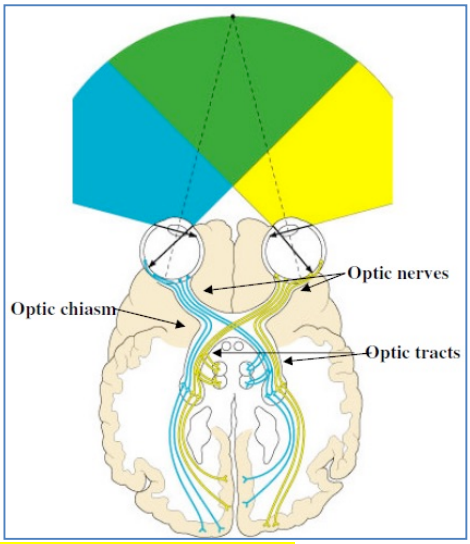


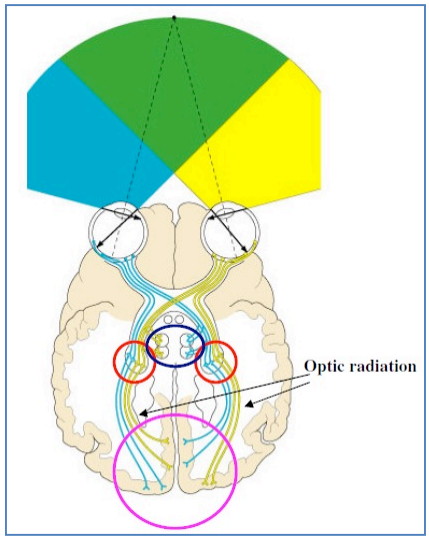
      - The Active Retinal Isomer ("all-trans" Isomer) causes Opsin to change shape to its activated form.
      - The Retinal-Opsin combination breaks down, allowing Retinal & Opsin to separate.
      - The "All-Trans"-Retinal activates an enzyme cascade → ↓**cGMP** levels → Closure of Na^+ Channels in Outer-Segment.
      - Current Flow Ceases → "Dark Current" disappears → Cell is repolarised to ≈-70mV
      - Cell is Inhibited → Stops releasing Glutamate → Removes Bipolar Cell Inhibition.
      - Active Bipolar Cell → Stimulates Ganglion Cell → Action Potential along Optic Nerve.



- **Light/Dark Adaptation:**
  - **Light Adaptation:**
    - Occurs when we move from Darkness into Bright Light. We are momentarily dazzled – as the retina is still "set" for dim light. At this point, both Rods & Cones are strongly stimulated, causing large amounts of Photopigment to be broken down → Floods the brain with signals → Glare.
    - To Compensate, the Rod system quickly desensitises and essentially turns off. The Cone system rapidly adapts, and takes over. Hence, overall the retina Desensitises.
    - Can take up to 60sec.
  - **Dark Adaptation:**
    - Occurs when we move from Brightness to Darkness. Initially we see nothing but black because:
      - 1. Cones stop functioning in low light. &
      - 2. Because Rods have been 'bleached' out by the bright light & are still turned off.
    - Once rhodopsin accumulates in the Rods, their function slowly increases.
    - Can take more than 30mins.
- **Retinal Processing:**
  - Most Direct Route of Info – Photoreceptor → Bipolar Cell → Ganglion Cell.
  - However, Lateral Inputs (Horizontal & Amacrine Cells) – Provide a level of Processing @ the Retina.
- **Pathways to the Brain:**
  - Ganglion Cell axons become the Optic Nerve.
  - Some of the Optic Nerve Fibres cross @ the **Optic Chiasm**.
  - After the Optic Chiasm, Optic Nerves become the **'Optic Tracts'**.

  - **Optic Tract fibres synapse in the:**
    - **Superior Colliculi** of the Midbrain (Blue Circles):
      - - Visual Reflex Centres controlling Extrinsic Eye Muscles
    - **Lateral Geniculate Nucleus of the Thalamus** (Red Circle):
      - - Sorts/Relays info Via the **Optic Radiation** to the **Primary Visual Cortex**. (Pink Circle)
      - Emphasis on Cone input
      - Sharpens Contrast
    - **Primary Visual Cortex** (Pink Circle):
      - Topographical map of the Retina (Similar to Homunculus)
      - Basic Processing Tasks:
        - Light Vs. Dark
        - Orientation of Object
        - **Sends Info to Visual Association Areas** – regarding Form, Colour & Motion.
    - **More Complex Processing occurs elsewhere:** (Temporal, Parietal & Frontal Lobes)





  - **Information Route/Pathway:** Photoreceptor → Bipolar Cell → Ganglion Cell → Optic Nerve → Optic Chiasm → Optic Tract → Superior Colliculus / Lateral Geniculate Nucleus of the Thalamus → Primary Visual Cortex → Visual Association Area → Perception.

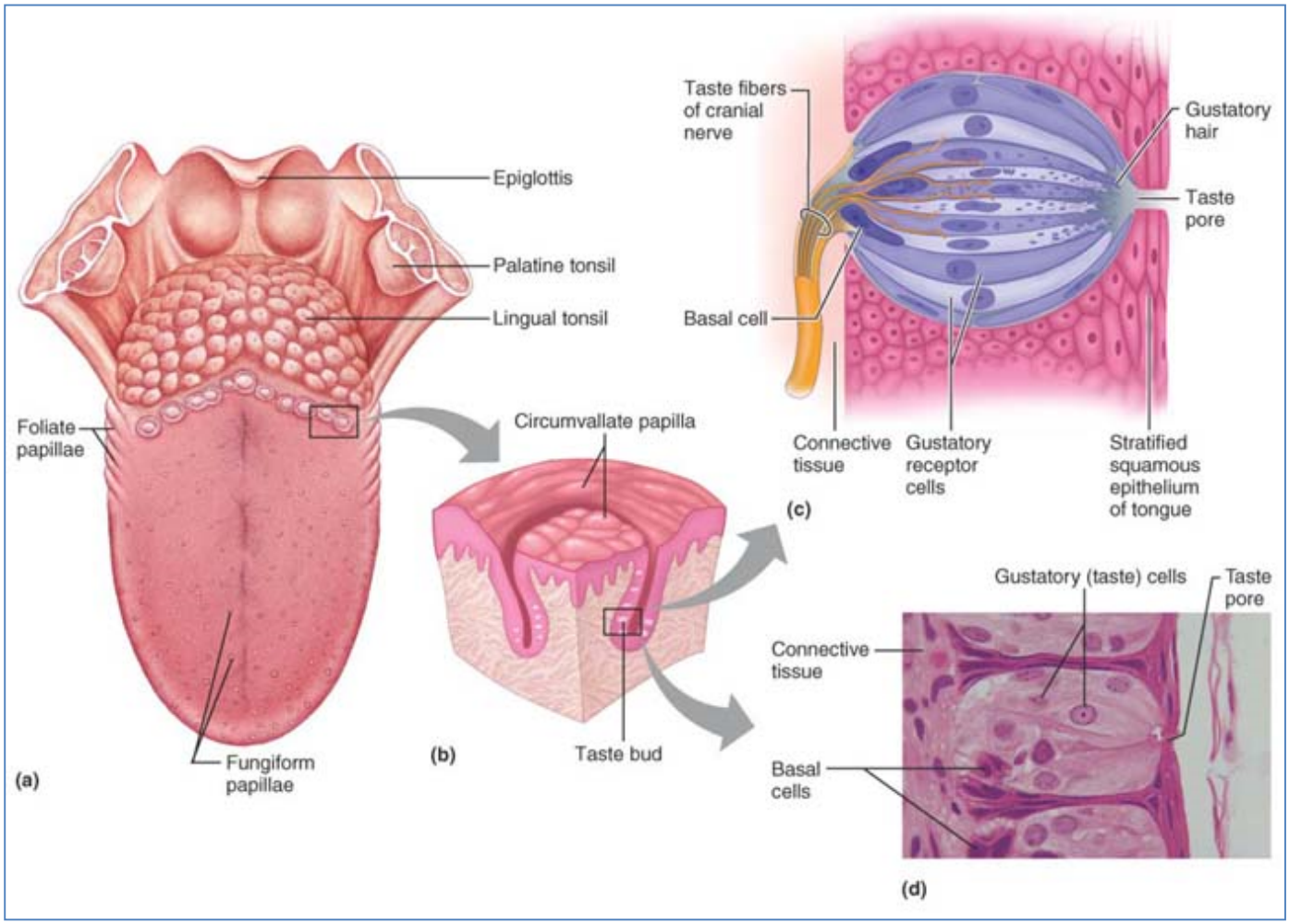
Taste/Smell:

Overview:

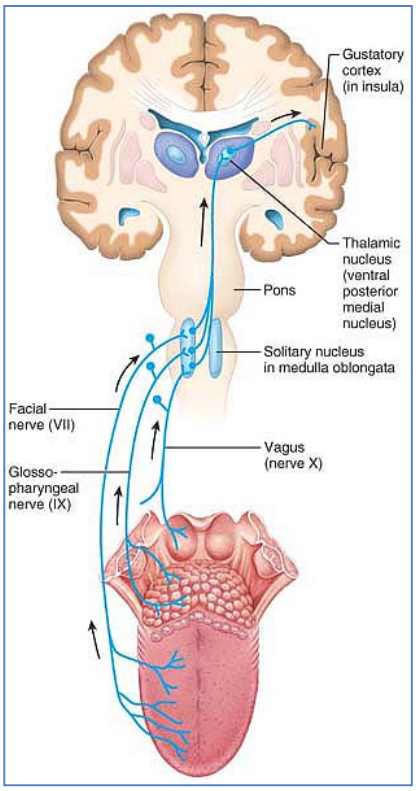
- **Function:** To alert us to whether stuff nearby/in our mouth is to be savoured or avoided.
- **Receptor Type:** Chemoreceptors (Respond to chemicals dissolved in solution)

Gustation (Taste):

- **Location of Taste Buds:**
  - Located primarily in the oral cavity:
    - Mainly on the Papillae of the Tongue
    - Also on Soft Palate
    - Inner surface of Cheeks
    - Pharynx
    - Epiglottis
  - Most taste buds are found on the Papillae of the Tongue:
    - On the tops of the Fungiform Papillae
    - On the side-walls of the Circumvallate Papillae
- **Structure of Taste Buds:**
  - *Each* taste bud consists of 50-100 epithelial cells. (3 Types of associated epithelial cells):
    - **Supporting Cells**:
      - Form the bulk of the taste bud.
      - Insulate the Receptor Cells from each other
    - **Receptor Cells:**
      - Have Long Microvilli that project from their tips, through a taste pore to the surface.
      - These Long Microvilli (Gustatory Hairs) are the sensitive portions of these cells.
      - Taste fibres of the Facial/Glossopharyngeal/Vagus Cranial Nerves coil around the Receptor Cells.
    - **Basal Cells:**
      - Act as stem cells
      - Divide & differentiate to replace the Receptor Cells every 7-10 Days

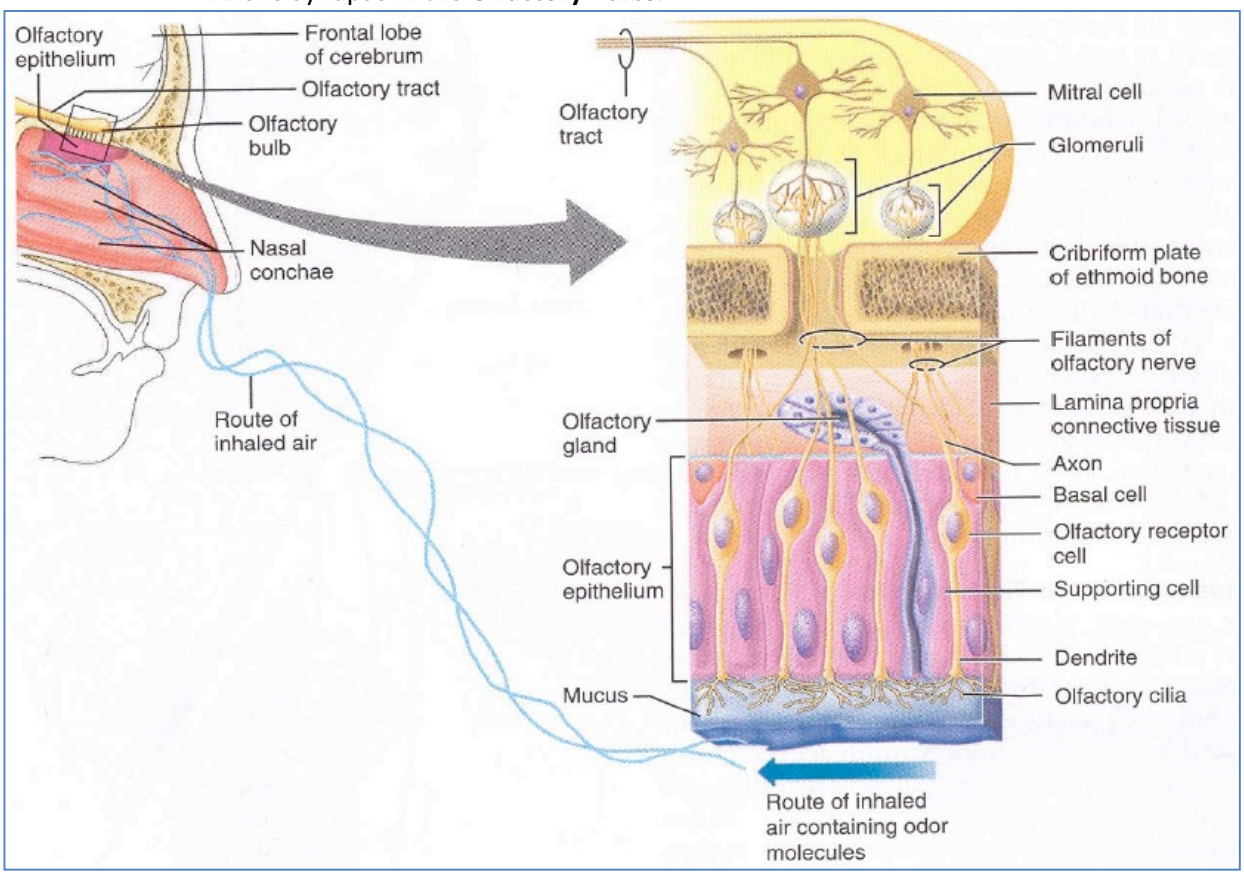


- **Basic Taste Sensations:**
  - **Sweet** - Sugars, some Amino Acids, Lead Salts
  - **Sour** - Acids
  - **Salt** - Metal Ions (Particularly Sodium)
  - **Bitter** - Alkaloids (Quinine, Caffeine, and Nicotine) – NB: Dislike for bitter is Protective.
  - **Umami** - "Delicious" - Glutamate (Steak, Cheese) & MSG.
  - NB: Most 'tastes' are a mixture of these basic taste sensations.
  - **NB: Taste 'likes/dislikes' have homeostatic values –**
    - Umami → leads to intake of Proteins
    - Sweet → leads to carbohydrate & mineral intake
    - Salt → leads to electrolyte intake
    - Sour → many sour (naturally acidic foods) are a rich source of Vit.C
    - Bitter → Many natural poisons & 'off' foods are bitter – hence a natural dislike is protective.
- **Physiology of Taste:**
  - Tasting requires a chemical to dissolve in the saliva, then diffuse through a **Taste Pore**, and contact **Gustatory Hairs**.
  - Binding of chemical induces a depolarising potential → Release of Neurotransmitter.
  - Neurotransmitter → Triggers dendrites of sensory nerves → Action Potentials.
  - NB: Different receptor cells have different thresholds (Eg. Bitter cells are very sensitive)
- **Taste Transduction:**
  - **Basic Overview:**
    - Stimulation of Gustatory Cell → leads to an ↑in intracellular [Ca^+] → Causes NT Release → Stimulates sensory nerves.
  - **Each taste-quality has its own way of stimulating the receptor cells:**
    - Salty – due to Na^+ influx → directly depolarises the Gustatory Cell.
    - Sour – due to H^+ either: 1) Entering the cell, 2) Opening Ion Channels, or 3) Blocking K^+ Channels.
    - Bitter, Sweet & Umami – G-Protein Linked Receptors that produce depolarisation.
- **Gustatory Pathway:**
  - Afferent fibres from taste buds run in 3 Cranial Nerves:
    - Facial (first 2/3 of tongue)
    - Glossopharyngeal (last 1/3 of tongue)
    - Vagus (Epiglottis & Lower Pharynx)
  - Afferent Fibres synapse in the Solitary Nucleus of the Medulla → Thalamus → Gustatory Cortex in Parietal Lobes.



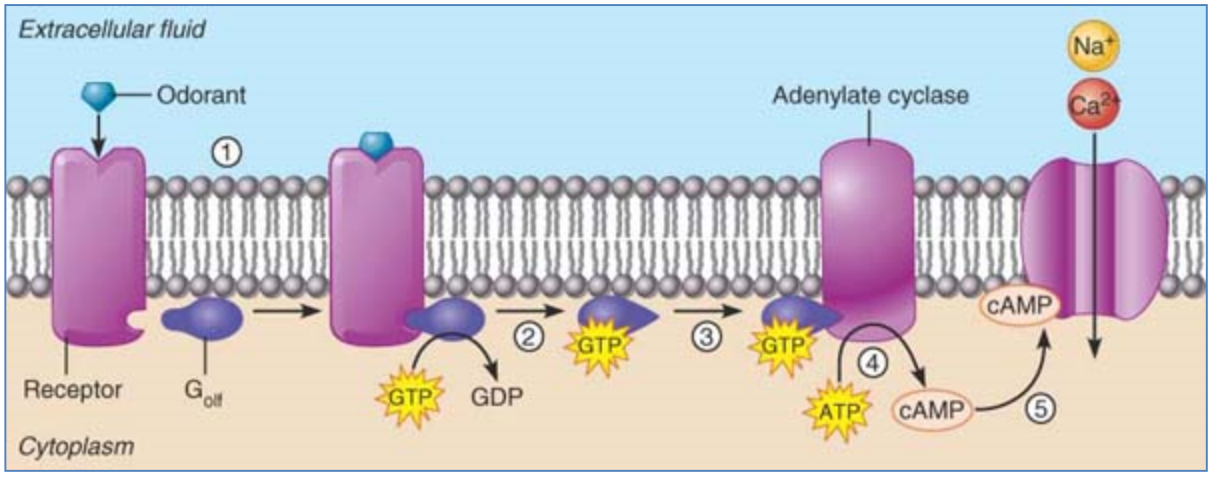
Olfaction (Smell):

- NB: ≈80% of taste is in fact *smell*.
- **Location of Olfactory Receptors:**
  - Located in the 'Olfactory Epithelium' – a 5cm^2 patch of Pseudostratified Columnar Epithelium in the roof of the Nasal Cavity.
  - Between the olfactory epithelial cells are the **Olfactory Receptor Cells.**
- **Olfactory Receptor Regeneration:**
  - Basal Cells in the basal side of the olfactory epithelium differentiate & replace Olfactory Receptor Cells every ≈60 days.
- **Structure of Olfactory Receptor Cells:**
  - They are Modified **Bipolar** Neurons
  - Have a thin apical dendrite, terminating in the olfactory mucus as **Olfactory Cilia.** (↑Surface Area)
  - Have thin, Unmyelinated Axons that collect to form the **Olfactory Nerve** (CN-I)
    - Filaments of the Olfactory Nerves project superiorly through the **Cribriform Plate**.
    - Axons Synapse in the **Olfactory Bulbs**.



- **Specificity of the Olfactory Receptors:**
  - Humans can distinguish ≈10,000 odours, but smell can't be classified like taste can.
  - Receptors are stimulated by different combinations of chemicals.
  - There are thought to be ≈1000 "smell" genes that code for special "**Odorant binding proteins**" (Special Receptor Proteins).
  - It is though that each receptor cell has only 1 type of receptor protein → Specificity.

- **Physiology of Olfactory Receptors:**
  - For an odorant to be smelt, it must dissolve in the olfactory mucus.
  - Once dissolved, odorants:
    - Stimulate the olfactory receptors by binding to Odorant Binding Proteins in the membranes of the Olfactory Cilia
    - Stimulated Odorant Binding Proteins → Activate G-Proteins → Activate Adenylate Cyclase
    - Active Adenylate Cyclase synthesises Cyclic AMP
    - cAMP → Opening Cation Channels → Depolarisation.
    - Depolarisation → Action potential → Stimulates the Olfactory Bulb.

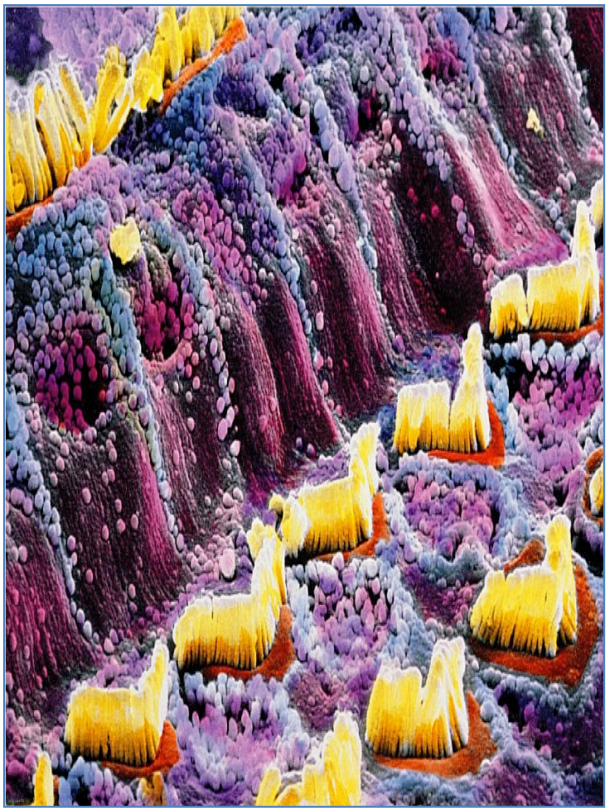


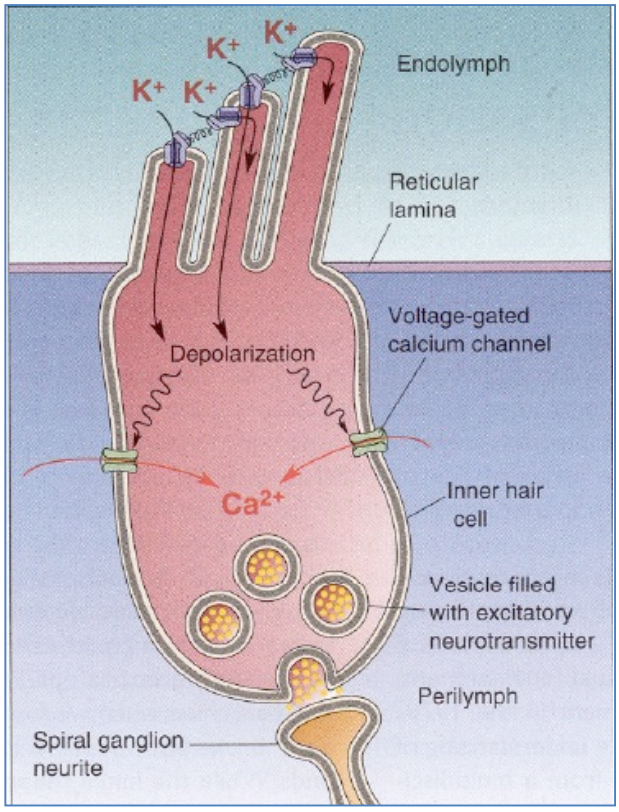
- **The Olfactory Pathway:**
  - Olfactory Receptors → Mitral Cells (in 'Glomeruli' – Each glomerulus receives only 1 type of odour) → Mitral Cell Axons (Olfactory Tracts) → Either:
    - 1) The Thalamus → Olfactory Cortex & Frontal Lobe (conscious interpretation/identification).
    - 2) The Hypothalamus, Amygdala & other Limbic System regions – Elicit emotional responses to odours.
- **Desensitisation:**
  - In the Olfactory Bulbs, there are **Granule Cells** that release **GABA** (Inhibitory NT) → Inhibits Mitral Cells.
  - This inhibition of Mitral Cells ensures that only *highly excitatory* impulses are transmitted.
  - This enables us to 'shut out' constant smells.

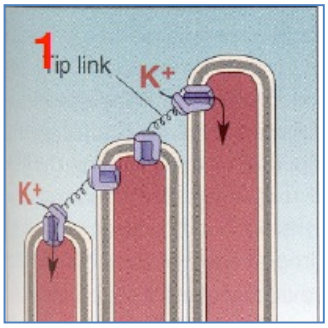
Neuroscience Notes
Special Senses II: Hearing & Equilibrium

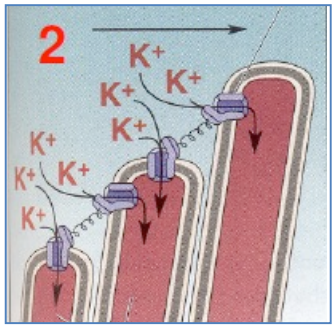
Functional Overview of the Ear:

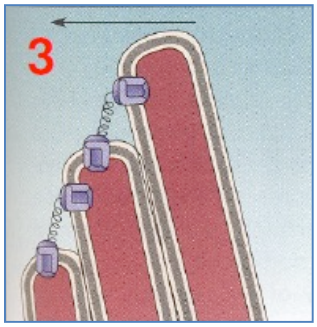
- **Ear is Responsible for 2 Special Senses:**
  - **Hearing** – Associated with Outer, Middle & Inner Ear (Cochlear) Structures.
  - **Equilibrium** - Associated with *just* the Inner Ear (Vestibular Apparatus)
- **NB: Receptors for both = "*Hair Cells*":** (NB: their functional differences are due to specialised anatomy)
  - **How they Work:**
    - Hair Cells have '*Cilia*' projecting from their apical surface into gelatinous masses:
      - Ie. Otolithic Membrane (in the Maculae of the Cochlea)
      - Ie. The Cupulae (in the Crista Ampullaris of the Vestibular Apparatus)
    - These 'Cilia' are distorted by movements in the gelatinous masses → Change in Membrane Potential (:. Hair Cells are Mechanoreceptors)
      - The Greater the distortion, the greater the change in Membrane Potential.
      - NB: The Polarity of the Change in Membrane Potential is determined by the Direction of the distortion.
  - **How Distortion of Cilia causes the Change in Membrane Potential:**
    - At the top of each cilia, there are Mechano-Gated **K^+ Channels**, joined together by '***Tip Links***'
    - **At Rest:** Half of the K^+ Channels are open, maintaining RMP.
    - **If Distorted & *Tip Links* are *Stretched*:** All K^+ Channels open → Depolarisation
    - **If Distorted & *Tip Links* are *Compressed*:** All K^+ Channels are closed → Repolarisation
  - **NB:** Neurotransmission from Hair Cells → Cochlear Nerve Dendrites is via ***Ca^+-Mediated Exocytosis***.





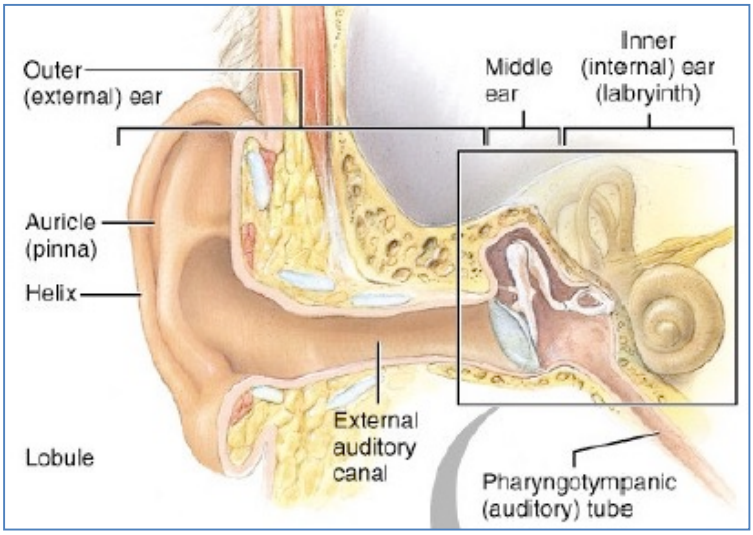




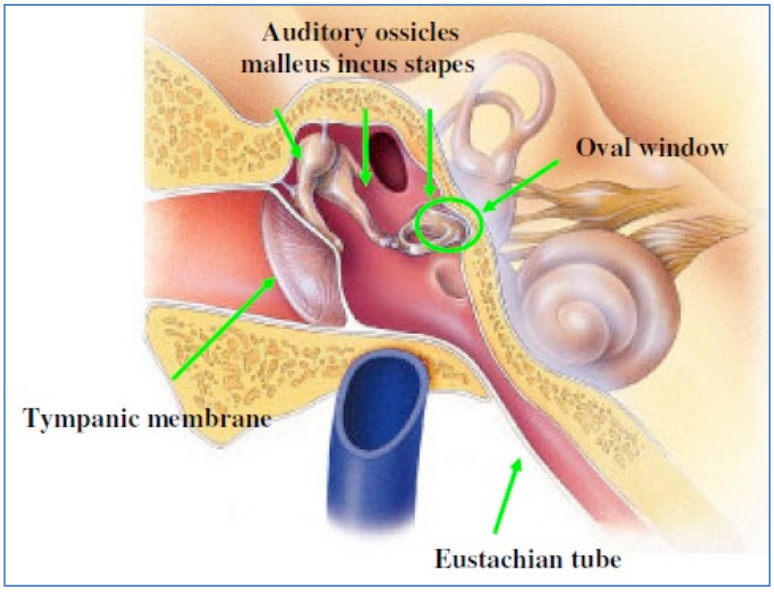


Ear Anatomy:

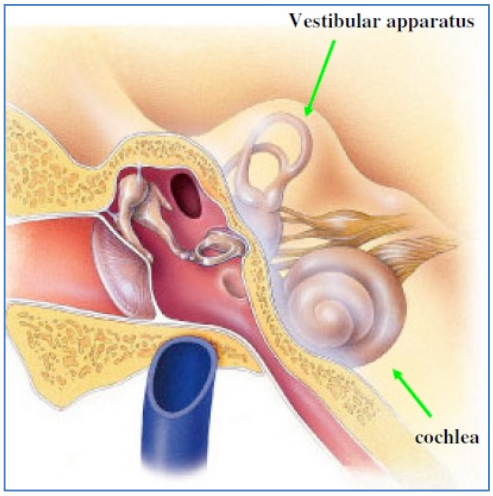
- **Outer Ear:**
  (Air-Filled)
  - **Pinna (Auricle):**
    - The Outermost part of the ear
    - The bit that funnels sound waves into the External Auditory Canal
  - **External Auditory Canal:**
    - The canal that conducts the soundwaves waves into the Tympanic Membrane (Eardrum)
    - Contains Ceruminous Glands – Secrete Cerumin (Earwax)
    - Abuts the Middle ear @ the Tympanic Membrane (Ear-Drum)

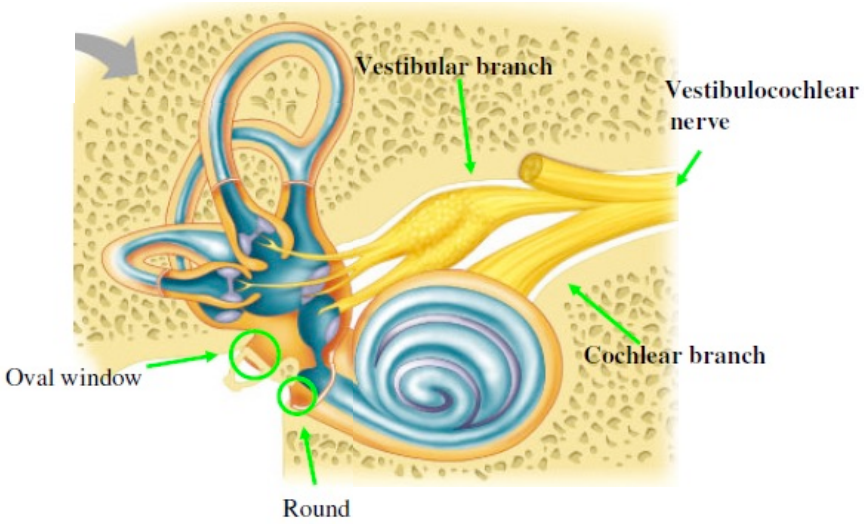


- **Middle Ear:**
  (Air-Filled Cavity within the Temporal Bone)
  - **Tympanic Membrane (Eardrum):**
    - Thin, translucent, connective Tissue Membrane (Skin on outside, mucosa on inside)
    - Connect to the 3 Auditory Ossicles
    - Soundwaves cause it to vibrate → Causes the Auditory Ossicles to Vibrate.
  - **The 3 Auditory Ossicles:**
    - Malleus ("Hammer"/"Mallet")
    - Incus ("Anvil")
    - Stapes ("Stirrup")
    - NB: 2 Skeletal Muscles (Tensor Tympani & Stapedius) Reflexively contract when ears are assaulted by loud sounds – Reduces Sound Conduction.
  - **Oval Window of the Cochlea:**
    - Transfers Vibration of the Stapes → Into the Cochlea.
  - **Eustachian (Pharyngotympanic) Tube:**
    - Equalizes pressure between the Outer & Middle Ear

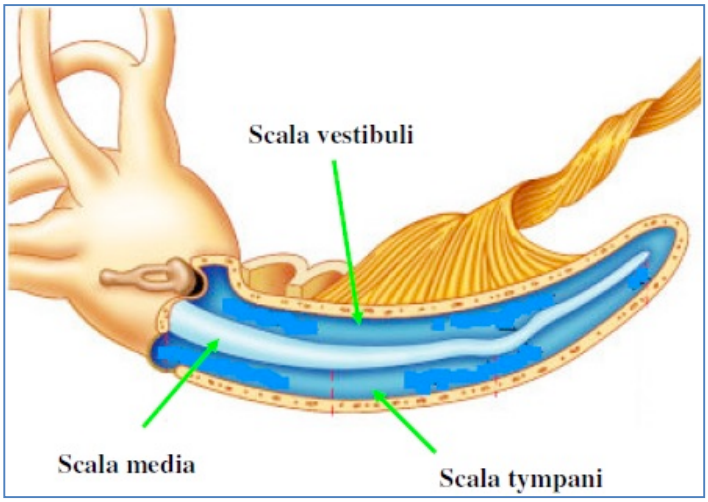


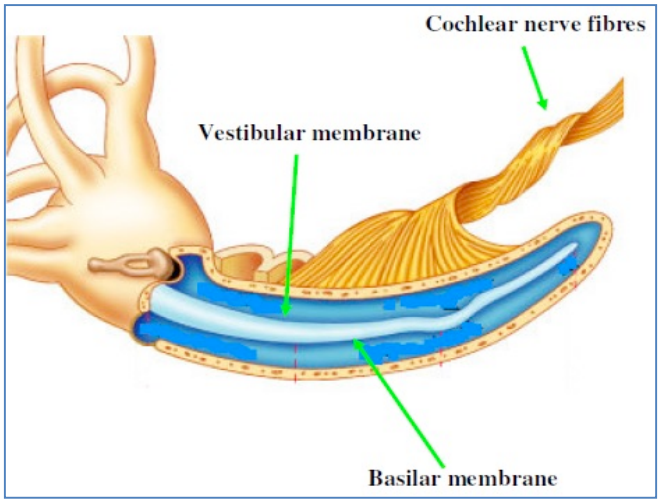
- **Inner Ear – (Cochlea & Vestibular Apparatus):**
  (Fluid-Filled Bony & Membranous Labyrinths)



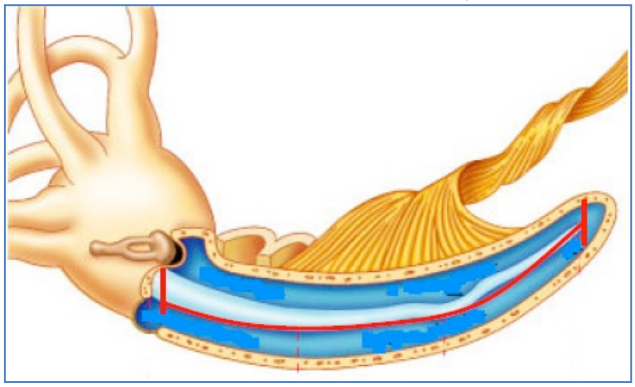


  - **Cochlea - HEARING:**
    - The Spiral-Shaped Organ
    - **Begins @ the *Oval Window*:**
      - The *Entry Point* of the Cochlea.
      - The hole covered by membrane
      - Separates the air-filled middle ear from the fluid-filled inner ear.
    - **Ends @ the Round Window:**
      - The Exit-Point of the Cochlea
      - Also covered by membrane
      - Also separates the air-filled middle ear from the fluid-filled inner ear.
    - **Consists of 3 Coiled Ducts – Separated by 2 Membranes:**
      - **Scala Vestibuli (Vestibular Duct):**
        - Begins @ the Oval Window
        - Ends @ the apex of the Cochlea
        - Filled with ***Perilymph***.
        - Separated from the Scala Media by the ***Vestibular Membrane***.
      - **Scala Media (Cochlear Duct):**
        - Runs through the middle of the Cochlea.
        - Separates the Vestibular Duct & Tympanic Duct.
        - Filled with ***Endolymph***.
        - Separated from the Scala Tympani by the ***Basilar Membrane***.
        - Contains the ***Spiral Organ of Corti*: (See Next Page)**
      - **Scala Tympani (Tympanic Duct):**
        - Begins @ the apex of the Cochlea
        - Ends @ the Round Window
        - Filled with ***Perilymph***.

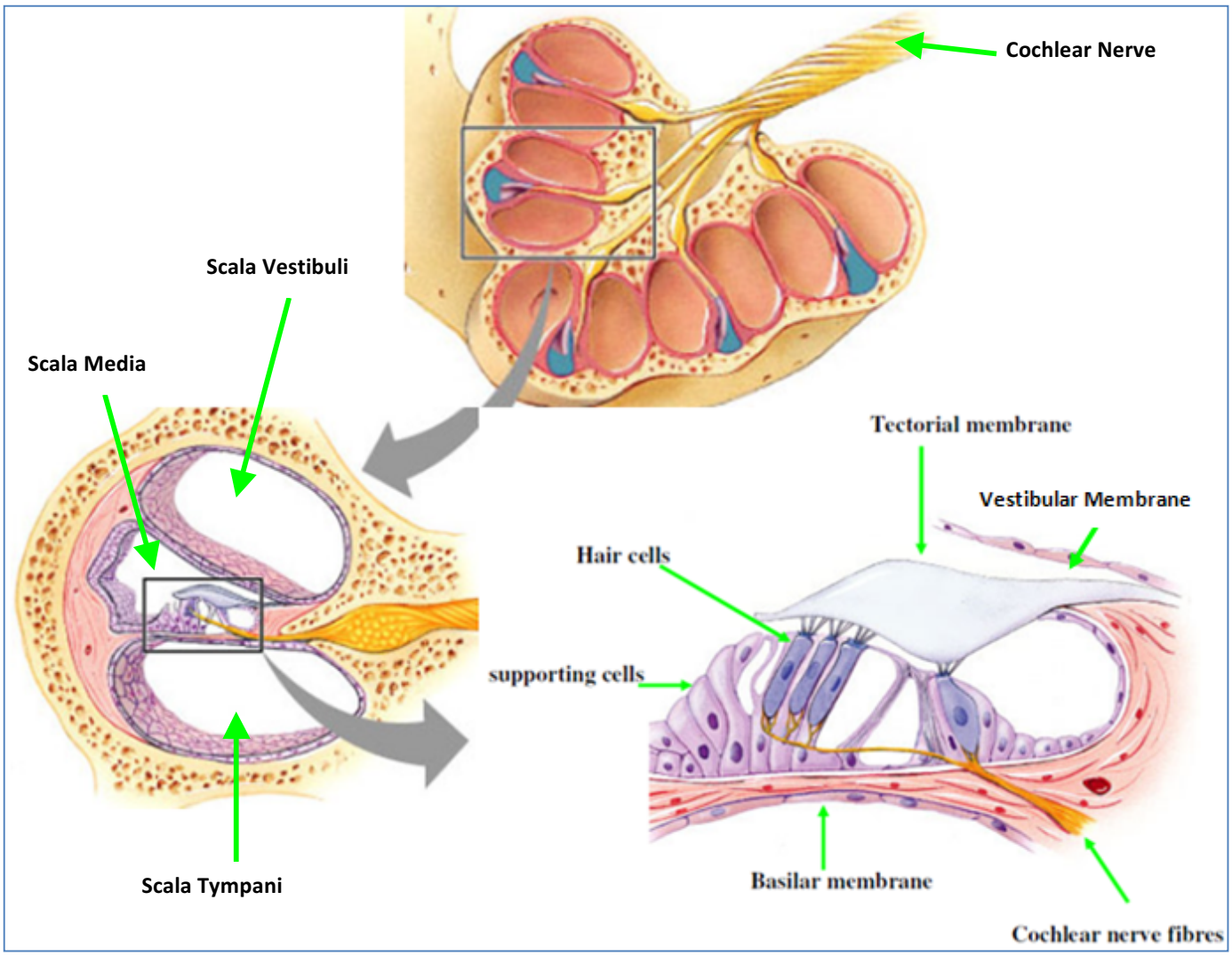




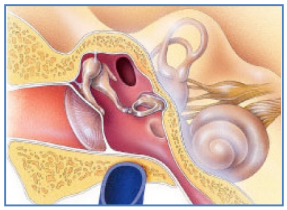
- ***The Spiral Organ of Corti*:**
  - Sits inside the Scala Media & runs along the Basilar Membrane.



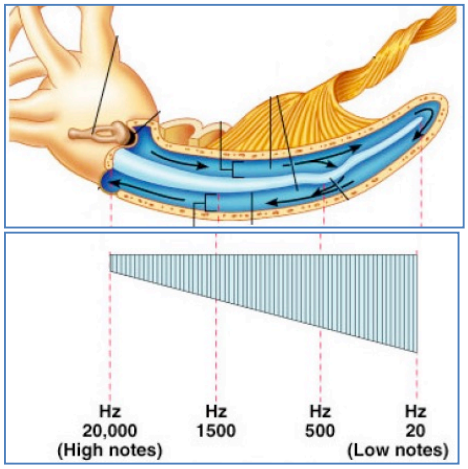
  - **Composed of:**
    - **The Tectorial Membrane** (Overlying the Hair Cells)
    - **Hair Cells** (Receptors for hearing) – Associated with cochlear nerve fibres:
      - **1x Row of Inner Hair Cells** – Has several inputs to the Spiral Ganglion
        - Sends most of the auditory info.
      - **3x Rows of Outer Hair Cells** – Has Only 1 input to the Spiral Ganglion
        - Plays a role in Signal Amplification
    - **Supporting Cells**
    - **The Basilar Membrane**
  - Cochlear Branch of the Vestibulocochlear Nerve Originates Here.

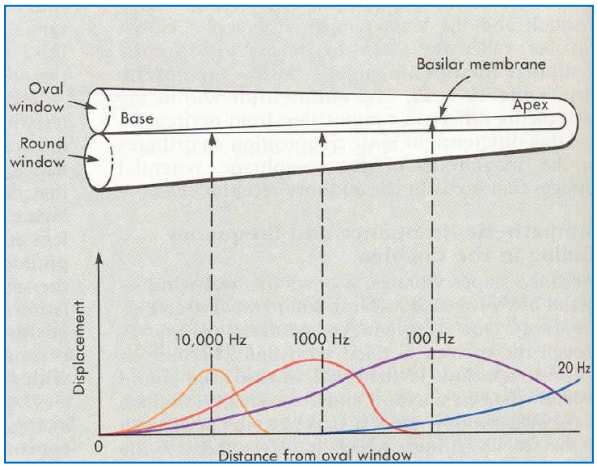


- **Audiotransduction:**

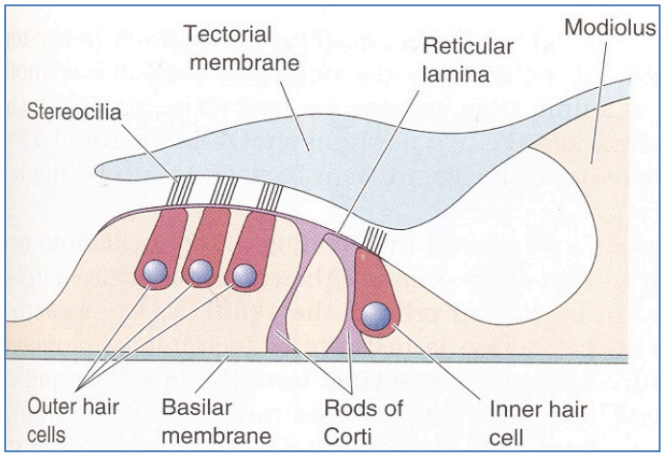


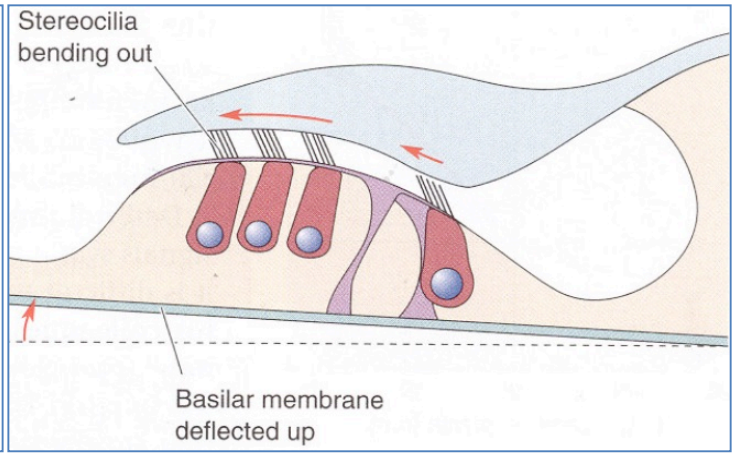
- Soundwaves are funnelled by the Auricle of the ear into the External Auditory Canal.
- → Soundwaves vibrate the Tympanic Membrane (Eardrum)
- → Eardrum vibration is passed through the Auditory Ossicles to the Oval Window.
  - NB: This transfer of vibration from the Eardrum→Oval Window *AMPLIFIES* it by ≈20x (As the eardrum surface area is ≈20x that of the Oval Window)
- → Oval Window vibration is transmitted into the Perilymph of the Scala Vestibuli.
- → Waves travelling through the Scala Vestibuli penetrate the Vestibular Membrane at different points relative its Resonant Frequency & enter the Scala Media:
  - High sounds resonate the Vestibular Membrane closer to the oval window
  - Low sounds resonate the Vestibular Membrane away from the oval window



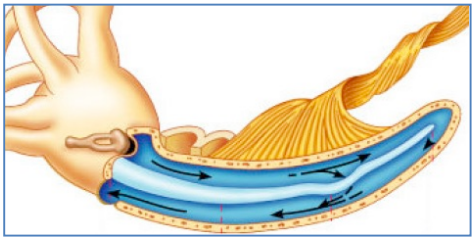


- → Waves exit the Scala Media by Penetrating the Basilar Membrane & enter the Scala Tympani:
  - The waves penetrating the Basilar Membrane cause it to Vibrate.
  - Vibration of the Basilar Membrane pushes the Hair Cells in the Organ of Corti up into the Tectorial Membrane, Distorting the Cilia & Initiating Graded Potentials in the Cochlear Nerve.





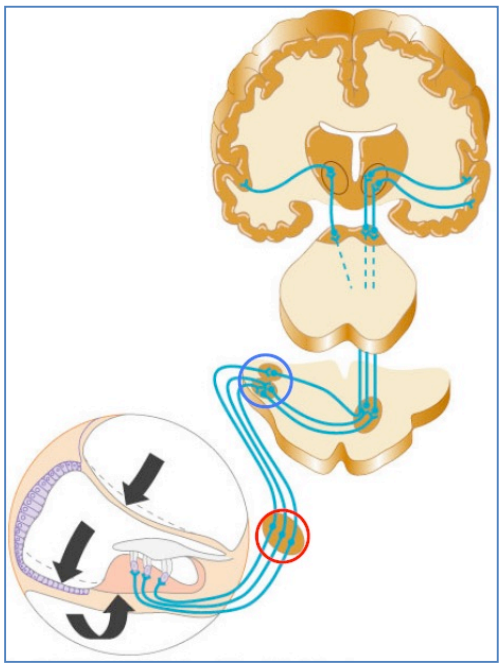
- → Waves continue down the Scala Tympani & leave the Cochlea via the Round Window – This prevents echoing of the sound waves within the Cochlea.



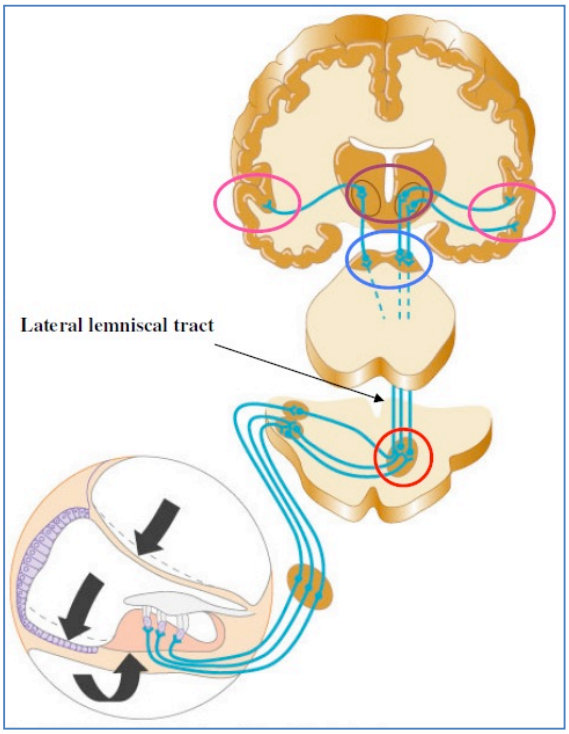
- **Pitch & Volume:**
  - **Pitch** – is coded in the ***area of the basilar membrane*** which is distorted by the wave.
  - **Volume** – is coded by the ***degree of distortion of the hair cells*** by the wave.

Pathway From the Cochlea to the Brain:

- Hair Cells → Cochlear Nerve (Incl. Spiral Ganglia) → Cochlear Branch of the Vestibulocochlear Nerve → Cochlear Nuclei of the Medulla →

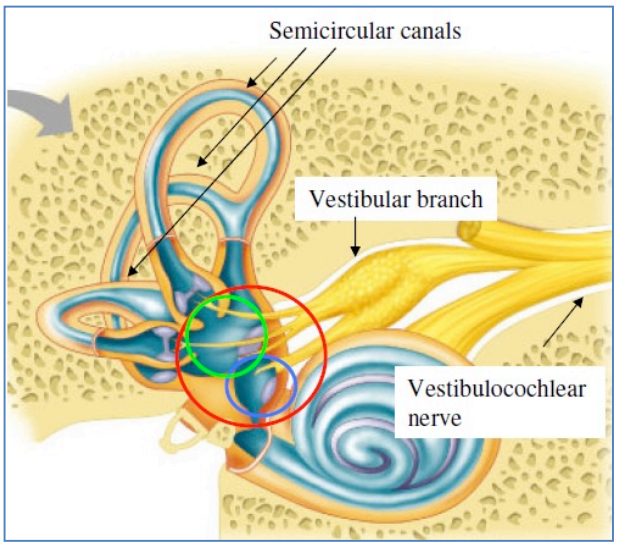


- → Superior Olivary Nucleus → Lateral Lemniscal Tract → Inferior Colliculus → Medial Geniculate Nucleus of the Thalamus →
    - Primary Auditory Cortex – (Conscious Sound)
    - Superior Colliculus – (Auditory Reflexes – Startle, Turning Head, etc.)

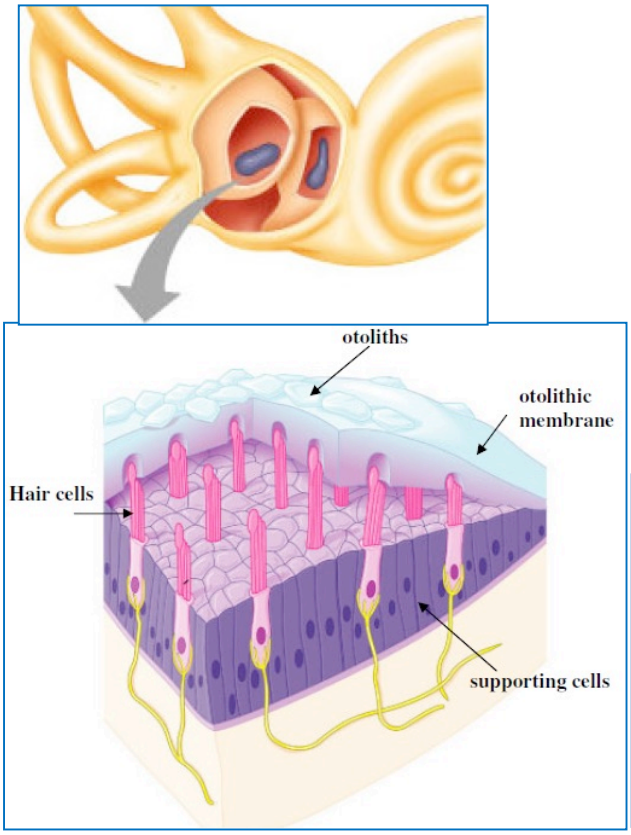


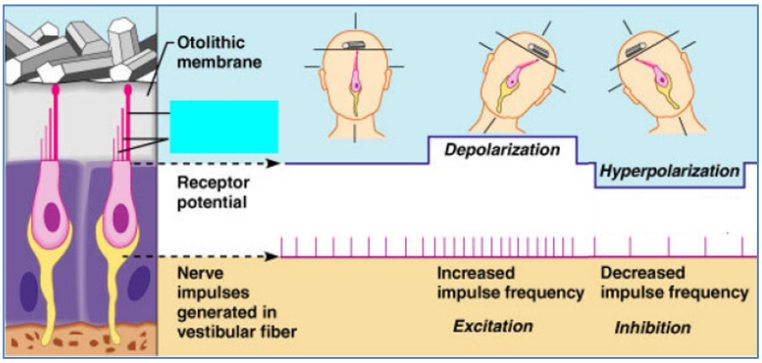
- **Deafness:**
    - **Conduction Deafness:**
        - Problem with Soundwave ***Conduction*** (Ie. Mechanical Structures)
            - Eg. Earwax
            - Eg. Perforated Ear Drum
            - Eg. Fused Ossicles
    - **Sensorineural Deafness:**
        - Problem with Soundwave ***Transduction*** (Ie. Neural Structures)
            - Eg. Damaged Hair Cells
            - Eg. Damaged Cochlear Nerve
            - Eg. Damaged Auditory Cortex

- **Vestibular Apparatus - EQUILIBRIUM:**
  - Vestibular Branch of the Vestibulocochlear Nerve Originates Here.
  - **Consists of:**
    - **A Vestibule, Containing:**
      - **1x Utricle:**
      - **1x Saccule:**
    - **& 3 Semicircular Canals.**

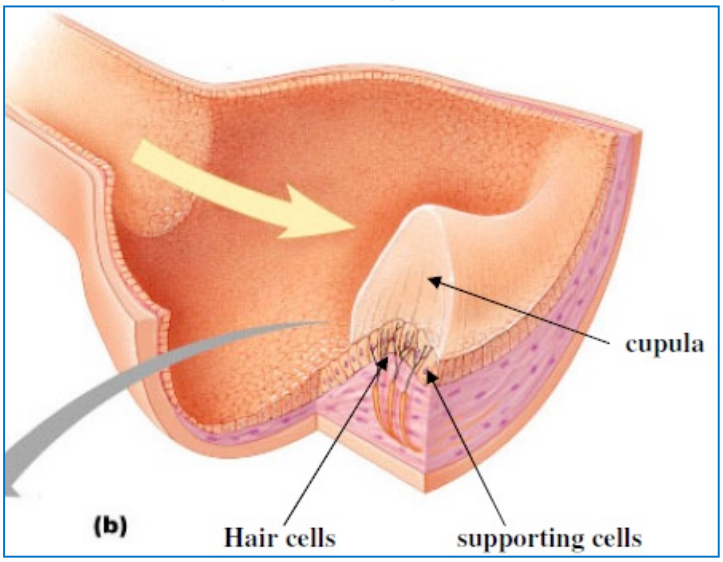


  - **The Vestibule: NB: Both the Utricle & Saccule have a Maculae:**
    - **Maculae =** Receptor Organs for Linear Acceleration (Static Equilibrium)
      - Provides Info about Orientation of the Head with respect to Gravity, Linear Acceleration & Angular Acceleration.
    - **Composed of:**
      - **Hair Cells** (Cilia Project into the Otolithic Membrane)
      - **Supporting Cells**
      - **Otolithic Membrane** - (Gelatinous Mass with 'Otoliths' – "Ear Stones" – of Calcium Carbonate Crystals resting on top. These 'Otoliths' provide the inertia required to move the Otolithic Membrane during head movement)

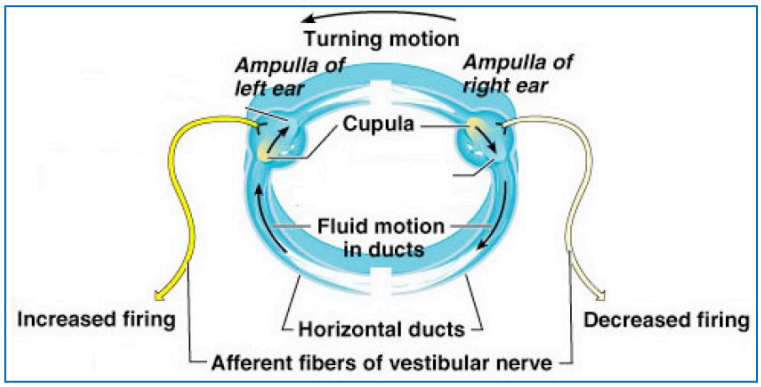




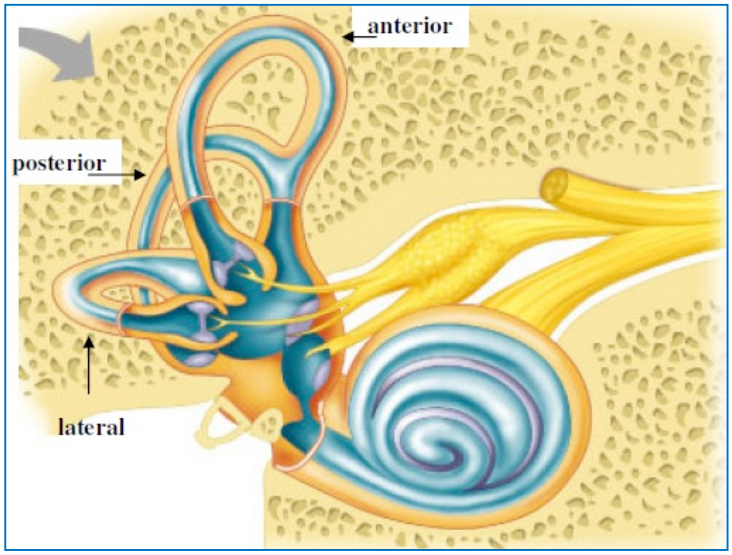
- **<u>The 3 Semicircular Canals:</u> NB: At the end of each Canal is a Swelling = "*Crista Ampularis*":**
  - **Crista Ampularis** = Receptors for Rotation (Dynamic Equilibrium).
  - **Composed of:**
    - **Hair Cells** (Cilia Project into the Cupula)
    - **Supporting Cells**
    - **Cupula** – (Gelatinous Mass encircling the entryway of each Crista Ampularis. Rotation of the head in the plane of the canal causes fluid movement over the Cupula, distorting the Hair Cells)



  - **NB: There are 2 Semi-Circular Canals for each *'Plane'* of Movement:**
    - One on each side of the head
    - This allows you to determine the ***Direction*** of head motion.



  - **NB: Each Semi-Circular Canal is Responsible for a different *Plane*:**
    - **Anterior –** ('Ear-to-Shoulder' Motion)
    - **Posterior-** ('Nodding' Motion)
    - **Lateral -** ('Shaking' ('no') Motion)



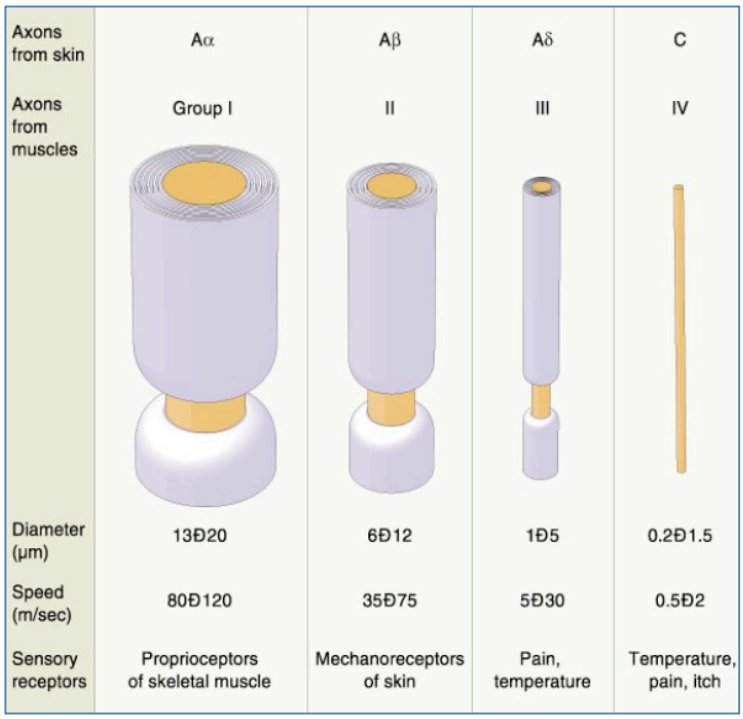
Equilibrium Pathways To the Brain:

- Equilibrium is Subconscious
- Info goes straight to the reflex centres in the **Brainstem** & **Cerebellum**:
    - **Vestibular Nuclei:**
        - Integrates Balance + Receive some Visual & Somatic Inputs
        - Sends commands to Brainstem Motor Centres controlling Eyes & Neck/Limb/Trunk Reflexes.

Neuroscience Notes
Pain & Nociception

Overview of Nociceptive Nerves:

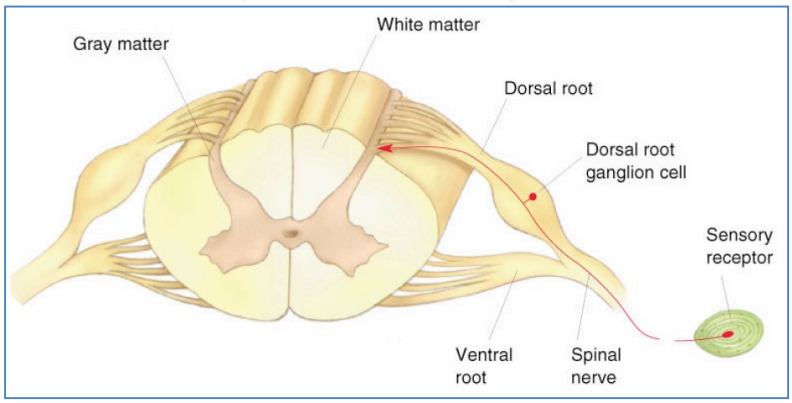
- = Sensory nerves that carry "Pain" information (Nociception)
  - → Tells the brain that tissues have been injured – Important for survival.
- **2 Types of Nociceptive Nerves:**
  - **Type-C Fibres:**
    - Very Thin, Un-Myelinated Fibres :. Slow Conduction :. Dull, Achy, Burning Pain
    - Poorly-Localised
  - **Type-Aδ Fibres:**
    - Relatively Thin, Myelinated Fibres :. Faster (-than C-Fibres) :. Sharp (Acute), Searing Pain
    - Well-Localised
- **NB: Conduction Speed increases with ↑Myelination & ↑Diameter.**
- **NB: Both Fibres are sensitive to the *same* stimuli.**
- **NB: *Both Fibres Respond to the Multiple Stimuli – Ie. Are Polymodal***

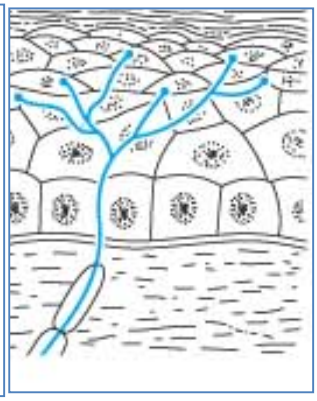


Fibre Type	Function	Diameter (mm)	Conduction Velocity (m/s)
Aβ	mechanoafferents	6 - 11	30 - 60
Aδ	convey "fast pain" nociceptive signals	1 - 6	2 - 30
C	convey "slow pain" nociceptive signals	0.5 - 1.5	0.25 – 1.5

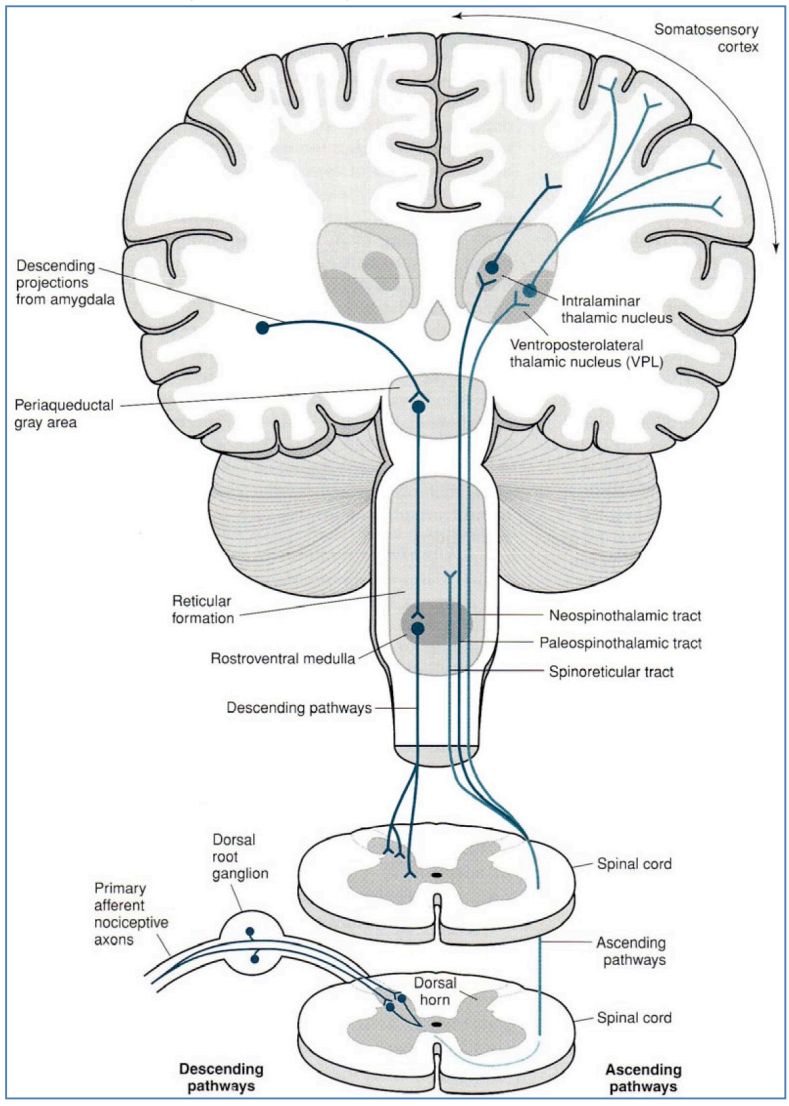
- **Nociceptors Are *Polymodal*:**
  - **Ie. Respond to a wide variety of stimuli:**
    - Eg. Mechanical
    - Eg. Chemical
    - Eg. Thermal
  - However, the stimulus must be sufficiently intense to stimulate Nociception. (Due to High Threshold)
    - Nociception is stimulated by Opening of cation channels → Brings nerve to threshold → Voltage-Gated Na^+ Channels open → Depolarisation (Action Potential).
  - **NB:** Much of this polymodality is due to the $TRPV_1$-Receptor's ability to respond to various stimuli. (Explained Later)

- **Organisation of Nociceptors:**
  - **1. Nociceptive Nerve:**
    - Distal Nerve Terminals = Simple, Un-encapsulated Nerve-Endings in Viscera/Periphery.
    - Cell Body is in Dorsal Root Ganglia

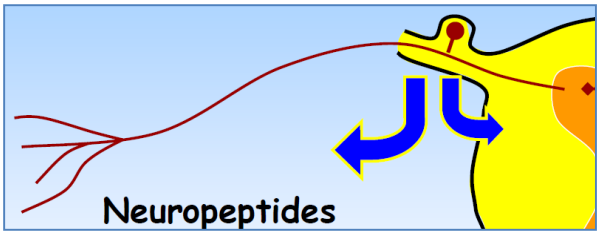




  - **2. Dorsal Horn of Spinal Cord:**
    - Proximal (Central) Nerve Terminal Synapses in Dorsal Horn of Spinal Cord.
    - The Substantia Gelatinosa Modulates Nociceptive Transmission – A whitish gelatinous mass at the apex of the dorsal horn – Plays a role in inhibiting the communication between Nociceptive Nerves & Ascending Pathways → Suppress Pain.
  - **3. Ascending Spinal Pathways:**
    - Nociceptive Nerves synapse with 1 of 2 Ascending Pathways transmits to the Brain:
      - Spinothalamic Pathways
        - Neospinothalamic
        - Palaeospinothalamc
      - Reticulospinal Pathway



- **Neurotransmitters:**
  - **Predominantly *Peptide* NT's (Neuropeptides):**
    - *Substance-P
    - Neurokinin-A (NKA)
    - CGRP (Calcitonin-Gene Related Peptide)
    - – and the Amino Acid: *Glutamate
  - **Synthesised in Cell Bodies:**
    - Peptides = Proteins :. Requires DNA for Synthesis :. Synthesis occurs close to the Nucleus.
    - NB: Neuropeptides are stored & transported in Vesicles.
  - **Bilateral NT Transport & Release:**
    - Released @ Dorsal Horn → Nociceptive Transmission
    - Released @ Distal-Terminal → 'Neurogenic Component of Inflammation' → Lowers Threshold → Ie. Makes the Nociceptor *Hypersensitive* → ***Potentiates Further Nociception***.

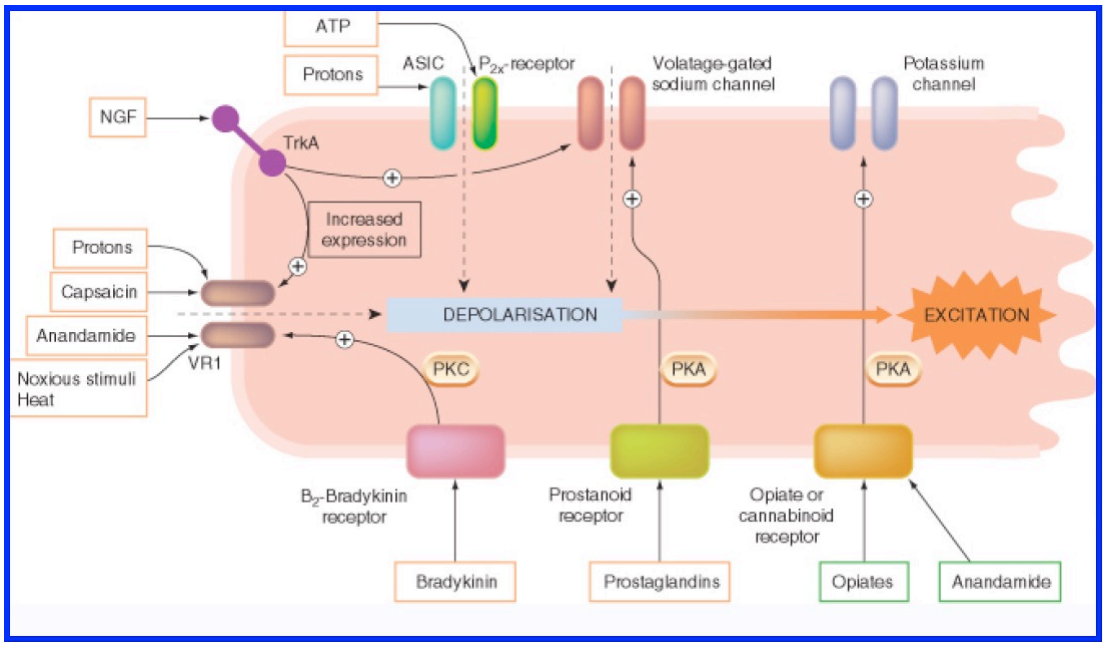


Process of Nociception:

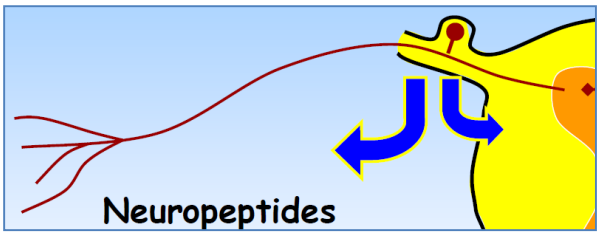
- **1. Noxious Stimulus @ Distal Nerve Terminal:**
  - **A Potentially Damaging Stimulus** (Or summation of multiple different potentially damaging stimuli) brings the Nerve to Threshold → Action Potential, leading to→
    - 1. NT release in Dorsal Horn (Glutamate & Substance P)→ Transmits to Ascending Pathways
    - 2. Bilateral Neuropeptide Transport to Central & Peripheral Nerve Terminals.
  - **"PRODUCTIVE PAIN" – Pain Associated with Initial Activation of Nociceptive Nerves :**
    - Via opening of Cation Channel Receptors in Distal Nerve Terminals → Depolarisation.
    - **Examples of Receptors & Their Stimulators That Stimulate/Modulate Nociception:**
      - ***TRPV$_1$-Receptor (Ca^+ Channel)("TRP Vanilloid Receptor$_1$"). Opened by:**
        - Capsaicin (from hot chillies)
        - H^+ (Acid)(Often a result of inflammation)
        - Heat
        - Mechanical (Mechanism unclear)
        - Eicosanoids (Lipid mediators of inflammation)

        } Hence, Polymodal. →Nociception
      - **Bradykinin Receptors:**
        - Sensitive to Bradykinin.
        - Bradykinin Activates TRPV$_1$-Receptor → Depolarisation → Nociception.
      - **Prostanoid Receptors:**
        - Sensitive to Prostaglandins.
        - Open Na^+ Channels →
        - Inhibit K^+ Channels →
        - Open TRPV$_1$-Receptors →

        } → ↑MP → :. Lowers Threshold → ↑Sensitivity
      - **Opiate/Cannabinoid Receptors:**
        - Sensitive to Opioid Peptides Cannabinoids.
        - Open K^+ Channels → K^+-Efflux → ↓MP (Hyperpolarises Cell) → ↓Sensitivity
        - NB: This is one of the targets of Opioid Analgesics.
      - **ASIC – ("Acid Sensitive (gated) Ion Channel"):**
        - Sensitive to H^+ Ions
        - Stimulation → Depolarisation of Cell → Nociception
      - **Also Exhibits Receptors for a Wide Range of Mediators (Most not shown):**
        - Glutamate
        - GABA
        - ACh
        - Serotonin
        - ATP
        - Noradrenaline
        - Histamine
        - Somatostatin



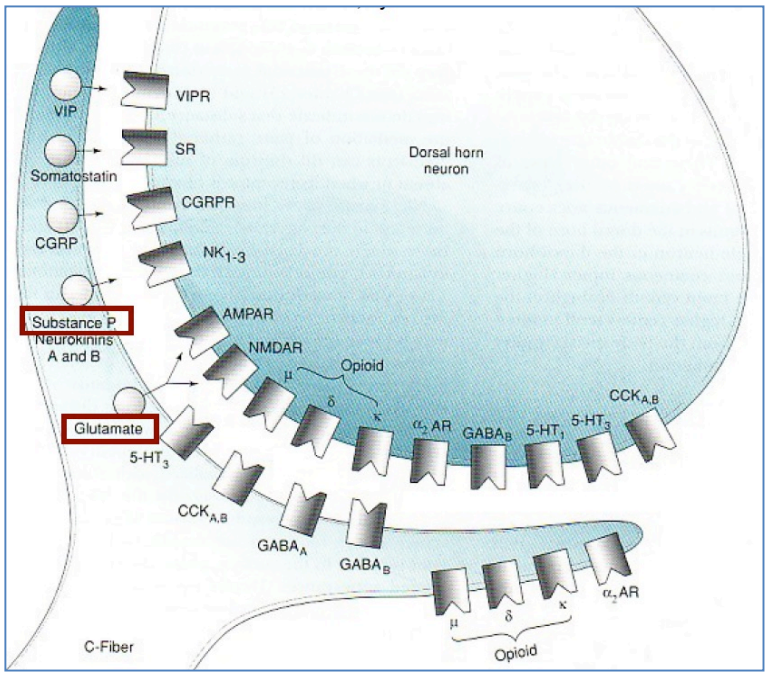
- **2. Bilateral Neuropeptide Transport:**
    - The Nociceptor Releases Neuropeptides (Substance-P, Glutamate, Neurokinin-A & CGRP) at both ends:
        - Release @ Dorsal Horn → Nociceptive Transmission
        - Distal-Terminal Release → 'Neurogenic Component of Inflammation' → Lowers Threshold → Ie. Makes the Nociceptor *Hypersensitive* → Potentiates Further Nociception.



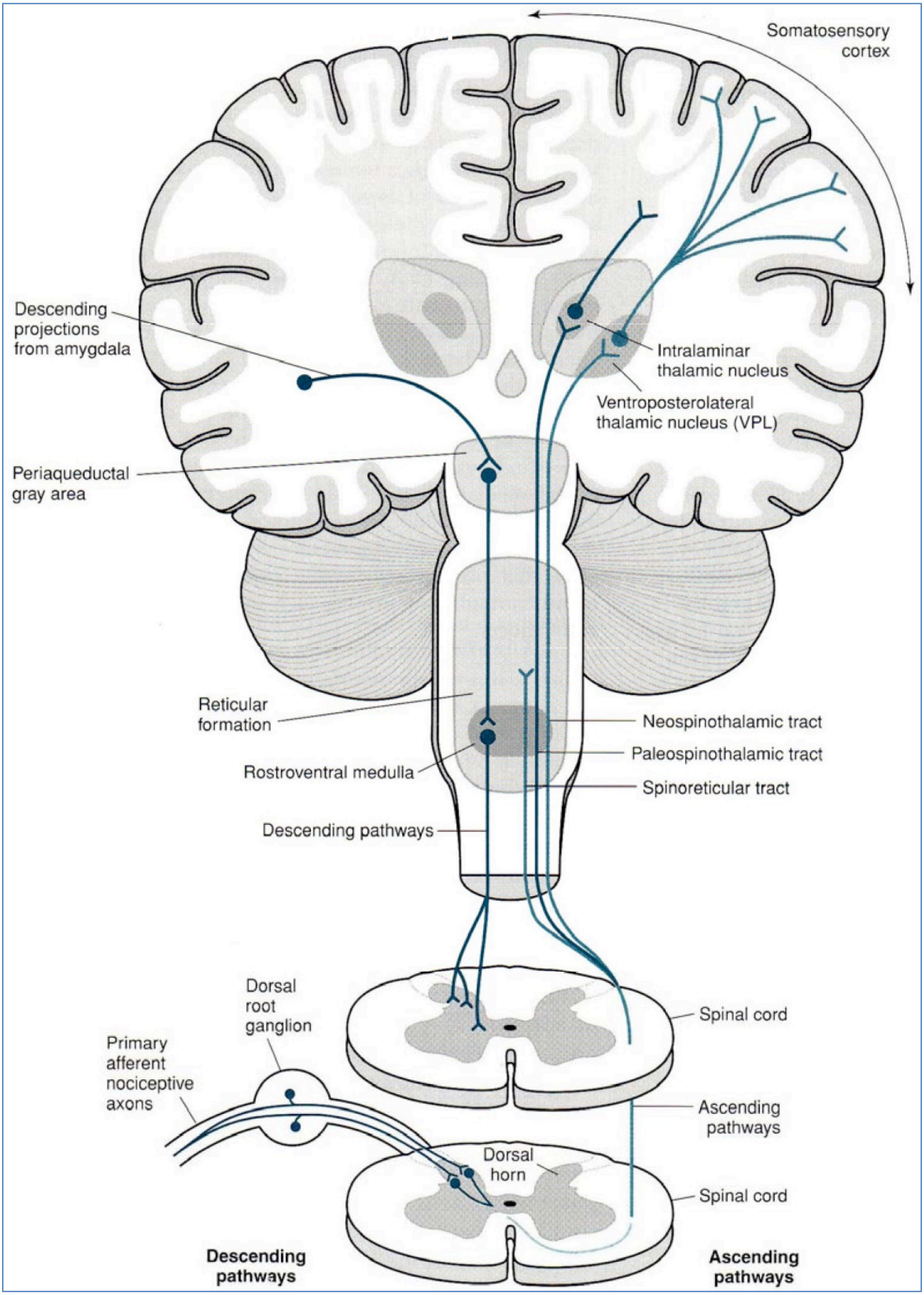
    - **"NON-PRODUCTIVE PAIN" – Pain Associated with *Ongoing* Chemical Stimulation (Potentiation):**
        - (Pain persists long after the initial noxious stimulus – particularly with Inflammation/Injury)
            - NB: Non-Productive Pain should dissipate as the injury heals.
        - **Chemical Factors Responsible:**
            - ***Nociceptor Neuropeptides (Potentiators):**
                - *Substance-P
                - Neurokinin-A (NKA)
                - CGRP
                - – And *Glutamate (Amino Acid)
            - ***Prostaglandins (Potent Pain-Enhancing Substances)**
                - Released during Inflammation & Ischaemia → Enhance the actions of other mediators (Esp. Bradykinin & Serotonin) → Hyper-sensitising Distal Nociceptive Nerve Terminals.
                - How? – By 1) Inhibiting K^+ Ion Channels,
                  And 2) Hypersensitising $TRPV_1$-Receptors to noxious stimuli.
            - **Kinins (Potent Pain-Producing Substances):**
                - ***Bradykinin**
                    - 1. Produces Pain - Triggers Action Potential in Nociceptive Neuron by activating $TRPV_1R$ Receptors (Ca^+ Influx → Depolarisation)
                    - 2. Triggers Prostaglandin & Bradykinin Release → enhances its own action on the Nerve Terminal
                - Kallidin
            - **Neurotransmitters (Mediators):**
                - Serotonin
                - Histamine
                - ACh
            - **Metabolites:**
                - Lactic Acid (eg. Ischaemic pain if stimulus damaged the tissue's blood supply)
                - K^+
                - H^+
                - ATP
                - ADP

                } Released by damaged/lysed cells
        - **Non-Chemical Factor:**
            - Primary Nociceptive Afferents inhibit the Substantia Gelatinosa → Inhibit Pain Suppression → Potentiate Pain.
        - **NB: NSAIDs (Non-Steroidal Anti Inflammatory Drugs)** – eg. Ibuprofen & Aspirin, elicit their effect by **Reducing Prostaglandin Synthesis** → Therefore preventing Sensitisation of Nociceptive Terminals.

- **3. Synaptic Transmission @ Dorsal Horn (Nociceptors Synapse with Ascending Fibre-Tracts in Spinal Cord):**
  - **The 2 Primary Neurotransmitters:**
    - *Substance-P
    - *Glutamate
  - **Other less-important NT's:**
    - VIP
    - Somatostatin
    - Serotonin
    - CCK
    - GABA
    - Opioids

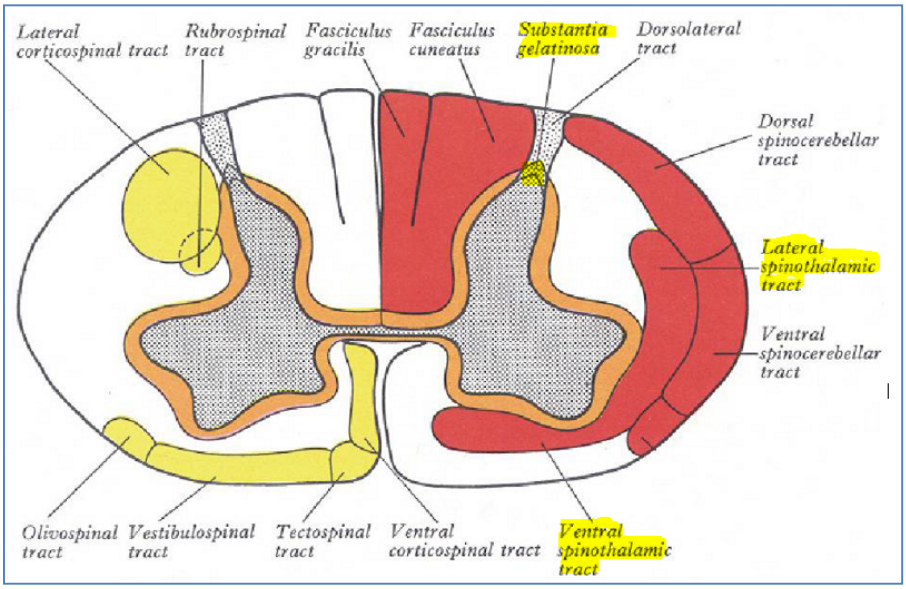


  - **Nociceptive Nerves synapse with 1 of 2 Ascending Pathways that transmit to the Brain:**
    - **1. Spinothalamic Pathways (Spine → Thalamus):**
      - **Neospinothalamic (Lateral):**
        - Somatotopical
        - Small Receptive Fields → Good Localisation
        - Aδ-Fibres = Main Afferents
        - Function = Localizing & Discrimination of Pain.
        - **Projections from the Thalamus Lead to:**
          - *Primary Somatosensory Cortex
      - **Palaeospinothalamic (Medial):**
        - Not Somatotopical
        - Broad Receptive Fields → Poor Localisation
        - C-Fibres = Main Afferents
        - Function = 'Alerting' – "We've been Injured"
        - **Projections from the Thalamus lead to:**
          - *Primary Somatosensory Cortex
          - Somatosensory Association Areas
          - Prefrontal Cortex
          - Cingulate Cortex
    - **2. Spinoreticular Pathway (Spine → Reticular Formation [RAS] in Brainstem) :**
      - Lacks Somatotopy.
      - Broad Receptive Fields → Poor Localisation
      - Function = 'Alerting' – "We've been Injured"
      - **RAS Function:**
        - Arousal/motivation/consciousness/circadian rhythms/HR/Respiration/etc.
        - Is also the ***FILTER*** between the *Conscious* & *Unconscious* mind, ignoring background 'Noise' & only bringing the 'Important' stimuli to Consciousness.
      - RAS Projects to many brain regions:
        - Including Thalamus & Hypothalamus → Changes body state
    - **NB: Both decussate at the spinal cord level & ascend on the Contralateral side.**
    - **NB: Thalamus receives *ALL SENSORY INPUTS* – only ≈10% is Nociceptive.**
    - **(3.) Trigeminal Nerve:**
      - Responsible for Nociceptive Info from Head & Face
      - Projects to Thalamus (Similar to Spinothalamic)

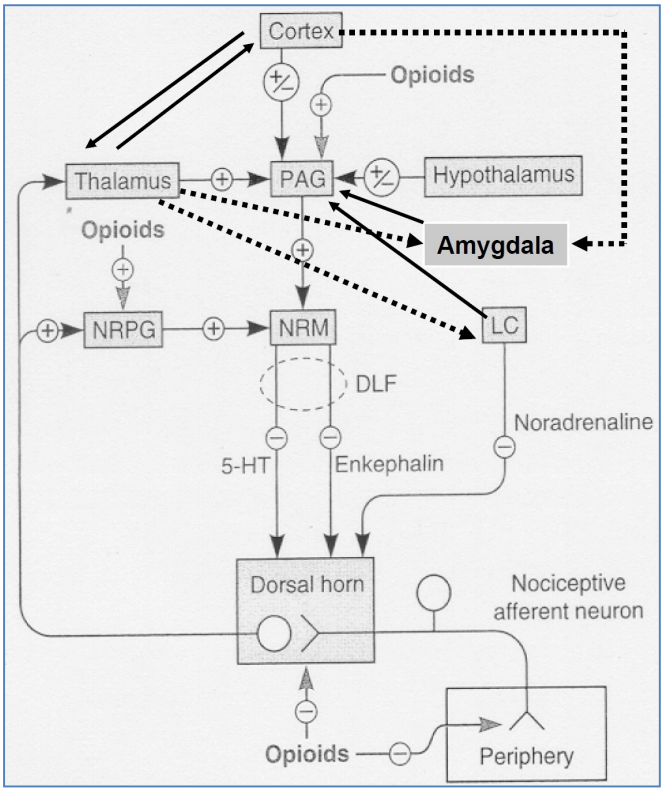


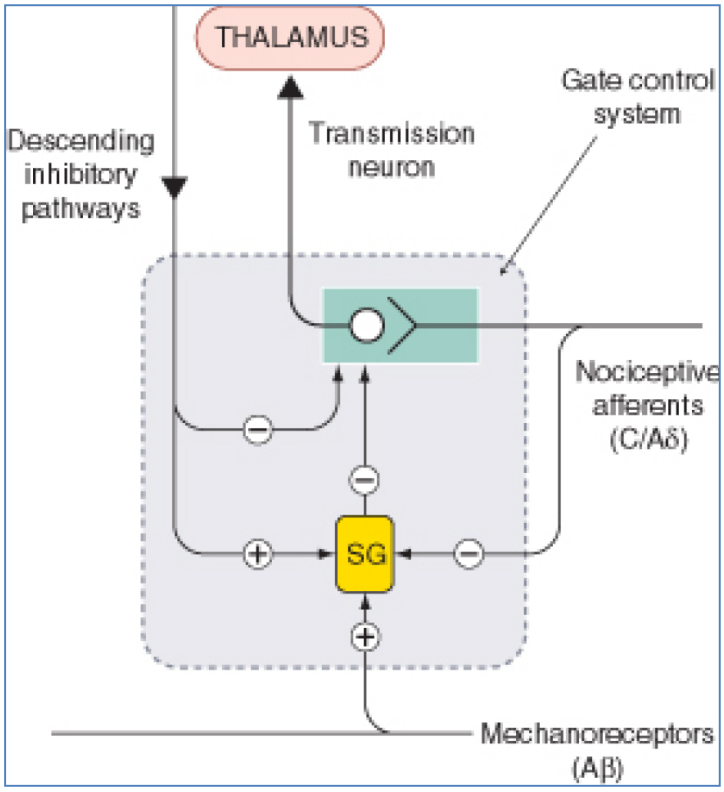
www.regentstudies.com

- **Regulating Nociceptive Transmission - *"The Pain-Gate Mechanism" & "Descending Inhibitory Pathways"*:**
  - **The Substantia Gelatinosa (Spinal Regulation of Nociceptive Transmission):**
    - A whitish gelatinous group of neurons at the apex of the dorsal horn
    - When *Active* → *Suppresses Pain*.
    - **Pain-Modulation @ the level of the Spinal Cord:**
      - **→Inhibiting Nociceptive Transmission → Suppressing Pain:**
        - Afferent Mechanoreceptors (Aβ-Fibres) & Descending Inhibitory Pathways → Stimulates the SG → Decreases Nociceptive Transmission → Decreases Pain.
        - NB: Exploited in Narcotic Analgesics
      - **→Potentiating Nociceptive Transmission → Potentiating Pain:**
        - Afferent Nociceptive Signals (C & Aδ-Fibres) → Inhibiting the SG → Increased Nociceptive Transmission → Increased Pain

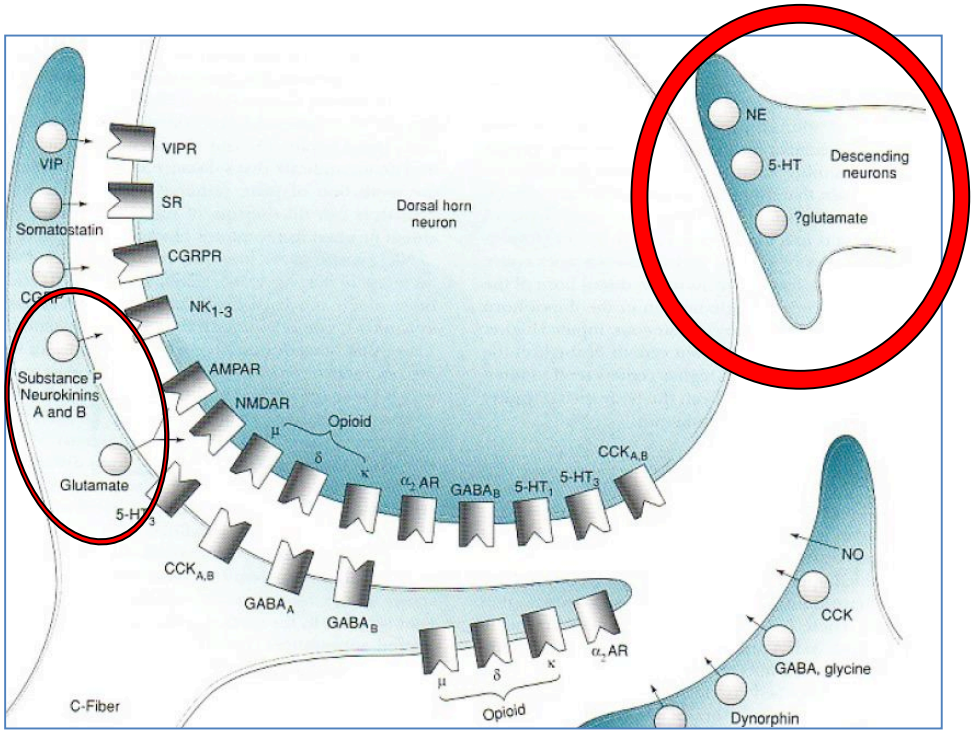


  - **Descending Inhibitory Pathways (Central Regulation of Nociceptive Transmission):**
    - **Pathway:** A Neuronal chain from the PAG (Midbrain) → NRM (Rostro-Ventral Medulla) → Substantia-Gelatinosa & Dorsal Horn of the Spinal Cord.
    - **Functions to** *Temporarily* Inhibit Nociceptive Transmission between Nociceptors & Spinal Cord (A few hours max).
    - **CNS Regions Involved:**
      - **PAG – Periaqueductal Grey matter (Midbrain):**
        - **Receives Inputs from:**
          - ***Locus Coeruleus***
          - Reticular Formation (Aka: Reticular Activating System – RAS)
          - Amygdala
          - Hypothalamus
          - Prefrontal Cortex
          - Insula
        - **Projects to –** 'Nucleus Raphe Magnus' (Raphe Nuclei) in the Rostro-Ventral Medulla.
        - **NB: It is Disinhibited (Activated) by Opioids & GABA-Antagonists** → Activates NRM → Inhibits Dorsal Horn Synapse.
      - **NRM – Nucleus Raphe Magnus (Rostro-Ventral Medulla):**
        - Projects to Dorsal Horn of Spinal Cord & acts in 2 Places:
          - 1. Directly Inhibits Nociceptive Transmission @ the Synapse.
          - 2. Stimulates Substantia Gelatinosa → Inhibits Nociceptive Transmission.
      - **Substantia Gelatinosa (Dorsal Horn of Spinal Cord):**
        - When activated, it directly suppresses Nociceptive Transmission @ the Synapse.

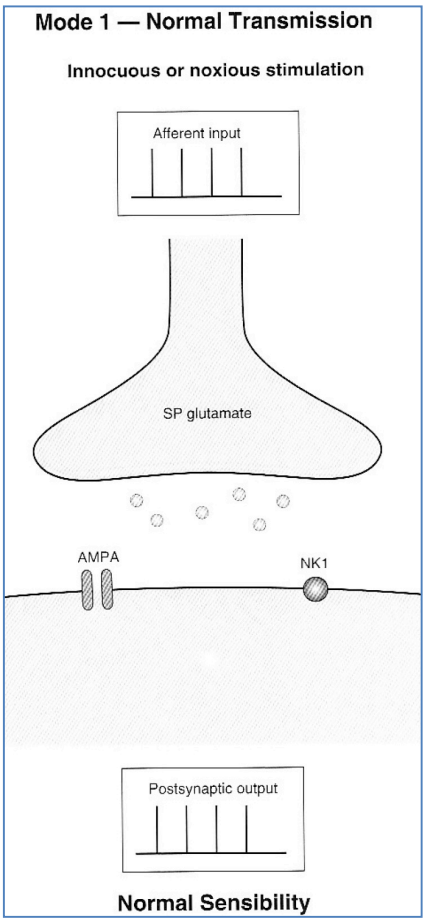


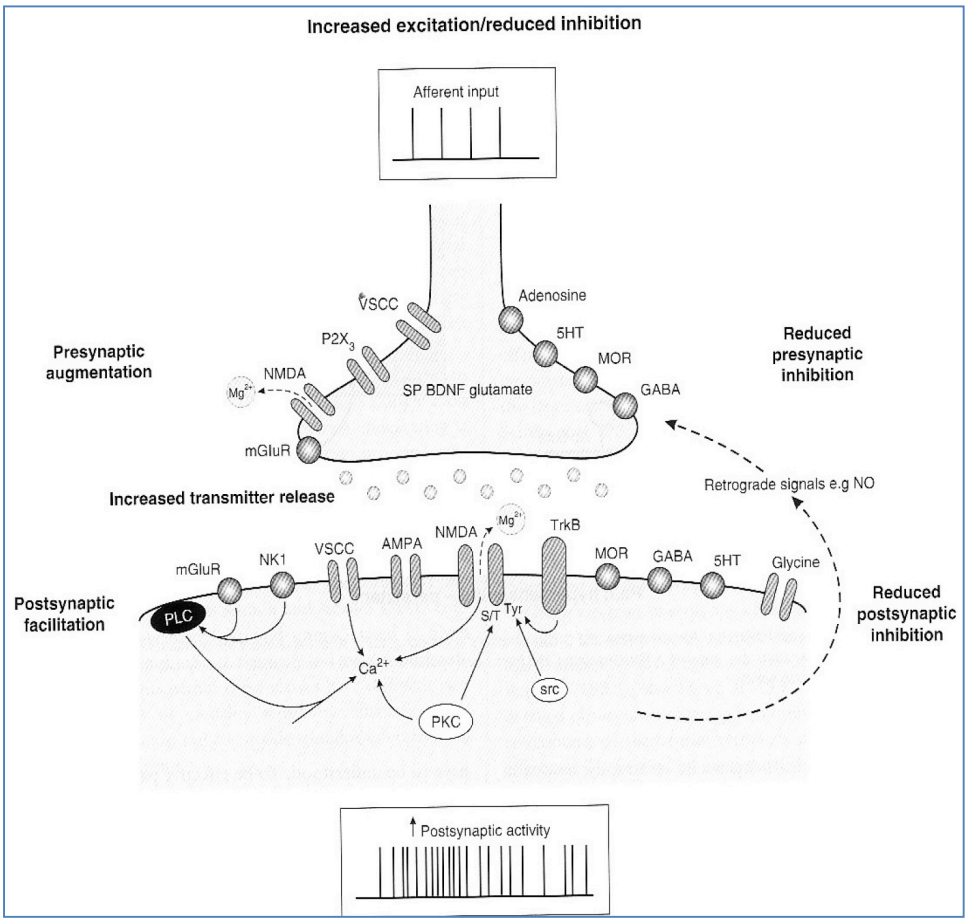


- **Neurotransmitters Involved:**
  - ***OPIOIDS*:**
    - 1. Remove Inhibition of PAG (Activates PAG) → Stimulate NRM → Inhibits Dorsal Horn Synapse
    - 2. Directly Inhibit Dorsal-Horn Synapse
    - – Hence, opioid analgesics work by activating Descending Inhibitory Pathways & Direct inhibition of Dorsal Horn Synapse.
  - ***Noradrenaline** – (From Locus Coeruleus – Directly Inhibits Dorsal-Horn Synapse)
  - ***Serotonin** (5-HT) – (From NRM – Directly Inhibits Dorsal-Horn Synapse)
  - ***Enkephalins** – (From NRM – Directly Inhibits Dorsal-Horn Synapse)
  - Adenosine ?
  - **NB:** Low-Dose Tri-Cyclic Anti-Depressants can treat Neuropathic pain by blocking re-uptake of NE, 5-HT, & Enkephalins in Dorsal Horn Synapse.

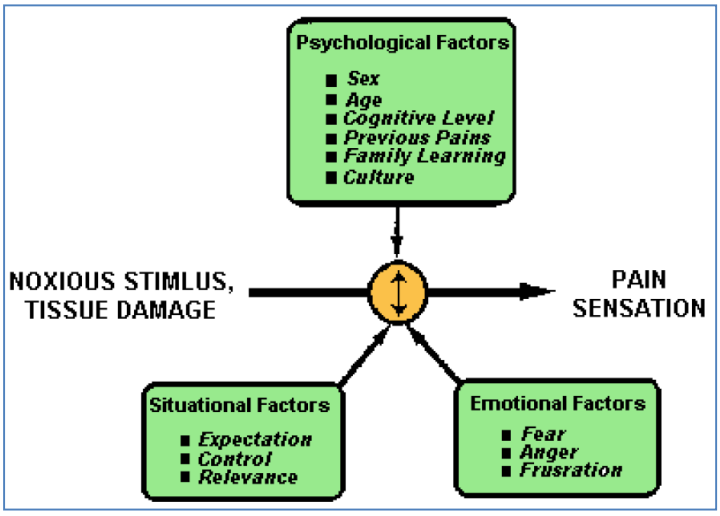


- **"Wind-Up":**
  - = Potentiation @ Synapses between C-Fibres & Dorsal Horn Nerves (Spinal Cord).
  - **Afferent Nociception → Release of Substance-P & Glutamate into Dorsal Horn Synapse → *Remodelling* of the synapse → ↓Threshold → Super-Sensitivity (↑Excitability).**
    - NB: Temporary(Normal)/Permanent(Abnormal)
  - **Remodelling Events:**
    - **Presynaptic:**
      - ↑Presynaptic NT Release
      - ↓Presynaptic Inhibition
    - **Postsynaptic:**
      - ↑Postsynaptic Facilitation (Lowered Threshold)
      - ↓Postsynaptic Inhibition
  - **NB: This 'Remodelling' is mediated by both:**
    - **Phosphorylation** of Proteins/Receptors → Changes Function.
    - **↑Transcription** due to Prolonged action of Second-Messengers (eg. cAMP) triggering Transcription Factors → ↑Number of proteins/New Proteins.
  - **NB: Very Similar To Long-Term Potentiation (LTP):**
    - A Long-Lasting Post-Synaptic Depolarisation, induced through Repetitive Stimulation & Summation of Excitatory Post-Synaptic Potentials."
    - Simply – "A Persistent Increase in Synaptic Strength & Excitability"
  - **Termination of "Wind-Up":**
    - Phosphorylated receptors/enzymes will be de-phosphorylated by Phosphatases.
    - The excess synaptic proteins will degrade (due to half-life) and be replaced by the correct number & type of proteins by normal transcription.

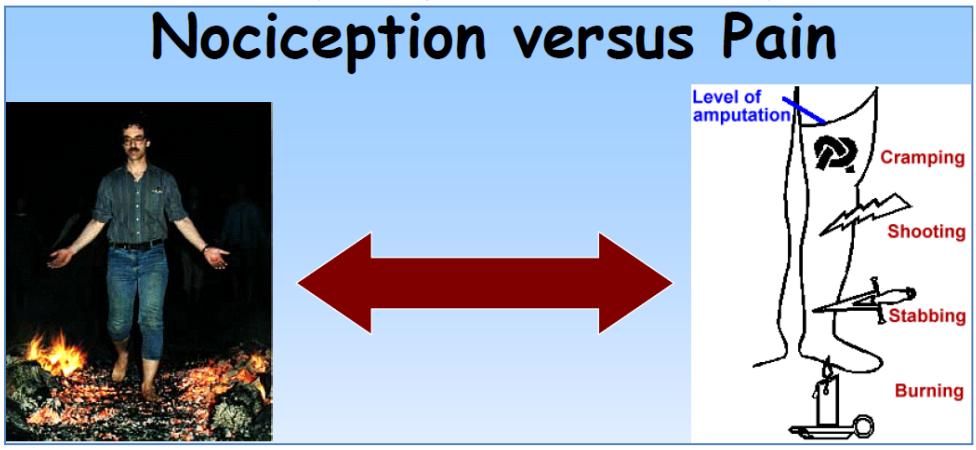




- **4. Processing of Nociceptive Signals by the Brain:**
  - **We Don't know much about Central Nociceptive Processing.**
  - **We Do Know:**
    - -that Thalamic neurons project to Limbic Structures & Hypothalamus (As well as Sens.Cortex)
    - -Incoming Nociceptive Signals are "Weighted" in terms of importance.
    - -The brain's "Response" depends entirely on comparison between the "Weight" of the signal and all other sensory input
    - -*Expectation/Anticipation* of a painful event heightens the pain sensation after stimulus.
    - -*Distraction* is often effective in reducing pain.
  - ***Pain* = a decision made by the brain – Based on more than just Nociception:**
    - Other Sensory Input
    - Context (Memory/Emotional/Danger (Survival)/Body Status/etc)



  - **There is no simple relationship between *Nociception* & *Pain*.**
    - Nociception without Pain = eg. Firewalkers
    - Pain without Nociception = eg. Phantom Limb Pain/Neuropathic Pain

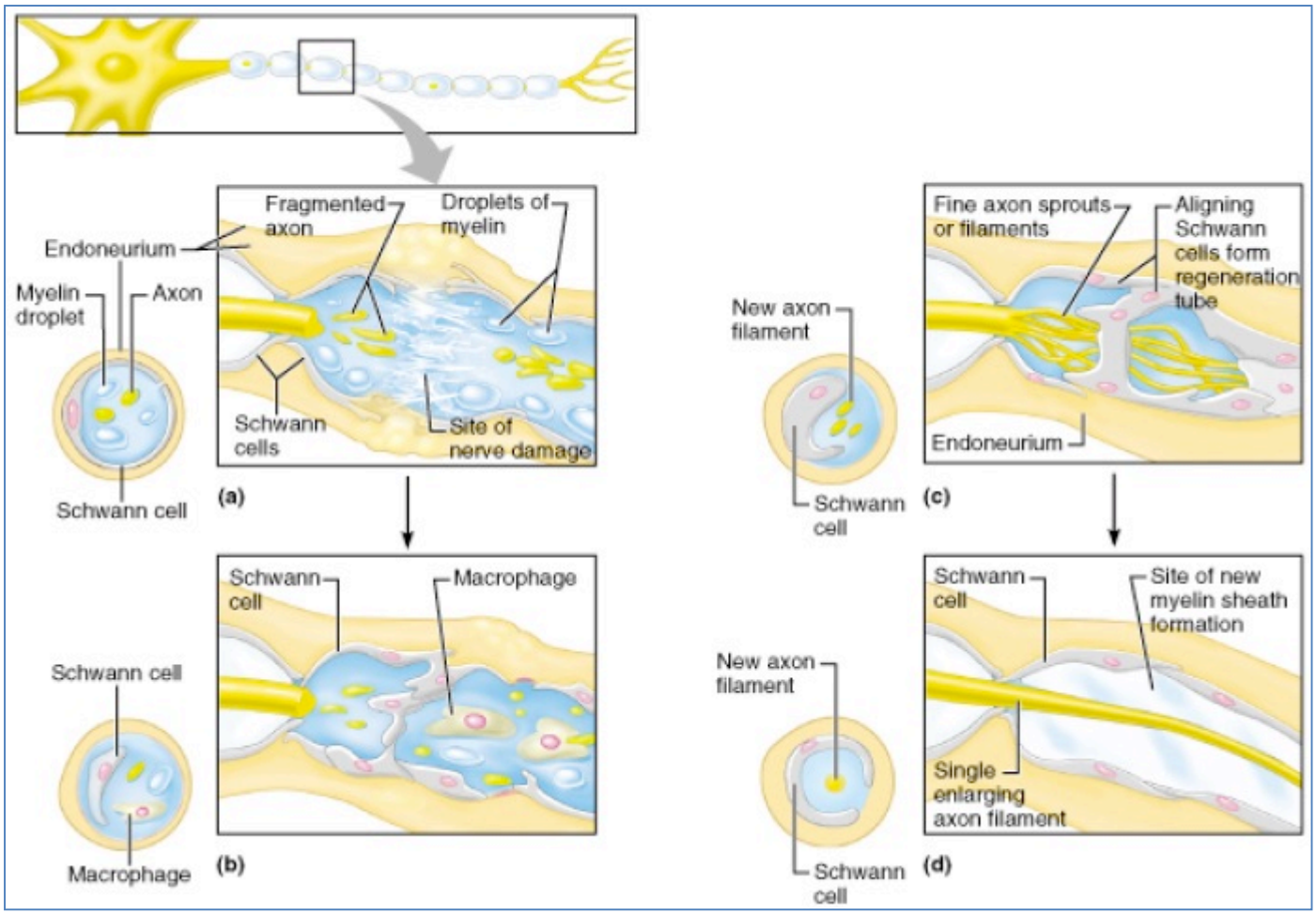


  - **Therefore *Pain is SUBJECTIVE*:**
    - 2 equal injuries will affect 2 people differently.
    - 2 equal injuries @ different times affect the *Same Person* differently.
      - Therefore, pain cannot be directly measured. Instead, a patient's rating of pain is the only measurement to go by (even if it is subjective).
  - **Q: How does the brain distinguish between 'Fast' (Aδ-Fibre) & 'Slow' (C-Fibre) input given that both fibres terminate in the dorsal horn?**
    - **A:** Hypothesis = 2 Ways:
      - 1. Although the different fibre types synapse in the same 'place' (Dorsal Horn), they synapse on *different ascending neurons* – Therefore, their individual info is carried to the brain along separate pathways.
      - 2. The brain uses the delay in the signals coming from the 2 fibre types (as they conduct at different speeds) to determine fibre-type origin.

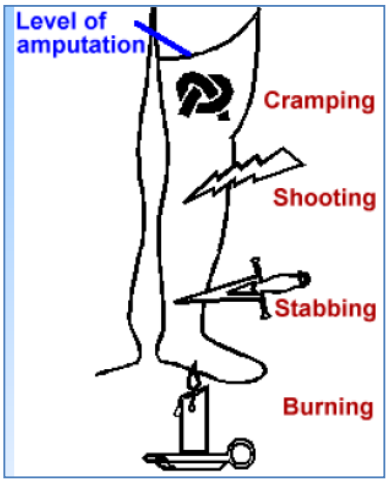
Clinical Relevance:

Neural Regeneration:

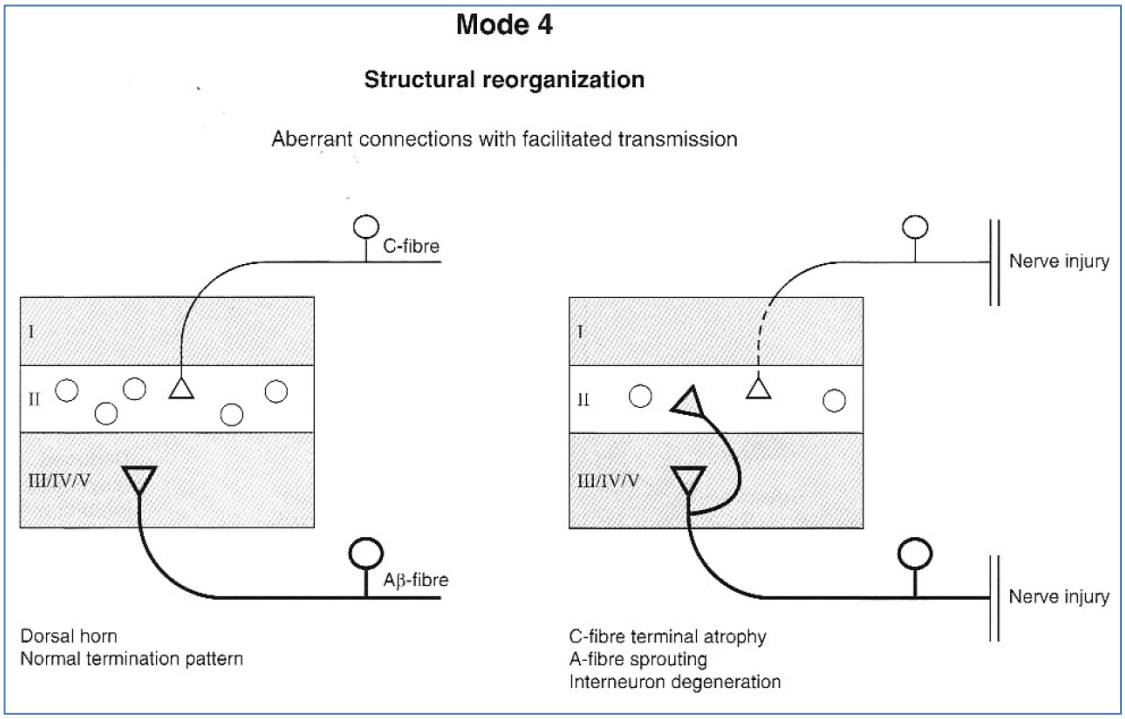
- **Body's attempt to re-connect severed/damaged nerves:**
  - Mediated by ***Schwann Cells***
  - Growth Factors are essential
  - **Aim** – to extend a new segment of ***Axon →Target***.
  - **Rate** – 1.5mm/day
- **Process:**
  - 1. Axon is severed
  - 2. Axon end seals & swells (as substances normally transported along the axon accumulate)
  - 3. Axon distal to injury degenerates due to lack of nutrients & fragments are phagocytosed.
  - 4. However, the Neurilemma in the Endoneurium remains Intact.
  - 5. Schwann Cells Proliferate around site of injury, release growth factors & form a *Regeneration-Tube*
    - A) Growth Factors encourage Axonal Regrowth – "Sprouting"
    - B) Regeneration Tube guides these 'Lamellopodia' (Sprouts) to their original contacts.
  - 6. Schwann Cells protect, support, and Re-Myelinate the Regenerating Axons.
  - 7. Excess 'sprouts' are culled once a connection is re-established.
- **Result:**
  - Never the same, but restores adequate sensitivity of sensory inputs
  - NB: The CNS isn't capable of Neural Regeneration.



- **NB: Neural Regeneration can become Corrupted:**
  - **Disrupted Neural Regeneration 1 – Neuromas:**
    - Sprout may overshoot the target, or the path forward may be blocked.
    - If no connection is made, sprouts can turn back on themselves → Forms a "***Neuroma***".
      - This can cause Sprout-ends to remodel→ changing subtypes of ion channels & receptors → Changing Sensitivity to stimulation.
        - Voltage-gated Na^+ channels go from high to low-threshold → ↑Sensitivity.
      - NB: Neuromas can be a source of ***Spontaneous Ectopic Discharge*** (Similar to Heart)
    - NB: Thought to be a major cause of ***Phantom Limb Pain***:
      - Shooting/Stabbing/Pricking/Squeezing/Burning pains in distal portion of missing limb



  - **Disrupted Neural Regeneration 2 – Wrong Connection:**
    - Relevant to Damaged Sensory Afferents close to DRG or Spinal Cord...
    - If Sprouts overshoot their target in the dorsal horn → they can synapse on the wrong ascending fibres → Changes the *Nature* of the Innervation → Signals are misinterpreted by the brain.
      - Eg. A Damaged Aδ-Fibre (Mechano-afferent) synapses onto an Ascending Neuron that is normally associated with C-Fibres.
      - **Result: Mechanical Sensory Input is now interpreted as Pain.**



Types/Features of Pain:

- **Altered Pain Sensitivity:**
  - Increased pain sensitivity to noxious/non-noxious stimuli → ↑Non-Productive Pain.
    - **Hyperalgesia:**
      - Where a mild noxious stimulus results in a heightened sense of pain.
      - Ie. Something that should only hurt a little, hurts a lot.
    - **Allodynia:**
      - Where pain is provoked by a non-noxious stimulus.
      - Ie. Something that shouldn't hurt, does.
  - **NB: Both can be Associated with Either:**
    - **A Healing Injury (Normal):**
      - Potentiation @ distal nerve terminals – Substance-P, Neurokinin-A & CGRP.
      - Pain Amplifiers – Prostaglandins & Bradykinin
      - **"Wind-Up":** Potentiation @ central nerve terminals – Substance-P & Glutamate – Temporary ***Remodelling*** of the synapse → ↓Threshold.
    - **Neuropathic Origin (Abnormal):**
      - **"Wind-Up":** Potentiation @ central nerve terminals – Substance-P & Glutamate – Permanent ***Remodelling*** of the synapse → ↓Threshold.
      - Other potential causes of *Permanent* Nociceptive Synapse Remodelling:
        - Injury (Mech. Damage)
        - Stroke (Ischaemic Damage)
        - Multiple Sclerosis
        - Diabetic Neuropathy
        - Shingles

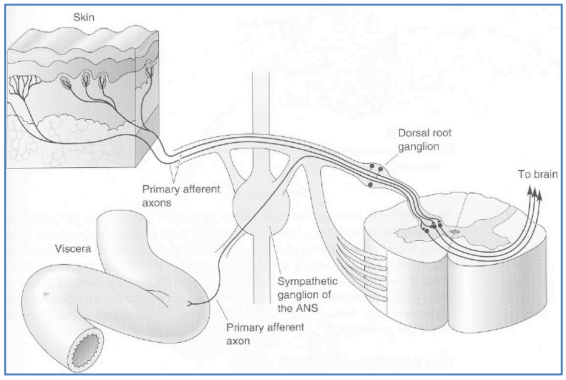
- **Altered Pain Sensation:**
  - **Dysthesia:**
    - Unpleasant, abnormal sensation – Burning/Wetness/Itching/Electric Shock/Incl.Paresthesia.
    - May be Spontaneous *Or* Evoked
  - **Paresthesia:**
    - Abnormal Tingling/Pricking/Numbness in Skin.
    - Eg. 'Pins & Needles'

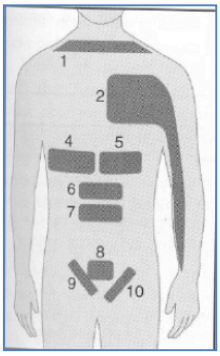
- **Neuropathic Pain:**
  - Severe, Chronic Pain that isn't associated with any current peripheral tissue damage. Rather, it is caused by a primary lesion/dysfunction of the Nervous System that is often impossible to identify.
  - Often results from ***Corrupted Neural Regeneration*** secondary to a past injury.
  - **Simply –** Pain that doesn't have an exogenous trigger.
  - **A Result of Permanent Synaptic Remodelling → Hypersensitisation:**
    - **Anatomical Malformations –** Eg. **Neuromas** (Tangle of Nerves) due to mechanical nerve injury & subsequent failed Neural Regeneration.
    - **Molecular Alterations –** Eg. Damaged nerve terminals begin to express α-Adrenergic Receptors (NB: Abnormal) →Become sensitive to Adrenaline.
      - Therefore, Sympathetic Activity → Systemic Adrenaline Release → Pain.
    - **Cellular Alterations** – Eg. Spontaneous Neuronal Discharges due to a change in number/type/& Sensitivity of Na^+ Channels.
    - **Physiological Alterations** – Eg. Permanent **"Wind-Up"** → ↓Threshold.
    - **Other potential causes of *Permanent* Nociceptive Synapse Remodelling:**
      - Injury (Mech. Damage)
      - Stroke (Ischaemic Damage)
      - Multiple Sclerosis
      - Diabetic Neuropathy
      - Shingles
  - **NB: Low-Dose Tri-Cyclic Anti-Depressants can treat Neuropathic pain** by blocking re-uptake of NE, 5-HT, & Enkephalins in Dorsal Horn Synapse → Maintained Inhibition of Nociceptive Transmission.

- **Chronic Pain:**
  - On-going pain associated with a Progressive Disorder or Non-Healing Injury.
    - Includes 'Neuropathic Pain'
  - Is often insensitive to Narcotic Analgesics (Opioids)
  - **NB:** There is often ***Discordance*** between Pain-Experience & Self-Report of Pain.

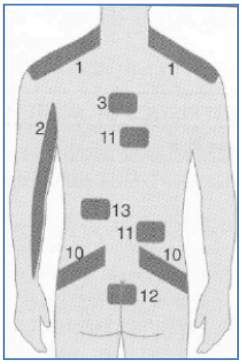
- **Visceral & Parietal Pain:**
  - **Visceral Pain:**
    - NB: Visceral Sensory Inputs are Primarily Nociceptive.
    - **NB: Primarily Associated with C-Fibres** (Dull, Aching Pain)
    - **Main Causes of Visceral Pain:**
      - Ischaemia
      - Chemical Stimuli (Eg. Gastric/Duodenal Ulcer Rupture)
      - Muscle Spasms in Hollow Organ
      - Over-Distension of Hollow Organ
    - **Most Sensitive to** Diffuse Organ Damage rather than Localised Organ Damage.
      - Ie. Diffuse organ damage → causes severe pain.
    - **Nature of Visceral Pain:**
      - Dull
      - Achy
      - Poorly Localised
  - **Parietal Pain:**
    - **NB: Primarily Associated with Aδ-Fibres** (Sharp, stabbing pain)
    - **Main Cause of Parietal Pain:**
      - Severely Diseased Organ → Spreads to Parietal Membranes:
        - Peritoneum
        - Pleura
        - Pericardium
        - Meninges (NB: Brain is impervious to pain, but Meninges & Vessels aren't)
          - NB: Meningitis is one of the most severe headaches known.
        - Etc
      - These Parietal Membranes have large numbers of Nociceptors.
    - **Nature of Parietal Pain:**
      - Sharp
      - Well-Localised

- **Referred Pain:**
  - = Pain experienced as being associated with a tissue/body part that isn't the actual site of injury:
    - Typically, Visceral Pain is felt in the Dermatomes of the Spinal Roots that also receive the Visceral Afferents.
  - Occurs due to Convergence of Visceral & Cutaneous Nociceptive signals @ the Spinal Cord:
    - Visceral C-Fibres synapse onto (and activate) the same Ascending Neurons as Cutaneous/Muscular Aδ-Fibres.
    - Therefore, Noxious Visceral Stimuli are felt as pain in the tissues covered by the Aδ-Fibres synapsing on the same Dorsal Horn Neuron.





1. Diaphragm
2. Heart
3. Esophagus
4. Liver
5. Stomach
6. Intestine
7. Colon
8. Bladder
9. Right ovary
10. Kidney
11. Gallbladder
12. Cervix of uterus
13. Spleen



Reporting Pain:

- **Paediatrics:**
  - **Children experiencing pain may not be able to accurately report on that pain for many reasons:**
    - May be Neonatal
    - May be unwilling to cooperate
    - May be incapable of understanding what you are asking when inquiring about their pain.
    - May be unable to describe their experience
    - They are afraid that if they report pain, they will get a needle (which they fear more)
    - May want to please Parents/Authority Figures (Docs/Nurses)
    - May be mentally/physically disabled
  - **This inability to accurately report on pain leads to "Discordance", a feature of Paediatric Pain:**
    - Where a child reports a certain degree (or lack) of pain that conflicts with observed behaviour and activities.
    - The temptation is to attribute this to attention-seeking, malingering or psychological problems.
    - However, discordance is simply a sign of a problem in pain evaluation (measurement/assessment) and indicates the need to pursue further investigations.
  - **Measuring Pain in Children:**
    - **Neonates/Very Young Children/Disabled Children:**
      - Reports by Parents/Care-Givers
      - 'The Oucher' Pain Scale – A 'Visual Analogue Scale' - Uses ethnically-specific photos of young children in various stages of distress.

    - **Children 8 Yrs^{+}:**
      - Variation of McGill Pain Questionnaire – Uses 56 Adjectives graded on a scale of 0-5.

- **Older Children & Adults:**
  - Self-Report Scales – Eg. The McGill Pain Questionnaire – Uses 78 Adjectives graded on a scale of 0-5.

McGILL PAIN QUESTIONNAIRE

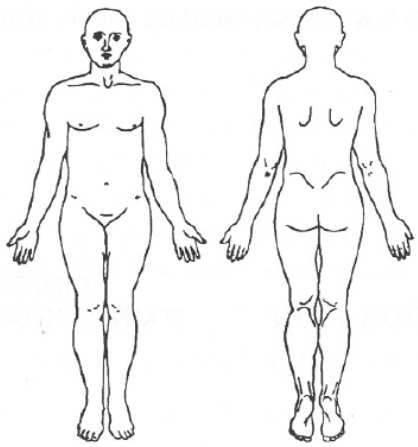
RONALD MELZACK

Patient's Name _____ Date _____ Time _____ am/pm

PRI: S _____ (1-10) A _____ (11-15) E _____ (16) M _____ (17-20) PRI(T) _____ (1-20) PPI _____

1	FLICKERING QUIVERING PULSING THROBBING BEATING POUNDING	11	TIRING EXHAUSTING
2	JUMPING FLASHING SHOOTING	12	SICKENING SUFFOCATING
3	PRICKING BORING DRILLING STABBING LANCINATING	13	FEARFUL FRIGHTFUL TERRIFYING
4	SHARP CUTTING LACERATING	14	PUNISHING GRUELLING CRUEL VICIOUS KILLING
5	PINCHING PRESSING GNAWING CRAMPING CRUSHING	15	WRETCHED BLINDING
6	TUGGING PULLING WRENCHING	16	ANNOYING TROUBLESOME MISERABLE INTENSE UNBEARABLE
7	HOT BURNING SCALDING SEARING	17	SPREADING RADIATING PENETRATING PIERCING
8	TINGLING ITCHY SMARTING STINGING	18	TIGHT NUMB DRAWING SQUEEZING TEARING
9	DULL SORE HURTING ACHING HEAVY	19	COOL COLD FREEZING
10	TENDER TAUT RASPING SPLITTING	20	NAGGING NAUSEATING AGONIZING DREADFUL TORTURING
		PPI	
		0	NO PAIN
		1	MILD
		2	DISCOMFORTING
		3	DISTRESSING
		4	HORRIBLE
		5	EXCRUCIATING

BRIEF	RHYTHMIC	CONTINUOUS
MOMENTARY	PERIODIC	STEADY
TRANSIENT	INTERMITTENT	CONSTANT



E = EXTERNAL
I = INTERNAL

COMMENTS:

© R. MELZACK, 1975

Treatment & Pain Management:

- **Effective Management ALWAYS STARTS with an Evaluation of the Pain Report:**
  - The Analgesic/Combination of Analgesics is ***Matched*** to the Pain Report.
- **3 Locations to Consider when Targeting Pain:**
  - **1. Peripheral Targets:**
    - **$TRPV_1R$ Receptors (Vanilloid Receptors – Sensitive to H^+/Capsaicin/Heat/Mech):**
      - **Capsaicin:**
        - Activates $TRPV_1R$ Receptors on C-Fibres → Causes Substance-P release
          - → Depletes the terminal of Substance-P (A Peptide)
          - → There will be a period of Analgesia while Sub-P is re-synthesised.
        - Useful For:
          - Topical Arthritis Cream
          - Some Neuropathic Pain
    - **Prostanoid Receptors (Sensitive to Prostaglandins):**
      - **Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) – (Aspirin/Ibuprofen)**
        - Mild Analgesic
        - Anti-Inflammatory:
          - ↓Prostaglandin Production by inhibiting the enzyme Cyclo-Oxygenase [COX]) → ↓Prostaglandin-Mediated Hypersensitivity of Nociceptive Neurons.
        - Useful For:
          - Mild-Moderate pain
          - Hyperalgesia
          - Allodynia
      - **COX-2 Inhibitors – (Celebrex)**
        - Mild Anti-Inflammatory Analgesic:
          - More specific than NSAID's – Target COX-2 Enzyme – Less Side-Effects)
          - ↓Prostaglandin Production by inhibiting the enzyme Cyclo-Oxygenase-2 [COX-2]) → ↓Prostaglandin-Mediated Hypersensitivity of Nociceptive Neurons.
        - Useful For:
          - Mild-Moderate pain
          - Hyperalgesia
          - Allodynia
    - **Opioid Receptors:**
      - **Opioid Drugs – (Codeine, Morphine, Fentanyl):**
        - Strong Analgesics - Act at all 3 levels (Periphery, Spinal Cord, Brain)
        - Activated Opioid Receptors on:
          - Distal Nerve Ending – (Periphery):
            - Opens K^+ Channels → K^+-Efflux → Hyperpolarisation.
        - May be used for Acute & Chronic Pain.
          - If used Acutely, a ***"Step-Down"*** Plan (to less potent agents) must be used to prevent addiction.
    - **Unknown:**
      - **Paracetamol – (Panadol)**
        - Mild Analgesic:
          - Mechanism is unknown.
        - WEAK Anti-Inflammatory:
          - Weak inhibit of Prostaglandin Synthesis
        - Useful For Analgesia when Inflammation isn't an issue.

- **2. Spinal Cord Targets:**
  - Substantia Gelatinosa
  - Dorsal Horn Synapse
  - **Effective Analgesics:**
    - **Opioids – (Codeine, Morphine, Fentanyl):**
      - Strong Analgesics - Act at all 3 levels (Periphery, Spinal Cord, Brain)
      - Activated Opioid Receptors on:
        - Distal Nerve Ending – (Periphery):
          - Opens K^+ Channels → K^+-Efflux → Hyperpolarisation.
        - Proximal Nerve Ending – (Spinal Cord):
          - Mimic Autoreceptors → Closure of Ca^+ Channels → ↓Ca^+-Mediated NT Release.
        - Periaqueductal Grey Matter (PAG) – (Brain):
          - Remove Inhibition of PAG (Activates PAG) → Activates NRM → Inhibits Dorsal Horn Synapse.
      - May be used for Acute & Chronic Pain.
        - If used Acutely, a ***"Step-Down"*** Plan (to less potent agents) must be used to prevent addiction.
    - **Tri-Cyclic Antidepressants:**
      - Low-Dose Tri-Cyclic Anti-Depressants can treat Neuropathic pain by blocking re-uptake of NE, 5-HT, & Enkephalins in Dorsal Horn Synapse → Maintained Inhibition of Nociceptive Transmission.
    - **Massage Therapy:**
      - Aβ-Fibre Mechano-Afferents directly activate the Substantia Gelatinosa → Inhibit Nociceptive Transmission @ Dorsal Horn Synapse.

- **3. Brain Targets:**
  - Periaqueductal Grey Matter (PAG)
  - Whole Brain
  - **Effective Analgesics:**
    - **Opioids – (Codeine, Morphine, Fentanyl):**
      - Strong Analgesics - Act at all 3 levels (Periphery, Spinal Cord, Brain)
      - Activated Opioid Receptors on:
        - Distal Nerve Ending – (Periphery):
          - Opens K^+ Channels → K^+-Efflux → Hyperpolarisation.
        - Proximal Nerve Ending – (Spinal Cord):
          - Mimic Autoreceptors → Closure of Ca^+ Channels → ↓Ca^+-Mediated NT Release.
        - Periaqueductal Grey Matter (PAG) – (Brain):
          - Remove Inhibition of PAG (Activates PAG) → Activates NRM → Inhibits Dorsal Horn Synapse.
      - May be used for Acute & Chronic Pain.
        - If used Acutely, a ***"Step-Down"*** Plan (to less potent agents) must be used to prevent addiction.
    - **General Anaesthesia:**
      - Knocks out the entire conscious NS.

Important Clinical Neurological Things:

Pattern-Recognition of Common Neuro Symptoms & Signs:

Headaches:

	Pattern:	**Probable Diagnoses:**
Isolated SEVERE Headache	History: Acute Onset Syx: "Thunderclap Headache", Pain 10/10, Vomiting, Meningism, ALOC.	?Subarachnoid Haemorrhage (Arterial)
Headache Following Head Injury	History: Acute Onset Syx: Acute LOC Following Severe Head Trauma → Lucid Interval → Rapid Deterioration + Vomiting + Seizures	?Extradural Haemorrhage (Arterial)
	History: Days-Weeks-Months Syx: Worsening Headache following Mild Head Trauma.	?Subdural Haematoma (Venous)
Subacute Onset Headaches	History: Days Syx: Headache + Constitutional Syx (Fever, Rash, N/V/D, Fatigue), + Meningism/Photophobia.	?Infective: - ?Meningitis - ?Encephalitis
Chronic or Recurrent Headaches	History: Months-Years Duration: Hours-Days Syx: Vague Muscle Tension/ Migraine/Sinus.	?Tension Headache (Muscular) ?Migraine (Functional) ?Sinusitis (Inflammatory/Pressure)
Pressure Headaches	History: Months-Years Syx: Pain worse Lying Down, Coughing, Straining or Sneezing. + Vomiting	?Intracranial Space-Occupying Lesion → ↑ICP
Headaches with Scalp Tenderness	History: Older Patient Syx: Headache + Extreme Tenderness over Scalp Vessels.	?Temporal Arteritis (Giant Cell Arteritis)

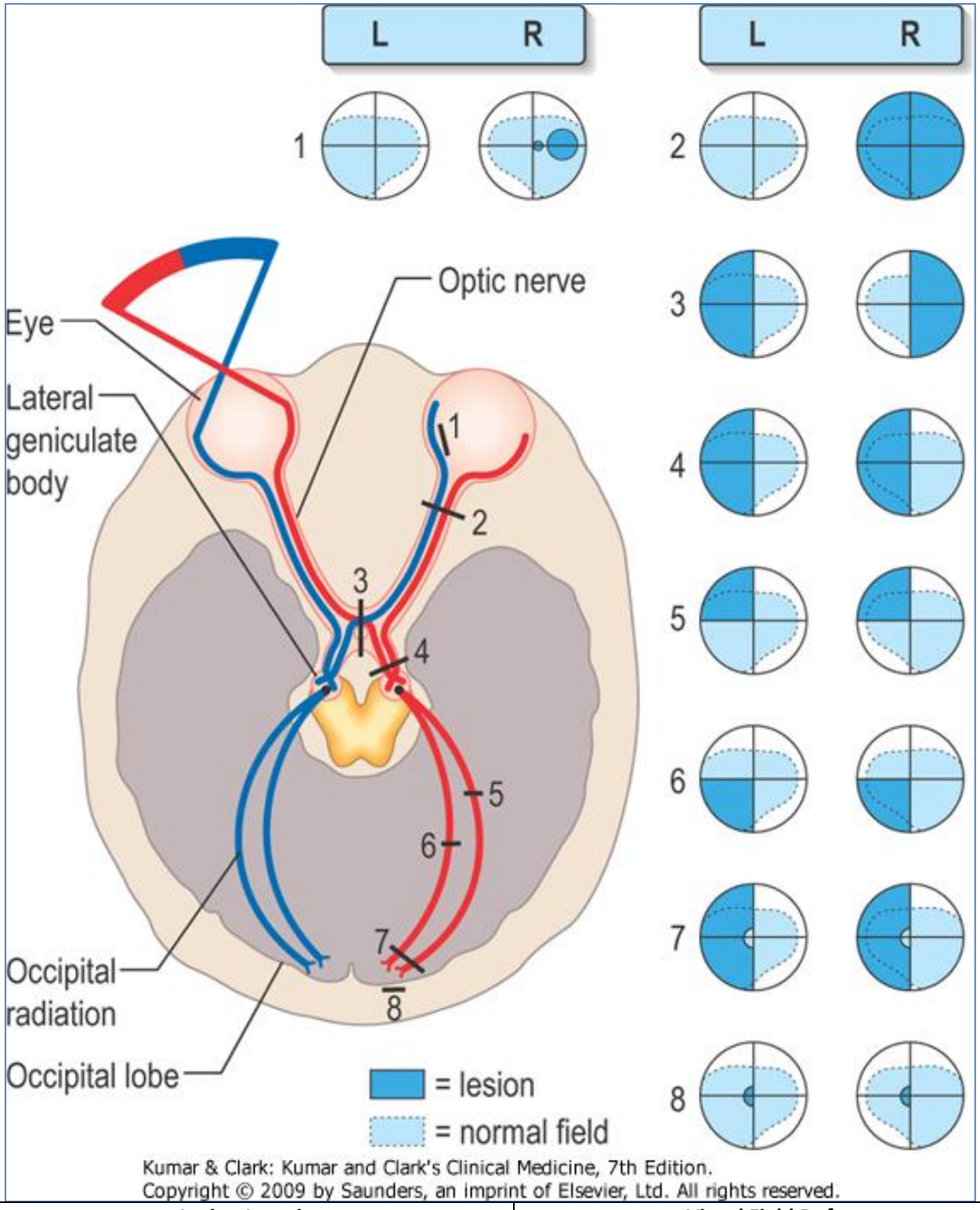
Dizziness, Vertigo & Blackouts

	Pattern:	**Probable Diagnoses:**
Dizziness	Vague Unsteadiness, Light-Headedness.	?Postural/Orthostatic Hypotension ?Panic/Anxiety ?Palpitations (Eg. Atrial Fibrillation) ?Anaemia
Vertigo	The Illusion of Movement, Sensation or Rotating/Tipping. + Nausea & Vomiting	?Otolith ?Vestibulocochlear Disease (Eg. Acoustic Neuroma)
Blackout	Implies ALOC, Visual Disturbance, or Falling	?Syncope ?Epilepsy ?Hypoglycaemia ?Anaemia

Difficulty Walking & Falls:

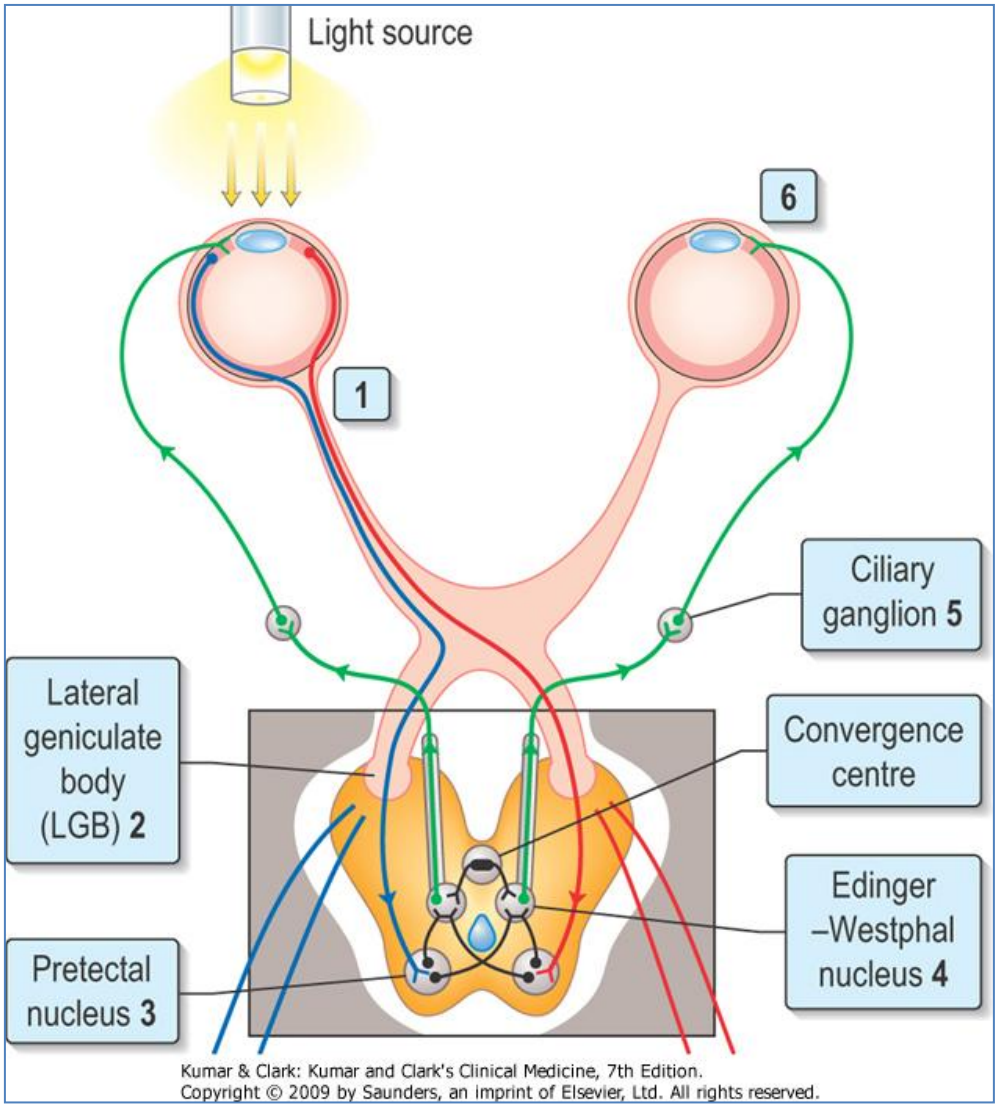
	Pattern:	**Probable Diagnoses:**
Spacticity	Stiff, Jerky Walking Toe-Scuffing and Catching Maintained Narrow Base	?Spastic Diplegia (Neonatal Asphyxia) ?Multiple Sclerosis ?Cerebral Palsy ?Bilateral Spinal Cord Injury
Hemiparesis	Unilateral Spacticity (See Above) + Circumduction of Spastic Leg to prevent Toe Dragging.	?Stroke (ACA) ?Unilateral Spinal Cord Injury
Parkinson's Disease: **Shuffling Gait**	Short Rapid Steps, Shuffling, Maintained Narrow Base, Stooping, Difficulty Turning Quickly	?Parkinson's Disease
Cerebellar Ataxia: **Broad-Based Gait**	**Broad-Based Ataxia**, Unstable, Tremulous	?Lateral Cerebellar Lobe Disease
	Truncal Ataxia (Unsteady Trunk without Limb Ataxia) + Tendency to fall Back/Sideways	?Midline Cerebellar (Vermis) Disease (*Remember Cpt. Jack Sparrow)
Sensory Ataxia: **Stamping Gait**	Broad-Based, High-Stepping, Stamping Gait. (Worse with Eyes Closed) (Romberg's Test Positive)	?Polyneuropathy & Loss of Proprioception
Lower Limb Weakness: **Slapping & Waddling Gaits**	**Slapping Gait:** Audible Sole-Slap when returned to Ground	?Distal Leg Weakness (Eg. Common Peroneal nerve Palsy)
	Waddling Gaits: Difficulty Rising from Sitting + Waddling	?Proximal Leg Weakness (Eg. Polyomyelitis, Muscular Dystrophy) (*Remember Maggie Grant)
Gait Apraxia	Failure to Initiate/Organize Walking, Shuffling Small Steps, Undue Hesitancy. (But Normal Leg Mvts when Sitting/Lying)	?Frontal Lobe Disease (Tumour, Hydrocephalus, Infarction)

Visual Field Defects + Causes:



	Lesion Location	Visual Field Defect
1	**Retinal Lesion (Eg. Retinal Haemorrhage)**	Paracentral Scotoma (Focal Visual Field Defect)
2	**Unilateral Optic Nerve Lesion**	Mononuclear Field Loss
3	**Optic Chiasm Lesion**	Bitemporal Hemianopsia
4	**Unilateral Optic Tract Lesion**	Contralateral Homonynous Hemaniopsia
5	**Temporal Optic Radiation Lesion (Upper Retinae; Lower Visual Field)**	Contralateral Homonynous Lower Quadrantanopsia
6	**Parietal Optic Radiation Lesion (Lower Retinae; Upper Visual Field)**	Contralateral Homonynous Upper Quadrantanopsia
7	**Full-Thickness Optic Radiation Lesion**	Contralateral Homonynous Hemaniopsia
8	**Occipital Pole Lesion (Visual Cortex Lesion)**	Contralateral Homonynous Hemiscotoma

Pupillary Defects + Causes:



Afferent Pupillary Defect:

- **(Ie. An Optic Nv/Optic Chiasm/Optic Tract Lesion)**
- **Eg. A Blind Left Eye:**
  - L-Pupil Unreactive to Light
  - Present Consensual Reflex in L-Pupil
  - R-Pupil Reactive to Light
  - Absent Consensual Reflex in R-Pupil

Efferent Pupillary Defect:

- **(Ie. Occulomotor Nv/Ciliary Nv Lesion)**
- **Eg. Left 3rd Nerve Palsy:**
  - L-Pupil Unreactive to Light
  - Absent Consensual Reflex in L-Pupil
  - R-Pupil Reactive to Light
  - Present Consensual Reflex in R-Pupil

Revision
Functional Areas of the Brain:

Frontal Lobe Functions:

- High level Cognition. (Reasoning, Abstraction, Concentration)
- Motor Control:
  - Contralateral Side (Motor Cortex)
  - Voluntary Eye Movement
  - Urinary Continence
- Expressive Speech Centre (Broca's Area) in Dominant Hemisphere.
- Memory
- Emotion and Personality (Limbic System)

Parietal Lobe Functions:

- Contralateral Sensation (Sensory Cortex)
- Contralateral Proprioception (Dorsal Column Medial-Lemniscal Pathway)
- Non-Dominant – Visuospatial Processing
- Dominant - Learned Motor Tasks

Temporal Lobe Functions:

- Smell (Olfactory Cortex)
- Hearing (Primary Auditory Cortex)
- In Dominant – Receptive Speech (Wernicke's)
- Memory
- Fear (Amygdala)

Occipital Lobe Functions:

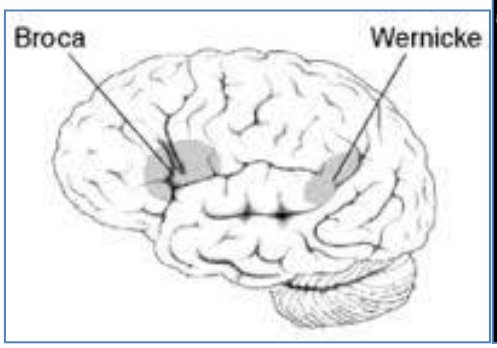
- Vision (Primary Visual Cortex)
- Visual Perception (Visual Association Areas)

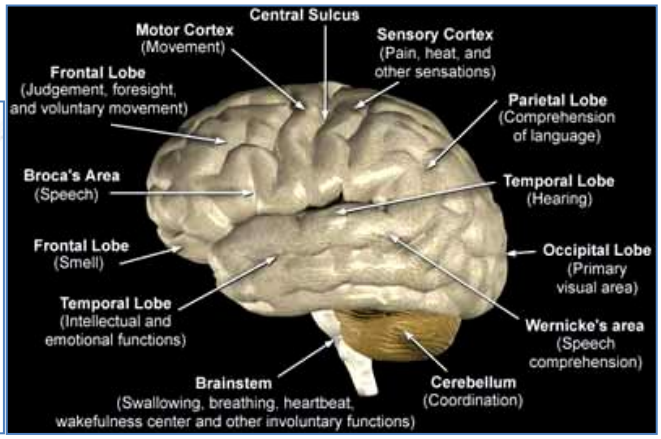
Brain Stem:

- Midbrain, Pons & Medulla
- 10 of the 12 cranial nerves arise from the brainstem → Ipsilateral signs
- Cortical pathway decussation → Contralateral Signs.
- **Major Functions:** Eye Movement, Swallowing, Breathing, Blood Pressure, Heart Rate, Consciousness

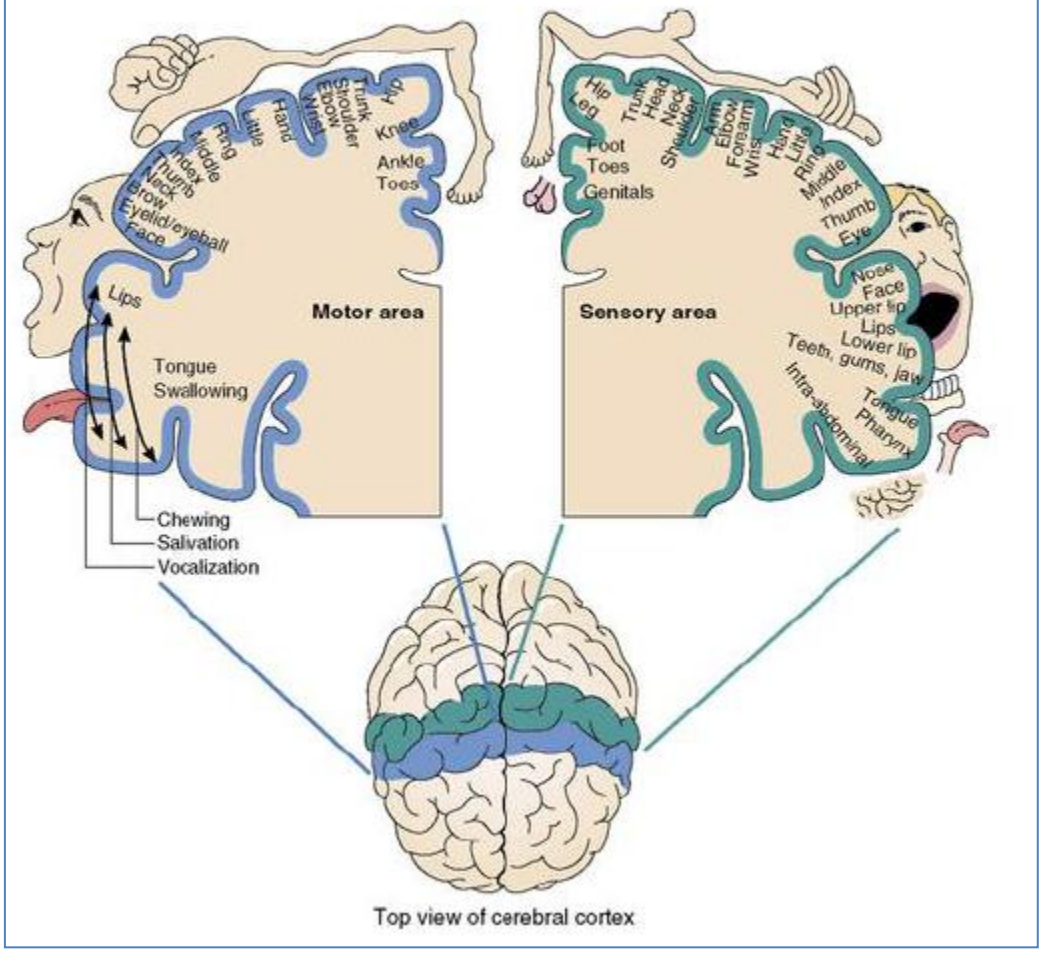
Cerebellum:

- Movement – Balance Coordination



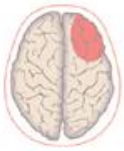


Coronal View of Motor and Sensory Cortex

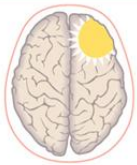
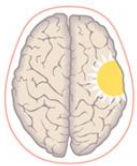
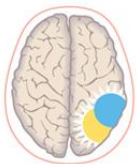
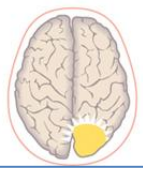


Clinical Features of Focal Brain Lesions:

Principal Features of Destructive Cortical Lesions:

Site of lesion	Disorder	R L
Frontal, either	Intellectual impairment Personality change Urinary incontinence Monoparesis or hemiparesis	
Frontal, left	Broca's aphasia	
Temporo-parietal, left	Acalculia Alexia Agraphia Wernicke's aphasia Right-left disorientation Homonymous field defect	
Temporal, right	Confusional states Failure to recognize faces Homonymous field defect	
Parietal, either	Contralateral sensory loss or neglect Agraphaesthesia Homonymous field defect	
Parietal, right	Dressing apraxia Failure to recognize faces	
Parietal, left	Limb apraxia	
Occipital/ occipitoparietal	Visual field defects Visuospatial defects Disturbances of visual recognition	

Effects of Irritative Cortical Lesions:

Site of lesion	Effects	R L
Frontal	Partial seizures–focal motor seizures of contralateral limbs Conjugate deviation of head and eyes away from the lesion	
Temporal	Formed visual hallucinations Complex partial seizures Memory disturbances (e.g. *déjà vu*)	
Parietal	Partial seizures–focal sensory seizures of contralateral limbs	
Parieto-occipital	Crude visual hallucinations (e.g. shapes in one part of the field)	
Occipital	Visual disturbances (e.g. flashes)	

Patterns of Motor Neuron Lesions:

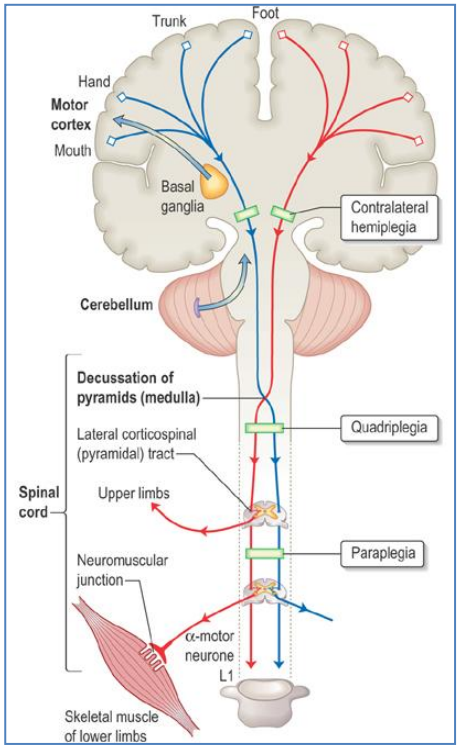
Upper Motor Neuron Lesions:

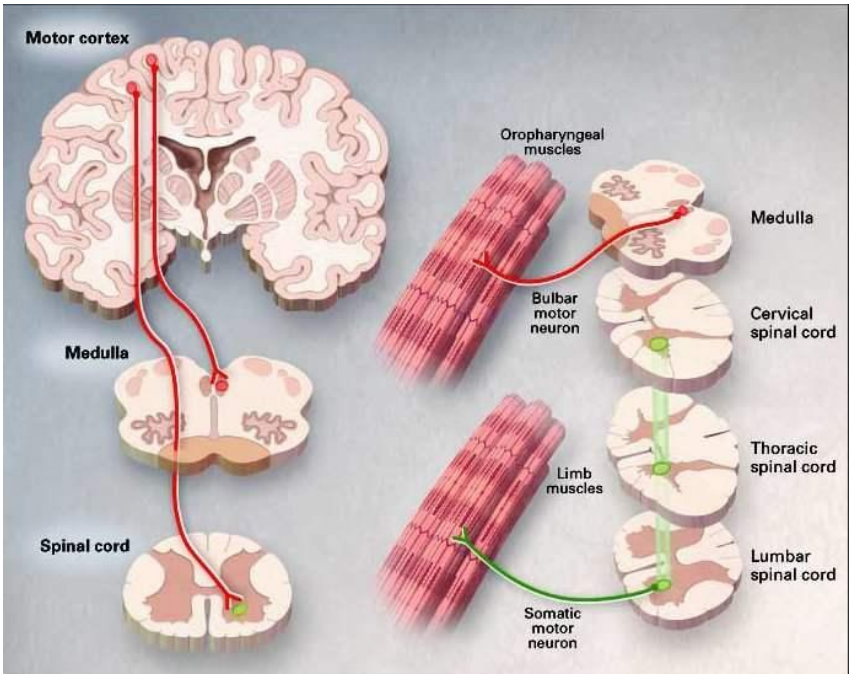
- = Lesions of the Neural Pathway *ABOVE* the Anterior Horn of the Spinal Cord (Or the Motor Nuclei of the Cranial Nerves)
- **Causes:**
  - Stroke
  - Traumatic Brain Injury
  - Cerebral Palsy
- **General Symptoms of UMN Syndrome:**
  - Muscle Weakness ('Pyramidal Weakness')
  - Hyperreflexia (Due to ↓CNS Inhibition)
  - Spasticity
  - Babinski Sign (Extension of Big Toe rather than Flexion)
  - Pronator Drift (Pt Flexes Arms to 90°, Supnates Forearms & Closes Eyes; Inability to maintain this position = Pronator Drift) (SideNB: Drifting *Upwards* is a Sign of a Cerebellar Lesion)
- **Specific UMN Lesion Locations & Their Consequences:**

Unilateral Motor Cortex Lesion (Eg. Stroke)	Contralateral Hemiplegia
Unilateral Internal Capsule Lesion (Eg. Tumour)	Contralateral Hemiplegia
Laceration of Spinal Cord Between Medulla & Brachial Plexus	Quadriplegia
Laceration of Spinal Cord Between Brachial Plexus & Sacral Plexus	Paraplegia

Lower Motor Neuron Lesions:

- = Lesions of the Neural Pathways *BELOW* the Anterior Horn of the Spinal Cord (Or the Motor Nuclei of the Cranial nerves)
- **Causes:**
  - Injuries/Trauma to Peripheral Nerves
  - Poliomyelitis (Virus Selectively Attacks the Anterior Horns of the Spinal Cords)
  - Guillain-Barre Syndrome
  - Botulism
- **General Symptoms of UMN Syndrome:**
  - Flaccid Paralysis of the Affected Muscle
  - Muscle Wasting of the Affected Muscle
  - Fasciculations
  - Areflexia

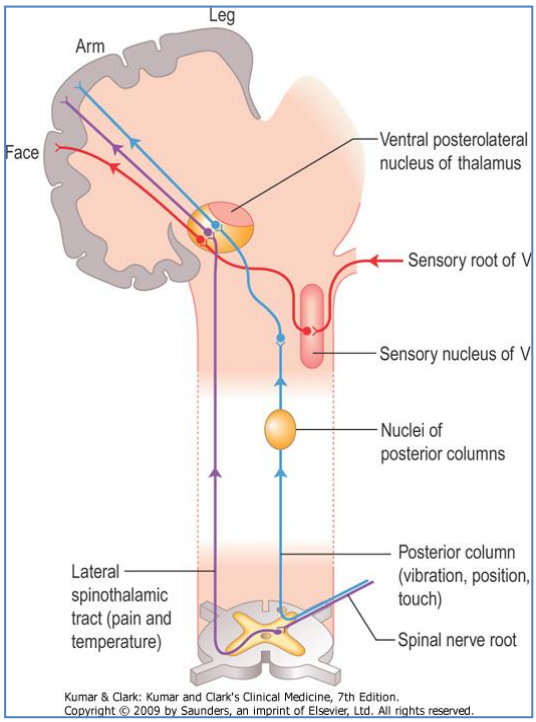




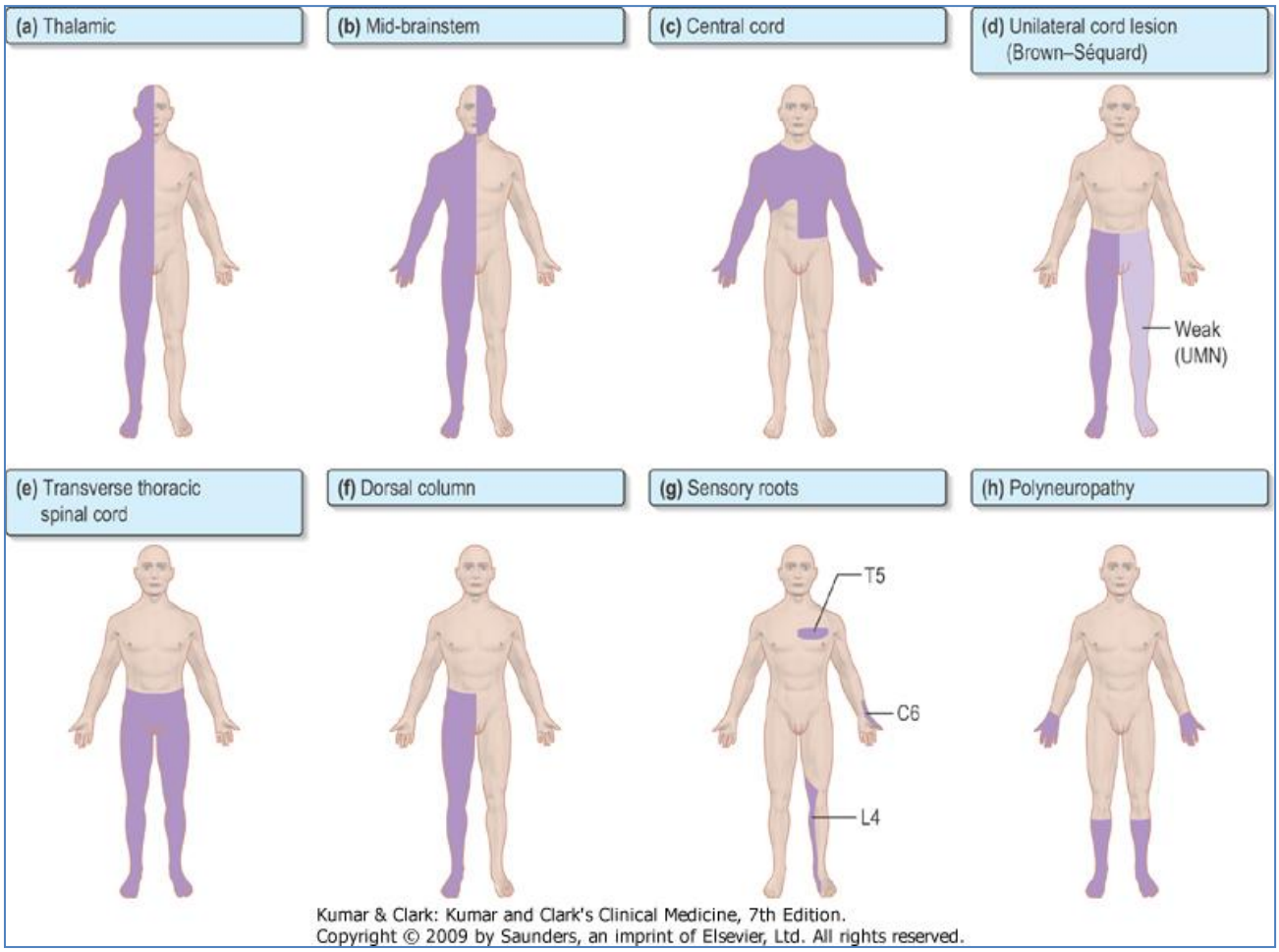
Patterns of Loss of Sensation:

Background:

- **3 Conscious Sensory Pathways:**
  - **Dorsal Column Medial-Lemniscal Pathway:**
    - Vibration, Proprioception, 2-Point Discrimination
    - Ascends Ipsilaterally → Decussates in Medulla → Thalamus → Sensory Cortex
  - **Spinothalamic Pathway:**
    - Pain & Temperature
    - Decussates @ Spinal Level → Ascends Contralaterally → Thalamus → Sensory Cortex
  - **Trigeminal Nerve:**
    - All Facial Sensation
    - Decussates in Medulla → Thalamus → Sensory Cortex
- **1 Unconscious Sensory Pathway:**
  - **Spinocerebellar:**
    - Role in Proprioception & Balance.

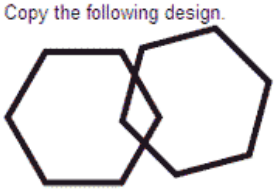


Kumar & Clark: Kumar and Clark's Clinical Medicine, 7th Edition.
Copyright © 2009 by Saunders, an imprint of Elsevier, Ltd. All rights reserved.



Kumar & Clark: Kumar and Clark's Clinical Medicine, 7th Edition.
Copyright © 2009 by Saunders, an imprint of Elsevier, Ltd. All rights reserved.

MMSE – Assessing Dementia:

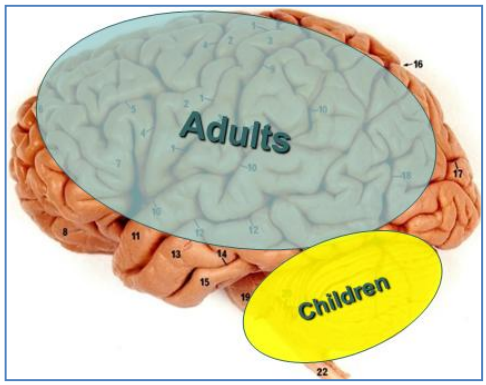
Maximum score	Score	
		Orientation
5	__	What is the (year) (season) (date) (day) (month)?
5	__	Where are we: (state) (county) (town or city) (hospital) (floor)?
		Registration
3		Name three common objects (e.g., "apple," "table," "penny"): Take one second to say each. Then ask the patient to repeat all three after you have said them. Give one point for each correct answer. Then repeat them until he or she learns all three. Count trials and record.
	__	Trials: ___
		Attention and clalculation
5		Spell "world" backwards. The score is the number of letters in correct order.
	__	(D___L___R___O___W___)
		Recall
3		Ask for the three objects repeated above. Give one point for each correct answer. (Note: recall cannot be tested if all three objects were not remembered during
	__	registration.)
		Language
2		Name a "pencil" and "watch."
	__	Repeat the following: "No ifs, ands or buts."
1	__	Follow a three-stage command:
3	__	"Take a paper in your right hand, fold it in half and put it on the floor."
1	__	Close your eyes.
1	__	Write a sentence.
1		Copy the following design.
		
	__	
	Total score: __	

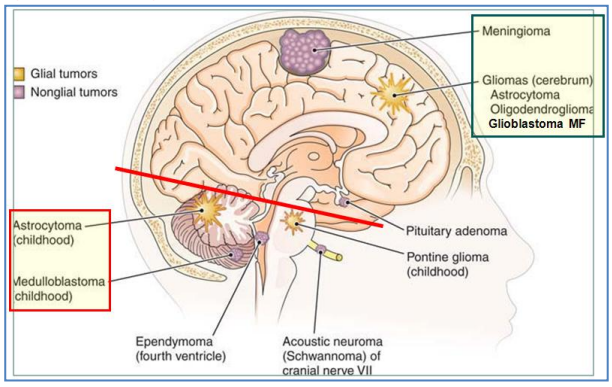
-
- **Interpretation:**
    - “No Cognitive Impairment” = 25-30MMSE
    - “Mild Cognitive Impairment” = 20-24MMSE – Relevant precursor sign to Dementia in early stages
    - “Moderate Cognitive Impairment” = 10-20
    - “Severe Cognitive Impairment” = <10MMSE

NEUROLOGICAL Pathology:
BRAIN TUMOURS

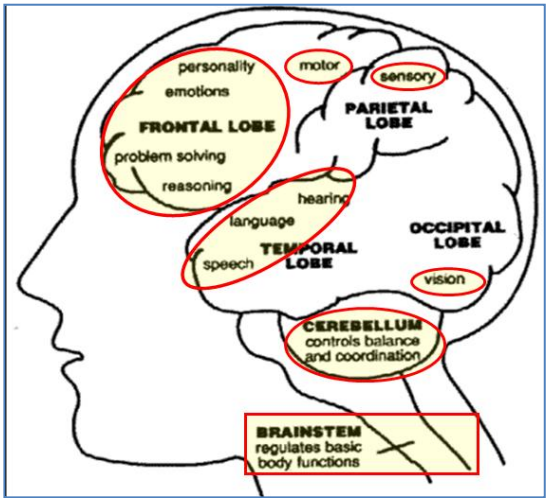
Common CNS Tumours:

- **General Features:**
  - **Adults** – Most are **Cerebral/Supratentorial**
  - **Children** – Most are **Infratentorial** (Cerebellum & Brainstem)
  - **NB: CNS tumours NEVER Metastasise to *Outside* the CNS.**
  - **Aetiologies:**
    - **Typically Secondary (Ie. Mets – Breast, Lung, GIT, Melanoma)**
    - **Some are Primary** (Gliomas are the Most Common) – NOT from Neurons!
  - **Types of Primary CNS Tumours – Only Covering 3 Types:**
    - **Adults – (NB: Most are Supratentorial – Cerebral):**
      - **1. Meningioma**
        - From the Arachnoid Layer
      - **2. Gliomas (Astrocytoma [& Glioblastoma Multiforme], Oligodendroglioma)**
    - **Children – (NB: Most are Infratentorial – Cerebellum & Brainstem):**
      - **2. Gliomas (Specifically Pilocytic Astrocytomas)**
      - **3. Medulloblastoma (Germ Cells)**





  - **Clinical Features:**
    - Slow, Progressive
    - Crescendo, Chronic, Morning Headache
    - **Local Damage →** Nerve & Tract deficits, Paralysis, Blindness, Anosmia, Seizures
    - **Raised ICP →** Headache, vomiting, papilodema & bradycardia.
    - **Irritation →** Seizures
  - **Clinical Features Depend on Tumour Location → Focal Deficits:**
    - **Brain stem Compression →** Drowsiness, Obtundation
    - **Frontal Lobe →** Personality, Memory, Executive, Intelligence
    - **Temporal Lobe →** Speech, Language & Hearing
    - **Motor Cortex →** Limb weakness
    - **Cerebellum →** Balance/Stumbling
    - **Occipital →** Vision, Eye Movements



Primary CNS Tumours:

Adult CNS Tumours:

- **MENINGIOMAS:**

Cell of Origin:	- Meningothelial Cells (Cells of the Arachnoid Granulations)
Morphology – Macro:	- Well Demarcated - Attached to the Dura - Hard, Fibrous Tumour with Calcification
Clinical Features:	- Very Common, But Clinically Benign - Non-Invasive, but Compresses the Brain → Symptoms (Headache) - **Chronic, Gradually Increasing Morning Headache (Years).** - **Oestrogen-Responsive** :. **Worse in Pregnancy/Menstruation.**
Treatment:	- Surgical Removal
Prognosis:	- Benign - Good Survival with Surgery

- **Adulthood Gliomas – *LOW-GRADE ASTROCYTOMA & GLIOBLASTOMA MULTIFORME*:**
  - **ASTROCYTOMAS:**

Cell of Origin:	- Astrocytes
- **Low-Grade ASTROCYTOMA:**	
Morphology – Macro:	- Usually Cerebral (Supratentorial) - Solid Tumour
Clinical Features:	- **Space-Occupying Syx** – Chronic Worsening Morning Headache, Vomiting, Altered Mental Status, Personality Change, ALOC. - **+ Focal Neurology** depending on Location in the Brain.
Treatment:	- Surgical Resection of Tumour
Prognosis:	- Benign - Good – 90% 5yr Survival

- **High-Grade Astrocytoma = "*GLIOBLASTOMA MULTIFORME*":**	
Morphology – Macro:	- Usually Cerebral (Supratentorial) - Solid Tumour – May see some Cystic Degeneration - Grows so fast, it looks encapsulated, but it is not.
Clinical Features:	- **↑Morning Headache, Nausea/Vomiting, Seizures, Hemiparesis** - + **Memory Loss & Personality Changes**. - + **Focal Neurology** (Language & Executive Fx)
Treatment:	- Palliative: Surgery + Chemo/Radiotherapy - + Anticonvulsants – To ↓Seizures - + Corticosteroids – To ↓Peri-Tumoural Oedema → ↓ICP - (NB: Total Surgical Resection Impossible due to diffuse Infiltration.)
Prognosis:	- Malignant – (Fast-Growing & Infiltrative) - Poor Prognosis - <1yr Survival Rate

Childhood CNS Tumours:

- **Childhood Glioma – *PILOCYTIC ASTROCYTOMAS*:**

Morphology – Macro:	- Usually **Cerebellar** (Infratentorial) – (Rather than Cerebral in Adults) - **Cystic Tumour** full of Mucoid FLuid- (Rather than Solid in Adults). - Well-Circumscribed
Clinical Features:	- **Gait Abnormality** (Wide Gait), **Uncoordination,** & Nystagmus - **Nausea, Vomiting, Irritability** - **Failure to Thrive -** Anorexia - (NB: Associated with Neurofibromatosis)
Treatment:	- Surgical Resection
Prognosis:	- Benign – (Low-Grade, Slow-Growing) - Good: >90% 10yr Survival Rate.

- **MEDULLOBLASTOMA:**

Cell of Origin:	- Neuroblast Cells (Ectoderm Cells of Neural Crest = **Neuroectoderm**)
Morphology – Macro:	- **Cerebellar** (Infratentorial) - **Usually Form in the 4th Ventricle**
Clinical Features:	- **Initial: Hydrocephalus (&↑ICP) due to 4th Ventricle Obstruction →** Listlessness, Morning Headache, Vomiting. - **Later: Cerebellar → Stumbling Gait, Falls, Diplopia, Nystagmus**
Treatment:	- Maximal Surgical Excision + Radiation + Chemotherapy
Prognosis:	- **High-Grade, Malignant Tumour →** CSF Seeding (Unique to Medulloblastom) & Infiltration through Meninges is Common. - **Poor:** 70% 5yr Survival, 50% 20yr Survival

Other CNS Tumours:

- **Acoustic Neuroma (AKA: *"Vestibular Schwannoma"*):**

Cell of Origin:	- Schwann Cells
Morphology – Macro:	- Schwannoma of the Vestibular Nerve (Part of CN8). - Usually in the Internal Auditory Canal - → May **Cerebellopontine Angle → CN 5,7,9 & 10 Compression**
Morphology – Micro:	- Homogenous Tumour – Only Schwann Cells - Tumour cells always stay on outside of Nerve, but may compress it against a bony structure → Damage.

Clinical Features:	- Typically 50-60yrs
	- → Sensorineural Hearing Loss/Deafness, Tinnitus
	- → Vertigo, Ataxia, Nausea & Vomiting
	- **Cerebellopontine Syndrome:**
	  ○ **CN 5 (Trigeminal) Palsy:** Ipsilateral ↓Corneal Reflex, Trigeminal Neuralgia, ↓Sensation
	  ○ **CN 6 (Abducens) Palsy:** Diplopia, Ipsilat. Inward-Facing Eye
	  ○ **CN 7 (Facial) Palsy:** Ipsilateral Facial Weakness
	  ○ **(CN 8 (V/C):** Ipsilateral Deafness, Tinnitus, Vertigo**)**
	  ○ **Ipsilateral Cerebellar Signs:** Nystagmus, Ataxia

Malignant/Benign:	- Benign, Slow-Growing
Treatment:	- Surgical + Radiotheraly (NB: Risk to Facial Nerve) - Conservative Monitoring if Elderly.
Prognosis:	- 100% Survival with Treatment. - But some morbidity.

-

- **PITUITARY ADENOMAS:**

Cell of Origin:	- Pituitary Gland Embryonic Tissue
Morphology – Macro:	- Partially Cystic with Solid Areas
Clinical Features:	- **Compression of Optic Chiasm:** 1. Bitemporal Inferior Quadrantanopsia → 2. Bitemporal Hemianopsia - **Headaches** - **+ Any Pituitary Endocrine Failure Symptoms**
Malignant/Benign:	- Benign – but hard to Treat & → Compressive Neurology
Treatment:	- Surgical Resection → Hormone Replacement
Prognosis:	- Benign but often recurrence. - Good Survival, but Morbidity.

- **NEUROFIBROMATOSIS – Type 1 & 2**

Cell of Origin:	- Neural Fibroblasts
Morphology – Macro:	- Encapsulated, Solid Nodular Tumours (Neurofibromas)
Morphology – Micro:	- Whorls of Fibroblasts Within Nerves - Well-Differentiated
Clinical Features:	- **NF1 – Familial & Sporadic** - **NF2 – Autosomal Dominant** - Associated with Acoustic Neuromas (Vestibular Schwannomas) o Tinnitus, Vertigo, Hearing Loss - Also Associated with Meningiomas & Juvenile Cataracts
Malignant/Benign:	- Benign
Treatment:	- Surgical Resection of Individual Lesions – But Recurrence is common
Prognosis:	- Benign – But can → Extreme Morbidity/Disfigurement

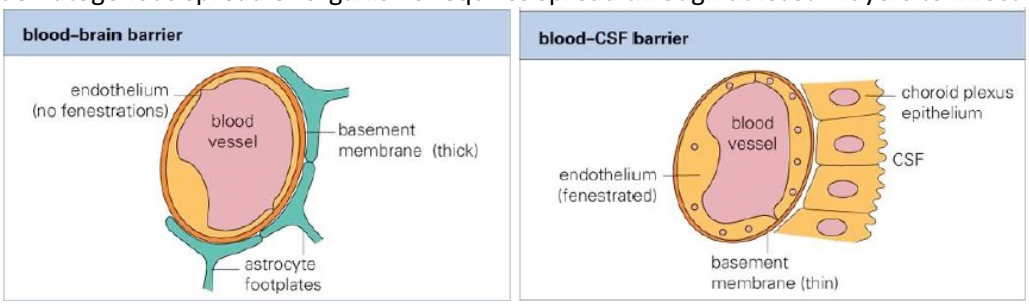
- **CNS Lymphoma:**

Cell of Origin:	- **B-Cell Non-Hodgkin Lymphomas**
Morphology – Macro:	- Multiple areas of tumour
Clinical Features:	- **Caused by EBV** + Immunocompromise (Ie. HIV) - **Symptoms:** Headache, Seizures, Cranial Nerve Palsies, ΔMental Status, Focal Neurology. - **+ Constitutional B-Syx:** Fever, Night Sweats, Weight Loss
Malignant/Benign:	- Malignant
Treatment:	- Chemo/Radiotherapy + Corticosteroids (Surgery is Impossible)
Prognosis:	- Poor – Due to High Grade + Concomitant Immunosuppression - Median survival = 10mths

Infectious Disease Notes
CNS Infections

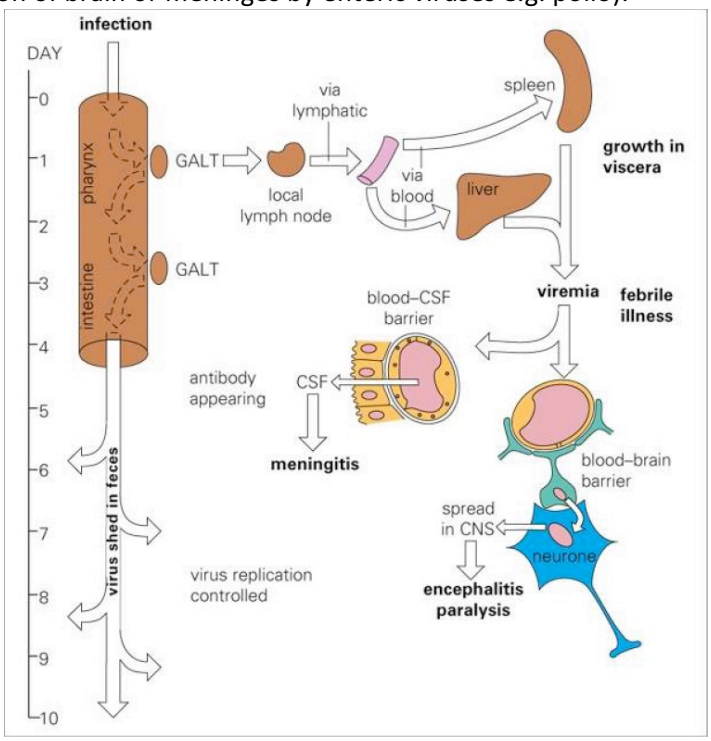
The blood brain barrier restricts the entry of pathogens into the brain and meninges:

- NB: Haematogenous spread of organisms requires spread through at least 2 layers to infect the brain.



Mechanisms of Entry into the CNS:

- **Haematogenous Spread (Bloodborne Invasion) into the CNS:**
  - **Growing across:**
    - Microbes can grow in the endothelial cells and then into the astrocytes or choroid plexus
  - **Passive:**
    - Transported across in intracellular vacuoles
  - **Carried in infected cells:**
    - Infected inflammatory cells can migrate into the brain and meninges, lyse and release the organism or the organisms may pass from cell to cell
  - (Eg. Infection of brain or meninges by enteric viruses e.g. polio):



- **Invasion Via Peripheral Nerves:**
  - Rabies and other Lyssaviruses may invade Muscle Cells @ The Bite Site →Move up the Nerves to the Dorsal Root Ganglia → Spinal Cord →Brain
  - Herpesviruses may migrate up the nerves using normal retrograde transport mechanisms

NB: The Blood Brain Barrier in Pharmacokinetics:

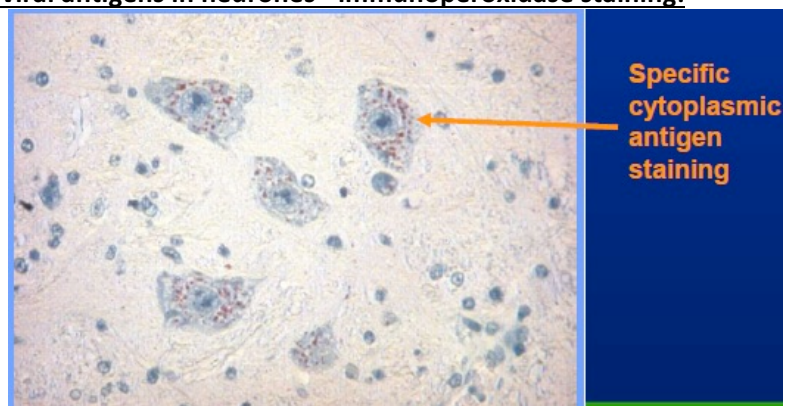
- The BBB Blocks access of certain chemicals to the CNS.
- :. Antimicrobial Drugs MUST be able to cross the BBB in order to fight CNS Infection.

Eg. Invasion of the CNS by Rabies – (Via Peripheral Nerves):

1) Myocytes are Infected @ the bite site
2) Growth up the Motor Nerves →Dorsal Root Ganglia
3) Growth up the Spinal Cord Nerves →Brain
4) Growth down the Cranial Nerves to the Salivary Glands
5) (Hence, CNS Invasion of the Rabies Virus is *REQUIRED* for transmission because it has to get from the Bite Site → Peripheral Nerves → CNS → Salivary Glands →Next Bite)

- **Rabies – Post Exposure Prophylaxis:**
  - **Administration of Human Rabies Immunoglobulin**
    - Used when there is a high risk of infection but insufficient time for the body to develop its own immune response.
  - **Vaccination:**
    - Rabies Vaccine → Promotes Active Humoral Immunity of the Host.

- **Bat lyssavirus - viral antigens in neurones - immunoperoxidase staining:**



Definitions:

- **Viral Meningitis:**
  - Inflammation of the Meninges of the brain due to viral aetiology.
  - (Eg. By Herpes Simplex Virus)
- **Bacterial Meningitis:**
  - Inflammation of the Meninges of the Brain due to Bacterial Aetiology.
  - (Typically: *Nesseria Meningitidis, Streptococcus Pneumoniae, Haemophilus Influenzae*)
- **Encephalitis:**
  - Inflammation of the Brain
  - (Typically due to Viruses – eg. Herpes Simplex)
- **Meningoencephalitis:**
  - Inflammation of the Brain & the Meninges
- **Myelitis:**
  - Inflammation of the Spinal Cord → Disrupts CNS functions liking the brain & limbs.
  - (Eg. Poliovirus (Poliomyelitis))
- **Encephalomyelitis:**
  - Inflammation of the Brain and Spinal Cord
  - Typically Immune-mediated following a viral infection.
  - (Eg. Acute Disseminated Encephalomyelitis – Following Influenza, enterovirus, measles, mumps, rubella, varicella zoster, etc.)
- **Brain Abscesses:**
  - Encapsulated Pus or Free-Pus in the Brain after an Acute Focal Purulent Infection.
    - (Focal Infections include: Otitis Media/Sinusitis)

MENINGITIS:

Presentation: Meningism:

- ***Neck Stiffness**
- ***Photophobia**
- ***Headache**
- (Fever/Malaise)

Meningitis - CSF Examination:

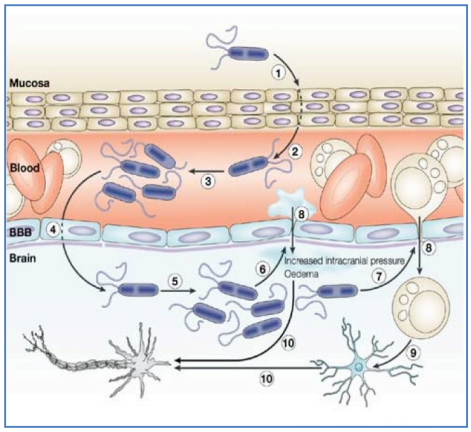
- **Three Successive Samples are Taken:**
  - To Eliminate Contamination
  - NB: By the 3rd Sample, there should be NO Contamination
  - NB: RBC indicates contamination
  - **Sample 1: Used for Serology**
    - Serology
    - or PCR
  - **Sample 2: Used for Biochemistry**
    - Glucose
    - Protein
    - Antigen Agglutination
  - **Sample 3: Used for Bacteriology – Most Precious**
    - Gram stain
    - Culture

CSF Changes During CNS Infection:

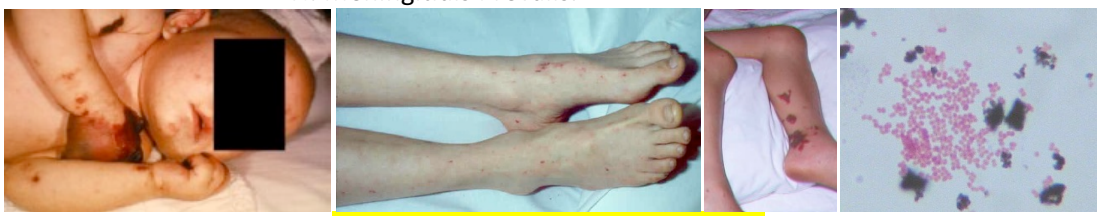
- **Septic Meningitis (Bacterial – *N.Meningitidis, H.Influenzae, S.Pneumoniae*)**
  - ↑Cells (Mainly Neutrophils & other Polymorphs)
  - ↑Protein (Exudate)
  - ↓Glucose (Due to Bacterial Metabolism)
  - Positive Culture & Gram Stain
- **"Aseptic" Meningitis (Typically Viral/Fungal)**
  - ↑Cells (Mainly Lymphocytes)
  - ↑Protein
  - Normal Glucose

Septic/Bacterial Meningitis:

- **More Severe than Viral**
- **Less Common than Viral**
- **Pathogenesis:**

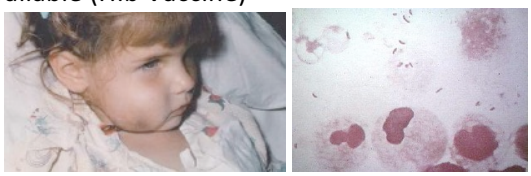


- **The 3 Common Bacterial Implicated in Bacterial Meningitis:**
  - **#1. Neisseria Meningitis:**
    - Gram Negative Diplococci
    - Usually in Stressed/Crowded
    - Severe toxin sequlae → Tissue damage
    - **Vaccine only for Serotypes A & C (Not B – Which is the most common)**
      - (NB: Serotype B Capsule molecules mimic Neural Tissue → Vaccine Cross Reacts)
    - **NB: Capsule Switching:**
      - By the time the immune system has mounted an Adaptive Immune Resposne, N. Meningitidis *Changes the Immunogenicity* of its Capsule.
      - → Immune System has to Start Again
      - → N. Meningitidis Prevails.

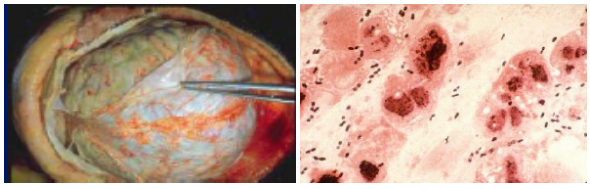


(Diplococci = Nesseria Meningitidis)

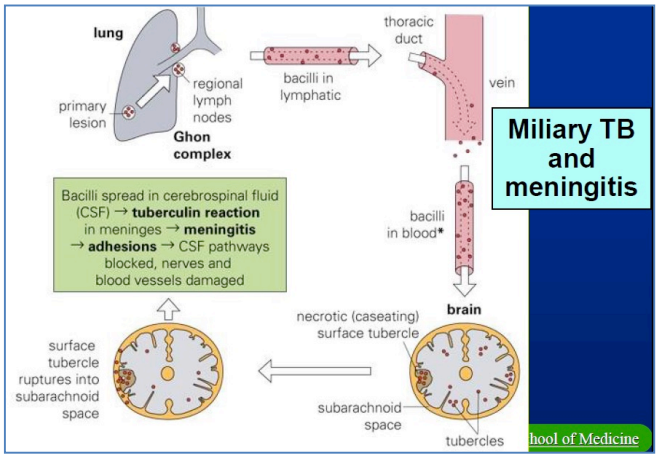
  - **2. Haemohpilus Influenza:**
    - Gram Negative Cocco-bacilli
    - Usually in Children / Babies
    - Toxin production→Tissue damage
    - Vaccine Available (HIb Vaccine)



  - **3. Streptococcus Pneumoniae:**
    - Gram Positive Cocci
    - Predisposed Adults
    - Neonates



- **Other Aetiologies:**
  - **Neonatal Meningitis:**
    - *Escherichia coli*
    - *Group B Streptococci*
    - (High Mortality Rates (35% of cases))
  - **Tuberculous Meningitis:**
    - ***Mycobacterium tuberculosis*:**
      - Acid fast bacilli (Stains with zheil Nielson stain)
      - Patients Typically have a Focus of Infection Elsewhere
      - :. Most of cases are associated with Miliary (disseminated) Tuberculosis



Features Suggestive of Aetiology

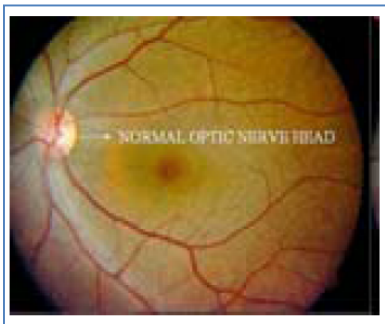
1. **Rash - erythematous, petechial / purpuric.**
   a. Suggests meningococcus (rarely Pneumococcus or Haemophilus influenzae type b)
2. **CSF rhinorrheoa or otorrhoea - basal skull fracture:**
   a. Pneumococcus, *H. influenzae*, Haemolytic Strep.
   b. (CSF Rhinorrhoea refers to the drainage of Cerebrospinal Fluid through the nose. It is a sign of Basal Skull Fracture.)
3. **Prominence of seizures or focal signs early:**
   a. Consider *Listeria monocytogenes*, Herpes simplex.

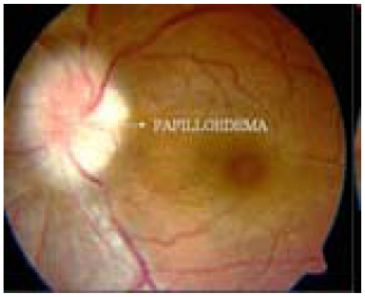
Aetiology Suggested by Age Group:

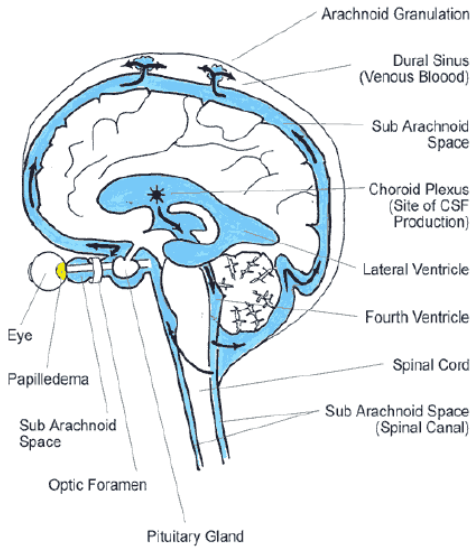
neonate	Group B Streptococcus *E. coli*, Salmonella *Listeria monocytogenes*
child< 6	***Neisseria meningitides* (meningococcus)** *Streptococcus pneumonia* (pneumococcus) *Haemophilus influenzae* B
child >6	***N. meningitidis*** *S. pneumonia*
Healthy Adult	*S. pneumoniae*, ***N. meningitides***
Immunosupressed, debilitated, elderly	*L. monocytogenes*, Gram negative enteric organisms e.g. *E. coli*

NB: Papilloedema < 1%:

- **= Swelling of the Optic Disc secondary to the ↑Intracranial Pressure during Meningitis.**
  - Usually Bilateral
  - May develop over hours to weeks.
- **How it Occurs?**
  - The subarachnoid space of the brain is continuous with the optic nerve sheath.
  - :. as CSF Pressure Increases → Pressure is transmitted to the optic nerve →Optic Nerve Sheath acts as a Tourniquet around the Axon.







Elevated CSF pressure is transmitted around the brain and along the optic nerve (sub-arachnoid space) producing papilledema.

Meningitis Management:

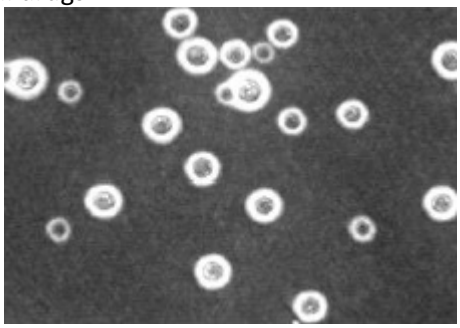
1. **Early Antibiotic Therapy is Essential for Good Outcome!!!**
   a. Even if they are Pre-Diagnosis.
2. **Always Do Blood Cultures!!**
3. **Antibiotics must be:**
   a. Effective Against Likely Pathogens
   b. Able to cross an Inflamed Blood Brain Barrier
   c. Given Parenterally and in high dose.
4. **Corticosteroids (Dexamethasone) are given prior to antibiotics →↓CNS Inflammation:**
   a. →Improves Neurological Outcome in all cases of suspected bacterial meningitis.
5. **Prophylactic Measures in close contacts:**
   a. Meningitis Prophylaxis: *Rifampicin, Ceftriaxone or Ciprofloxacin*:
   1. Prophylaxis with the above antibiotics WILL NOT abort infection in those already infected.
   2. *RATHER,* It aims to Eliminate Nasopharyngeal Carriage →Prevent subsequent transmission.
   3. Offered to Household, child care and CLOSE CONTACTS.
   4. No evidence for salivary spread.

Brain Abscesses:

- Incapsulated or free-pus in the substance of the brain after an acute focal purulent infection is known as a brain abscess.
    - **Sites of Focal Infection that could lead to brain abscesses:**
        - Otitis Media
        - Sinusitis
        - Penetrating trauma
        - Haematogenous dissemination
    - **Given the Possible Sites of Entry, Which Organisms are Most Likely to be Involved?**
        - Otitis Media – Strep Pneumoniae
        - Sinusitis – Strep Pneumoniae
        - Penetrating Trauma – Probably Staph Aureus
    - **Diagnosis:**
        - Blood culture should be performed, but often is not diagnostic
        - CT or MRI are Essential for Diagnosis.
        - Lumbar Puncture is Contraindicated (Due to ↑ICP)
        - Inflammatory Markers WBC, CRP & ESR are raised.

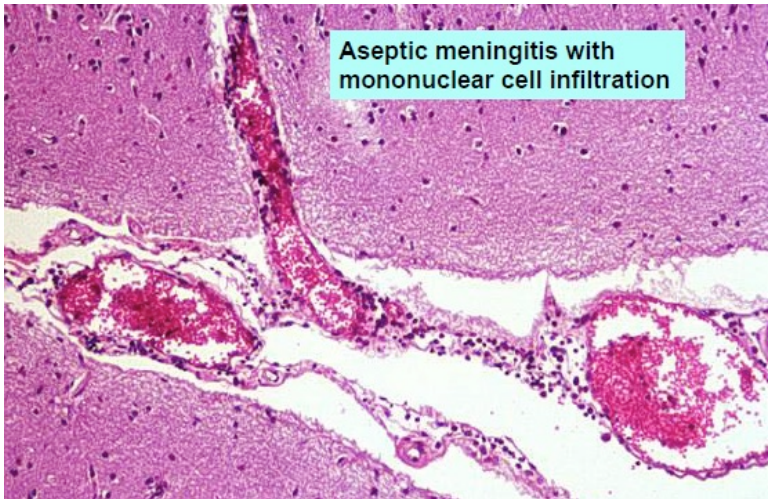
Fungal Meningitis:

- **Mainly *Cryptococcus Neoformans***
- Typically in Immunosuppressed
- Can be treated with antifungal drugs



Viral Meningitis:

- **Less Severe than Bacterial**
- **More Common than bacterial**
- **Presentation:**
  - Usually are milder disease than bacterial meningitis
  - Headache, fever and and general illness but less neck stiffness
  - Generally Complete Recovery
- **Examination of CSF:**
  - The CSF is clear and free of bacteria
  - CSF Contains Mainly Lymphocytes
- **Viruses Implicated in Viral Meningitis:**
  - **Herpes Simplex**
    - Uncommon; may follow congenital infection with HSV2
  - **Mumps**
    - A quite common complication
  - **Poliovirus, cocsackievirus, echovirus**
    - Commonly seen especially due to echoviruses
  - **Enterovirus 71**
    - May follow hand foot and mouth disease
  - **Japanese encephalitis**
    - India, Southeast Asia, Japan
  - **Eastern and Western equine encephalitis**
    - Eastern and Western USA
  - **HIV**
    - May occur early after infection

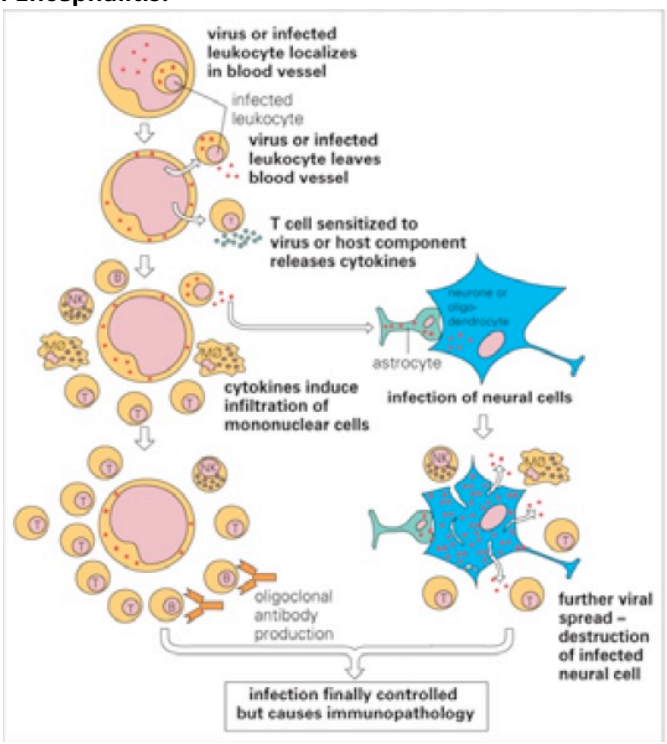


(NB: "Perivascular Cuffing" by monocytes around the vessels)

ENCEPHALITIS:

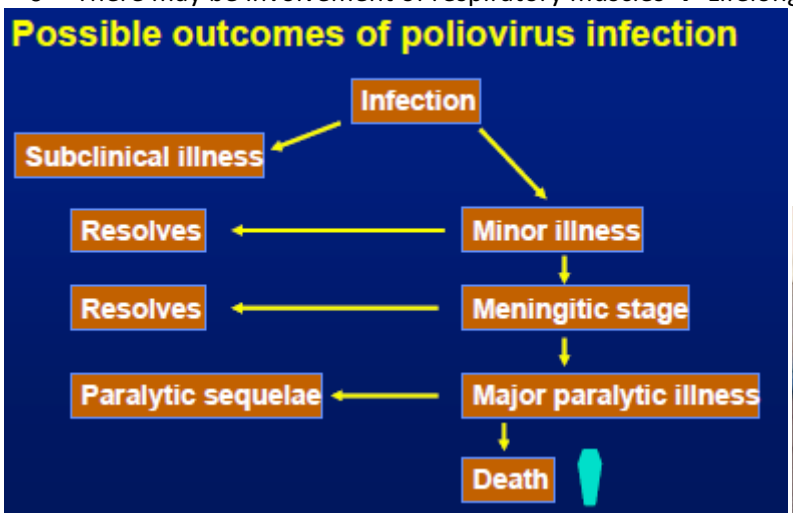
Encephalitis – Infection of the Brain:

- **Encephalitis Is Usually Caused By Viruses:**
  - ****Herpes Simplex Virus**
    - The infection progresses back to the temporal lobe of the brain
    - 70% mortality rate in untreated patients
    - Treatment with Acyclovir → ↓Mortality rate
    - **(Including Varicella Zoster, & Cytomegalovirus)**
    - **VZV:** Encephalitis generally occurs as a sequel to reactivation
    - **CMV:** Either during primary infection (in utero) or reactivation due to immunodeficiency (HIV)
  - **Poliovirus:**
  - **Rabies:**
- **Other causes of encephalitis can include:**
  - **Parasites** such as Toxoplasma gondii and Plasmodium falciparum
  - **Fungi** such as Cryptococcus neoformans
  - **Bacteria** such as Treponema palidum
- **Pathogenesis:**
  - **→Characteristically there are signs of cerebral dysfunction:**
    - Abnormal Behaviour
    - Seizures
    - Altered Consciousness
    - Nausea/Vomiting
  - **and fever**
- **Pathogenesis of Viral Encephalitis:**



Poliovirus:

- **Epidemiology:**
  - Non Existent in Aus (A single case would be an epidemic)
- **Prevention:**
  - **Vaccination Available**
    - **Live Attenuated (Oral Polio Vaccine):**
      - Advantages:
        - Easy Administration - Given Orally
        - Cheap
        - Induces intestinal local immunity
        - More Robust Immune Response
      - Disadvantage:
        - Rarely causes paralysis (1 in 2.5million)
    - **Inactivated Polio Vaccine (IPV):**
      - Advantages:
        - Carries NO risk of Vaccine-Associated Polio Paralysis
        - Very Robust Immune Response
      - Disadvantage:
        - Difficult Administration - Has to be injected
        - Confers little Mucosal Immunity in the Intestinal Tract.
        - 5 Times more expensive than OPV.
  - (NB: 1 in 2.5Mil recipients develop paralysis)
- **3x Serological Types:**
  - PV1, PV2, PV3.
  - **Have little cross-reaction :. Vaccination must contain ALL 3 Serotypes for Full Immunity.**
  - (NB: Serotype 1 causes most of the problems – Ie. Paralysis)
- The major lesion results in a flaccid paralysis
- **Transmission:**
  - **Faecal Oral
  - Respiratory
- **Pathogenesis:**
  - Poliovirus Acquired ***Faecal-Orally* or *Respiratory Route***.
  - Virus Replicates in *Lymphoid Tissue* in the Pharynx and Gut.
  - Viraemia follows → Extension to the Nervous System
  - → Lytic Infection of Neurons → Paralysis
    - Anterior Horns of Spinal Cord are Most Affected.
- **Clinical features:**
  - The incubation period = 7 to 14 days
  - A minor illness with malaise, fever and a sore throat may occur
  - Paralysis may extend from a single muscle to virtually every skeletal muscle
  - There may be involvement of respiratory muscles → Lifelong Assisted Ventilation



Rabies Encephalitis:

- **Organism:**
  - Rhabdovirus (A Bat Virus)
- **Transmission:**
  - by the bite of an infected animal
  - The virus is present in the saliva of the infected animal (Dogs, foxes and other wild species)

Flavivirus Encephalitis:

- **Japanese Encephalitis (JEV) is the most common cause of this infection:**
  - A vaccine is available for this virus
  - This virus is common throughout Asia
  - *Of particular importance in North Queensland
- **Other members of the encephalitic subgroup of the flaviviruses include:**
  - Kunjin
  - Murray Valley encephalitis
  - West Nile virus
  - St Louis encephalitis

Togavirus Encephalitis:

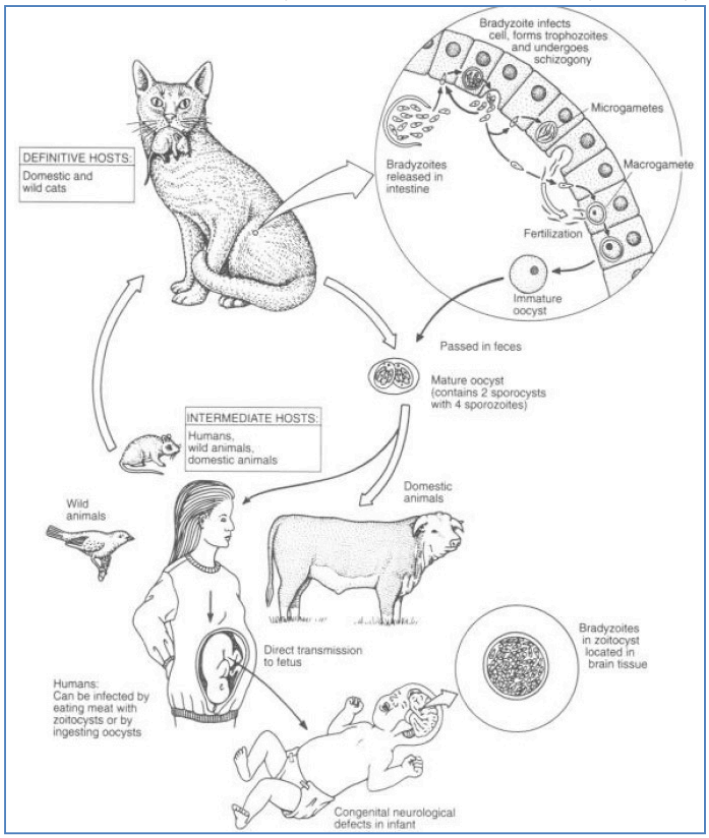
- Some of the togaviruses in the Americas (Eastern and Western encephalitis) can produce encephalitis
- These viruses usually infect various animal species and occasionally infect humans
- Vaccines are available for the animal species
- No vaccines are available for humans

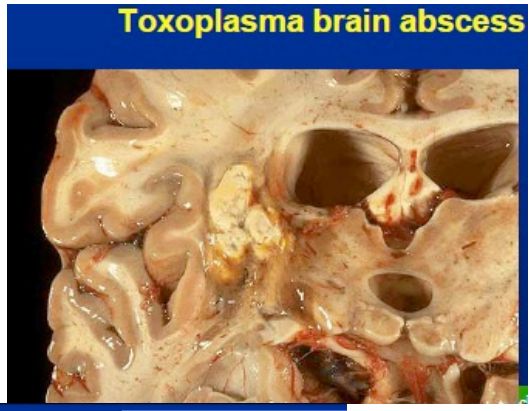
Acute Flaccid Paralysis:

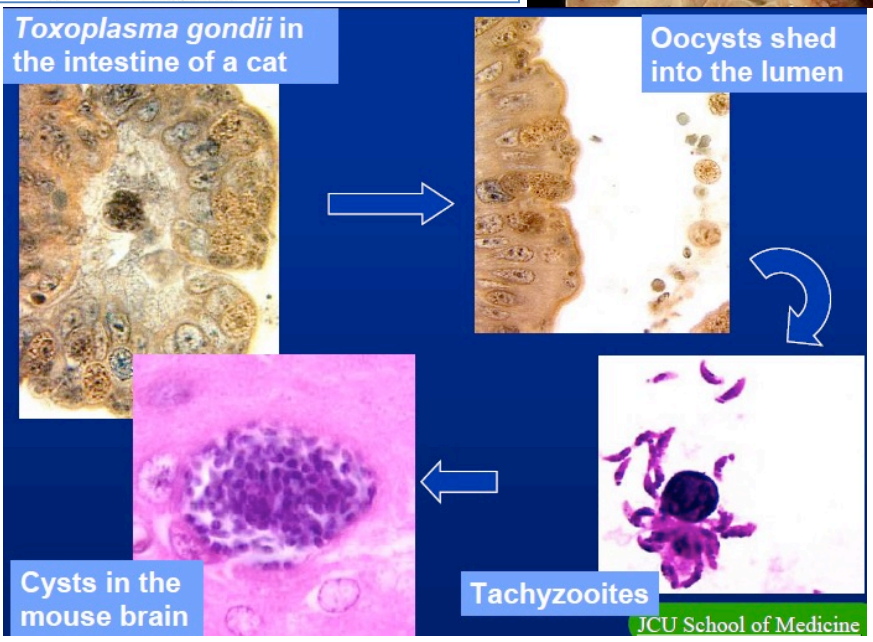
- While acute flaccid paralysis is a key clinical feature of polio infection, this syndrome can be produced my several other factors:
- These include other picornaviruses such as enterovirus 71
- This virus also produces the syndrome hand foot and mouth disease
- In 1998 an outbreak in Taiwan involving 300,000 children resulted in 56 deaths
- In 1999 an outbreak in Perth resulted in six cases of acute flaccid paralysis

PARASITIC INFECTIONS OF THE BRAIN:

- **Toxoplasma Gondii:**
  - **Life cycle:**
    - → Cysts in Brain (Contained by Macrophages & Helper T-Cells)





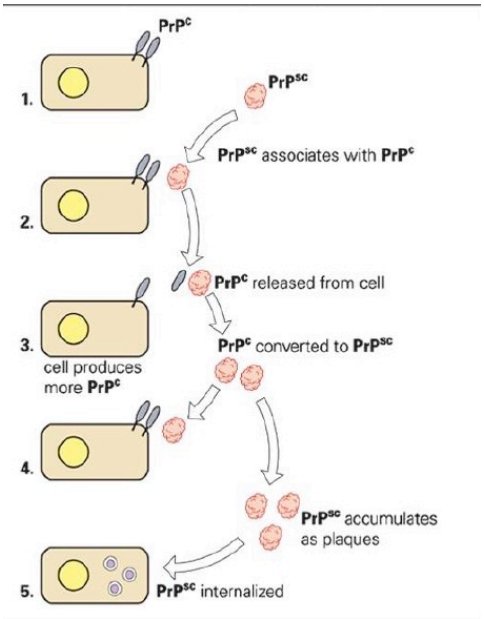


Helminthic & Protozoal Organisms Capable Of Causing CNS Infections:

Helminth	Reservoir	Neurological symptoms	Method of diagnosis	Treatment
Tapeworm	Eating uncooked Pork	Cysts in Brain → Convulsions	Detectino of specific antibody in serum or CSF Visual detection of cysts by MRI	Albendazole or praziquantel + Corticosteroids
Roundworm	Cats and dogs	Cysts in Brain → Convulsions Retinal Detachment → Blindness	Serum can be tested for Antibodies by ELISA	Antihelmentic therapy (But not in ocular)
Protozoan				
Malaria	People + Mosquitoes	Convulsions Coma	RDT Antigen Test	Artemesinin
Toxoplasma Gondii	Cats and mice	Hydrocephalus Inctracerebral calcification	PCR of blood samples Immunostaining	Antibiotics Antimalarials Atovaquone → Kills Cysts
Trypanosome	Kissing bug	Abnormal gait Abnormal speech Mental state change Other abnormal movement Sleep Disturbance	Microscopy of: Blood Smears CSF Lymph Node Aspirates RDT Antibody Detection test.	Melarsoprol Eflornithine

PRION INFECTIONS OF BRAIN:

- Scrapie like agents referred to as prions can produce infections in a range of domestic animals and in humans
- NO DNA or RNA!! (Important for Exams)
- The disease is produced when there is a conformational change in the proteins referred to as prion protein C
- **The PrP^{SC} protein:**
  - **The two forms of the protein have different properties**
    - **PrP^{C}** is anchored to the cell membrane by a glyco-phospho-inositol (GPI) anchor
    - **PrP^{SC}** accumulates in plaque deposits in the brain of affected individuals
  - The two proteins have the same posttranslational modifications and cannot be distinguished by monoclonal antibodies
- **How the prions damage the cells:**
  - Accumulation in Neurons → Death of Neurons



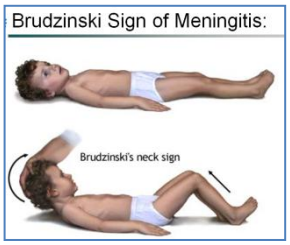
- **Human prion diseases:**
  - **There are four human diseases classified as TSEs (Transmissible Spongiform Encephalopathies):**
    - (NB: All are Progressive and Fatal.)
    - Creutzfeldt-Jacob disease (CJD) (Most Common In Humans)
      - Iatrogenic (Person-Person – Eg. Transplant)
      - Inherited
      - Sporadic
    - Gertsmann-Straussler syndrome (GSS)
    - Fatal familial insomnia (FFI)
    - Kuru confined to one tribe in New Guinea and related to cannibalism in the past

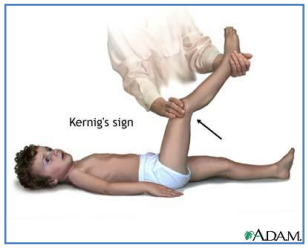
OTHER INFECTIOUS DISEASES AFFECTING THE CNS:

- **Toxins produced by bacterial infections can affect the CNS:**
  - **Eg. Tetanus**
    - **Organism:**
      - *Clostridium tetani*
      - Found in Soil & Faeces of Domestic Animals
      - Like Anaerobic Conditions
    - **Pathogenesis:**
      - → Toxin → Tetanic Spasms (Acts on the nerves)
      - (Acts by binding to Ganglioside Receptors → Blocking Release of Inhibitory NTs → Convulsive Contractions of Voluntary Muscles)
    - **Prevention:**
      - Tetanus Vaccine
  - **Eg. Botulism**
    - **Organism:**
      - *Clostridium Botulinum*
    - **Pathogenesis:**
      - → Toxin → Flaccid Paralysis
        - Most commonly absorbed in the gut.
      - (Blocks Acetylcholine Release from Peripheral Nerves → Paralysis)
    - **Presentation:**
      - Weakness and paralysis
      - Dysphagia
      - Diplopia
      - Vomiting
      - Vertigo
      - Respiratory muscle failure
    - **Treatment:**
      - Antibodies (Antitoxins)
      - Respiratory Support

NEUROLOGICAL Pathology:
CNS INFECTIONS

MENINGITIS:

- **Aetiology:**
  - **Bacterial/Septic Meningitis – Nesseria meningitides**, Haemophilus influenza, Group B Streptococci.
    - **Adults = Neisseria meningitides** (NB: Vaccine preventable – Meningococcal A & C)
    - **Children = Haemophilus influenza** (Vaccine Preventable – HIB Vaccine)
    - **Neonates = Group B Streptococci (or E.coli)**
  - **Viral/Aseptic Meningitis – Herpes Simplex Virus**, Enteroviruses (Echo/Coxsackie), Influenza
  - **Chronic Meningitis –** Miliary Tuberculosis
- **Pathogenesis:**
  - **Meningeal Infection →** Inflammation & Oedema → ↑ICP → Vomiting, Drowsiness.
  - **NB: Meningococcal Sepsis** can → **Thrombocytopaenia** → Maculopapular Rash ... →DIC
- **Morphology:**
  - **Bacterial →** Exudate within Meninges (Pus beneath the meninges)
  - **Viral →** No pus
  - Engorged Meningeal Vessels
- **Clinical Features:**
  - ******Meningism:***
    - ***1. Neck Stiffness** (Due to Inflammation of the Meninges)
      - **:. Brudzinski's Sign Positive** (Flex the Neck → Pt bends knee)
      - **:. Kernig's Sign Positive** (Flex the hip and attempt knee extension → Pain
      - 

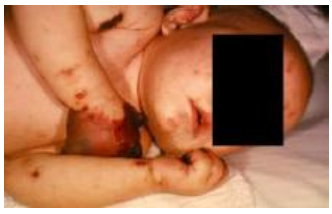
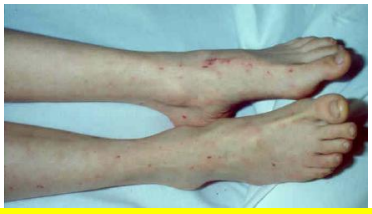
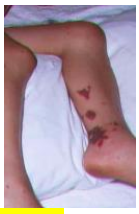
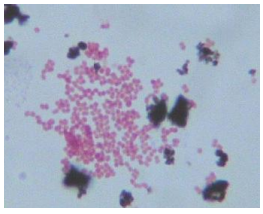
        

    - ***2. Photophobia**
    - ***3. Headache**
  - **+ Constitutional Syx:**
    - Fever/Malaise
    - Nausea/Vomiting
    - May eventually have loss of consciousness. (Rare)
    - Irritability
    - Poor Feeding
  - **Features Suggestive of Aetiology**
    - **Non-Blanching Maculopapular Rash →** Suggests Meningococcus
    - **CSF Rhinorrheoa/Otorrhoea - basal skull fracture →** Suggests Pneumococcus, HiB, Strep.
- **Diagnosis:**
  - ****Clinical Suspicion:** (Meningism +/- Rash +/- Fever/Malaise/Vomiting +/- Headache/ALOC
    - +/- (Brudzinski's Sign +, Kernig's Sign +)
  - **Blood Cultures BEFORE IV Antibiotics!!**
  - **L3-L5 Lumbar Puncture → CSF Examination:**
    - **LP can → Coning if ↑ICP :. DO NOT do LP if:**
      - **1. Papilloedema**
      - **2. Cushing's Response (Triad – ↑*BP*, ↓*HR*, *Irregular Breathing*)**
      - **3. Unresponsive Pupils**
    - **Can → "Cerebral Herniation" (Aka: Cistern Obliteration) → Often Fatal**
  - **CSF Samples (Take 3):**
    - **Sample 1 → Serology** (or PCR)
    - **Sample 2 → Biochemistry** (Glucose, Protein)
    - **Sample 3 → Bacteriology – Most Precious** (Gram Stain + Culture)

- **CSF Interpretation:**

	Normal	Bacterial Meningitis	Viral/Aseptic Meningitis (Usually Herpes Virus)
CSF Pressure	Normal	Normal-Raised	Normal-Raised
White Cell Count	Normal	Raised (Polymorphs)	Raised (Lymphocytes)
Glucose	Same as Serum	Lower than Serum (Hungry Bacteria)	Normal
Protein	Normal	Raised (produced by the organisms)	Raised (produced by the organisms)
Gram Stain	None	Presence of Bacteria	Nothing ("Aseptic Meningitis")

- **Treatment:**
  - **(Bacterial Meningitis = Emergency – Can be Fatal)**
  - **(Viral Meningitis = Usually Self-Limiting & Less Fulminant Clinically)**
  - ******Treat on Suspicion!! –*** (Don't wait for lab results!)
  - ***1. Blood Cultures BEFORE IV Antibiotics!!***
  - **2. Early Antibiotic Therapy is Essential for Good Outcome!!!**
    - ***IV Benzylpenicillin G***, or ***IV Cephtriaxone*** (why? – Because they can enter the BBB)
  - **3. Corticosteroids (*Dexamethasone*) *WITH* the Antibiotics →↓CNS Inflammation:**
    - →Improves Neurological Outcome of bacterial meningitis.
  - **4. Fundoscopy, Then Lumbar Puncture –** (Check for Papilloedema before doing LP)
    - **CSF – MCS**
  - **(+ Prophylactic Measures for Close Contacts):**
    - **Meningitis Prophylaxis: *Rifampicin, Ceftriaxone or Ciprofloxacin*:**
    - Offered to Household, child care and CLOSE CONTACTS.
- **Prognosis:**
  - **Good prognosis** with Aggressive Treatment.
    - **:. Treatment on Suspicion:** Empirical Antibiotics (or Antivirals).
- **Complications:**
  - **Acute:**
    - Encephalitis
    - Cerebral infarction
    - Oedema
    - Herniation
    - **Waterhouse-Frederichson Syndrome (Acute Adrenal Infarction)**
      - (→Petechial Haemorrhages, DIC, Septic Shock)
  - **Late:**
    - Abscess
    - Subdural Empyema
    - Epilepsy
    - Leptomeningeal Fibrosis & Consequent Hydrocephalus

(Diplococci = Nesseria Meningitidis)

ENCEPHALITIS:

- **Aetiology:**
  - **Almost Always Viral – (**Herpes Simplex Virus, VZV, CMV, Poliovirus, Rabies [Rhabdovirus], JEV)**
- **Pathogenesis:**
  - Viraemia → Crosses BBB → CNS Infection →→ Cerebral Oedema → ↑ICP → Neurological Signs
- **Clinical Features:**
  - **Infective Syx – Fever, Nausea, Vomiting**
  - **+ Cerebral Syx – *Encephalopathy – (Altered Mental State/Abnormal Behaviour/ALOC/Drowsiness)***
    - +/- Seizures
- **Treatment:**
  - **Treat on Suspicion – (*Acyclovir* + *Dexamethasone*)**
- **Prognosis:**
  - **Poor -** Once symptomatic, rapid inflammation & necrosis → Brain-Death or Neurological Deficit
  - **70% Mortality Untreated**
- **Investigations:**
  - **FBC – (Lymphocytosis)**
  - **LP – (↑Lymphocytes, Normal Glucose, ↑Protein, Negative Cultures)**

	Normal	Bacterial Meningitis	Viral Meningitis (Usually Herpes Virus)	Encephalitis (typically viral)
CSF Pressure	Normal	Normal-Raised	Normal-Raised	Markedly Raised
White Cell Count	Normal	Raised (Polymorphs)	Raised (Lymphocytes)	Raised (Lymphocytes)
Glucose	Same as Serum	Lower than Serum (Hungry Bacteria)	Normal	Normal
Protein	Normal	Raised (produced by the organisms)	Raised (produced by the organisms)	Raised
Gram Stain	None	Presence of Bacteria	Nothing ("Aseptic Meningitis")	Nothing

BRAIN ABSCESSES:

- **Incapsulated pus within the brain occurring after an acute focal purulent infection.**
  - **Sites of Focal Infection that could lead to brain abscesses:**
    - Otitis Media
    - Sinusitis
    - Penetrating trauma
    - Haematogenous dissemination
  - **Given the Possible Sites of Entry, Which Organisms are Most Likely to be Involved?**
    - Otitis Media – Strep Pneumoniae
    - Sinusitis – Strep Pneumoniae
    - Penetrating Trauma – Probably Staph Aureus
  - **Diagnosis:**
    - Blood culture should be performed, but often is not diagnostic
    - CT or MRI are Essential for Diagnosis.
    - Lumbar Puncture is Contraindicated (Due to ↑ICP)
    - Inflammatory Markers WBC, CRP & ESR are raised.

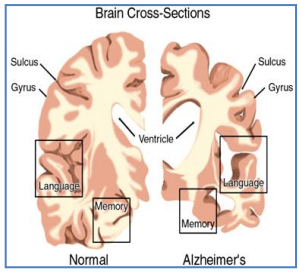
NEUROLOGICAL Pathology:
DEMENTIAS

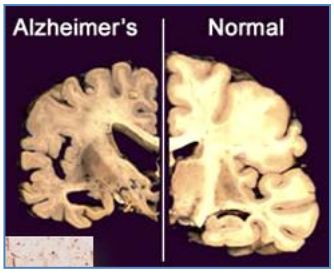
Global Degeneration – Dementias (Age-Related (Senile), Alzheimers, Lewy-Body, & Fronto-Temporal/Pick's):

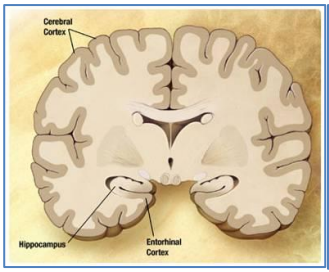
- **Dementia:**
  - = Acquired *Global Impairment* of Intellect, but with no ALOC.
- **Epidemiology:**
  - 5% of >55yrs are demented
  - 20% of >80yrs are demented
  - Prevalence Doubles every 5yrs Beyond Age:60.
  - 50% of dementia pts have clinically significant behavioural/psychological symptoms.
- **Common Symptoms:** (In order of prevalence):
  - **Early – Cognitive:**
    - **Memory loss
  - **Later – Non Cognitive:**
    - Apathy/Depression
    - Delusions (False Beliefs)
    - Anxiety
    - Agitation/Aggression
    - Hallucinations
- **Types of Primary Dementias:**
  - Age-Related (Senile) Dementia
  - Alzheimers Disease
  - Lewy-Body Dementia
  - Fronto-Temporal Dementia ("Pick's Disease")
- **Clinical Diagnosis:**
  - Timeline of Symptom Progression (Memory Loss → Agitation/Aggression, Wandering, Apathy)
  - Impact on ADLs (Especially *Medications & Financials*)
  - MMSE (Mini-Mental State Examination)

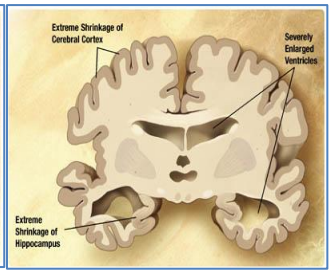
- **AGE-RELATED (SENILE) DEMENTIA:**
  - **Aetiology:**
    - Old Age
  - **Pathogenesis:**
    - Old-Age → Neuronal Atrophy (Particularly Cortex & Hippocampus) → Progressive Neuronal Loss with Time →
      - →↓Brain Mass & ↓Dendritic Branches
      - →Neurons are replaced by glial cells
  - **Morphology:**
    - **Macro:**
      - Cortical atrophy
      - Enlarging of ventricles ("Compensatory Hydrocephalus")
      - Thickening of Leptomeninges (Pia Mater & Arachnoid Mater) (*The "Thin" Meninges*)
  - **Clinical Features:**
    - **Dementia:** All Spheres of Intellect affected

- **ALZHEIMERS DISEASE:**
  - Commonest Cause of Dementia
  - **Aetiology:**
    - Exact Aetiology Unknown
    - Genetic & Environmental Components
    - (NB: Inevitable in Down-Syndromes)
  - **Pathogenesis:**
    - **Excess β-Amyloid Protein Formation** (A Degradation product of Amyloid Precursors)
      - → **β-Amyloid** Protein Deposition around Neurons → ***Neuritic Plaques***
      - → **β-Amyloid** Protein Deposition in Blood Vessels → ***Amyloid Angiopathy***
  - **Morph:**
    - Severe Cortical Atrophy (Widened Sulci, Narrow Gyri)
      - Typically Starts around Broca's Area + Frontal Area → Extends to the rest of the brain (Affecting motor and sensory areas – may even have paralysis)
    - Secondary Ventricular Dilation (Compensatory Hydrocephalus)





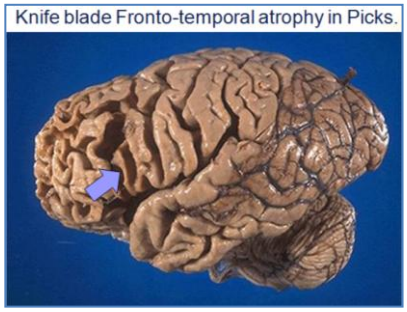




  - **Clinical Features:**
    - May be as young as 50yrs old
    - SLOW Insidious Onset (Years) – (Cf. Lewy-Body Dementia)
    - **Early Signs:** (Neuronal Atrophy Starts in the Hippocampus)
      - → Memory Loss is :. the First Sign
    - **Progressive Signs:** (Neuronal Atrophy Progresses to the Cortex)
      - **Mild Cortical Atrophy:**
        - →*Increased* Memory Loss
        - →Confusion, Apathy, Anxiety
        - →Difficulty Handling Money
      - **Moderate Cortical Atrophy:**
        - →Difficulty Recognising People
        - →Difficulty with Language
        - →Wandering & Disorientation
    - **Late Signs:** (Extreme Global Cortical Atrophy)
      - →Seizures, Incontinence
      - →Groaning/Moaning/Grunting
  - **Treatment:**
    - ***Acetylcholine-Esterase Inhibitors***
  - **Prognosis:**
    - Mean Survival = 7yrs from Onset.
    - →Death Typically From Aspiration Pneumonia or Other Infections.

- **DIFFUSE LEWY-BODY DEMENTIA:**
  - 3rd Most Common (Behind Alzheimers & Vascular)
  - **Aetiology:**
    - Unknown – But Genetic Link.
  - **Pathogenesis:**
    - Development of Abnormal Proteins (Alpha-Synuclein) in Neurons throughout the Brain → Impair the Functioning of Neurons → Rapid Decline in Cognition, Memory, Attention & Motor
  - **Morphology:**
    - **Macro:**
      - Significant Cortical Atrophy
      - Typically Starts around Broca's Area → Extends to the rest of the brain
  - **Clinical Features:**
    - **Rapid Onset (within few months)** – (Cf. Alzheimer's Disease)
    - **Early:**
      - Fluctuating Cognition/Dementia (↓STMemory, Confusion, Language Problems)
      - Vivid Visual Hallucinations (Eg. Strange Faces, Frightening Creatures, or Children)
      - Impairment in Attention
    - **Later:**
      - Parkinsonism – with shuffling gait & cog-wheel rigidity..
      - Delusions
      - Transient ALOC's.
  - **Treatment:**
    - Pharmacological – ***Cholinesterase Inhibitors*** are promising.

- **FRONTO-TEMPORAL DEMENTIAS (Incl. Pick's Disease):**
  - 4th most common dementia after Alzheimer's, Vascular & Lewy-Body
  - **Aetiology:**
    - Other Fronto-Temporal Dementias = Genetic
    - "Pick's Disease" = Unknown
  - **Pathogenesis:**
    - Selective Build-up of Tau Proteins within Frontal & Temporal Lobe Neurons →
      - Frontal Lobe Dysfunction → **↓Executive Function, ΔPersonality, Disinhibition**.
      - Temporal Love Dysfunction → **Aphasias (Expressive & Receptive)**
  - **Morphology:**
    - **Macro:**
      - Selective Atrophy of Frontal & Temporal lobes
      - Sparing of the Parietal & Occipital Lobes
  - **Clinical Features:**
    - Younger Patients (40-65yr olds)
    - **Dysexectutive Syx:** Inability to Coordinate & Execute Tasks
    - ****Behaviour Changes:** Behaviour & Personality Change & Disinhibition
      - (NB: A Defining feature of Pick's Disease is that Behaviour/Personality Changes occur PRIOR to Memory Loss. Cf. Alzheimer's, where Memory Loss occurs First.)
    - **Language Changes:** Progressive Aphasia (Expressive & Receptive)
    - **NB: Memory is Preserved until *Late Stages*.**



- **VASCULAR DEMENTIA (Multi-Infarct Dementia):**
  - **Epidemiology:**
    - 2nd Most Common (behind Alzheimer's); 25% of All Dementias.
  - **Aetiology:**
    - Cumulative Ischaemic Brain Damage
      - (Mostly due to Hypertension & Atherosclerosis)
  - **Pathogenesis:**
    - **Either Sudden** Onset Following a CVA
    - **Or Gradual** Deterioration after Successive (often unnoticeable) CVAs.
      - → Generalised Intellectual Loss → Dementia
  - **Morphology:**
    - **Macro:**
      - May have Necrotic/Fibrotic Foci (If Multi-Infarct) – Often Visible on MRI/CT
      - May have a single, large Necrotic/Fibrotic Focus (Single, Large Infarct)
      - May have Hypertensive Lacunar Lesions
  - **Clinical Features:**
    - Memory Loss
    - ↓Cognitive Function
    - Confusion
    - Mood Changes (Depression/Irritability)
    - Language Problems
    - Executive Dysfunction → ↓ADLs (Eating, Dressing, Shopping, etc)
    - Rapid Shuffling Gait (Sometimes called 'Atherosclerotic Parkinsonism')
    - Hx of Vascular Pathology (Past Hx of CVA, TIA, HTN & Focal Neurology)
  - **Treatment:**
    - No Cure, but Preventable
  - **Prevention:**
    - Control Hypertension
    - Reduce Cholesterol
    - Control Diabetes
    - Stop Smoking
    - Antiplatelet Drugs (Aspirin/Clopidogrel)

- **DEMENTIA PUGILISTICA = "Punch Drunk Syndrome":**
  - **Aetiology:**
    - Repetitive Trauma/Concussion
  - **Pathogenesis:**
    - Repeated Concussive/Sub-Concussive Blows to the Head → Cumulative Loss of Neurons, Fibrosis, Hydrocephalus, Diffuse Axonal Injury & Cerebellar Damage.
  - **Morphology:**
    - Hydrocephalus
    - Thinning of Corpus Callosum
  - **Clinical Features:**
    - Slow Progression (Over Decades)
    - Dementia (↓Memory, ↓Cognition, ΔPersonality)
    - Parkinsonism (Tremors, ↓Coordination)
    - Unsteady Gait
    - Dysphasias

- **WERNICKES-KORSAKOFF SYNDROME (Alcoholic Encephalopathy):**
    - **Aetiology:**
        - Alcohol Abuse → **Vit B1[Thiamine]** Deficiency
    - **Pathology:**
        - Alcohol Abuse → Vit B1[Thiamine] Deficiency
        - Vit B1[Thiamine] is a cofactor for Glucose Metabolism :. Deficiency → Neuronal ATP → Neuronal Atrophy (Particularly Cortex & Mamillary Bodies)
        - (Vit B1[Thiamine] Deficiency) → Ataxia
    - **Morphology:**
        - Cortical Atrophy
        - Mamillary Body Atrophy & Haemorrhages
        - Cerebellar Atrophy
    - **Clinical Features:**
        - Cortical Atrophy → **Impaired Memory** (Anterograde & Retrograde) + **Confabulation**
        - Mamillary Body Damage → **Vision Changes, Nystagmus, Unequal Pupils**
        - Cerebellar Atrophy → **Ataxia**
    - **Treatment:**
        - Supplemental ***Thiamine + B12***
            - (NB: B12 to prevent subacute degeneration of the cord)
    - **Prognosis:**
        - By the time Amnesia & Psychosis are apparent, complete recovery is unlikely.

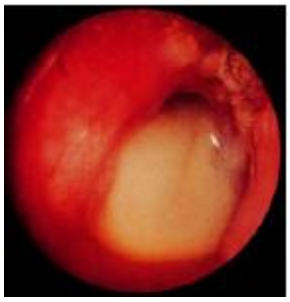
Amnesia:

- **Typically Declarative Memory Loss**. (Therefore Hippocampal Damage)
- Commonly caused by Temporal Lobe Damage (Hippocampus and/or Thalamus)
    - **NB: L-Hippocampus** = Language
      R-Hippocampus = Spatial Memory
- **Anterograde:**
    - - Inability to form new memories from time of Injury/Damage ***Onwards.***
    - Non-Declarative Memory is Unaffected
- **Retrograde:**
    - - Inability to recall memories from time of Injury/Damage ***Backwards.***

NEUROLOGICAL Pathology:
EAR PATHOLOGY

Ear Complaints:

- **Deafness:**
  - **Conductive:**
    - Due to a condition that blocks the conduction of sound through the Outer & Middle Ear.
      - **Originating in the Outer Ear:**
        - External auditory canal obstruction. (Wax/Foreign Bodies/Infection/Pus)
      - **Originating in the Tympanic Membrane:**
        - Perforation or Scarring due to Infection or Trauma.
      - **Originating in the Middle Ear:**
        - Otitis Media → Fills the Tympanic Cavity with pus.
        - Otosclerosis → Ossicles become fused together

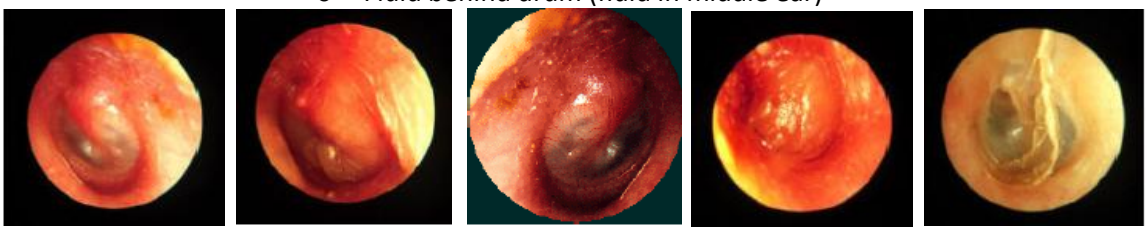


  - **Sensorineural:**
    - Due to a disorder of the inner ear, the cochlear nerve, or its central connections to the brain.
      - **Noise-Induced** Damage to Cochlear Hair Cells.
      - **Stroke in the Auditory Cortex** causing hearing loss.
      - **Acoustic Neuroma** (tumour of CN8) causing deafness on the affected side.
      - **Ototoxic Drugs** → Damage to Cochlea Nerve
      - **Meningitis**
      - **'Presbycusis' –** Progressive age-related hearing degradation.

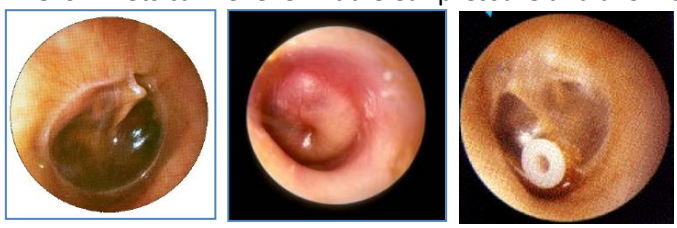
- **Tinnitus:**
  - A 'Percieved' Ringing in the ears. (Or buzzing, hissing, clicking, roaring, etc)
  - Commonly occurs immediately after Acoustic Trauma (Eg. Clubbing)
  - Is a problem of the *Peripheral* auditory system (Not the brain)

- **Vertigo:**
  - Sensation of 'Spinning'. (Distinct from faintness)
  - Usually a problem of the Vestibular Apparatus or the Vestibulocochlear Nerve (CN8)
    - **Benign Paroxysmal (sudden onset) Positional Vertigo**
    - **Vestibular Neuronitis**
    - **Drugs (Eg. Alcohol)**
    - **Brainstem Lesions, Multiple Sclerosis, Migraine.**

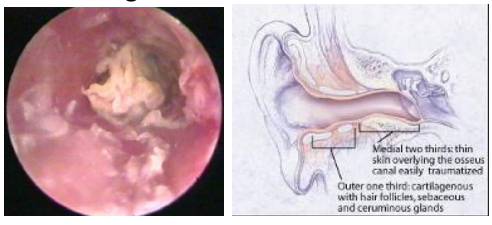
- **Otalgia:**
  - "Pain of the Ear"
  - Most often caused by some form of Otitis:
    - **Acute Otitis Media** – (Acute Middle Ear Infection).
      - Caused by Respiratory Pathogens which enter via Eustachian Tube.
      - Can Present with:
        - URTI; Rhinitis; Cough; Fever
        - Ear ache; 'Ear-pulling'
      - Otoscopy may show:
        - Swollen, bulging, red Ear-drum.
        - Fluid behind drum (fluid in middle ear)



    - **Chronic Otitis Media –** (Chronic Middle Ear Infection):
      - Caused by:
        - Chronic Respiratory Infections
        - Nasopharyngeal colonisation in early infancy.
        - Eustachian tube dysfunction
      - Can Present with:
        - Chronic ear discharge.
        - Hearing loss
        - Developmental delay/poor school performance.
      - Can result in a variety of Conditions:
        - Retraction or Perforation of Eardrum.
        - Loss of Eardrum Elasticity
        - Fluid behind an intact eardrum.
        - Scarring of ossicles.
        - Erosion of the bony cavity of the middle ear.
        - Cholesteatoma (Keratinizing Squamous epithelioma in mid.ear or eardrum)
      - Grommets can relieve middle ear pressure and allow draining of exudate.

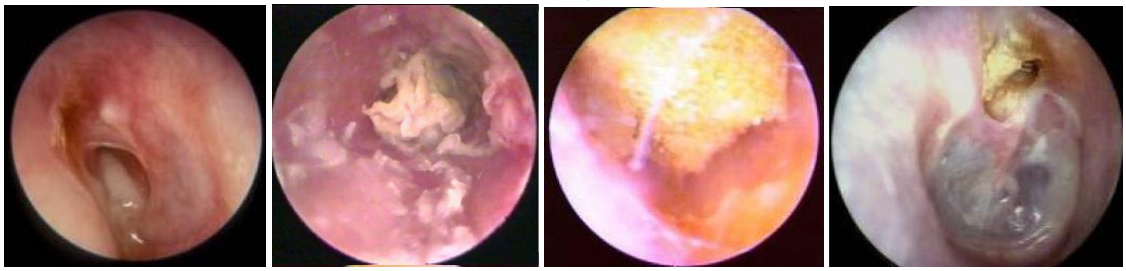


    - **Otitis Externa –** (External Ear Infection):
      - Caused by:
        - Humidity/Swimming → Bacterial/Fungal Infection.
      - Can Present with:
        - Itch; Pain; Ear Pulling
        - Fever
        - Discharge



- **Otorrhoea:**
  - "Runny Ear"

- Can be Caused by:
  - Otitis Media:
    - Acute – with perforation
    - Chronic
  - Otitis Externa
  - Foreign Body
  - Cholesteatoma → Chronic Infection/Erosion



Ear-Related History:

- **Past Medical:**
  - Ear Infections?
  - Ear Trauma?
  - Diabetes?
  - MS?
- **Past Surgical:**
  - Ear Surgery?
- **Medication?**
  - NB: Some are ototoxic.
- **Noise Exposure:**
  - Occupational
  - Recreational

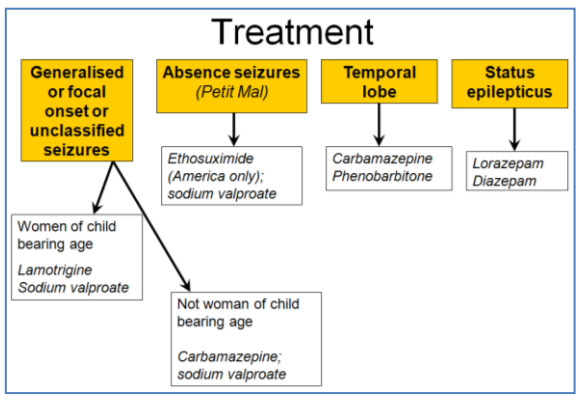
Ear Examination:

- **External Ear:**
  - Inspection
  - Palpation (tenderness) + Cervical & Occipital Lymph Nodes.
- **Otoscopy:**
  - Inspection of Tympanic Membrane & Middle Ear
- **Hearing Tests:**
  - Whisper Test
  - Tuning Fork Tests
  - Testing for Nystagmus (Involuntary eye movement due to head movement)
  - Romberg's Test (standing, feet together, then closing eyes. Loss of balance = positive)
  - Tympanometry (tests the eardrum & ossicle mobility)
  - Audiometry (tests a person's responses to different pitches & volumes.)

NEUROLOGICAL Pathology:
EPILEPSY

EPILEPSY:

- **Terminology:**
  - **"Epilepsy" =** *A Recurrent Spontaneous Seizure Activity, NOT Attributable to External Cause*.
    - (Clinical Dx Depends on the an arbitrary cutoff, usually 3/more seizures)
  - **"Seizures" =** *Spontaneous Abnormal Electrical Activity within the Brain*.
- **Aetiology:**
  - 70% Idiopathic (Often Familial)
  - Others: Post-Injury, Developmental, Tumour, Stroke, Febrile Convulsion, Trauma, Stroke, ↑ICP, Alcohol Withdrawal, Metabolic, Infection, Drugs.
- **Common Triggers (Among Epileptics):**
  - **Strobe Lights are most common → (Often used for Diagnosis)
- **Common Triggers (Among Non-Epileptics):**
  - Drug/Caffeine OD
  - Fever
  - Alcohol Withdrawal
  - Toxins
  - Head Injury
  - Metabolic/Electrolyte Disturbances
  - **NB: The above triggers have to be eliminated before Epilepsy is Diagnosed.**
    - (Epilepsy is an 'Innocent until proven guilty' disease.)
  - **NB: 1x Seizure ≠ Epilepsy.**
- **Pathogenesis:**
  - Hyperexcitable Neurons (Lower Threshold, Ion-Channelopathy, or Neurotransmitter Imbalance) → Inappropriate, uncontrolled, spontaneous Electrical Activity within the Brain (Seizure)
- **Clinical Features:**
  - **Prevalence:** 0.5 - 1% of Adults
  - **Age of Onset:**
    - Generally before 20yrs.
    - 1st seizure before 10yrs
  - **Presentation:**
    - **1. Pre-Seizure '*Aura*':** Eg. Deja-vu, Abdominal Discomfort, Flashing Lights, Strange Smells, Sounds, Tastes.
    - **2. Seizure – Many Different Types**
    - **3. Post-Ictal Symptoms:** Eg. Headache, Confusion, Myalgia, Temporary Weakness
- **Diagnosis: a *Clinical Diagnosis*; Requiring:**
  - **>2 Seizures**, for which all external triggers have been eliminated.
  - **Positive EEG**
  - **Seizure Induction Test**
  - **(+ Detailed History)**
  - **(+ Detailed Description (or video) of the Seizures)**
  - (No single test is enough to diagnose.)
  - NB: 1x Seizure ≠ Epilepsy.
- **Treatment:**



(NB: Valproate = "Epilim"; Carbamazepine = "Tegretol")

Types of Seizures:

- **ICES-Classified Seizures:**
  - **"Simple Partial Seizure" – (Conscious & Localised):**
    - **Symptoms:**
      - Typically – Small, Rapid Muscle Movements
      - May include - Focal Motor/Sensory/Autonomic/Psychic Symptoms
    - **Duration:** Very Short Duration (Less than 1min)
    - **NB:** Preservation of Consciousness & Memory is Key.
  - **"Complex Partial Seizure" – (ALOC & Localised):**
    - **Symptoms:**
      - '*Impaired* Consciousness' = Dazed/Dopey.
      - + Purposeless Movements – (Hand-Wring/Pill-Rolling/Face-Washing)
    - **Duration:** Less than 2 min
    - **NB:** Impaired Consciousness → Little/No Memory of Seizure.
  - **"Partial with Secondary Complex-Generalised Seizure" - ("Tonic-Clonic"):**
    - Ie. Simple *or* Complex Partial Seizure, Progressing to Complex (Unconscious) Widespread (Generalised) Seizure.
    - **4 Phases:**
      - **1. Pre-Seizure Period – (Aura)**
      - **2. Tonic Phase – (Sustained Generalised Tonic Contraction)**
      - **3. Clonic Phase – (Repetitive Generalised Synchronous Jerks)**
      - **4. Post-Ictal Coma – (Sustained Post-Seizure Unconsciousness)**
      - (May include Central Apnoea & Incontinence)
    - **Duration:**
      - 1-2mins
      - However, can last for many minutes.
- **Unique Seizure Types:**
  - **"Myoclonic":**
    - **Symptoms:**
      - Brief, Marked Contraction of Muscles (Ie. A "Shock-Like Jerk" or a "Startle")
      - Typically Upper Body
      - Typically Bilateral
      - (May be in a specific muscle group/s)
    - **Duration:**
      - Typically 1-5sec
  - **"Temporal Lobe Epilepsy":**
    - **Symptoms:** Typically Behavioural Alteration:
      - - Automatic Activity but Without Consciousness or Memory
      - - Sexually Inappropriate Behaviour
      - - Religiosity
      - - Aggression
      - - Relived Experiences
    - **Duration:**
      - Can last for hours
    - **Treatment:**
      - *Carbamazepine (Tegretol)*
  - **"Absence Seizures" - (The *Classic* "Petit Mal"):**
    - **Symptom:**
      - Abrupt Onset of Impaired Consciousness + Amnesia
      - Pt appears to "Zone Out"
      - May → Purposeless Movements (Eg. Lip Smacking, Eye Blinking)
      - **Then Pt resumes *Exactly* where they left off** (unaware of time lapse)
    - **Duration:**
      - Up to 30sec
    - **Treatment:**
      - ***Ethosuximide*** (Thalamic Ca-Channel Blocker)

- **"Status Epilepticus" – (Unremitting Seizure; or Multiple Successive Seizures):**
  - **= An Episode of Seizures of Any Type that Either:**
    - 1. Seizures Don't Stop Spontaneously.
    - 2. Seizures Occur in Rapid Succession Without Recovery.
  - **A *Status Epilepticus* Seizure = Absolute Neurological Emergency:**
    - High Risk of Cerebral Hypoxia
    - High Risk of Permanent Brain Damage
    - Often Results in Permanent Loss of Neurons due to Excito-Toxicity.
      - (Hippocampus & Pyramidal Tracts are Particularly Sensitive → ↓Memory & Motor)
    - Surviving Neurons may exhibit Synaptic Reorganisation.
  - **The Problem = Cell Death:**
    - Seizures can Trigger Cell Death; **How?:**
      - **↑Intracellular Ca^+** from ↑Ca-Mediated-NT-Release. → Release of Cytochrome-C from Mitochondria → Triggers Apoptotic Pathway.
      - **Energy Depletion → ↑Free Radicals** → Widespread Protein/Membrane/DNA Damage.
    - Also, Attempts made by the brain to Restore Function favour The Excitatory Pathways → ↑Seizures.
  - **Occurs mostly in the Young and the Elderly (Typically not middle-aged)**
    - NB: Mortality is highest in Elderly Patients.
    - Average Mortality Rate ≈20%
  - **Treatment:**
    - **1st Line: *Benzodiazepines* (GABA-Channel Agonist)**
      - ***Diazepam*** – (Generally #1; But Short Acting)
      - ***Lorazepam*** – (Some argue that it's #1 due to Higher Seizure-Termination Rate)
      - ***Midazolam***
    - **+/- *Phenytoin* – As an Adjunct to 'Benzos' (Usage Dependent VG-Na Channel Blocker)**:
      - **(Unless Absence Seizures or TLE)**

- **Treatment - Anti-Convulsants:**
  - **The Jack of All Trades – (*Valproate*):**
    - **3 Mechanisms of Action -** (Na^+ Channel Blocker, Ca^+ Channel Blocker & GABA Activator):
      - → ↓Repetitive Firing of Neurons.
      - → Prevents Spread of Signals from Epileptic Focus.
      - → General Neuronal Inhibition of the Brain.
    - **ALL Seizure Types**
  - **VG-Na^+ Channel Blockers – (*Carbamazepine*[*Tegretol*], *Lamotrigine*, Phenytoin):**
    - Use Dependent VG-Na^+ Channel Blockers
    - Useful in **All Seizures EXCEPT Absence** Seizures
  - **VG-T-Ca^+ Channel Blockers – (*Ethosuximide*):**
    - Blocks VG-T-Ca^+ Channels in the Thalamus → Prevents Propagation of Seizure Activity.
    - Used **ONLY in Absence Seizures**
  - **GABA Channel Modulators – (Benzodiazepines - *Diazepam*):**
    - Activate GABA Channel → ↑Cl^- Influx → Hyperpolarises & :. Stabilises Neuron.
    - Useful in All Seizures EXCEPT Absence Seizures
    - **NB: Benzodiazepines (Diazepam) = 1ST LINE FOR STATUS EPILEPTICUS**
  - **GABA Analogues – (Gabapentin):**
    - Activate GABA Channel → ↑Cl^- Influx → Hyperpolarises & :. Stabilises Neuron.
    - Useful in Partial Seizures

Surgical Interventions:

Why Surgery:

- Up to 30% of Epilepsies are Unresponsive to Pharmacological Treatment
- If the Epilepsy is Unresponsive to drugs, Surgery is Essential to prevent Permanent Progressive Brain Damage
    - NB: Risk of Brain Damage Increases the longer the condition continues.
    - NB: Seizures bring about More Seizures. (Ie. Untreated Seizures make Future Seizures more Likely)

Surgical Options:

- **1. Resections:**
    - **Removal of Epileptic Focus.**
    - **Hemispherectomy** (Removal of an entire Hemisphere)
    - **Anteromedial Temporal Lobectomy**
- **2. Disconnections:**
    - **Cut the Corpus Callosum** (Bridge between Hemispheres)
    - **Multiple Sub-Pial Transections** (Small cuts made into cortex hoping to isolate neuronal networks)

Prognosis:

- ≈80% of Surgery Patients are Seizure-Free 10yrs later.
- **(NB:** Precise mapping of the Epileptic Focus is an Essential Prerequisite to Surgery to ensure that removal won't render the patient Paralysed/Unable to Speak/Other Serious Deficit.)

Dietary Intervention: The Ketogenic Diet:

What is the Ketogenic Diet?

- 1gram/$Kg_{Body\text{-}Weight}$ of Protein.
- 5-10grams of Carbs/Day. (Ie. Virtually NO Carbs)
- Remainder of Calories is made up in Fats.
- **NB: Side Effect** – Bloating & Constipation (Lack of Fibre).

Proposed Mechanism/s of Action:

- **↑GABA Availability:**
    - Through ↑Metabolic Conversion of Ketone Bodies → GABA.
        - ↑GABA Availability →General Inhibition of Neuronal Activity.
- **Altered Metabolic Activity:**
    - ↑Protein & ↓Carbs → Forced Re-Adaptation of Energy-Utilisation → ↓Glutamate Availability.
        - ↓Glutamate Availability → Decreased Stimulation of Neuronal Activity.
- **↑Activity of Na/K-ATPase**:
    - → Drives Neurons *Away* from Threshold → Hyperpolarises.

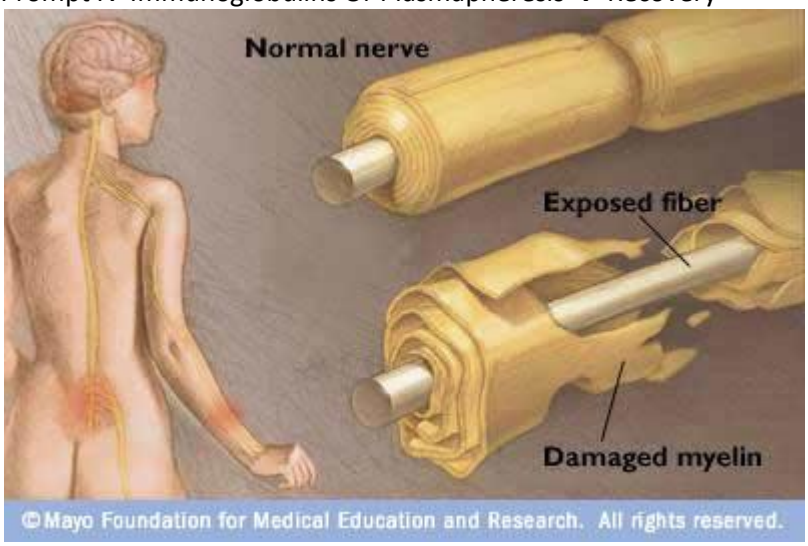
SENSORY Pathology:
EQUILIBRIUM DISORDERS

Common Equilibrium Disorders:

- **Vertigo:**
  - Hallucinatory sensation of movement (Referred to dizziness)
  - Labyrinthitis or vestibular neuronitis (subsequent to viral/bacterial infection/metabolic disturbance – eg. hypoglycaemia)
  - Elderly patients – due to reduced blood supply to the labyrinth.
- **Meniere's Syndrome:**
  - Labyrinthine disorder – affects both semicircular canals & cochlea:
    - Repeated attacks of vertigo, nausea & vomiting
    - Tinnitus is common & hearing is impaired
- **Positional Vertigo:**
  - May often follow trauma
  - May follow drug overdose
  - Anxiety & depression may contribute (psychogenic)
- **Motion Sickness:**
  - Mismatch between visual & vestibular information.

NEUROLOGICAL Pathology:
GUILLIAN-BARRE SYNDROME

- **Guillain-Barre Syndrome:**
  - **Aetiology:**
    - **Post-Viral Autoimmune**
    - An **Acute Inflammatory Demyelinating *Peripheral* Polyneuropathy** that occurs **following an Acute Viral Illness**
  - **Pathogenesis:**
    - Acute Viral Illness Triggers a Misdirected Immune Response
    - → T-cell Mediated, Autoimmune Attack & Demyelination of **Peripheral** Nerves →
      - **Motor:** Ascending Paralysis (Weakness beginning in Feet & Hands → Migrating toward the Trunk)
      - **Sensory:** Ascending Paraesthesia, ↓Proprioception & Areflexia (Altered Sensation in Feet/Hands → Trunk)
    - (NB: Distinct from Multiple Sclerosis since it does not affect the CNS)
  - **Clinical Features:**
    - Hx of Recent Viral Illness
    - Acute – Progresses over Hours → Days
    - Rapid, Symmetrical Ascending Paralysis & Paraesthesia (Initially Distal Limbs only, then Proximal Muscles)
    - Areflexia
    - NO Fever
    - Is Life threatening - Death usually due to respiratory paralysis
  - **Diagnosis:**
    - LP → ↑CSF Protein
    - EMG (Electromyography) & Nerve Conduction Studies.
  - **Treatment:**
    - Hospitalisation
    - **Ventilation
    - Prompt IV-Immunoglobulins Or Plasmapheresis → Recovery



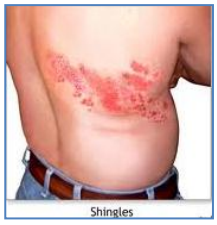
SENSORY Pathology:
HEARING DISORDERS

Common hearing deficiencies:

- **Ageing:**
  - Progressive loss of hearing receptors
- **Acute Damage:**
  - Hair cells can be destroyed by a single explosive sound or continuous high-intensity sound → tears at the cilia
- **Drugs:**
  - Some are ototoxic (damage the hair cells)
- **Tinnitus:**
  - Ringing in the ear in the absence of auditory stimulus
  - Symptom of nerve degeneration/inflammation of middle/inner ear.
  - Can be caused by drugs. (Damage can be permanent)
    - Some antibiotics (Streptomycin, neomycin)
    - Loop diuretics (transient)
    - Salycilates
- **Otitis Media:**
  - Inflammation of middle ear lining
  - Is a common result of throat infections in infants & children (due to short Eustachian tube).
  - Can be bacterial viral or bacterial
  - Eardrum becomes inflamed and bulges – can perforate
  - When large amounts of fluid - pus accumulate behind the eardrum, grommets may be inserted.
- **Deafness:**
  - **Conduction Deafness:**
    - Problem with Soundwave ***Conduction*** (Ie. Mechanical Structures)
      - Eg. Earwax
      - Eg. Perforated Ear Drum
      - Eg. Fused Ossicles
  - **Sensorineural Deafness:**
    - Problem with Soundwave ***Transduction*** (Ie. Neural Structures)
      - Eg. Damaged Hair Cells
      - Eg. Damaged Cochlear Nerve
      - Eg. Damaged Auditory Cortex

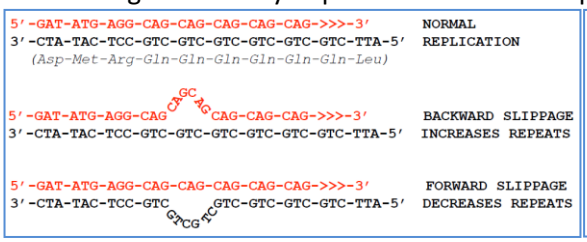
NEUROLOGICAL Pathology:
HERPETIC NEURALGIA (SHINGLES)

- **Herpetic Neuralgia ("Shingles"):**
  - **Aetiology:**
    - Herpes Zoster Virus Infection in Neural Ganglia
  - **Pathogenesis:**
    - Trigger (Stress/Sunlight/Immunocompromise) → Reactivation of Latent HZV Infection in Neural Ganglia → HZV Migrates down the Axons → Painful Vesicular Lesions in the Sensory Dermatome (Often Trigeminal Nerve)
  - **Morphology:**
    - Vesicular Lesions over Sensory Dermatome
  - **Clinical Features:**
    - Initially just paraesthesia & burning pain over Sensory Dermatome
    - Then Painful Vesicular Lesions over Sensory Dermatome
  - **Treatment:**
    - **Antivirals:**
      - Famciclovir → Shortens course of disease.
    - **Pain Management:**
      - Antidepressants / Anticonvulsants (For Neuropathic Pain)
      - Topical Anaesthetics (Lidocaine Patches / Capsaicin Lotion)
      - Opioid Analgesics


Shingles

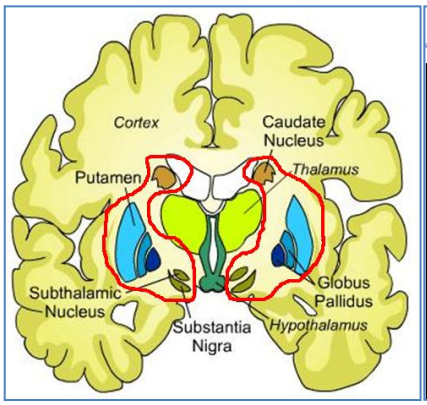
NEUROLOGICAL Pathology:
HUNTINGTONS DISEASE

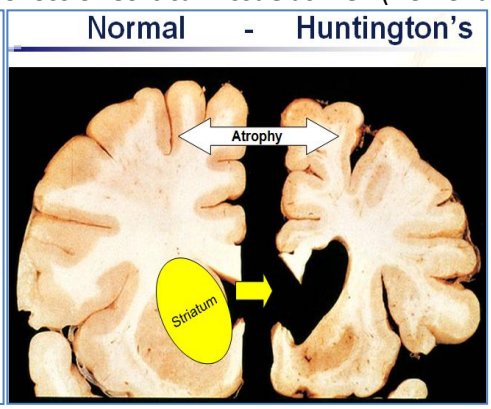
- **Huntingtons Disease:**
  - **Aetiology:**
    - **Genetic - Autosomal Dominant**
    - Defective Huntungton Gene (Chromosome 4) – Excess CAG Tandem Repeats
    - Onset Age & Severity depends on # of CAG Repeats in mutation.

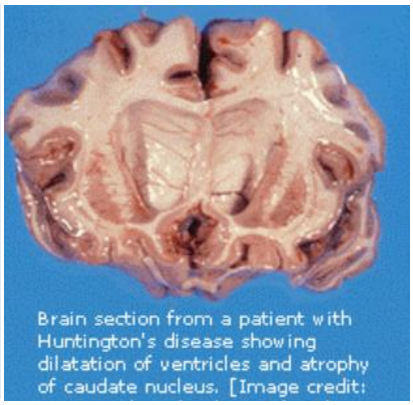


No. Repeats	Median age of onset
39 repeats	66 yrs
40 repeats	59 yrs
41 repeats	54 yrs
42 repeats	49 yrs
43 repeats	44 yrs
44 repeats	42 yrs
45 repeats	37 yrs
46 repeats	36 yrs
47 repeats	33 yrs
48 repeats	32 yrs
49 repeats	28 yrs
50 repeats	27 yrs

  - **Pathogenesis:**
    - Excess CAG Tandem Repeats in Huntington Gene → Production of Mutant Huntingtin Proteins in the Brain → Increases *Decay Rate* of Certain Types of Neurons →
      - →**Selective Marked Degeneration of the *Basal Ganglia (incl. The Striatum [Caudate + Putamen], Globus Pallidus & Substantia Nigra).***
        - NB: Loss of Basal Ganglia → Dysfunctional Action Selection → Chorea
      - →**Also loss of Cortical Tissue as well** (Dementia as well as chorea)







  - **Morphology:**
    - **Macro:**
      - Atrophy of Basal Ganglia (Striatum [Caudate & Putamen], Globus Pallidus & Substantia Nigra)
      - Some Atrophy of Cortical Tissue as well.
      - Compensatory Hydrocephalus of Lateral Ventricles (Lateral Ventricular Dilatation)
  - **Clinical Features:**
    - Onset in 40's (NB: The more CAG repeats, the younger the onset & faster the progression)
    - **Huntington's Triad:**
      - Dementia (Intellectual Decline)
      - Depression
      - Coreiform Movement (Involuntary Jerking) → Unsteady Gait
    - **Late Stages:**
      - Slurred speech
      - Difficulty swallowing.
  - **Treatment:**
    - Incurable
    - Tetrabenazine, Neuroleptics, Benzodiazepines Can → ↓Chorea
  - **Prognosis:**
    - <20yr life expectancy after Symptoms Begin.

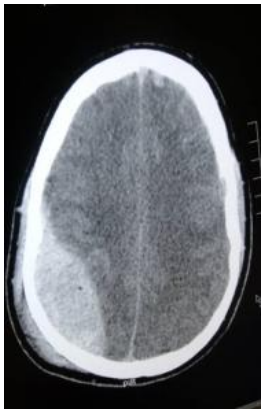
NEUROLOGICAL Pathology:
INTRACRANIAL HAEMORRHAGES

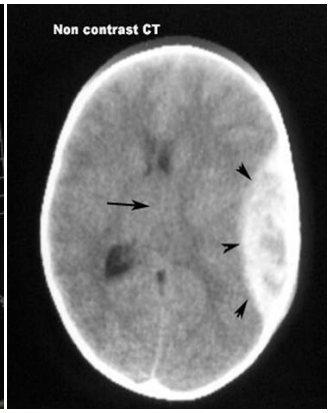
INTRACRANIAL HAEMORRHAGES:

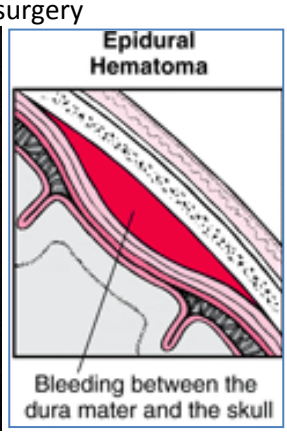
- **Aetiologies:**
  - **Trauma:**
    - Eg. Skull Fracture → **Extradural Haemorrhage** (Arterial)
    - Eg. Low-Force Trauma → **Subdural Haemorrhage** (Venous)
  - **Congenital Vascular Conditions:**
    - Eg. **Congenital Berry Aneurysms** → Rupture → **Subarachnoid Haemorrhage** (Arterial)
    - Eg. **Congenital AV Malformations** → Rupture → **Intracerebral Haemorrhage** (Arterial)
  - **Hypertension:**
    - → Hypertensive **Intracerebral Haemorrhage** (Arterial)

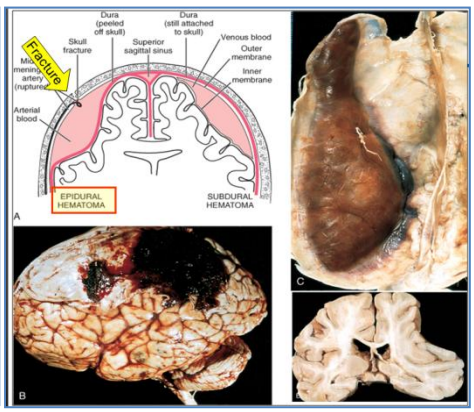
EPIDURAL/EXTRADURAL HAEMORRHAGE:

- **Aetiology:**
  - **Trauma/Cranial Fracture** → Arterial Rupture →Separation of Dura from the Skull → Haematoma
- **Pathogenesis:**
  - → High pressure bleed → Forced Splitting of the Dura Mata → ↑Intracranial Pressure
- **Morphology:**
  - Dura Mata gets separated from the skull
  - Extent of Bleeding is Limited by Attached Dura, :. Clearly Defined Margin.
  - Lens-shaped area
  - Brain Underneath is Compressed
- **Clinical Features:**
  - →Severe headache, vomiting and altered consciousness.
  - **Course:**
    - **Rapid progression** (due to arterial source of blood)
    - 1. Acute Loss of Consciousness
    - 2. Then Lucid Interval (Temporary Improvement)
    - 3. Then Sudden Deterioration if Herniation (Vomiting, Ipsilateral Pupil Dilation, LOC)
  - **Signs:**
    - Fixed & Dilated Pupil on side of injury.
    - Eye on side of injury may be down & out (CNIII Palsy)
    - Contralateral Weakness of Extremities
    - Contralateral Homonymous Hemianopsia (Loss of Contralateral Visual Field)
    - If ↑↑ICP → Cerebellar Tonsillar/Uncal Herniation → Respiratory Arrest
- **Investigations:**
  - **Head CT – (**Biconvex Lens Appearance)
- **Management:**
  - **Good prognosis with Surgery – (*Burrhole Craniotomy* → Drainage)**
    - Will 'Cone' & Die without surgery



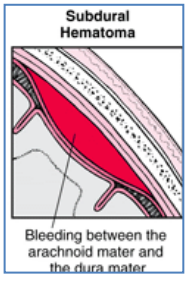


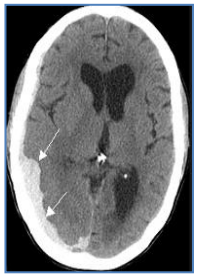
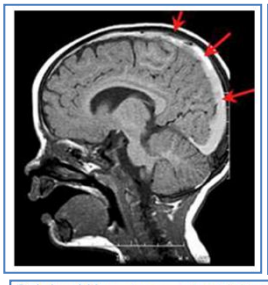
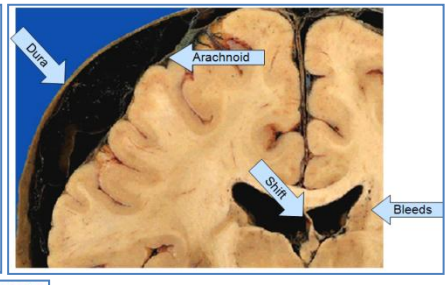


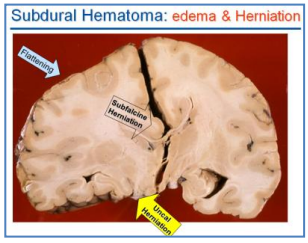


SUBDURAL HAEMATOMA (typically a venous bleed; happens slowly)

- **Aetiology:**
  - Elderly + Low force trauma (Eg. Whiplash Injuries) → Slow **Venous Bleed**
- **Pathogenesis:**
  - Bleeding between the Dura Mata and the Arachnoid Mater
- **Morphology:**
  - **Wide distribution** – ie. Over the entire hemisphere
  - **Cerebral Oedema** → Flattening of the gyri, narrowing of sulci, shift of midline
  - **Abnormal Brain underneath** (Ie. Pt. Is often demented, or alcoholic, or have severe cerebral atrophy)
- **Clinical Features:**
  - **Acute Subdural Haematomas:**
    - Typically Due to Mild Trauma
    - → Acute Neurologic Dysfunction (Within Minutes)
    - High Mortality Rate
  - **Chronic Subdural Haematomas:**
    - Typically a Spontaneous, Slow Venous bleed (Days – Weeks)
    - → Gradual headache, Somnolence, Confusion, Focal Deficits, Seizures.
    - Common in Elderly.
    - Signs/Symptoms **within Days-Weeks**.
  - **Signs/Symptoms:**
    - Gradually Increasing Headache and Confusion
    - Dizziness/Tinnitus/Numbness
    - Blurred Vision
    - Disorientation/Amnesia
    - Weakness/Lethargy/Ataxia
    - Nausea/Vomiting/Anorexia
    - Irritability/Seizures
- **Investigations:**
  - **Head CT:**
    - **Acute Subdural =** Crescent-Shaped Density.
      - Can compress lateral ventricle and cause midline shift
    - **Chronic Subdural =** Bleeding has Spread Throughout the Subdural Space → Follows the curve of the brain.
- **Management:**
  - **If Severe Bleed:** Drill & Drainage of Blood to ↓ICP
  - **If Small Bleed:** Conservative Management and Monitoring
- **Prognosis:**
  - Brain is typically *Abnormal* Underneath, Therefore the prognosis is worse

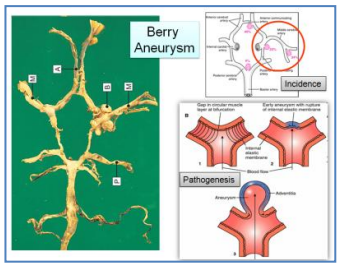


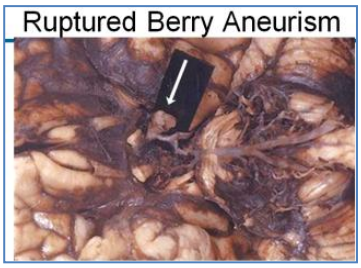






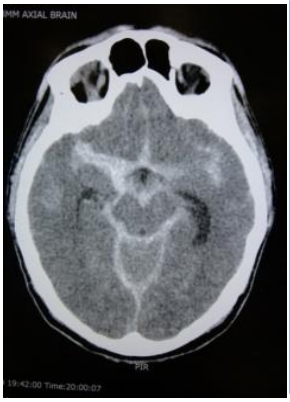
Subarachnoid Haemorrhage

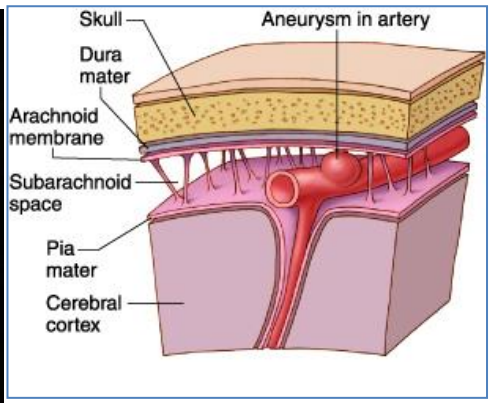
- **Aetiology:**
  - **Berry Aneurysm Rupture** in Circle of Willis
  - **Hypertension** is a Contributing Factor
- **Pathogenesis:**
  - **#Congenital Berry Aneurysm** (Rupture of Saccular Aneurysm on circle of willis)
    - **MCA is Commonest**, then ACA, then PCA rare





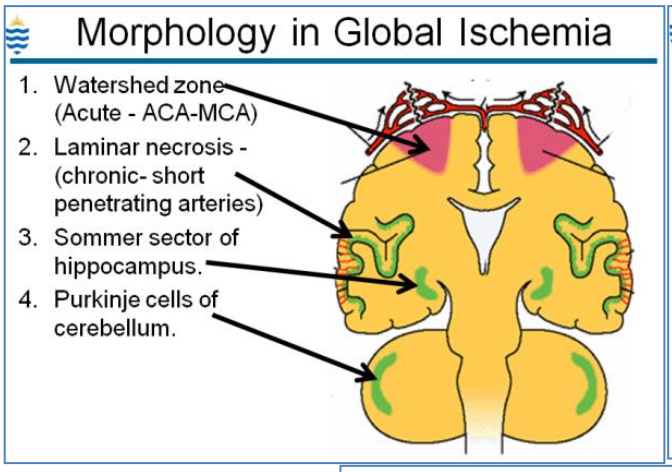
- **Morphology:**
  - Blood in the sulci
  - Blood pools around the **Basal Cistern** of the brain
- **Clinical Features:**
  - **(Pre-Rupture):**
    - Fatigue, Loss of perception/balance, Dysphasia
  - **Post-Rupture:**
    - **"Thunderclap Headache"** – Sudden, Severe, Pulsating Headache
      - + Vomiting
      - **+ Meningism**
      - + Hemiparesis
      - + Diplopia
    - **→Followed by Confusion → Loss of Consciousness – (+/- Seizures)**
- **Specific Investigations:**
  - **Head CT/MRI:** Blood *Within* the Sulci & Fissures
  - **Lumbar Puncture:** Blood in CSF
  - **CT Angiography:** To Identify Aneurysms
- **Management:**
  - **Stabilise Patient** (Ie. Intubate/Ventilation, ICU Admission)
  - **Urgent Neurosurgical Consult & Intervention**
  - **Prevent/Rx ↑ICP**
- **Prognosis:**
  - <50% are Fatal.

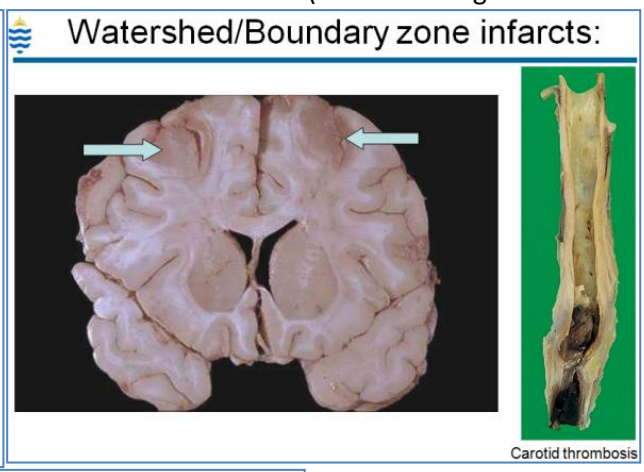


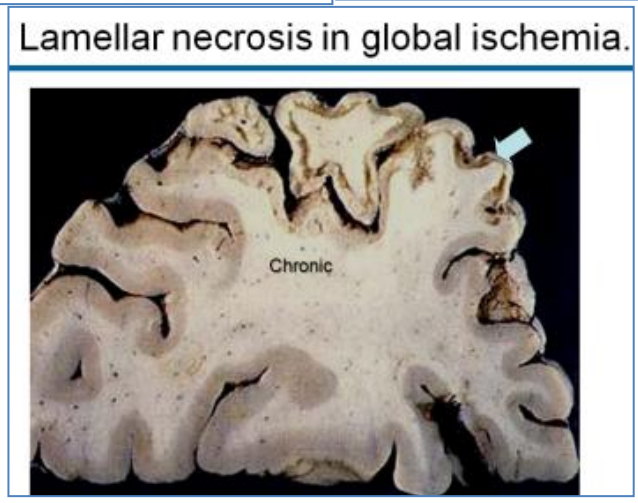


NEUROLOGICAL Pathology:
ISCHAEMIC ENCEPHALOPATHY

- **Global Ischaemia – (Ie. Hypoxemic Encephalopathy):**
  - **Aetiology:**
    - Impaired blood supply – Eg. Heart Failure, Hypotension, Shock, Carotid Thrombosis.
    - Impaired O2 carrying – Eg. Anemia, Hypoxia.
    - Impaired O2 utilization – Eg. Cyanide/Carbon-Monoxide Poisoning.
    - Excessive Neuronal Activity – Eg. Epilepsy/Seizure
  - **Pathogenesis:**
    - Heart Failure, Anaemia, Hypotension, Hypoxia, Shock, Etc → Global Brain Ischaemia →
    - **Sensitive Areas:**
      - **Adults:**
        - Watershed Zone (Between ACA & MCA Perfusion Zones)
        - 3^{rd}, 5^{th}, 6^{th} Layers of Cortex
        - Hippocampus
        - Purkinje Cells – Cerebellum Border Zone (watershed areas)
      - **Infants:**
        - Brainstem Nuclei
  - **Morphology:**
    - Watershed Zone Necrosis (Between ACA & MCA Perfusion Zones)
    - Laminar Necrosis – (Chronic – Short penetrating arteries) – the nuclear layers of the cortex
    - Hippocampus
    - Purkinje Cells of the Cerebellum
  - **Clinical Features:**
    - Mild Transient Confusion → Severe Irreversible Brain Death (Flat EEG = Vegetative = Coma)

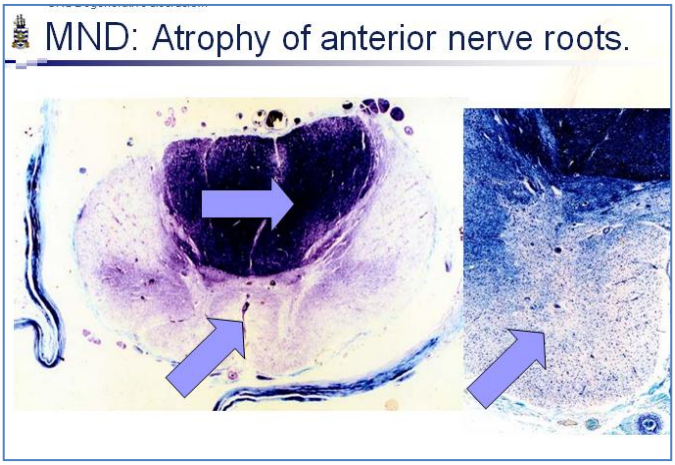


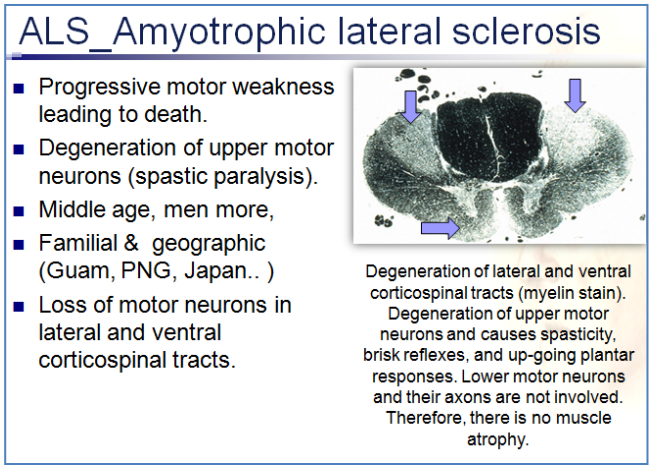




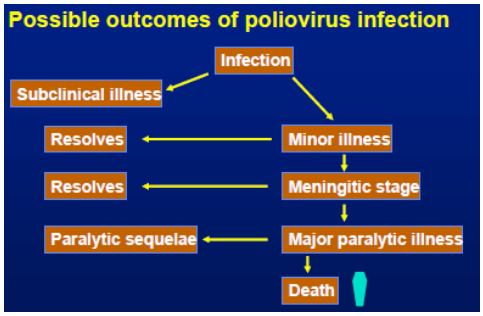
NEUROLOGICAL Pathology:
MOTOR NEURONE DISEASES & POLIO

- **Motor Neurone Disease (MND)/Amyelotrophic Lateral Sclerosis (ALS):**
  - ***Remember:**
    - Skeletal Muscles are Innervated by Lower Motor Neurons (Ventral Spinal Root → Muscle)
    - LMN's are innervated by Upper Motor Neurones (From the Corticospinal Tract)
  - **Aetiology:**
    - 90% Sporadic; 10% Genetic
  - **Pathogenesis:**
    - Progressive Degeneration of LMN's & UMN's in the Spinal Cord
      - (+ Cranial Nerve Nuclei in the Spinal Cord)
    - UMN & LMN Degeneration → Progressive Weakness, Muscle Wasting, Fasciculations, Spasticity/Stiffness & Hyperreflexia.
      - → Affects Voluntary Muscles (Ie. Walking, Speaking, Breathing, Swallowing)
  - **Morphology:**
    - **Macro:**
      - Degeneration of the Ventral Horns of the Spinal Cord (Ie. LMN)
      - Degeneration of the Ventral Spinal Roots (Ie. LMN)
      - Degeneration of Ventral & Lateral Corticospinal Tracts in Spinal Cord (UMN)
    - **Micro:**
      - Neurons may show Spongiosis
      - Higher #s of Astrocytes
      - Neuronal Inclusions – "Skein-like" Inclusions, Bunina Bodies & Vacuolisation.
  - **Clinical Features:**
    - Highly Aggressive (Normal → Severe within 1yr)
    - Voluntary Motor Only; Sensory System is Spared
      - **LMN Signs:**
        - Progressive Muscle Weakness
        - "Amyotrophy" (= No Muscle Growth) = Muscle Atrophy/Wasting
        - Fasciculations & Cramps
        - Hyporeflexia – if Mostly LMN's are Affected (↓ Muscle Innervation)
      - **UMN Signs:**
        - Spacticity/Stiffness/Rigidity
        - Hyperreflexia - if Mostly UMN's are Affected (Due to ↓Cortical Inhibition)
          - (+ *Up-Going Plantars (Babinski Sign)*)
    - Clinical Diagnosis
  - **Treatment:**
    - Supportive (Ventilation, Parenteral Nurtition)
  - **Prognosis:**
    - Incurable
    - Death within 3yrs



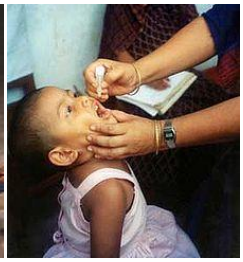


- **Poliomyelitis:**
  - **Aetiology:**
    - Poliovirus Infection
  - **Epidemiology:**
    - Non Existent in Aus (A single case would be an epidemic)
  - **Prevention:**
    - **Vaccination Available**
      - **Live Attenuated (Oral Polio Vaccine):**
        - Advantages:
          - Easy Administration - Given Orally
        - Disadvantage:
          - Rarely causes paralysis (1 in 2.5million)
      - **Inactivated Polio Vaccine (IPV):**
        - Advantages:
          - Carries NO risk of Vaccine-Associated Polio Paralysis
        - Disadvantage:
          - Difficult Administration - Has to be injected
  - **Pathogenesis:**
    - **Transmission:**
      - Faecal-Oral
      - or Respiratory
    - Initially Enteric Infection → Spreads to Bloodstream → Spinal Cord → Preferentially Infect & Destroy **Motor Neurons**
  - **Clinical Features:**
    - 90% Asymptomatic
    - <10% Minor Viral Illness:
      - Headache
      - Neck/Back pain
      - Abdominal Pain
      - Fever, Lethargy, Vomiting
    - 1% CNS Infection → Paralysis
      - Acute Asymmetrical Flaccid Paralysis + Areflexia
      - If 'Spinal Polio' → Paralysis of Legs(unilateral)
      - If 'Bulbar Polio' → Cranial Nerve Paralysis (eg. Dysphagia, Dysphasia, Dyspnoea)
      - Or Combination of Both.



  - **Treatment:**
    - Self-Limiting, but Lasting Disability – Only Supportive Rx (Eg. Ventilation, Physiotherapy)
    - But Vaccine Preventable

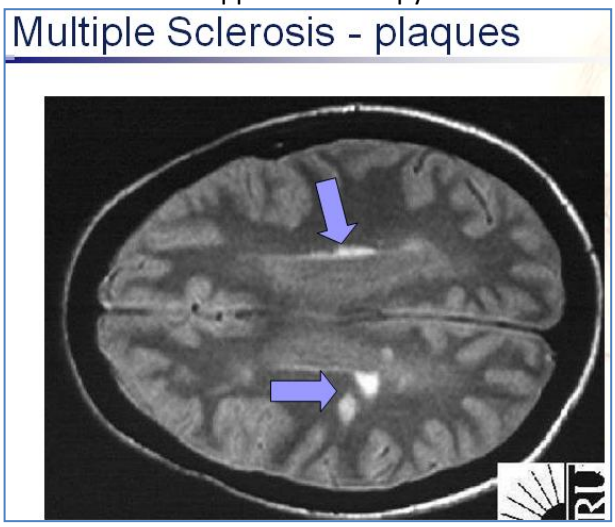


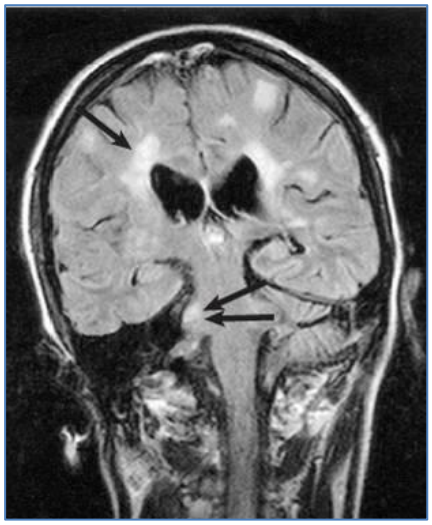


NEUROLOGICAL Pathology:
MULTIPLE SCLEROSIS & LEUKODYSTROPHIA

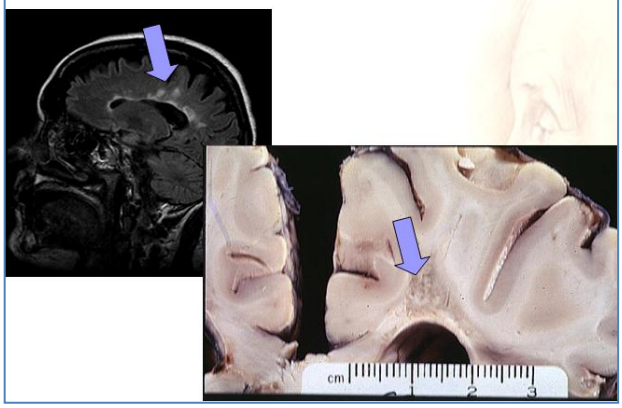
Multiple Sclerosis – (Demyelinating Disorder):

- (Formed Meylin gets Destroyed)
- **Aetiology:**
  - Chronic Autoimmune Inflammatory Disease of the CNS
  - Some Genetic Concordance
- **Pathogenesis:**
  - Precise Mechanism Unknown.
  - Autoimmune Demyelination within the Brain & Spinal Cord (Stripping of Wire's Insulation) → Defective Impulse Transmission & Short-Circuits.
  - Affects the CNS ONLY!!
- **Morphology:**
  - **Macro:**
    - Patches/islands of Grey-matter-like material in the white matter (Demyelination)
    - Multiple Soft Pink plaques of Demyleination (Periventricular) (Seen as white periventricular patches on MRI)
  - **Micro:**
    - Areas of Loss of Myelin Firstly *Around the blood vessels, extending outwards.*
    - Perivascular Inflammation: T-Lymphocytes, Macrophages & Plasma Cells
    - Reactive Gliosis
- **Clinical Features:**
  - Onset @ 20-40yrs
  - Affects White Matter Only
    - Limb weakness
    - Ataxia
    - Paraesthesia
    - Optic Neuropathy
    - Vertigo + Nystagmus, but *Without* Tinnitus or Deafness.
  - Relapsing & Remitting
  - Progressive → Spastic Quadraparesis → Death in years (Typically due to paralysis of chest muscles → pneumonia)
- **Diagnosis:**
  - MRI – Visible Plaques around the Ventricles in the White Matter.
  - CSF Examination – Oligoclonal IgG
- **Treatment:**
  - Currently Incurable
  - Home Care & Supportive Therapy

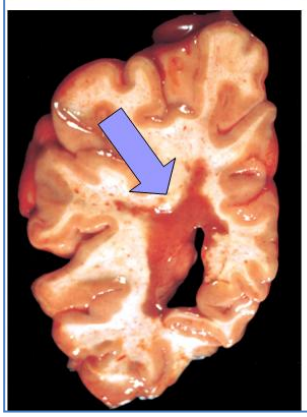




Multiple Sclerosis - plaques

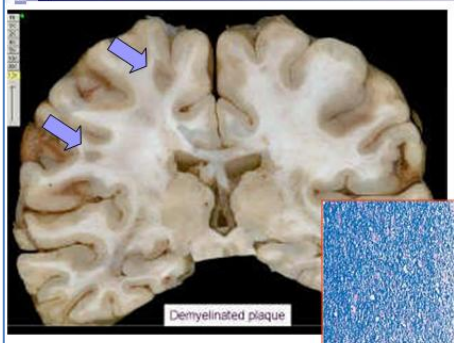


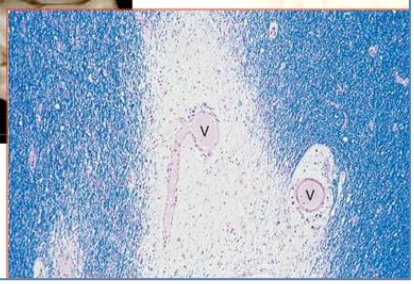
Multiple Sclerosis Plaque:



Section of fresh brain showing brown plaque around occipital horn of the lateral ventricle.

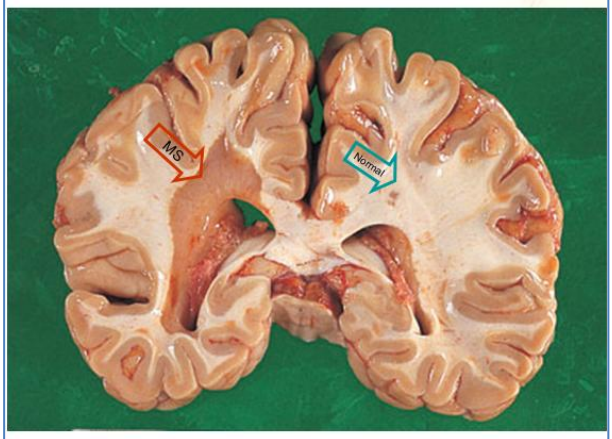
Multiple Sclerosis: Demyelinated plaques





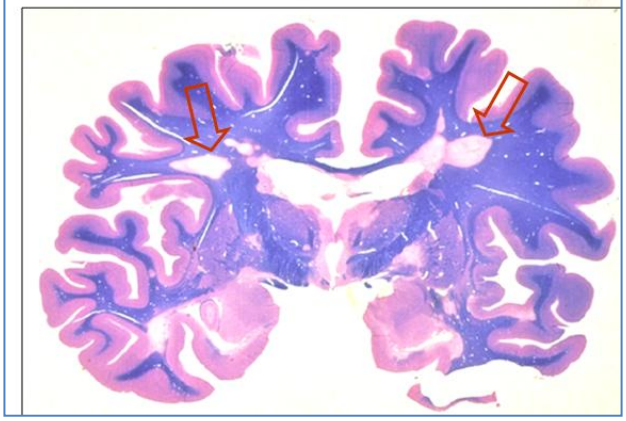
Microscopy showed loss of myelination with many lipid macrophages.

MS – Periventricular plaque



Like patches of grey matter within white matter…!

MS- Plaques – Myelin stain.



Leukodystrophies – (Myelin Production Disorders):

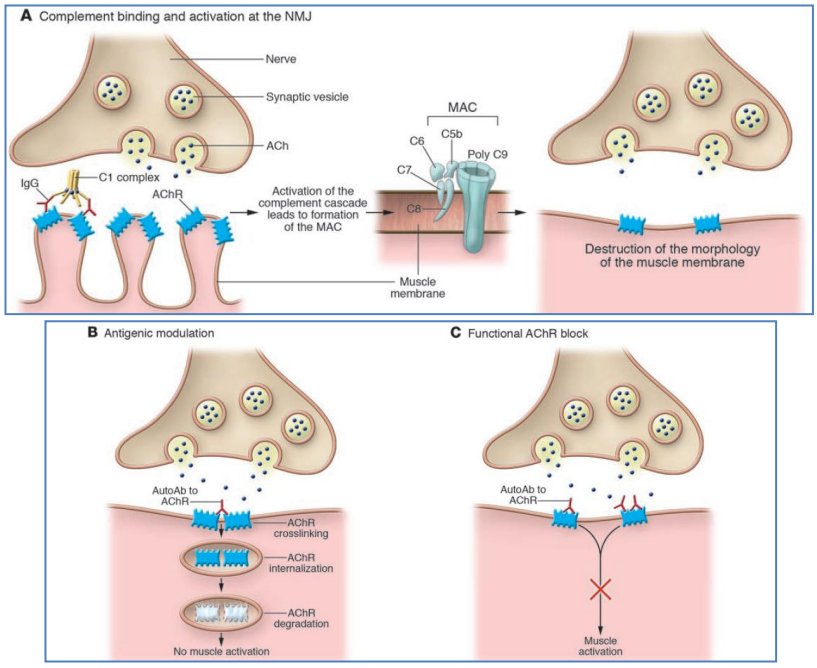
- (Insufficient Production of Myelin)
- Many, Many Types
- **Aetiology:**
  - Genetic Defect
- **Pathogenesis:**
  - Insufficient Production of Myelin (Insufficient Insulation around Wires) → Defective Impulse Transmission & Short-Circuits.
- **Morphology:**
  - **Macro:**
  - **Micro:**
- **Clinical Features:**
  - Gradual Decline in a Previously-Well Infant/Child:
    - ↓Body Tone
    - ↓Movements
    - ΔGait
    - Dysphasia
    - Dysphagia
    - Sensory Impairment (Vision/Hearing)
    - Behaviour Δ
    - Slowed Mental/Physical Development
- **Treatment:**
  - Incurable



NEUROLOGICAL Pathology:
MYAESTHENIA GRAVIS

Myasthenia Gravis

- **= "Severe Muscle Weakness"**
  - Myo(Muscle)
  - Asthenia (Weakness)
  - Gravis (Grave/Severe)
- **Pathophysiology:**
  - MG is an Antibody-Mediated Autoimmune Disease which attacks the ACh-Receptors @ the NMJ, leading to Failure of Neuromuscular Transmission.
  - **How? By 3 Mechanisms:**
    - **A) Complement Binding & Activation @ the NMJ:**
      - Ab-Binding to the AChR activates the Complement Cascade.
        - → ↓Receptor Density & Changed Physical Architecture of the Muscle
          - → Failure of Neuromuscular Transmission.
    - **B) 'Antigenic Modulation':**
      - Ab-Binding → Cross-Links AChRs on NMJ.
        - → Causes Endocytosis & Destruction of the Cross-Linked AChRs.
        - → Leads to a Reduced Number of AChRs on the NMJ.
          - → Failure of Neuromuscular Transmission.
    - **C) Functional AChR-Block by Antibodies:** (Relatively Rare)
      - Ab-Binding to AChR @ the ACh-Binding Sites.
        - → Causes functional block of the AChR by preventing ACh binding @ the NMJ.
          - → Failure of Neuromuscular Transmission.



- **2 Types of Myasthenia Gravis:**
  - **Ocular MG:**
    - Fatigable Muscle Weakness limited to Extrinsic Ocular Muscles of the Eye.
    - In 75% of Cases, Ocular MG is the Initial Manifestation of Generalised MG.
      - Ocular Muscles are susceptible due to constant rapid neuronal stimulation.
    - **Symptoms:**
      - Double Vision (Diplopia)
      - Drooping Eyelids
  - **Generalised (Whole Body) MG:**
    - Fatigable Muscle Weakness involving Other Muscle Groups Including the Eye Muscles.
    - As mentioned above, Generalised-MG typically begins as Ocular-MG, and then progresses to the rest of the body.

        - **Symptoms (In addition to Ocular MG):**
            - Unstable/Waddling Gait
            - Weakness in Arms/Hands/Fingers
            - Weakness in Legs
            - Weakness in Facial Muscle
            - Difficulty Swallowing
            - Shortness of Breath

- **Diagnosis:**
    - **Clinical (Pharmacological) Test:**
        - **Edrophonium (Short-Acting ACh-Esterase Inhibitor):**
            - → Repeated stimulation of remaining receptors.
            - If symptoms improve, then it's MG.
    - **Serology Testing:**
        - **Test for Antibodies Against:**
            - **AChR (Acetylcholine Receptors)**
            - **MuSK (MuSK = Muscle-Specific $_{Tyrosine}$ Kinase)**
            - **Anti-Muscle (eg. Actin) Antibodies**
    - **Electrophysiological Tests:**
        - **Repetitive Stimulation of Peripheral Nerves:**
        - **Single-Fibre Electromyography:**
- **Treatment:**
    - **Acetyl-Cholinesterase Inhibitors:**
        - Drugs that Inhibit the Cholinesterase Enzyme from degrading ACh in the Synapse.
        - **Eg. Physostigmine/Organophosphates**
        - **Mechanism of Action:**
            - → Prolonged Action of ACh in the Synapse
            - → ↑[ACh] in the Synapse
        - **Side Effects:**
            - **Short Term → Excessive ACh-Signalling:**
                - **Increases Mainly Parasympathetic Activity:**
                    - Increased Secretions (Salivary/Lacrimal/Bronchial/Intestinal)
                    - Increased Peristaltic Activity
                    - Bronchoconstriction
                    - Bradycardia & Hypotension
                    - Pupillary Constriction (→ Fall in Intraocular Pressure)
            - **Long Term → Desensitisation of AChRs:**
                - **Decreased Parasympathetic Activity.**
                - **In Cholinergic Crisis →Muscle & Respiratory Paralysis:**
                    - ***(Cholinergic Crisis* =** AChR Desensitisation due to ↑ACh-Stimulation)
                    - ACh-E-Inhibitors Potentiate further Desensitisation.
            - **In Myasthenic Crisis → Original Dose is Ineffective:**
                - ***(Myasthenic Crisis*** = Disease Progression →↓Number of ACh-Rs **)**
                - → Requires higher Dose for Therapeutic Effect.
    - **Immunomodulation:**
        - **Goal –** To Remove the Source of the Antibodies or the Antibodies Themselves.
        - **Variety of Options:**
            - Thymectomy
            - Plasma Exchange
            - Intravenous-Ig
            - Immunoadsorption.
    - **General Immunosuppression:**
        - **Goal –** To dial down the whole immune system → slow progression of disease.
        - **Immunosuppressive Drugs:**
            - ***Prednisone**:

        - Prednisone = A Corticosteroid = Powerful Anti-Inflammatory
    - ***Azathioprine:**
        - A Purine-Analogue → ↓ DNA Synthesis in Clonally Dividing Cells (B/T-Cells).

- **Complications:**
    - **Cholinergic & Myasthenic Crises:**
        - **Cholinergic Crisis:**
            - Rapid Desensitisation of the AChRs due to ↑↑ ACh-Stimulation.
            - → Requires Instant Cessation of Acetyl-Cholinesterase Inhibitors.
        - **Myasthenic Crisis:**
            - The point at which the Disease Progression has rendered the current ACh-E-Inhibitor Useless
            - Often causes Paralysis of Respiratory Muscles → Pt. Requires Assisted Ventilation.
            - → Ie. Requires a higher dose of ACh-E-Inhibitor to Maintain Therapeutic Effects.
    - **Rectifying these Complications:**
        - **Cholinergic Crisis:**
            - Cessation of ACh-E-Inhibitors.
        - **Myasthenic Crisis:**
            - ↑Dose of ACh-E-Inhibitors.

NEUROLOGICAL Pathology:
NEUROSYPHILIS

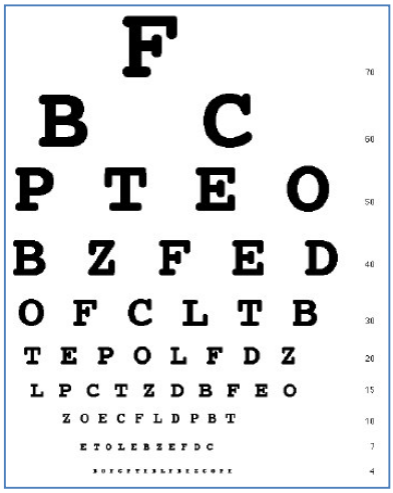
NEUROSYPHILIS:

- **Aetiology:**
  - Infection of the Brain/Spinal Cord by Bacteria: *Treponema pallidum*.
- **Pathogenesis:**
  - Chronic, Untreated Syphilis – Usually after 10-20yrs → *Tertiary Syphilis* → Brain/Spinal Cord
- **Clinical Features:**
  - Weakness, Abnormal Gait
  - Blindness, Argyll-Robertson Pupils (Bilateral Miosis, responsive to accommodation, but not to light)
  - Confusion, Dementia, Irritability
  - Depression
  - Headache
  - Paraeshtesia in Toes/Feet/Legs
  - Seizures
- **Treatment:**
  - 2wk Course of **IV/IM Penicillin**.

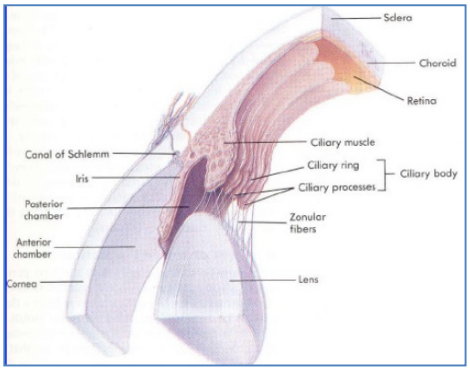
Disorders of the Special Senses:

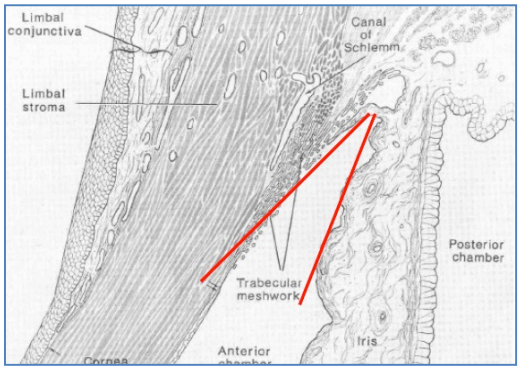
Visual Disorders

- **Visual Acuity:**
  - The ability to discriminate fine detail in a visual image.
  - Refers to the ability of one cone to be stimulated without its neighbour being stimulated
  - Disorders are typically due to imperfections in lens/eyeball shape.
  - Measured Using Snellen's Charts @ 6m distance (See lecture notes for full description)
    - 20/20 (20ft) (6m) = Normal Acuity
    - 20/15 = Better than Normal Acuity
    - 20/60 = Less than Normal Acuity



- **Glaucoma:**
  - A group of diseases characterised by raised intraocular pressure due to an imbalance between Aqueous Humour Production & Drainage (via Canal of Schlemm)
  - IOP produces ocular tissue damage
  - One of the leading causes of blindness
  - **3 Categories:**
    - **Angle-closure**
      - Aqueous humour produced by the ciliary body normally is emptied through the canal of schlemm.
      - Angle-Closure is an imbalance between production & drainage → ↑IOP
      - "Angle" = the angle between the inside of the cornea & the iris.
      - "Closure" = the angle is too small → blocks off the canal of schlemm.





    - **Open angle**
      - The 'angle' is fine.
      - But the part of the canal of schlemm is blocked → obstruction to drainage → ↑IOP
    - **Congenital/juvenile**
      - Hereditary
      - Infections can do it too.
  - IOP → pressure on nerve fibres → axonal necrosis
    - → pressure on the blood vessels → ↓Blood flow

- **Diabetic Retinopathy:**
  - Change in basement membranes of the retinal capillaries:
    - Microaneurysms
    - Microvascular obstruction
    - Non-perfusion of capillaries
    - Narrowing of arterial walls
    - Increase in Retinal Vein Calibre
- **Cataracts:**
  - Opacity in the crystalline lens
  - Causes are multifactorial:
    - Metabolic disease (eg. Diabetes)
    - UV Light
    - Smoking
    - Ocular diseases (eg. Glaucoma)
    - Skin diseases (eg. Dermatitis)
    - Drug induced (Eg. Corticosteroids)
    - Ageing (Idiopathic – unknown cause)
  - Prevention is important –
    - Improving nutrition
    - Reducing diarrhoea
    - Wearing sunglasses with UV filters.

Common hearing deficiencies:

- **Ageing:**
  - Progressive loss of hearing receptors
- **Acute Damage:**
  - Hair cells can be destroyed by a single explosive sound or continuous high-intensity sound → tears at the cilia
- **Drugs:**
  - Some are ototoxic (damage the hair cells)
- **Tinnitus:**
  - Ringing in the ear in the absence of auditory stimulus
  - Symptom of nerve degeneration/inflammation of middle/inner ear.
  - Can be caused by drugs. (Damage can be permanent)
    - Some antibiotics (Streptomycin, neomycin)
    - Loop diuretics (transient)
    - Salycilates
- **Otitis Media:**
  - Inflammation of middle ear lining
  - Is a common result of throat infections in infants & children (due to short Eustachian tube).
  - Can be bacterial viral or bacterial
  - Eardrum becomes inflamed and bulges – can perforate
  - When large amounts of fluid - pus accumulate behind the eardrum, grommets may be inserted.
- **Vertigo:**
  - Hallucinatory sensation of movement (Referred to dizziness)
  - Labyrinthitis or vestibular neuronitis (subsequent to viral/bacterial infection/metabolic disturbance – eg. hypoglycaemia)
  - Elderly patients – due to reduced blood supply to the labyrinth.
- **Meniere's Syndrome:**
  - Labyrinthine disorder – affects both semicircular canals & cochlea:
    - Repeated attacks of vertigo, nausea & vomiting
    - Tinnitus is common & hearing is impaired
- **Positional Vertigo:**
  - May often follow trauma
  - May follow drug overdose
  - Anxiety & depression may contribute (psychogenic)
- **Motion Sickness:**
  - Mismatch between visual & vestibular information.

NEUROLOGICAL Pathology:
PARKINSON'S DISEASE

PARKINSON'S DISEASE ("Shaking Palsy")

- **Aetiologies:**
  - **Parkinsonism "Shaking Palsy" = The Clinical Syndrome**
    - (Drugs/Toxins/Post Encephalitis)
  - **Parkinson's Disease = Primary Atrophy of Substantia Nigra (Dopaminergic System)**
    - (Idiopathic)
- **Pathogenesis:**
  - **Loss of Substantia Nigra (Dopamine makers) Neurons → Dopamine Deficiency in the Basal Ganglia → Basal Ganglia Dysfunction.**
    - Dopamine is required by the basal ganglia to coordinate complex movements, therefore, a loss of the basal ganglia's function → symptoms of Parkinson's.
  - **More Specifically**:
    - → Supplementary Motor Area isn't activated to Fine-Tune Movement.
- **Morphology:**
  - **Macro:**
    - Loss of Pigment Neurons (Melanin) in the Striatum

- **Clinical Features:**
  - **Onset:** In second half of life (mean age of onset = 55yrs)
  - **Parkinson's Triad:**
    - **1. *Resting* Tremor** (May be a 'Pill-Rolling' tremor)
    - **2. Rigidity** (Hypertonia → ↑Resistance to Passive Joint Movements)
      - May be "Lead-Pipe Rigidity" (Constant) or "Cog-Wheel Rigidity" (Fluctuating)
    - **3. Brady/Akinesia** (Slowness/Inability to Initiate/Execute Movement)
  - **Other Symptoms:**
    - +Diminished Facial Expressions
    - +Stooped Posture
    - +Shuffling/Hurried Gait
    - +Declined intellectual function
    - +Depression
    - + Inability to pick up small objects, cups, do up buttons, write in small font etc.




→


- **Treatment:**
  - **Aim:** To ↑ Dopamine Levels in the Brain, or to mimic the effect of Dopamine.
  - **Oral *Levodopa*:** (L-Dopa can cross the bbb → Converted to Dopamine in the Brain)
  - ***Dopamine Agonist*:** Drugs that mimic Dopamine, binding to Dopamine receptors.
  - **Side effects:**
    - By ↑Dopamine in the Basal Ganglia, Dopamine is ↑Globally → Side Effects
    - "On Off Phenomenon" – Symptomatic Relief is Random & Fluctuating
      Over time, Levodopa's Efficacy Decreases, But Side Effects Increase.

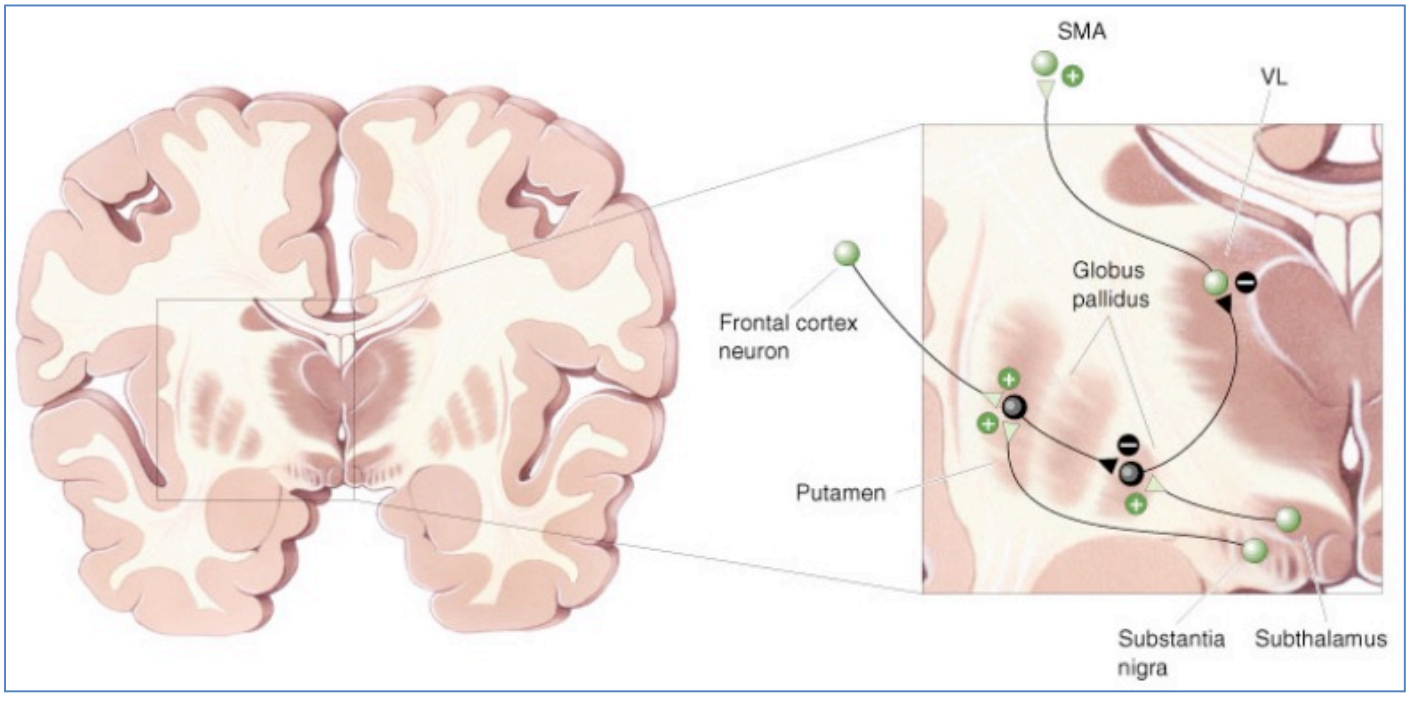
Neuroscience Notes
Parkinson's Disease ("Shaking Palsy")

What is it?

- **Onset:**
  - Insidious (Menacing/Unstoppable)
  - In second half of life (mean age of onset = 55yrs)
  - Progression is variable.
- **Characterised by:**
  - Slowly progressive akinesia
  - Rigidity (stiffness)
  - Postural abnormality (Leaning forward, stiff, difficult to move, weight loss – difficult to swallow without aspirating)
  - Tremor
- **2nd most common neuro-degenerate disease after Alzheimer's**
- **Prevalence:**
  - 1/1000 non-elderly
  - 1/200 in elderly

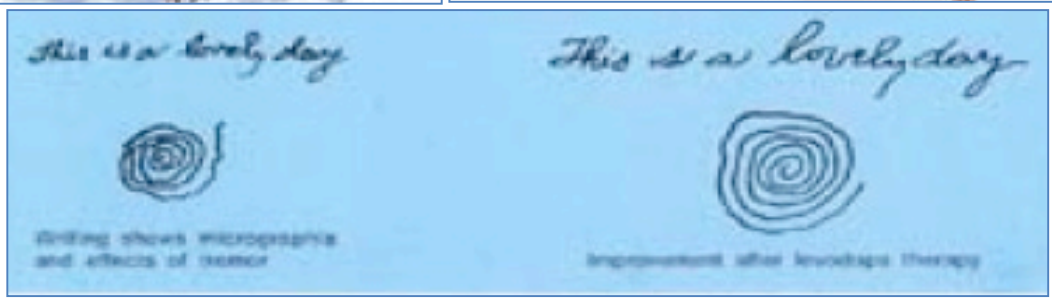
Biochemistry – Basal Ganglia Dysfunction due to:

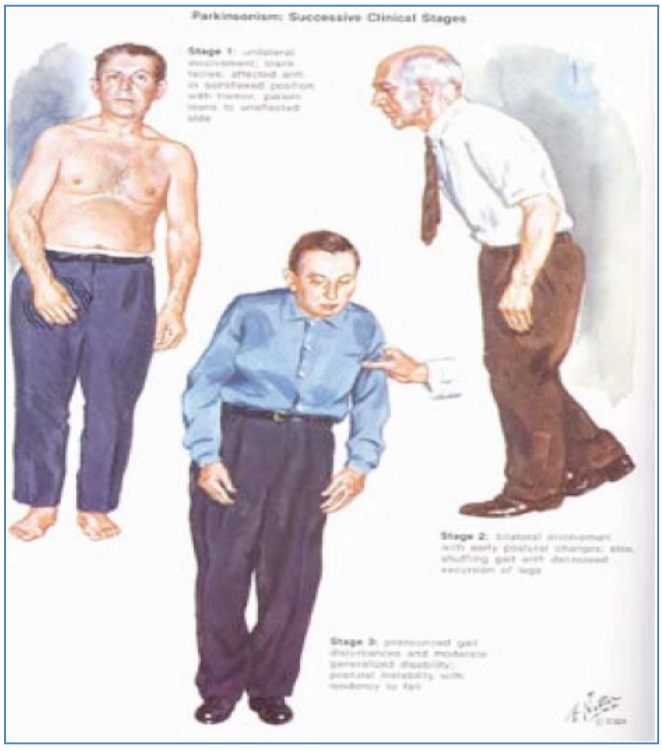
- **Loss of Substantia Nigra (Dopamine makers) Neurons → Dopamine Deficiency in the Basal Ganglia.**
  - These neurons project to the striatum (Caudate & Putamen) – Part of the Basal Nuclei – Normally involved in coordinating movements.
  - 50-60% loss of Nigral neurons are required for symptoms.
  - Dopamine is required by the basal ganglia to coordinate complex movements, therefore, a loss of the basal ganglia's function → symptoms of Parkinson's.
- **Unknown Aetiology**
- **Secondary Causes** – eg. Illicit drug
- **More Specifically**:
  - Without input from the Substantia Nigra, there's no activation of Inhibitory Neurons of the Putamen, meaning there's No Inhibition of Inhibitory Neurons of the Globus Pallidus, Meaning Inhibitory Neurons of the Globus Pallidus are unopposed in inhibiting Neurons of the VL-Thalamus that usually activate the SMA (Supplementary Motor Area).
  - → Supplementary Motor Area isn't activated to Fine-Tune Movement.
- **NB: Loss of Dopamine release in Striatum creates a NT Imbalance that favours ACh :. Anticholinergic Drugs are used to treat Parkinson's Disease.**



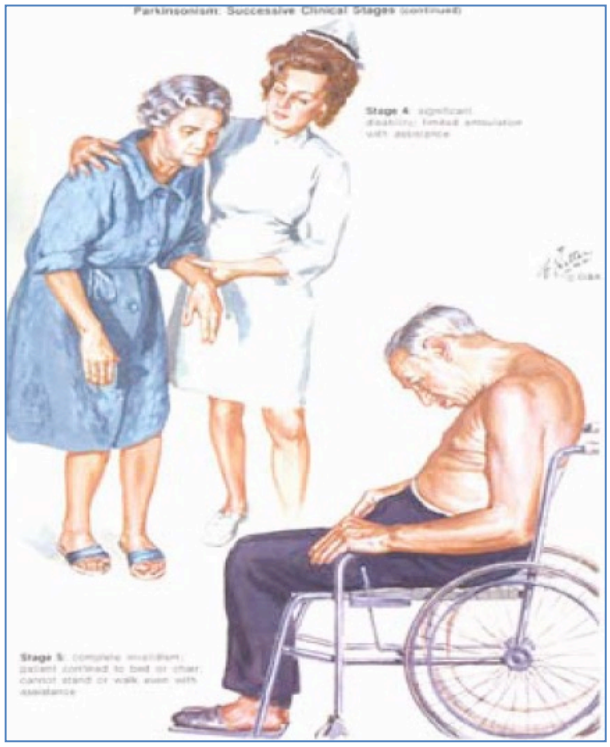
Symptoms:

- **Most common presenting feature = Tremor:**
  - Usually unilaterally
  - Present at rest
  - Increased by emotion & stress
  - 'Pill rolling' tremor (with fingers)
- **Rigidity:**
  - Stiff muscles
  - Cogwheel phenomenon (ratchet-like feeling during passive pronation)
- **Slowness of movement**
- **Postural Chances**
- **Decline in intellectual function**
- **Depression**
- → Inability to pick up small objects, cups, do up buttons, write in small font etc.





→

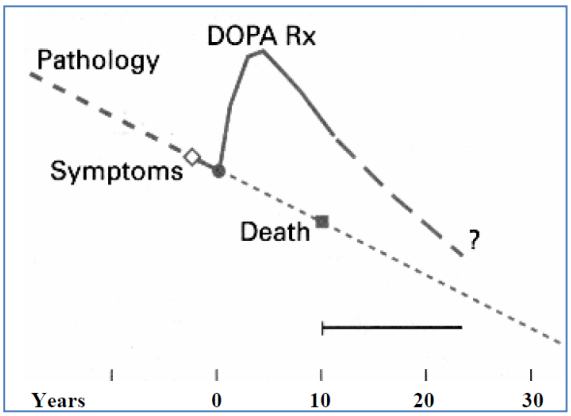


Treatment:

- **Aim:** to try to increase the level of Dopamine in the brain, or to mimic the effect of Dopamine, or to relieve competition of dopamine receptors by anticholinergics.
- **Oral Levodopa (Dopamine – NB: L-dopa can cross the bbb, but dopamine can't)**
    - Converted to dopamine in the brain by dopa-decarboxylase.
    - However, if taken orally, less than 5 % reaches the brain as most is converted to dopamine systemically. Therefore, it is usually administered with decarboxylase inhibitors to prevent conversion in systemic.
- **Dopamine Agonist:**
    - Drugs that mimic Dopamine, binding to Dopamine receptors.

NB: Remember, The Dopamine Deficit is only in the Striatum. Other Dopamine pathways are Unaffected. Hence this poses a problem of side-effects with Dopamine supplementation & Dopamine Agonist drugs.

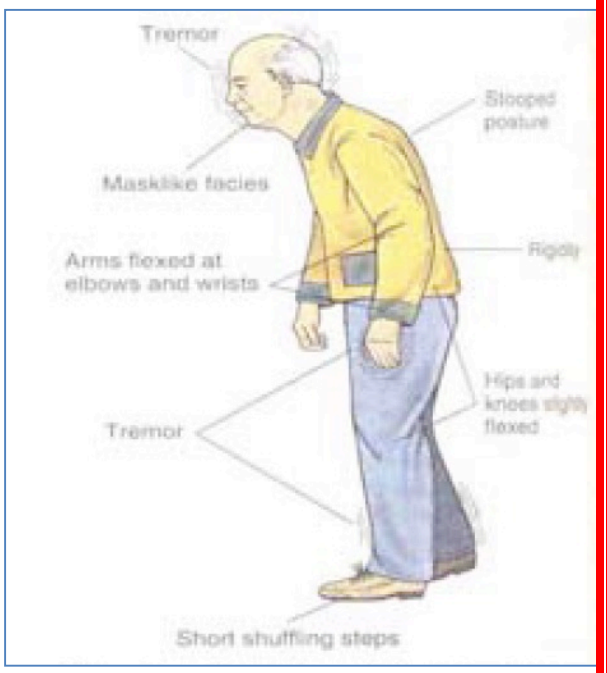
- **Anticholinergic drugs** – to prevent competition in the brain. **(Loss of Dopamine release in Striatum creates a NT Imbalance that favours ACh :. Anticholinergic Drugs are used to treat Parkinson's Disease)**
- **Surgery**
    - Sterotactic – using instruments to make a lesion to the brain resulting in decreased symptoms.
    - Today – rather than making a physical lesion, an electrical probe is inserted into the brain → 'lesions' the brain → stimulates response.
    - However, the aim is to 1. Find the area of the brain you want to target, & 2. Find a way to get there safely while minimising the damage to the brain.
    - Benefits – Good control of tremor and on/off phenomenon – stimulator inhibits the sub-thalamic nuclei (can also be used in some severe OCD's and other psychiatric disorders)
    - Disadvantage – dangerous, and only beneficial for a small subgroup of parkinsons patients.
- **Physical Therapy**
- **Side effects:**
    - **On off phenomenon** – Symptoms range from either well controlled or poorly controlled at random times
    - Over time, Levodopa decreases in Efficacy & Side effects Increase.
    - Increased severity of symptoms after a while of DOPA administration
    - Therefore, treatment is delayed until symptoms are sufficient to impact on the person's life.



Other Facets of Parkinson's: By Speech pathologist

Psychosocial Impact:

- **Myths:**
  - Only old people get it. – wrong - +10% of diagnoses are in people under 40yrs.
  - They only get shaking – wrong – people have postural, balance, speech, swallowing, breathing problems.
  - Sufferers are unemotional and non-feeling – wrong – this is often due to inability to show facial expression
- **Personal Impact:**
  - Tremor
  - Stooped posture
  - Masklike face
  - Rigidity
  - Arms flexed at elbows & wrist
  - Bradykinesia
  - Postural/balance instability
  - Short shuffling steps
  - Other CNS symptoms:
    - Speech difficulties (Disarthria of speech muscles)
    - Swallowing difficulties (dysphagia)
    - Masklike facial expression
    - Constipation/urinary problems
    - Sweating
    - Pain & sensory disturbances.
  - Behavioural/Psychological:
    - Sleep disturbances
    - Fatigue (Fatigue very quickly)
    - Mood/depression
    - Anxiety & obsessiveness
    - Thought & memory disturbances (dementia in the end-stage)
    - Psychosis.



- **Impact on Carers:**
  - Depression
  - Financial stress
  - Strained relationships
  - Frustration
  - Anger
  - Change in roles
  - Changed plans for the future
- **Impact on families:**
  - Helplessness
  - Financial stress
  - Change in roles
  - Frustration
  - Resentment
- **Impact on community:**
  - Loss of social capital
  - Increased healthcare costs
  - Increased social benefits
  - Loss of productivity
  - Ageing population.

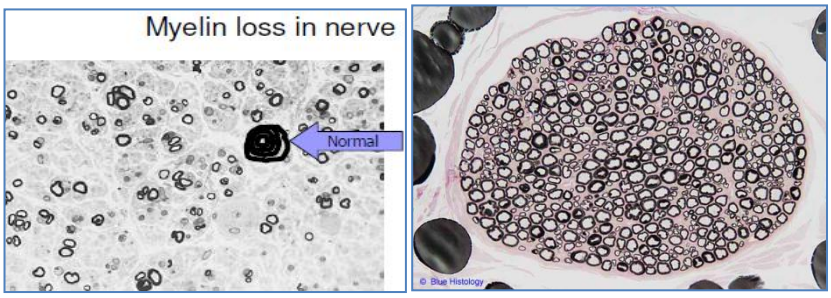
Role of Health Professionals:

- **Role of the GP:**
  - Coordinate lifetime, holistic care
  - Plan of management
  - Give patient an idea of what the future may hold
  - Aim of management:
    - Encourage healthy lifestyle
    - Help the family & patient
    - Manage symptoms as they arise
- **Allied Health:**
  - Specialist (Neurologist)
  - Geriatrician
  - Physiotherapy
  - Occupational therapy
  - Speech path
  - Social work
  - Psychologist
- **Other management issues:**
  - Conselling
  - Continuing to work
  - Continuing to drive
  - Help for carers.

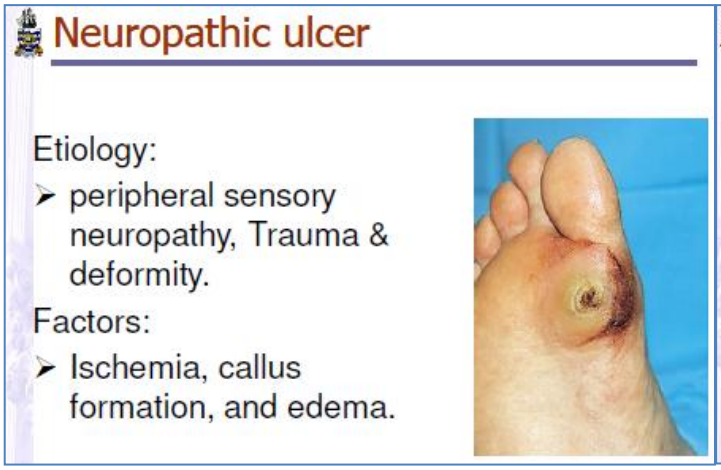
NEUROLOGICAL Pathology:
PERIPHERAL NEUROPATHIES

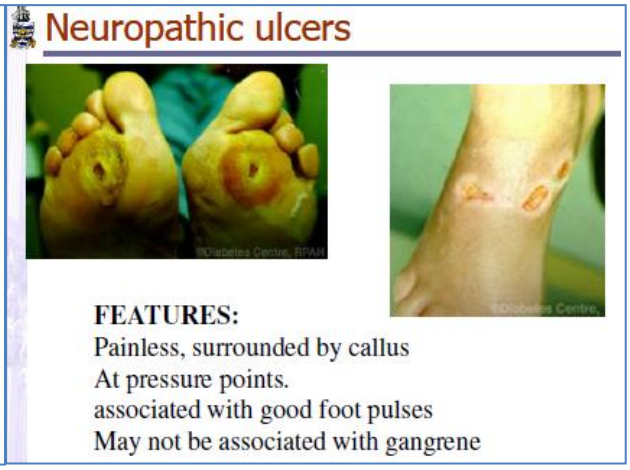
- **Diabetic Neuropathy:**
  - **Aetiology:**
    - **Chronic Hyperglycaemia →**
      - Demyelination
      - & Arteriolosclerosis
  - **Pathology:**
    - 1. Hyperglycaemia → Focal Osmotic Demyelination of Axons → Exposure of axon →
      - Affects SENSORY nerves first – because they are the ones covered with myelin. (Remember Motor neurons aren't covered in myelin)
    - 2. Hyperglycaemia → Arteriolosclerosis in Vasa-Nervorum (Nerve Blood Supply) →Ischaemic Neuropathy
  - **Morphology:**
    - Arteriolosclerosis (Amyloid Thickening of the Basement Membrane of Capillaries)
    - Myelin Loss in Nerve – Seen on *Myelin Stain* (Myelin Stains Black)

Diabetic Neuropathy **Normal**

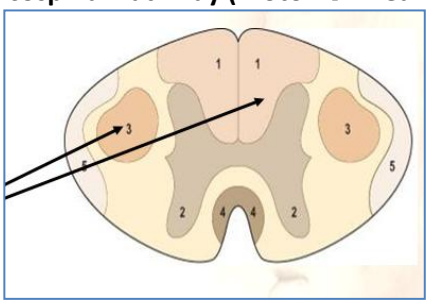


  - **Clinical Features:**
    - Distal, Symmetric Sensory Neuropathy (Paraesthesia, Loss of Sensation)
    - Autonomic Neuropathy
      - **Progression:**
        - **1. Sensory Neuropathy**
          - "Glove & Stocking" Paraesthesia/Pain/Night-Time Pain
          - Loss of Proprioception
          - → Risk of Ulcers due to Chronic Painless Injuries.
          - NB: Bilateral, Symmetrical
        - **2. Motor Neuropathy**
          - Muscle Atrophy
          - 3rd Nerve Palsy (Eye is Down & Out)
        - **3. Autonomic Neuropathy**
          - Postural Hypotension
          - ↓GI Motility (Constipation/Diarrhoea)
          - Urine Retention/Urgency/Incontinence
          - Erectile Dysfunction





- **B12 Deficiency:**
  - **Aetiology:**
    - B12 Deficiency – Due to:
      - ↓Dietary Intake (↓Eggs, meat, milk, shellfish – Ie. Vegetarian/Vegan)
      - Malabsorption (Eg. Pernicious Anaemia/GI Surgery/Coeliac/Crohn's)
      - ↑Loss
  - **Pathogenesis:**
    - B12 is necessary for Maintenance of the CNS
    - :. B12 Deficiency → Demyelination, Axonal Oedema, Neuronal Sclerosis
    - **Particularly Affects Spinal Cord:**
      - **(1) Dorsal Column ML Pathway (Sensory → Paraesthesia)**
        - (↓Vibration, Proprioception, & [fine touch])
      - **(3) Corticospinal Pathway (Motor → Weakness)**



  - **Clinical Features:**
    - Weakness and Paraesthesiae in the Lower Limbs
    - Loss of Balance
    - Megaloblastic Anaemia
  - **Treatment:**
    - Supplemental B12

NEUROLOGICAL Pathology:
PRION DISEASES

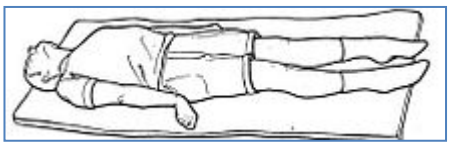
- **Eg. Creutzfeldt Jackob Disease, Gertsmann-Straussler Syndrome, Fatal Familial Insomnia, Kuru Kuru:**
  - **Aetiology:**
    - Prion Infection of the Brain
    - **"Prions" =** Proteinaceous, Infectious + 'on'
      - = **Abnormally folded Host-Proteins** that accumulate in the brain
      - NO DNA or RNA!! (Important for Exams)
    - ***Prion* Proteins (PrP):**
      - **Normal Form = PrP^{c} (Cellular)**
        - Normal α-Helix form. (Functional & Denaturable)
        - Found throughout the body (Also in mammals).
      - **Abnormal Form = PrP^{sc} (Scrapie)**
        - Abnormal β-Sheet form. (Non-Functional & Non-Denaturable)
        - Accumulates in plaques in the brain → Tissue Damage & Cell Death.
        - *EXTREMELY STABLE* – Resists denaturation :. Difficult disposal.
  - **Pathogenesis:**
    - Prions cause Neurodegenerative Disease by aggregating Extra-Cellularly in the CNS → form amyloid plaques → Plaques are Internalised → Vacuole formation in Neurons → Spongy Architecture.
    - **Propagation: Conversion of Normal Proteins (α-helix → β-sheet):**
      - Prions propagate by transmitting a ***Mis-Folded Protein State,*** not replicating.
      - Ie. They convert *Pre-Existing, Normal* forms of the protein to the *Abnormal Form*.
  - **Morphology:**
    - **Macro:**
      - Empty cystic lesions in the brain → Spongiform Encephalopathy
    - **Micro:**
      - Neuronal Vacuolation & Plaque Formation
  - **Clinical Features:**
    - Initially Subtle Memory & Behavioural Changes → Then Rapidly Progressive Dementia
    - Convulsions (Myoclonus)
    - Dementia
    - Ataxia, Dysarthria, Dysphagia, Nystagmus
    - Behavioural/Personality Changes
  - **Prognosis:**
    - **All** known Prion Diseases **affect the Brain** and are **currently Untreatable** & **Universally Fatal**
    - **7mths life expectancy**

NEUROLOGICAL Pathology:
RAISED INTRACRANIAL PRESSURE

Intracranial Pressure:

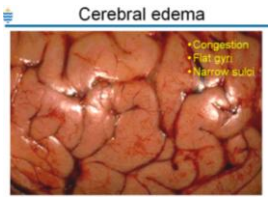
- **Normal ICP:**
  - 10mmHg
- **↑ICP leads to→:**
  - **↓Cerebral blood flow** (Due to reduced perfusion pressure)
    - (Perfusion Pressure = Sys.BP – Intracranial Pressure)
    - (NB: Perfusion only occurs when Perfusion Pressure is *Positive*)
  - ***ICP may* = Arterial Pressure?**
    - If Arterial Pressure = ICP…then Perfusion Pressure = 0.
    - Nil Perfusion
- **Signs of Raised Intracranial Pressure:**
  - ***Cushings Response/Reflex (Cushing's Triad):***
    - *Hypertension*
    - *Bradycardia*
    - *Irregular Breathing*
- **Treating Raised ICP:**
  - **Osmotic Diuretics (Eg. *Mannitol*)**
  - ***Hyperventilation* → Hypocapnia → Vasoconstriction of Cerebral Vessels**
  - **Continuous *CSF Drainage/Surgical CSF Shunt***

- **NB: DON'T do a Lumbar Puncture if Intracranial Pressure is High:**
  - **If ICP is high, and you drain CSF → Can cause "Coning":**
    - Aka. "Cerebral Herniation" (Aka: Cistern Obliteration)
    - → Brain can herniated through the foramen magnum → Puts extreme pressure on parts of the brain and thereby cuts off their blood supply.
    - **Is often Fatal**
  - **Signs:**
    - **ALOC** (GCS 3-5)
    - **Vomiting** (Compression of Emetic Centre in Medulla)
    - **Can cause 3rd Nerve (Oculomotor) Palsy:**
      - **Ptosis** = Unable to Open Eyelid (Levator Palpebrae Superioris)
      - **'Blown Pupils' (Dilated) & Unresponsive to Light.**
      - Eye faces ***Downwards & Outwards***
    - **'Decerebrate' Posturing** (Abnormal Extension to Pain)



CEREBRAL OEDEMA:

- **Cerebral Oedema =** Fluid Accumulation in the Intracellular and/or Extracellular Spaces of the Brain
- **Aetiologies & Pathogeneses – 4 Types:**
  - **Vasogenic -** ↑Cap.Permeability – (Ie. Trauma, Ischaemia/Infarction, Infection/Inflammation)
  - **Cytotoxic –** Na & H_2O Retention in Injured Neurons– (Eg. From Hypoxia or Neurotoxin)
  - **Osmotic –** CSF Osmolality > Plasma Osmolality – (Eg. Overhydration, Hyponatraemia)
  - **Interstitial –** Obstructive Hydrocephalus
- **Clinical Features:**
  - **(Features of Aetiology –** Fever if Meningitis, Concussion if Trauma, Stroke if Infarction, etc**)**
  - **Features of ↑ICP:**
    - **Cushing's Triad** - (Hypertension, Bradycardia, Cheyne-Stokes Respiration)
    - **Headache**
    - **ALOC**
    - **Vomiting**
    - **Pupil Dilation**
- **Management:**
  - **Osmotic Diuretics (Eg. *Mannitol*)**
  - ***Hyperventilation*** **→ Hypocapnia → Vasoconstriction of Cerebral Vessels**
  - **Continuous *CSF Drainage/Surgical CSF Shunt***



Chronic ↑Intracranial Pressure – Due to Space-Occupying Lesions *(See Wk 3 for Cerebral Oedema & Herniation)*:

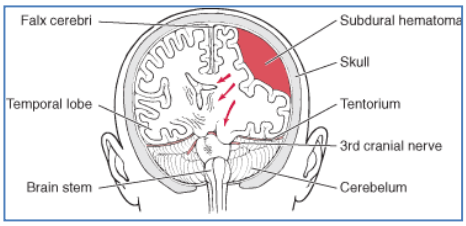
- **Aetiologies:**
  - ***Space-Occupying Tumours**
- **Clinical Features of Raised Intracranial Pressure:**
  - **Signs – (*Cushings Response/Reflex/Triad*):**
    - *1. Hypertension*
    - *2. Bradycardia*
    - *3. Cheyne-Stokes Respiration*
  - **Symptoms:**
    - *Headache; Drowsiness; Altered level of Consciousness (GCS 3-5)*
    - *Vomiting*
    - *Seizures*
- **Treating Raised ICP:**
  - **Elevate Head 30-40°**
  - **Hyperventilate** → ↓Hypercapnia → Vasoconstriction of Cerebral Vessels
  - **Neurosurgery (if Trauma → Haemorrhage)**
  - **Continuous CSF Drainage/Surgical CSF Shunt**
  - **Osmotic Diuretics** (Eg. Mannitol)→↑Plasma Osmolarity → Extracts Water from Brain Tissue.

BRAIN HERNIATIONS:

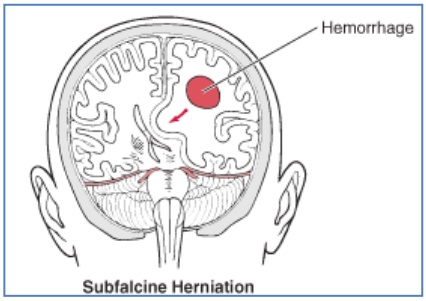
- **Aetiology – Anything that Causes ↑ICP:**
  - Eg. Cerebral Haemorrhage
  - Eg. Cerebral Oedema
  - Eg. Obstructive Hydrocephalus
  - Eg. Space-Occupying Lesions

- **1. "Cerebellar Tonsil Herniation"/"Coning":**
  - **Pathogenesis:**
    - **General ↑ICP** → Herniation of Cerebellar Tonsils through Foramen Magnum → Compresses the Brainstem → Brainstem Ischaemia → Cardio/Respiratory-Centre Dysfunction → (Death)
  - **Specific Signs/Symptoms:**
    - 'Decerebrate' Posturing (Abnormal Extension to Pain)

    - ALOC (GCS 3-5)
    - One/Both Pupils 'Blown' (Dilated) & Unresponsive to Light.
    - Vomiting (Compression of Emetic Centre in Medulla)
- **2. "Uncal Herniation":**
  - **Pathogenesis:**
    - **Unilateral Lesion** → Lateral Herniation of the 'Uncus' (Inferomedial Temporal Lobe) against the midbrain →Then, Inferior Uncal Herniation below the Tentorium Cerebelli.
  - **Specific Signs/Symptoms:**
    - **May compress the Occulomotor Nerve → 'Third Nerve Palsy' →**
      - **Ipsilateral Pupil Dilation** & Unresponsive to Light
      - **Ptosis** = Unable to Open Eyelid (Levator Palpebrae Superioris)
      - **Eye *Down & Out***
  - **NB: May Progress to Cerebellar Tonsil Herniation → Coning → Death**

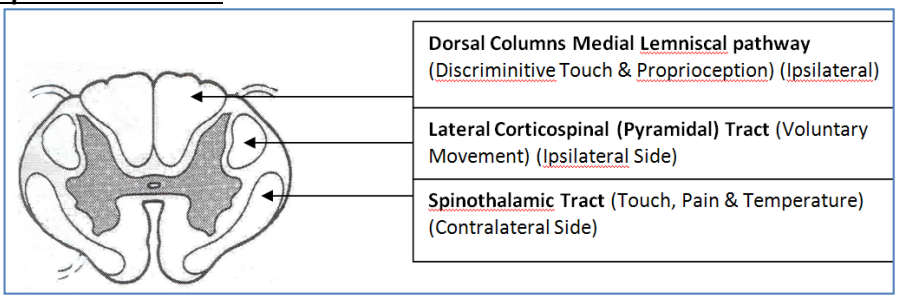


- **3. "Subfalcine Herniation":**
  - **Pathogenesis:**
    - **Frontal Lesion →** Posterio-Lateral Herniation of the Cingulate Gyrus (Medial Frontal Lobe) under the Rigid Falx Cerebri.
  - **Specific Signs/Symptoms:**
    - May compress the ACA → Stroke → Contralateral Para-Hemiplegia
    - Abulia (Frontal Dysexecutive Symptoms)



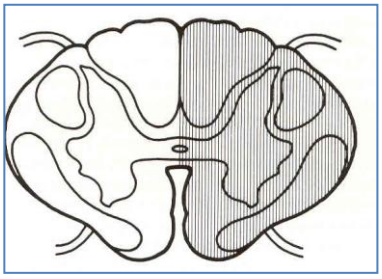
NEUROLOGICAL Pathology:
SPINAL CORD SYNDROMES

- **Revision of Spinal Cord Tracts:**

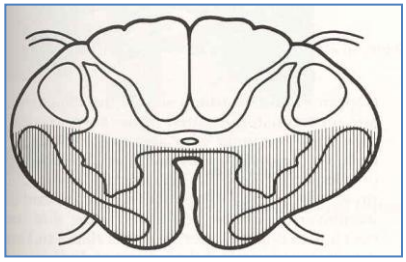


- **Changes in Motor Reflexes with Spinal Cord Injury:**
  - **Immediate Consequences:**
    - Reflexes are conserved since they aren't mediated by the brain.
    - (NB: Reflexes are only lost if the lesion is @ the level of that reflex)
  - **Consequences Over Time:**
    - Muscle movement diminishes over a period of time
    - Due to Progressive Muscle Atrophy (not Nerve Atrophy)

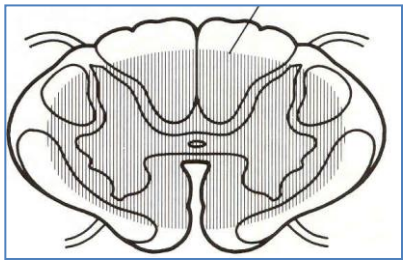
- **Different Spinal Cord Lesions (Pathways Affected & Clinical Consequences):**
  - **'Brown-Sequard' Syndrome:**
    - (seen if someone is stabbed in the back with a knife or shot with a handgun causing a hemi-transection of the spinal cord)
    - **Pathways Affected & Clinical Consequences:**
      - Dorsal Column Medial Lemniscal Pathway
        - Loss of Discriminative Touch & Proprioception
        - (Ipsilateral to & below the level of the lesion)
      - Spinothalamic Tract
        - Loss of somatosensation (Touch, Pain, Temperature)
        - (Contralateral to & below the level of the lesion)
      - Lateral Corticospinal:
        - Loss of voluntary movements
        - (Ipsilateral to the side of the lesion. Because it decussates in the pyramidal tracts)



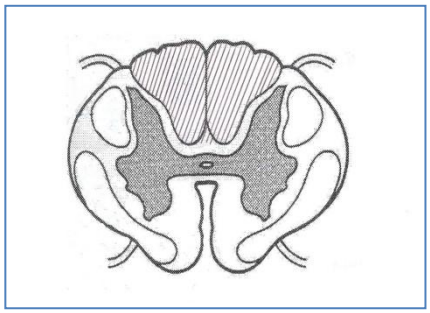
  - **Anterior Spinal Artery Syndrome:**
    - (Due to Lesion of the Anterior Spinal Artery. Eg. Diving injury)
    - **Pathways Affected & Clinical Consequences:**
      - Doesn't affect the Dorsal Column Medial Lemniscal pathway.
        - No loss of Discriminitive Touch & Proprioception
      - Doesn't Affect the Corticospinal Tract
        - Conserves Motor Function)
      - Affects Spinothalamic Tract
        - Loss of Somaosensation Contralateral to & below the level of the lesion.



- **Central Cord Syndrome:**
  - (Usually secondary to spinal trauma and, affects the centre of the spinal cord.)
  - **Pathways Affected & Clinical Consequences:**
    - Mainly Corticospinal Tracts
      - → Motor Impairment (Mostly in Upper Extremities)
      - (Why? Motor Fibres supplying Upper limbs tend to be more Central than those supplying the lower limbs)
    - Dorsal Column & Spinothalamic Tracts:
      - Variable sensory losses below the Lesion.



- **Dorsal Column Syndrome:**
  - (Very Unusual)
  - **Pathways Affected & Clinical Consequences:**
    - Dorsal Column Medial Lemniscal Tracts:
      - Ipsilateral Loss of Discriminitive Touch & Proprioception Below the Lesion
    - Doesn't Affect Spinothalamic Tract:
      - Somatosensation (Touch, Pain, Temperature) Unaffected.
    - Doesn't Affect Corticospinal Tract:
      - Motor Functions Conserved



NEUROLOGICAL Pathology:
STROKES

Strokes:

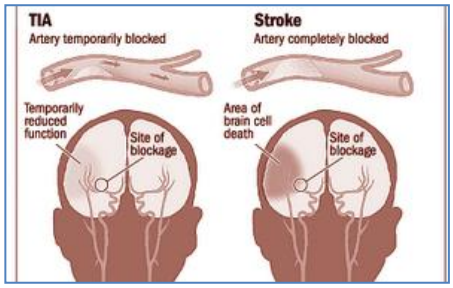
- **TIA vs. CVA vs. Stroke:**
  - **TIA = TRANSIENT ISCHAEMIC ATTACK ("Mini-Strokes") =** A brief stroke (<24hrs)(episode of neurologic dysfunction) due to a temporary focal cerebral ischemia NOT associated with cerebral infarction.
    - **Typically Thromboembolic**
    - **Clinical Course:**
      - **Temporary Ischaemia, Resolves within 24hrs**
  - **CVA = CEREBRO-VASCULAR ACCIDENT =** Any cerebro-vascular pathology that leads to lack of blood supply to the brain → Stroke >24hrs
    - **Clinical Course:**
      - **Evolving CVA = Increasing Ischaemia, Longer than 24hrs, Typically Thrombosis**
      - **Completed CVA= Complete Ischaemia, No Change, Typically Embolism**
  - **Stroke =** "Rapid Loss of Brain Function(s) due to Disturbance in the Blood Supply to the Brain."
    - (Stroke is the clinical syndrome of a CVA)

- **Common Causes of Stroke:**
  - **1. Ischaemic Strokes – (Focal, Thrombo/Embolic):**
    - **Atherosclerosis –**
      - **→ Rupture → *Thrombosis* → Cerebral Ischaemia → Stroke.**
      - **→ Or Athero-Emboli** in a Cerebral Artery **→ Cerebral ischaemia → Stroke**
    - **Heart Disease –**
      - **Eg. Atrial Fibrillation** →Thrombo-Emboli **→ Cerebral Ischaemia → Stroke**
  - **2. Haemorrhagic Strokes – (Global, ↑ICP → Hypoperfusion):**
    - **Hypertension –**
      - **Blood vessel bursts** under pressure → Bleeding → ↑ICP → Compresses other Cerebral Arteries → **↓Blood Flow → Cerebral Ischaemia → Stroke**.
    - **Congenital Vascular Conditions –**
      - **Eg. Congenital Berry Aneurysms** → Rupture → **Subarachnoid Haemorrhage** (Arterial) → ↑ICP → Compresses other Cerebral Arteries → **↓Blood Flow → Cerebral Ischaemia → Stroke**.
      - **Eg. Congenital AV Malformations** → Rupture → **Intracerebral Haemorrhage** (Arterial) → ↑ICP → Compresses other Cerebral Arteries → **↓Blood Flow → Cerebral Ischaemia → Stroke**.
    - **Trauma –**
      - **Eg. Skull Fracture → Extradural Haemorrhage** (Arterial)
      - **Eg. Low-Force Trauma → Subdural Haemorrhage** (Venous)

CAUSES OF ALOC – VASCULAR:

TRANSIENT ISCHAEMIC ATTACK ("Mini-Strokes"):

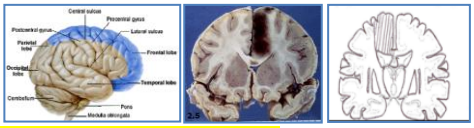
- **Aetiology – Typically Transient Embolism:**
  - Thrombo-Embolism from Carotids
  - Cardioembolism from a mural thrombus (Post-MI, AF, Valve disease, Prosthetic Valve)
- **Pathogenesis:**
  - Thrombo-Emboli → Lodged in Cerebral Artery → **Ischaemia** → Temporary Neurological Deficit (TIA) → When Blood Flow Returns, Neurons are still Functional → Recovery
    - NB: Prolonged Ischaemia → **Infarction** → Stroke.
- **Morphology:**
  - No Physical Changes – Only Metabolic.
- **Clinical Features:**
  - **Signs/Symptoms:**
    - **Mimic those of stroke (But <24hrs)**
      - Cerebral hemisphere → Contralateral Hemiplegia
      - Brainstem → Quadriplegia, Vision Disturbances etc
      - Lacunar (Basal Ganglia) → Pure Motor, Pure Sensory etc
    - **Emboli in Retinal Artery → *Amaurosis Fugax* (Unilateral Descending Curtain of Blindness)**
  - **DDX:**
    - Hypoglycemia
    - Migraine Aura
    - Focal Epilepsy
    - Hyperventilation
    - Retinal Bleeds
- **Investigations:**
  - **Physical Examination:**
    - Causes? – Carotid Bruit, HT, Murmur, ECG (AF?), Fundoscopy
  - **Lab:**
    - FBC, ESR, U&Es, Glucose, Lipids,
  - **Imaging:**
    - **CT Brain – (Rule out Haemorrhagic – *Since Rx Contradict Each Other)***
    - **Carotid Doppler +/- Angiography**
- **Management:**
  - **Control CV risk factors**
    - Lower lipids – (***Simvastatin*** / ***Atorvastatin***)
    - Stop smoking – (***Champix***)
    - Lower BP – (***Perindopril***/***Candesartan*** +/- ***Atenolol***)
    - Antiplatelet – (***Aspirin***)
  - **Anticoagulation – (*Warfarin* with *Heparin* Cover)**
  - ***+/- Carotid Endarterectomy***



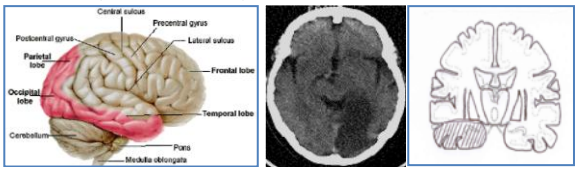
80% ISCHAEMIC STROKE (Thrombo/Embolic → Infarction):

- **Aetiologies:**
  - **50% Thrombotic Infarct (Sudden Onset *At Rest*)**
    - Eg. Rupture of Atherosclerotic Plaque
    - Eg. Hypercoagulable Syndromes (Eg. Oral Contraceptives, Clotting Disorders)
  - **30% Embolic Infarct (Sudden Onset *Following Exercise*)**
    - Eg. Embolus from Atherosclerosis (eg. From internal carotid)
    - Eg. AF → Blood Stasis in Atria → Thrombus Formation
    - Eg. Paradoxical Embolism (Embolus from DVT → Through ASD → CVA)
- **Pathogenesis:**
  - Thrombosis/Embolism → Focal Ischaemia → Infarction → Focal Neurology
- **Locations:**
  - **MCA (Most Common)**
  - ACA (Common)
  - PCA (Rare - 4% clinically)
- **Morphology:**
  - **Early:** Oedema (Narrow Sulci, Flattened Gyri)
  - **NB:** Thrombolytic Therapy can → Pin-point Haemorrhages around Capillaries
  - **1wk:** Liquefactive Necrosis & Cavitation
- **Clinical Features – (Depend on *which arteries/functional areas* are affected/occluded):**
  - **Middle CA Stroke (#1 Most Common):**
    - **Contralateral *Whole Body* Hemiplegia (Primary Motor Cortex) +/- Dysarthria**
    - **Generalised Reduced Sensation (Primary Somatosensory Cortex)**
    - **Homonymous Hemianopia (Or sometimes Homonymous Quadrantonopia)**
    - **Expressive Aphasia If on LEFT (Dominant) Side – *Left*. (Broca's Area)**

  - **Anterior CA Stroke (#2 Most Common)**
    - **Contralateral *Lower-Limb* Hemiplegia (Primary Motor Cortex)**
    - ***Lower-Limb* Numbness (Primary Somatosensory Cortex)**
    - **Dysexecutive Syndrome ("Abulia" = Slowness/Prolonged Delays to Perform Acts)**
    - **Cognitive Impairment (Frontal)**
    - **Flat Affect (Limbic System)**



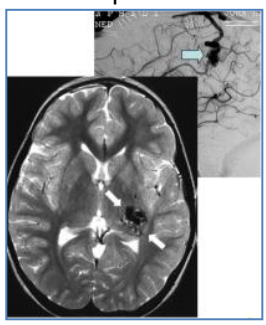
  - **Posterior CA Stroke (#3 - Rare - 4% clinically)**
    - **Primarily Visual Defects**
    - **Memory Deficits (Short Term)**



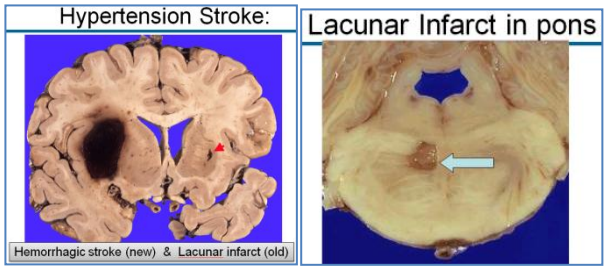
- **Investigations:**
  - **Clinical Examination**
  - **FCB, Coags, Lipids**
  - **CT Brain – (Rule out Haemorrhagic)**
- **Treatment:**
  - **Supportive – (**O2, Fluids)
  - **Rapid Reperfusion – (**Thrombolysis [***Tissue Plasminogen Activator***] +/- ***Thrombectomy***)
  - **Anticoagulation – (*Clopidogrel*/*Aspirin* + *Warfarin with Heparin Cover*)**
  - **Stroke Rehabilitation – (**Speech Therapy, OT, Physio**)**
- **Prognosis/Complications:**
  - 40% Mortality; 75% Mobidity (Eg. Hemiplegia, Aphasia, Dementia, Epilepsy, Mental Dysfunction)

20% HAEMORRHAGIC STROKES (Bleeds):

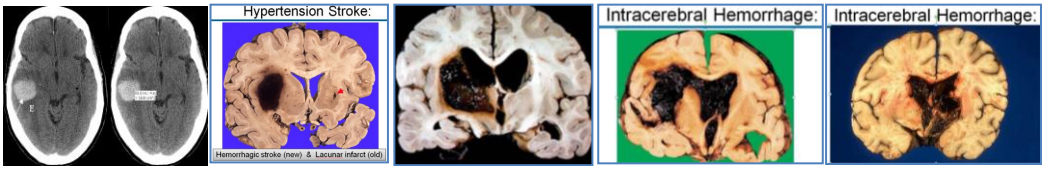
- **INTRACEREBRAL HAEMORRHAGE (ICH) ("Haemorrhagic Stroke"/CVA):**
  - **Aetiologies:**
    - **Head Trauma.**
    - **Congenital Arteriovenous Malformations**
      - = Tufts of Blood Vessels where they shouldn't be
      - Highly Susceptible to Rupture → Intracerebral Haemorrhage & Cystic Change



    - **Hypertension**
      - Hypertension → Vessels Burst → Bleeding → ↑ICP → Compresses other Cerebral Arteries → **↓Blood Flow → Cerebral Ischaemia → Stroke**.
      - **Morphology:**
        - **Slit Haemorrhages** – Microhaemorrhages heal as slits with pigment
        - **Lacunar Infarcts in the Brainstem** – Small cavity-like areas of pale infarcts



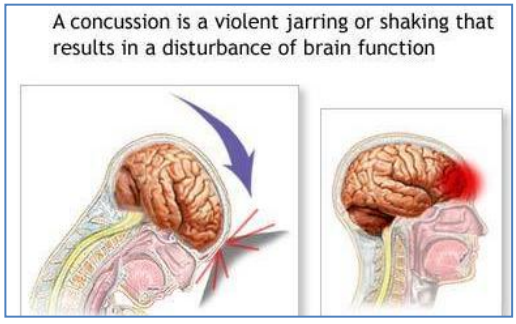
  - **Clinical Features:**
    - **Sudden onset Headache**/Vomiting/Meningism
    - **Anisocoria** (Uneven Pupils), Nystagmus
    - **Signs of ↑ICP** (Hypertension, Bradycardia & Cheyne-Stokes Respiration)
    - **+ Potentially Fatal Herniation Syndromes** (Cerebellar Tonsillar/Uncal/Subfalcine).
    - **ALOC**
    - **+Focal Neurological Deficits:**
  - **Investigations:**
    - **Head CT/MRI – (**Bleeding within the Brain or Ventricles**)**
    - **Transcranial Doppler**
  - **Management:**
    - **Supportive – (**Intubation, IV Fluids)
    - **Medical:**
      - **Antihypertensives – (*B-Blocker*, *ACEi/ARB*, *Ca-Ch-Blocker*)**
      - ***Coagulation Factor VIIa***
      - ***Mannitol* (Osmotic Diuretic)** → ↓ICP
      - ***Paracetamol*** → ↓Hyperthermia
      - ***FFP, Vit.K, Platelets*** (if Coagulopathy)
      - ***Corticosteroids*** → ↓Swelling
    - **Surgical (If Haematoma >3cm)**
  - **Prognosis:**
    - >40% Mortality
    - 75% of Survivors are Disabled



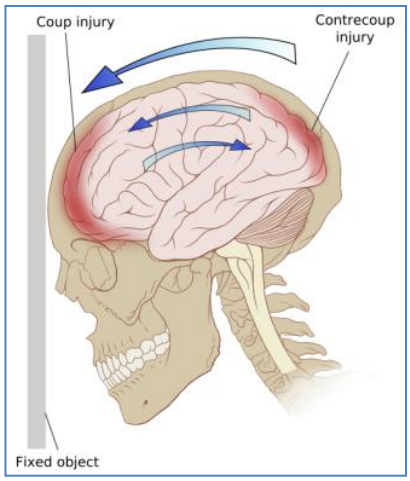
NEUROLOGICAL Pathology:
TRAUMATIC BRAIN INJURIES

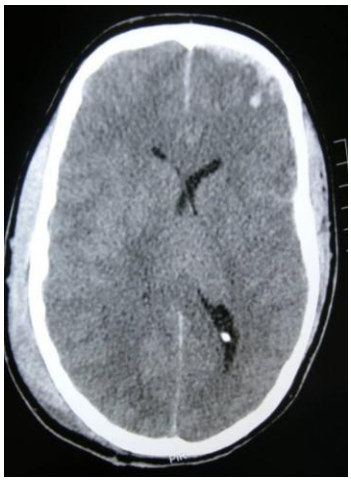
Focal Primary Injury:

- **CONCUSSION:**
  - **Aetiology:**
    - Moderate-Force Blunt Trauma to Head
  - **Pathogenesis:**
    - Brain Trauma → Metabolic/Ionic/Neurotransmitter Disruption → Impaired Neurotransmission
  - **Morphology:**
    - **Macro:**
      - No structural damage
      - No visible Bleed
  - **Clinical Features:**
    - **Course =** Acute, Temporary Unconsciousness (Secs-Mins)→ Normal Arousal
    - **Symptoms:**
      - Temporary Loss of function
      - Likely to fully recover (unless secondary injury)
      - Anterograde & Retrograde Amnesia (↓Memory before & after Injury)
      - Headache
    - **"Post Concussion Syndrome" <3wks Post injury**
      - Memory Problems
      - Dizziness/Loss of Balance
      - Visual Disturbances/Photophobia
      - Tiredness
      - Sickness
      - Depression/Irritability/Restlessness
      - Rarely, Post-Traumatic Seizures
  - **Investigations:**
    - History (Mechanism & Duration of LOC)
    - Concussion Grading Systems:
      - Grade I: Confusion, No LOC
      - Grade II: Confusion, Amnesia, No LOC
      - Grade III: Any LOC
    - Physical Examination
    - Neurological Examination
      - Including GCS
    - If GCS is <14 → CT
  - **Management:**
    - Usually Benign :. Just Supportive Treatment (Analgesics, Rest, Sleep, Avoid Drugs/Alcohol)
    - Avoid Further Head Trauma to Prevent *"Second-Impact Syndrome"* (Dangerous cerebral oedema following second impact. Occurs days-weeks after an initial concussion)

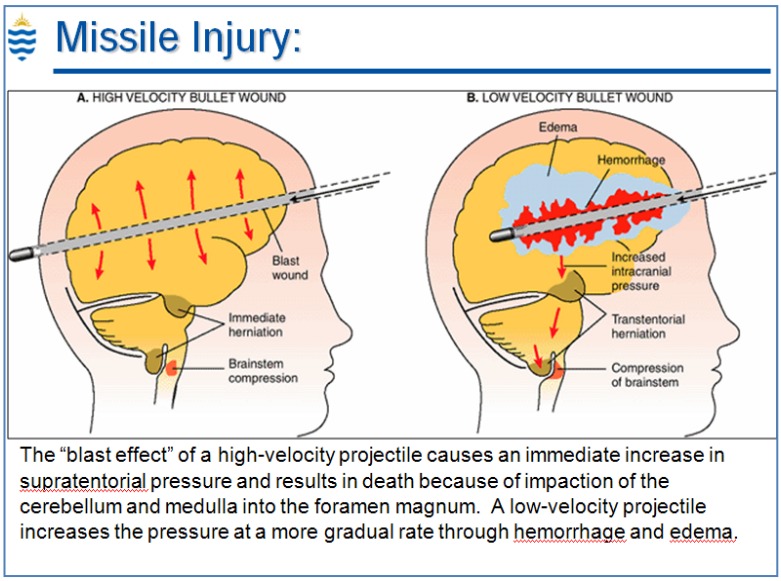


- **CONTUSION:**
  - **Aetiology:**
    - Higher-Force Blunt Trauma to Head
    - **(Often a "Contre-Coup injury" =** Brain Injury on the Opposite Side of Impact – Due to Rebound of the Brain**)**
    - **(NB: "Coup Injuries" =** Brain Injury on the Side of Impact)
  - **Pathogenesis:**
    - Higher-Force Trauma → Coup &/or Contre-Coup Injury → *Bruising* & Swelling of the Brain.
  - **Morphology:**
    - **Macro:**
      - Contusion = Local Injury + haemorrhage
      - Some damage
      - Localised, Visible Injury with Bleeding (Bruising)
  - **Clinical Features:**
    - Headache
    - Confusion/Sleepiness/Loss of Consciousness
    - Dizziness/Nausea/Vomiting
    - Cognitive Impairment
    - Sensory Impairment
    - Seizures
    - Ataxia
  - **Specific Investigations:**
    - **CT/MRI:**
      - Focal Cerebral Oedema and often Surrounding Brain tissue
      - Transtentorial Herniation
  - **Management:**
    - **ICU management**
    - **Goal = Treat ↑ICP**
      - Prevent Hypotension, Hyponatraemia, Hypercapnia.
      - May require surgical Intervention
    - Usually heal without other treatments.
  - **Prognosis:**
    - Expect a reasonable recovery (but decreased memory, concentration; but still retain normal function)





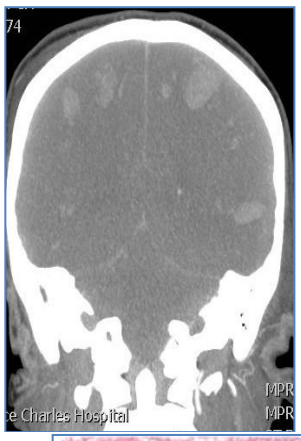
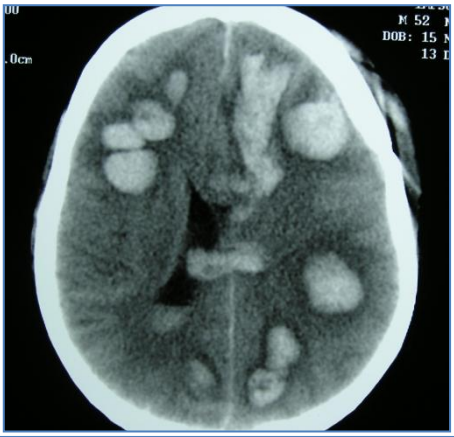
- **LACERATION:**
  - **Aetiology:**
    - Penetrating Head Trauma
    - An incised wound of brain tissue (Eg. Bullet/knife/etc)
  - **Pathogenesis:**
    - Mechanical Destruction of Brain Matter due to Invading Object
    - Usually SEVERE damage
  - **Morphology:**
    - **Macro:**
      - Visible tear in the tissue
      - Haemorrhage
  - **Clinical Features:**
    - **High Velocity:**
      - Instant Death due to "Blast Effect" → Immediate ↑Supratentorial Pressure → Brainstem Herniation through Foramen Magnum.
    - **Low Velocity:**
      - May have Lucid Interval and No LOC
      - May have LOC as the laceration bleeds into the skull (↑ICP)
  - **Specific Investigations:**
    - **CT:**
      - Frequently Associated with Skull Fractures &/or Diffuse Axonal Injury
      - Cerebral Laceration
      - Large amounts of Blood
  - **Management:**
    - Prevent ↑ICP
  - **Prognosis:**
    - Typically a Poor Prognosis.

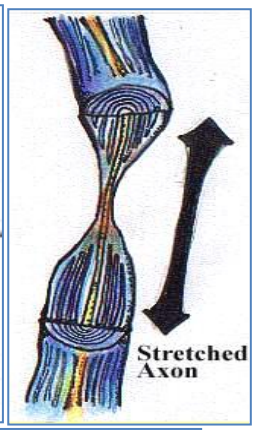


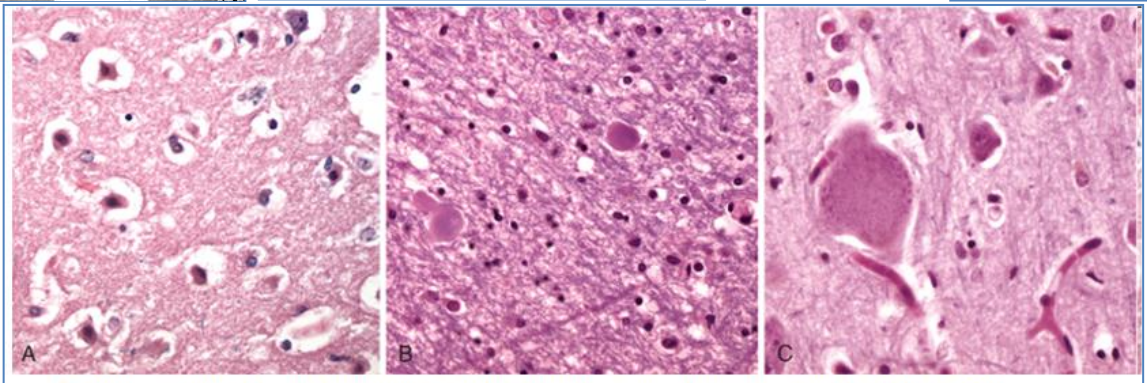
The "blast effect" of a high-velocity projectile causes an immediate increase in supratentorial pressure and results in death because of impaction of the cerebellum and medulla into the foramen magnum. A low-velocity projectile increases the pressure at a more gradual rate through hemorrhage and edema.

Diffuse Primary Injury:

- **DIFFUSE AXONAL INJURY:**
  - **Aetiology:**
    - High-Force Blunt Trauma to Head
  - **Pathogenesis:**
    - Shearing of neurons.
    - (Grey matter of whole areas of the brain have been sheared right off)
  - **Morphology:**
    - **Macro:**
      - Small Haemorrhagic Lesions – In the Corpus Callosum and Dorsolateral Brainstem
  - **Clinical Features:**
    - Unconsciousness
    - Persistent Vegetative State (Coma) – NB: 90% Never regain constiousness.
    - 10% Regain Constiousness – BUT significant mental impairment.
  - **Specific Investigations:**
    - Difficult – Doesn't show up well on CT/MRI.
    - CT may appear normal initially
    - May see small bleeds in Basal Ganglia/Corpus Callosum/Cerebral Cortex on MRI.
  - **Management:**
    - No Specific Treatment Exists
    - (Stabilise Patient, & Control ICP)
  - **Prognosis:**
    - Poor (Brain Damage → GCS 3 → Organ donor)



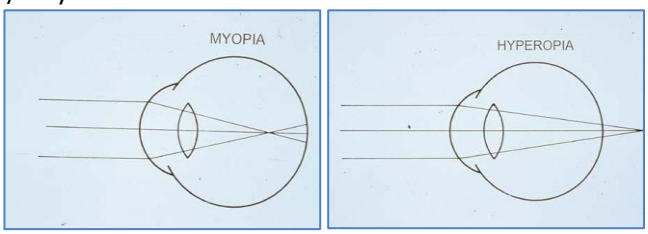


A, Hypoxic/ischemic injury in cerebral cortex - "red neurons." shrunken cell
B, Axonal spheroids at points of axonal disruption
C, Swollen cell body and peripheral dispersion of Nissl substance (chromatolysis)

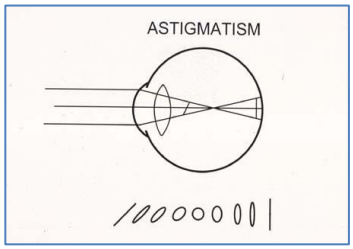
SENSORY Pathology:
VISION DISORDERS

Focal Disorders:

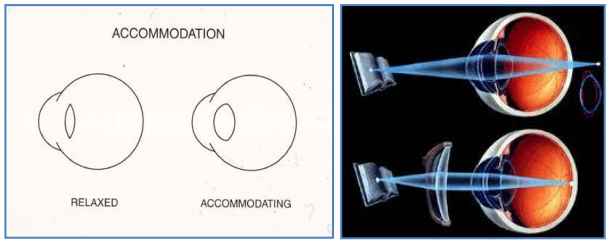
- **Myopia** (Short Sighted) – Eye is too long
- **Hyperopia** (Far Sighted) – Eye is too short



- **Astigmatism:**
  - The lenses are not perfectly round (more football shaped)
  - Corrected by a 'Toric' (Football shaped) lens which is oriented in the opposite direction

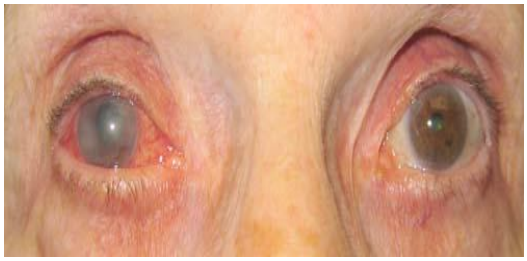


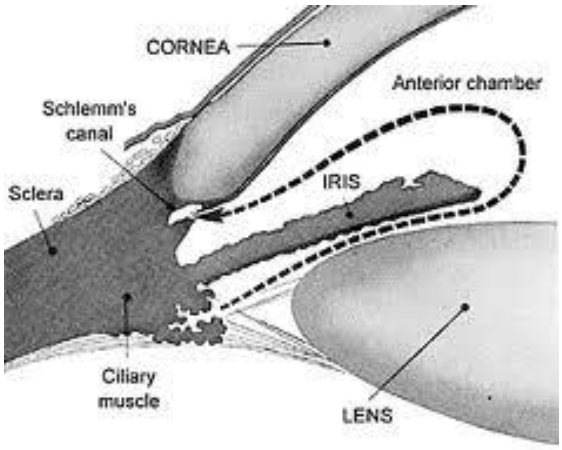
- **Presbyopia:**
  - As you get older, the ability to *Accommodate* gets less → "*Presbyopia*"
    - Ie. A progressively diminished ability to focus on near objects with age.
    - Why? – Because the lens loses its elasticity with age.
  - → Inability to focus on Near Objects (Similar to Hyperopia, but different aeitiology)
  - Corrected by Corrected by *Plus* lenses.

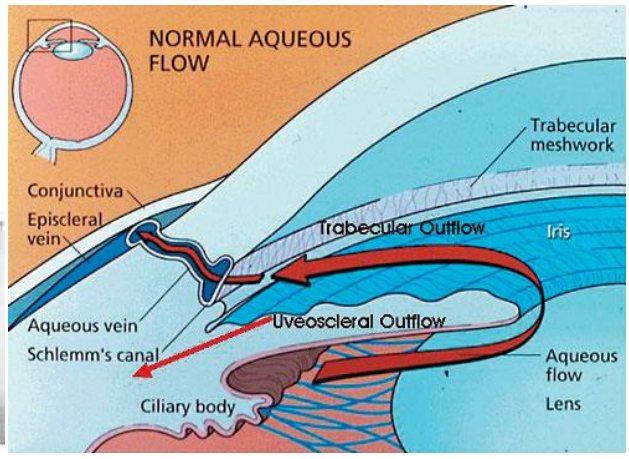


Glaucoma:

- **= A State of Increased Intraocular Pressure**
- **Aetiology:**
  - Imbalance between Aqueous Humour Production & Drainage (via Canal of Schlemm)
- **Pathogenesis:**
  - Imbalance between Production & Drainage → ↑IOP → Damages Optic Nerve & Causes Retinal Ischaemia → Loss of Vision (Typically Peripheral Vision First)
- **3 Categories:**
  - (Depends on the "Angle" between the Cornea & The Iris – Which determines patency of the Canal of Schlemn)
  - **Open Angle Glaucoma:**
    - The 'angle' is fine, But the Canal of Schlemm is Blocked for another reason → obstruction to drainage → ↑IOP
    - NB: Progresses slower and vision loss may be insidious until the disease has progressed significantly.
  - **Closed Angle Glaucoma:**
    - The 'Angle' is too acute → Blocks Canal of Schlemn → ↓Drainage → ↑IOP
    - NB: Acute onset - Often Painful; visual loss can progress quickly but the discomfort often leads patients to seek medical attention before permanent damage occurs.
  - **Congenital/juvenile**
    - Hereditary
    - Infections can do it too.
- **Acute Glaucoma Symptoms:**
  - **Sudden onset headache, nausea, vomiting**
  - **Loss of vision**
  - Red Eye
  - Commonly Unilateral
  - **Pupils are Dilated**
- **Treatment:**
  - Pupillary Constrictors
  - NB: Pupillary Dilation will make glaucoma worse; or precipitate glaucoma in predisposed individuals. (Eg. At night)



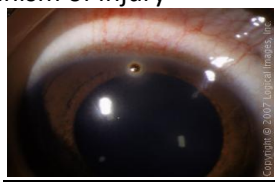




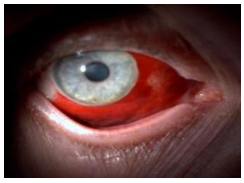
Production of aqueous humour & drainage through canal of schlemn

"Red Eye"

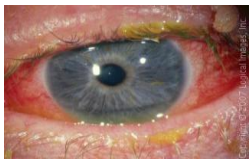
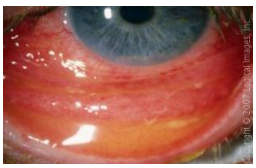
- **Common Causes:**
  - Foreign bodies
  - Conjunctivitis(baterial,viral,allergic)
  - Sub-conjunctival haemorrhage
  - Corneal abrasion
  - Corneal ulcer(bacterial/viral)
  - Uveitis
  - Acute Glaucoma
- **Questions to ask:**
  - **Ascertain History of Injury:**
    - Have you been welding
    - Have you been using contact lenses (notorious for causing problems)
    - Have you been handling acids/alkalines?
  - **Is it Uniocular or Binocular?:**
    - If Binocular – Probably conjunctivitis
    - If Monocular – These are the ones to be concerned about:
      - Uveitis
      - Glaucoma
  - **Watery or Sticky?**
    - If watery – More concerning – Eg. Uveitis, Glaucoma, corneal ulcer
    - If Sticky - Less concerning – Prob Conjunctivitis
  - **Painful/Sensitive to light *OR* Just uncomfortable?**
  - (If Vision is Blurred & Painful, Flourescein is used to determine corneal staining)
- **Red Flags:**
  - Unilateral
  - Blurred vision
  - Severe pain
  - Photophobia
  - Haloes.
- **Common Causes of Red-Eye:**
  - **Foreign Body:**
    - Must know the mechanism of injury



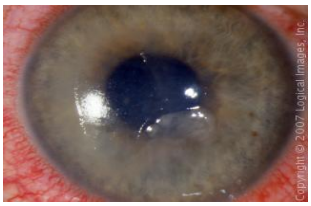
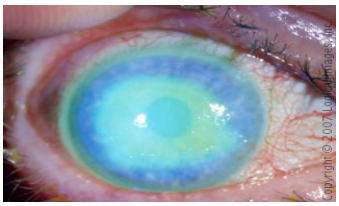
  - **Subconjunctival haemorrhage:**
    - Just a simple bruise
    - Common Causes
      - Coughing fit
      - Hypertensive
      - Anticoagulants
    - Requires no treatment – but check BP & whether they're on anticoagulants.



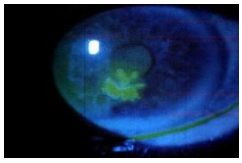
- **Conjunctivitis:**
  - Inflammation of conjunctiva
  - Sticky eyes common due to exudates (sometimes purulent)
  - NB: The cornea is nice and clear
  - **Common Causative Organisms**
    - Staph epiderm
    - Staph aureus
    - Strep
    - adenovirus

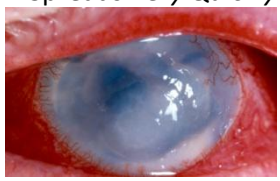
- **Corneal Abrasion:**
  - Diagnosed by Flourescine + Blue Light
  - → Stains areas of epithelial loss
  - Must be able to distinguish between a simple corneal abrasion & a corneal ulcer
  - Superficial abrasions Heal within 24hrs and don't scar.

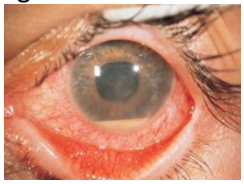
- **Corneal Ulcers:**
  - Require *Urgent* Specialist Care
  - **Viral:**
    - Commonest is Herpetic (Herpes Simplex Virus)
    - Characteristic feature = has branches :. A *Dendritic Ulcer*.



  - **Bacterial:**
    - More concerning
    - Most dangerous organism is Gonorrhea (Can penetrate the eye even without break in the epithelium)
    - Pseudomonas – Spreads *Very Quickly*→ Opaque (Most sight-threatening)



- **Uveitis:**
  - Very common cause of Red Eye
  - Inflammation of the entire uveal tract
  - Different from iritis
  - Very sensitive to light
  - Watery Eyes
  - NB: There is pus collecting in the anterior chamber.



Diabetic Retinopathy:

- Change in basement membranes of the retinal capillaries:
    - Microaneurysms
    - Microvascular obstruction
    - Non-perfusion of capillaries
    - Narrowing of arterial walls

Cataracts:

- Opacity in the crystalline lens
- Causes are multifactorial:
    - Metabolic disease (eg. Diabetes)
    - UV Light
    - Smoking
    - Ocular diseases (eg. Glaucoma)
    - Skin diseases (eg. Dermatitis)
    - Drug induced (Eg. Corticosteroids)
    - Ageing (Idiopathic – unknown cause)

- **Chalazion:**
    - A cyst in the eyelid that is caused by inflammation of a blocked meibomian gland, usually on the upper eyelid.

- **Strabismus:**
    - Where eyes are not properly aligned with each other.
    - Very important to treat in children because it can cause Amblyopia (Where the brain ignores input from the deviated eye. Can also be a cosmetic problem)

SS Quiz Cases: - What is Most Likely in Each Patient?

1.A 23 yr old male presented to A&E with a red left eye .He was grinding metal at work.
- Foreign Body

2.A 13 yr old girl presented with complaints of a red right eye and blurred vision. She has also noticed some cold sores around her lips.
- Herpetic ulcer

3.A 65yr old male presents with a painless red right eye following a coughing fit. He happens to be on anticoagulants for a heart condition.
- Subconjunctival Haemorrhage

4.A 35yr old lady who wears contact lenses comes with a 2 day history of a painful red left eye. Her vision is blurred and her eye is watery.
- Acanthomeba or Pseudomonas infection

5.A 27 yr old male comes with a 2 day history of red eyes. Both eyes are affected. He tells you that his vision appears OK but they are sticky. He has recently had a sore throat.
- Conjunctivitis (Probably Bacterial)

6. 78 yr male presents with sudden loss of vision in the right eye.Over the past few months he has episodes of loss of vision lasting for a couple of minutes. He has raised cholesterol.
- transient ischaemic attacks due to embolic atherosclerotic lesions lodging in the eye.

7. 80 yr old woman presents with blurring of central vision.She complains that whem she looks at your face she cant see anything clearly but can see around it.She tries to read but all the letters are wavy and distorted.
- Age Related Macular Degenration

Continue Reading For Bonus Supplementary Study Materials…

Neurology

Adi Kartolo, Yi (Emma) Quan, and **Jeremy Zung,** chapter editors
Hart Stadnick and **Kevin Yau,** associate editors
Alex Cressman, EBM editor
Dr. Mark Boulos, Dr. Alfonso Fasano, Dr. Lorraine Kalia, and **Dr. Peter Tai,** staff editors

www.regentstudies.com

Acronyms

ACA	anterior cerebral artery
ACh	acetylcholine
AD	Alzheimer's disease
ADL	activities of daily living
AED	antiepileptic drugs
AION	acute ischemic optic neuropathy
ALS	amyotrophic lateral sclerosis
AVM	arteriovenous malformation
AVPU	alert, verbal, pain, unresponsive
CJD	Creutzfeldt-Jakob disease
CN	cranial nerve
CNS	central nervous system
CRVO	central retinal vein occlusion
CSF	cerebral spinal fluid
CVD	cerebrovascular disease
DBS	deep brain stimulation
DLB	dementia with Lewy bodies
DM	diabetes mellitus
EOM	extraocular movement
EtOH	ethanol
FEF	frontal eye field
FTD	frontotemporal dementia
GBS	Guillain-Barré syndrome
GCA	giant cell arteritis
GCS	Glasgow coma scale
GPe	Globus pallidus pars externa
GPi	Globus pallidus pars interna
HD	Huntington's disease
IADL	instrumental activities of daily living
ICH	intracranial hemorrhage
ICP	intracranial pressure
IIH	idiopathic intracranial hypertension
INO	internuclear ophthalmoplegia
IVIG	intravenous immunoglobulin
JC	John Cunningham virus
LEMS	Lambert-Eaton myasthenic syndrome
LGB	lateral geniculate body
LMN	lower motor neuron
LOC	level of consciousness
LP	lumbar puncture
MCA	middle cerebral artery
MG	myasthenia gravis
MLF	medial longitudinal fasciculus
MMSE	mini mental status examination
MoCA	Montreal cognitive assessment
MS	multiple sclerosis
NCS	nerve conduction studies
NMJ	neuromuscular junction
NPH	normal pressure hydrocephalus
PComm	posterior communicating artery
PD	Parkinson's disease
PICA	posterior inferior cerebral artery
PLMS	periodic limb movement in sleep
PPA	primary progressive aphasia
PPRF	paramedian pontine reticular formation
PSP	progressives supranuclear palsy
RAPD	relative afferent pupillary defect
REM	rapid eye movement
RLS	restless legs syndrome
ROM	range of motion
SAH	subarachnoid hemorrhage
SDH	subdural hematoma
SNc	substantia nigra pars compacta
SNr	substantia nigra pars reticulata
STN	subthalamic nucleus
TBI	traumatic brain injury
TIA	transient ischemic attack
UMN	upper motor neuron
VEGF	vascular endothelial growth factor
VZV	varicella zoster virus

Approach to the Neurological Complaint

- **Two questions:** Where is the lesion? What is the lesion?

Lesion Localization

- cortical
  - contralateral paresis (with differential effect on face and arm vs leg)
  - UMN injury (normal tone, hyperreflexia, Babinski sign, spasticity, no atrophy)
  - homonymous hemianopia midline
  - cortical sensory loss (hemisensory loss, position sense, two-point discrimination, graphesthesia, stereognosis)
  - dominant hemisphere (aphasia, alexia, agraphia, acalculia, left-right disorientation)
  - non-dominant hemisphere syndromes (hemineglect, dysprosody, amusia, constructional apraxia)
  - homonymous hemianopia/quadrantanopia
  - gaze deviation (eyes look toward infarct side of the lesion)
  - partial seizure
  - agnosia (visual, auditory)
  - apraxia
  - dominant hemisphere (aphasia, syndromes (alexia, without agraphia, acalculia, Gerstmann syndrome)
  - non-dominant hemisphere syndromes (denial, hemineglect, constructional apraxia)
  - alien hand syndrome
- subcortical white matter:
  - internal capsule: contralateral paresis with equal face, arm, leg involvement without sensory/cortical deficits; contralateral dysmetria/clumsiness and leg paresis
  - basal ganglia: pill-rolling tremor, bradykinesia, festinating gait, hemiballismus, chorea, dystonic posture (basal ganglia)
  - thalamus: dense sensory loss (thalamic), contralateral severe pain
- brainstem: (bulbar)
  - cranial nerve deficits
  - crossed hemiplegia or sensory loss (i.e. (ipsilateral face, contralateral body)
  - crossed sensory loss
  - dysmetria
  - ipsilateral cerebellar (rapid alternating movements, tandem gait)
  - nystagmus toward lesion, diplopia, INO (impaired adduction on contralateral gaze)
  - dysphagia
  - dysarthria (impaired speech articulation)
  - hearing loss
  - vertigo
- cerebellum
  - ipsilateral ataxia (unsteadiness, incoordination)
  - dysmetria
  - intention tremor
  - dysdiadochokinesia
  - wide-based gait, truncal titubation (staggering, reeling, lurching)
  - scanning speech (explosive speech with noticeable pauses and accentuated syllables)
  - nystagmus, distorted smooth pursuit, oscillopsia

www.regentstudies.com

- spinal cord
  - absence of facial involvement with bilateral motor and /sensory deficits below the lesion without facial involvement
  - sphincter dysfunction
  - ataxia, sensory level (sharp line below which there is decreased sensation)sensory deficits exist); suspended "cape-like" sensory level
  - LMN signs (flaccid paresis, hypotonia, hyporeflexia, atrophy, fasciculations) at level of lesion; UMN signs below lesion (marked spasticity and Babinski)
  - bowel, bladder incontinence, sexual dysfunction
  - saddle anesthesia
  - ataxia
  - cord compression symptoms
- nerve root
  - multiple peripheral nerve involvement
  - radicularmyotomal/dermatomal deficits
  - radiating back/neck pain
- peripheral nerve
  - distal "stocking-glove distribution" sensory loss
  - distal paresis
  - LMN signs (hypotonia, hyporeflexia, fasciculations, atrophy)
- neuromuscular junction
  - fluctuating ocular and proximal muscle weakness
  - fatigable upgaze and diplopia
  - bulbar involvement (bulbar symptoms
  - dysphonia, dysarthria)
- muscle
  - symmetric proximal weakness without sensory deficits +/- (climbing stairs, up from chair, combing hair)
  - muscle tenderness
  - muscle atrophy

Differential Diagnosis

- vascular: ischemia, hemorrhage, vasculitis (temporal arteritis), aneurysm, vasospasm, hematologic, embolic, thrombotic
- infectious/post-infectious: meningitis, encephalitis, sinus, osteomyelitis, abscess; viral, (herpes simplex, HIV, JC, polio, rabies), bacterial, (meningococcal, Lyme, botulism), mycobacterial (TB), spirochete (syphilis), parasitic, (cysticercosis), protozoal, mycobacterial, (malaria), fungal, spirochete, (histoplasmosis, cryptococcus), prion, (CJD), post-infectious (GBS)
- neoplastic/paraneoplastic: metastatic (breast, lung, kidney, lymphoma, melanoma, kidney, breast) or primary (glioblastoma multiformeglioma, meningioma, schwannoma, primary CNS lymphoma)
- paraneoplastic: small cell lung carcinoma, testicular, breast, gastrointestinal, ovarian
- degenerativeAD, ALS, FTD, HD, PD, PSP
- demyelinating: MS, GBS
- drugs: Alzheimer's, Parkinson's, ALS, medications/drugs, (anticholinergics, opiates, sedatives, chemotherapy), substance use,/exposure (stimulants, hallucinogens, EtOH, heavy metals, carbon monoxide), withdrawal, pernicious anemia (levodopa, benzodiazepine)
- deficiencies: thiamine, niacin, pyridoxine (B_6), vitamin B_{12}, vitamin D, vitamin E
- inflammatory/auto-immune: polymyositis, myasthenia gravis, GBS, MS,dermatomyositis, MG, post-radiation therapy, granulomatous, collagen vascular, auto-immune
- ictal: epilepsy
- congenital/hereditary: hydrocephalus, cerebral palsy, fragile X syndrome
- anatomic/structural: ICP, cauda equina syndrome, herniation, HTN, decreased pressure (tonsillar, disc), Arnold-Chiari malformation, space-occupying lesion: tumour, pus, blood
- autoimmune
- traumatic: concussion, vertebral fracture, SDH, SAH, epidural hemorrhage
- endocrine/metabolic: DM, cirrhosis, hypoglycemia, uremia, hepatic encephalopathy, hypercapnia, thyroid, electrolyte, liver function test abnormality, endocrine, enzyme defect/ deposition (lysosomal and other), (Na^+, K^+, Ca^{2+}, Mg^{2+}), mitochondrial, nutrient deficiency
- toxic: medications/drugs, toxins, withdrawal
- movement disorder (dystonia, dyskinesia)
- sleep disorder
- ictal
- sleep: obstructive sleep apnea, restless leg syndrome, narcolepsy
- psychiatric
- psychiatric: depression, schizophrenia, anxiety, psychosomatic, malingering, pseudoseizure
- idiopathic

www.regentstudies.com

The Neurological Exam

General Exam and Mental Status

- **vitals:** pulse (especially rhythm), BP, RR, temperature
- **H&N:** meningismus, head injury/bruises (signs of basal skull fracture: Battle's sign, raccoon eyes, hemotympanum, CSF rhinorrhea/otorrhea), tongue biting
- **CVS:** carotid bruits, heart murmurs
- **mental status:** orientation (person, place, time), LOC (GCS) (see Emergency Medicine, ER4)
  - GCS/15 – Motor/6, Verbal/5 (T= intubated), Eyes/4
- **cognition**
  - Folstein MMSE – /30 (note: dementia is a clinical diagnosis and is not diagnosed by cognitive testing)
  - MoCA – /30 (≥26 is considered normal)
  - frontal lobe testing (for perseveration)
  - clock drawing

See Online Atlas for Cranial Nerves Exam, Motor Exam, and Sensory Exam Techniques

Battle's sign = mastoid ecchymosis

Raccoon eyes = periorbital ecchymosis

If patient has not brought their glasses, have them look through a pinhole for best corrected vision

Cranial Nerve Exam

- **olfactory (CN I):** odour sensation (test each nostril separately)
- **optic (CN II)**
  1. visual acuity: test each eye individually using best corrected vision
  2. visual fields by confrontation
  3. pupil: direct and consensual pupillary reaction (afferent limb), accommodation, swinging flashlight test (see *Relative Afferent Pupillary Defect*, Ophthalmology, OP33)
  4. fundoscopy: optic disc edema, optic disc pallor, venous pulsations, hemorrhages
- **oculomotor** (CN III), **trochlear** (CN IV), and **abducens** (CN VI)
  1. **oculomotor (CN III):** levator palpebrae superioris, medial rectus, superior rectus, inferior rectus, inferior oblique, efferent limb of pupillary light response
  2. **trochlear (CN IV):** superior oblique
  3. **abducens (CN VI):** lateral rectus
- **trigeminal (CN V)**
  1. sensory: V1 (above supraorbital ridge), V2 (buccal area), V3 (mandible), corneal reflex (afferent)
  2. motor: temporalis, masseter, pterygoids, jaw jerk reflex
- **facial (CN VII)**
  1. inspect for facial asymmetry, widening of palpebral fissure, flattened nasolabial fold, drooping mouth, and involuntary facial movements
  2. sensorimotor: muscles of facial expression, hyperacusis (stapedius), corneal reflex (efferent)
  3. visceral sensory: taste of anterior 2/3 of tongue
  4. visceral motor: salivary and lacrimal glands
- **vestibulocochlear (CN VIII)**
  1. vestibular: nystagmus, caloric reflexes
  2. cochlear: whisper, Rinne, Weber
- **glossopharyngeal (CN IX) and vagus (CN X):** palatal elevation, gag reflex, vocal cord function, swallowing, taste of posterior third of tongue
- **accessory (CN XI):** trapezius and sternocleidomastoid strength
- **hypoglossal (CN XII):** tongue muscle bulk, fasciculations, strength

When testing CN I, avoid noxious smells like ammonia, as this tests CN V

Screening Neurologic Exam
- mental status: orientation (person, place, time), obeys commands, GCS
- head and neck: examine for lacerations, contusions, deformities, signs of basal skull fracture (periorbital or mastoid ecchymosis, oto/rhinorrhea), flex neck for meningismus if c-spine injury has been ruled out
- cranial nerve exam: visual fields ± fundoscopy, pupil size and reactivity, extraocular movements, facial strength, hearing to finger rub
- motor: power in deltoids, triceps, wrist extensors, hand interossei, iliopsoas, hamstrings, ankle dorsiflexors, pronator drift
- coordination: finger tapping, finger-to-nose, heel-knee-shin
- gait: tandem gait, heel walking
- reflexes: plantar, biceps, triceps, patellar, ankle
- sensation: all 4 limbs, including double simultaneous stimulation, vibration sense at great toes

Motor Exam

- **bulk:** atrophy, asymmetry
- **tone:** hypotonia (flaccid), hypertonia (spasticity, rigidity, paratonia), cogwheeling
- **power:** pronator drift, asymmetric forearm rolling test
- **reflexes:** deep tendon reflexes, abdominal reflexes, primitive reflexes, Babinski, Hoffmann, clonus
- **abnormal movements:** tremors, chorea, dystonia, dyskinesia, hemiballism, myoclonus, athetosis, tics, fasciculations
- **abnormal posturing:** decorticate (flexion upper extremities, extension lower extremities), decerebrate (extension)

CN Innervation of EOM
LR: CN VI, SO: CN IV, Other: CN III

Contraction of the left sternocleidomastoid turns the head right

Calorics: Brainstem Test
Describe nystagmus by direction of fast component

COWS
Cold
Opposite
Warm
Same

www.regentstudies.com

Table 1. Localization of Motor Deficits

	LMN	UMN	Extrapyramidal
Muscle Tone	Flaccid	Spastic	Rigid
Involuntary Movements	Fasciculations	None	None
Reflexes	Decreased	Increased	Normal
Plantar Reflex	Down-going (flexor)	Up-going (extensor, i.e. Babinski sign)	Down-going (flexor)
Pattern of Muscle Weakness	Proximal, distal, or focal	Pyramidal pattern: look for hemiparetic gait (flexed arm, extended legs) **Upper extremities**: extensors weaker than flexors **Lower extremities**: flexors weaker than extensors	None

Table 2. Overview of Neuromuscular Diseases

	Upper and Lower Motor Neuron Disease	Peripheral Neuropathy	Neuromuscular Junction	Myopathy
SIGNS AND SYMPTOMS				
Weakness	Segmental and asymmetrical, distal → proximal	Distal (except GBS) but may be asymmetrical	Proximal and fatigable (e.g. MG), or weak then recovers (e.g. LEMS)	Proximal
Fasciculations	Yes	Yes	No	No
Reflexes	Increased	Decreased/absent	Normal	Normal (until late)
Sensory	No	Yes	No	No
Autonomic*	No	Yes	No	No
TESTS				
EMG	Denervation and reinnervation	Signs of demyelination ± axonal loss	Decremental response in MG Jitter on single fibre EMG	Small, short motor potentials
NCS	Normal	Abnormal	Normal	Normal
Muscle enzyme	Normal	Normal	Normal	Increased

*e.g. orthostatic hypotension, anhidrosis, visual blurring, urinary hesitancy or incontinence, constipation, erectile dysfunction

Table 3. Approach to Strength Testing of Radiculopathies vs. Peripheral Neuropathies

How to use this table: For each nerve root, learn two (or more) peripheral nerves (and their associated muscles/movements). In radiculopathies, all associated peripheral nerves (and their movements) will be impaired, whereas in peripheral neuropathies, only one of the nerves (and its movement) will be impaired, sparing the other nerve. Particularly useful peripheral nerve "pairs" are bolded for emphasis.

Root	Peripheral Nerve	Movement	Muscle
C5	Axillary	Shoulder abduction	Deltoid
C6	Musculocutaneous (C5/6) Radial (C6)	Elbow flexion Elbow flexion Wrist extension	Biceps Brachioradialis Extensor carpi radialis longus
C7	Radial Posterior interosseus	Elbow extension Finger extension	Triceps Extensor digitorum communis
C8, T1	***Median*** ***Ulnar***	Thumb flexion Thumb abduction Opposition Finger abduction	Flexor pollicis longus (look for thenar wasting) Abductor pollicis brevis (look for thenar wasting) Opponens pollicis (look for thenar wasting) First dorsal interosseus (look for wasting in first dorsal webbed space)
L2, 3, 4	***Femoral*** ***Obturator***	Hip flexion Hip adduction	Iliopsoas Adductor muscles
L3, 4	Femoral (L3/4) Deep peroneal (L4/5)	Knee extension Dorsiflexion	Quadriceps Tibialis anterior
L5	Sciatic (L5, S1) ***Tibial*** ***Superficial peroneal*** Deep peroneal	Hip extension Ankle inversion Ankle eversion Big toe extension	Gluteus maximus Tibialis posterior Peroneal muscles
S1	Sciatic Tibial	Knee flexion Plantar flexion	Hamstring muscles Gastrocnemius and soleus

Upper Motor Neuron Tests

Babinski Reflex: 'Up-going' big toe ± fanning of toes indicates an UMN lesion
Hoffmann's Reflex: Flexion of IP joint of the thumb when tapping/flicking/flexing the nail of the index or ring finger may indicate an UMN lesion if asymmetrical
Pronator Drift: Unable to maintain full arm extension and supination; side of forearm pronation reflects contralateral pyramidal tract lesion; closing eyes accentuates effect

Pyramidal Pattern of Muscle Weakness (i.e. UMN)

Weaker arm extensors: shoulder abduction, elbow extension, wrist extension, finger extension, finger abduction

Weaker leg flexors: hip flexion, knee flexion, ankle dorsiflexion

MRC Muscle Strength Scale

5 Full power
4 Submaximal power against resistance (ranging 4+, 4, 4-)
3 Full ROM against gravity without resistance
2 Full ROM with gravity removed
1 Muscle flicker
0 No muscle contraction

Primitive Reflexes

Grasp, palmomental, root, glabellar tap, snout

Deep Tendon Reflexes

Root	Muscle Tendon
C5/6	Biceps
C6	Brachioradialis
C7	Triceps
C8	Finger flexors
L2/3	Hip adductors
L3/4	Knee extensors
S1/2	Plantar flexion

Deep Tendon Reflex Scoring

0	Absent
1+	Depressed
2+	Normal
3+	Increased
4+	Clonus (≥4 beats)

Interpreting a Slow or Uncoordinated Rapid Alternating Movement (RAM)

- Slow RAMs without fatiguing is suggestive of weakness (especially if it is asymmetric)
- Slow RAMs with fatiguing (i.e. decreasing amplitude over time) is suggestive of Parkinsonism
- Uncoordinated RAM is suggestive of cerebellar disorder (i.e. ataxia and irregularly irregular rhythm) or ideomotor apraxia

www.regentstudies.com

Sensory Exam

- **primary sensation**
  - spinothalamic tract: crude touch, pain, temperature
  - dorsal column-medial lemniscus pathway: fine touch, vibration, proprioception
- **cortical sensation**
  - graphesthesia, stereognosis, extinction, 2-point discrimination

Coordination Exam and Gait

- **coordination exam**
  - finger-to-nose, heel-to-shin, rapid alternating movements
- **stance and gait**
  - gait: antalgic, hemiplegic, ataxic, apraxic, festinating, foot drop, broad-based
  - tandem gait (heel-to-toe walking)
  - Romberg test
  - pull test for postural instability

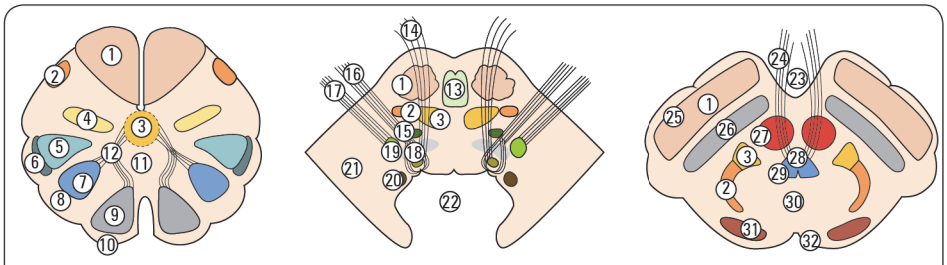
Common Cerebellar Findings
Frontal executive dysfunction/ disinhibition, scanning speech, nystagmus, hypo- or hyper-metric saccades, hypotonia, pendular reflexes, terminal tremor, ataxic finger-nose/ heel-shin/tandem, wide based stance, positive rebound

Romberg Test
Stable with eyes open and closed = normal

Stable with eyes open, falls with eyes closed = positive Romberg, suggesting loss of joint position sense

See Functional Neuroanatomy software

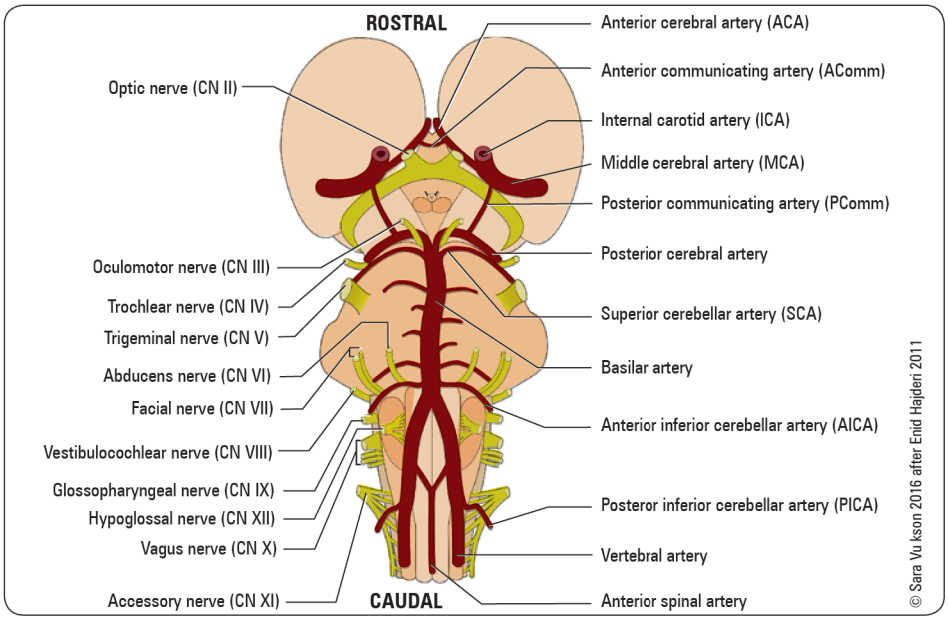
Basic Anatomy Review



Medulla		Pons		Midbrain	
1	Corticospinal tract	13	Pontine nucleus	23	Interpeduncular fossa
2	Spinothalamic tract	14	Abducens (VI) nerve fibres	24	Oculomotor (III) nerve fibres
3	Medial lemniscus	15	Nucleus of facial (VII) nerve (motor)	25	Cerebral peduncle
4	Reticular formation	16	Facial (VII) nerve fibres	26	Substantia nigra
5	Nucleus of spinal tract of trigeminal (V) nerve (descending)	17	Trigeminal (V) nerve fibres	27	Red nucleus
6	Spinal tract of trigeminal (V) nerve	18	Nucleus of abducens (VI) nerve	28	Edinger-Westphal nuclei
7	Nucleus cuneatus	19	Nucleus of spinal tract of trigeminal (V) nerve	29	Oculomotor (III) nucleus complex (motor)
8	Fasciculus cuneatus	20	Lateral vestibular nucleus	30	Cerebral aqueduct
9	Nucleus gracilis	21	Middle cerebellar peduncle	31	Pretectal area
10	Fasciculus gracilis	22	Fourth ventricle	32	Superior colliculus
11	Central canal				
12	Arcuate fibres				

© Meriem Benlamri 2016 after Frances Yeung 2005

Figure 1. Brainstem (axial view)



© Sara Vu kson 2016 after Enid Hajderi 2011

Figure 2. Brainstem (posterior view)

www.regentstudies.com

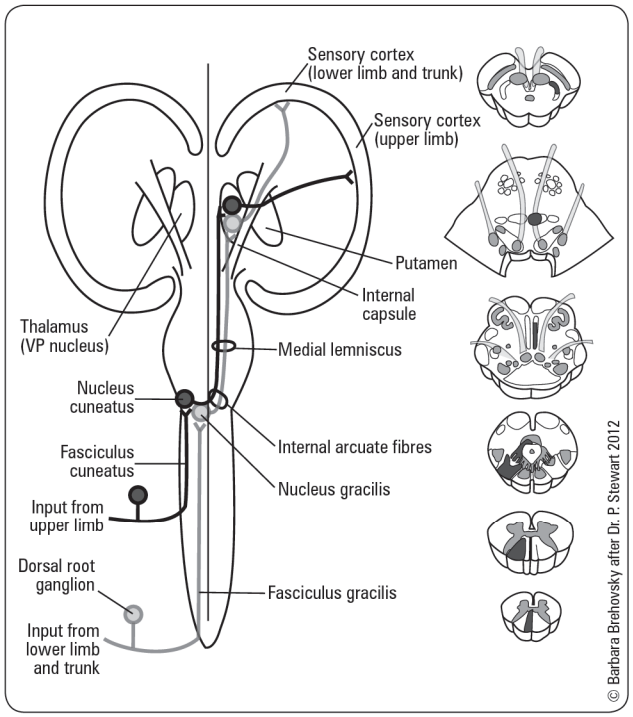


Figure 3. Discriminative touch pathway (dorsal column) from body

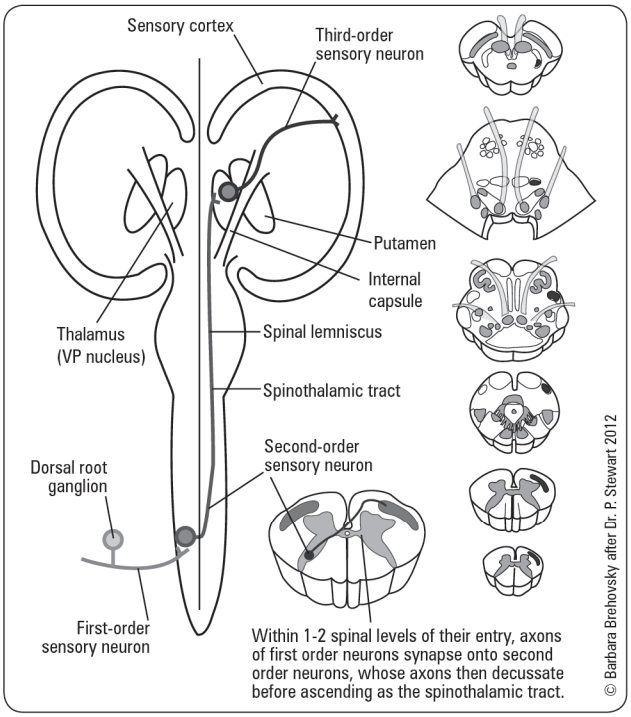


Figure 4. Spinothalamic tract from body

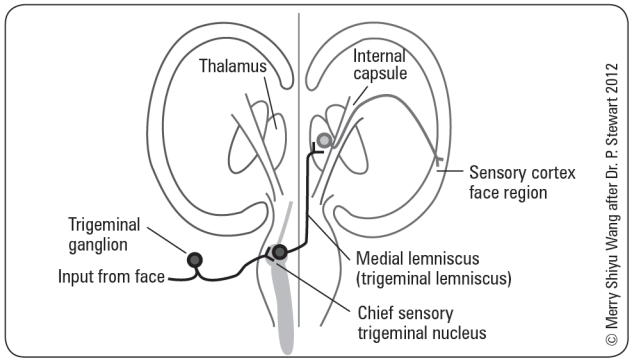


Figure 5. Discriminative touch pathway (dorsal column) from face

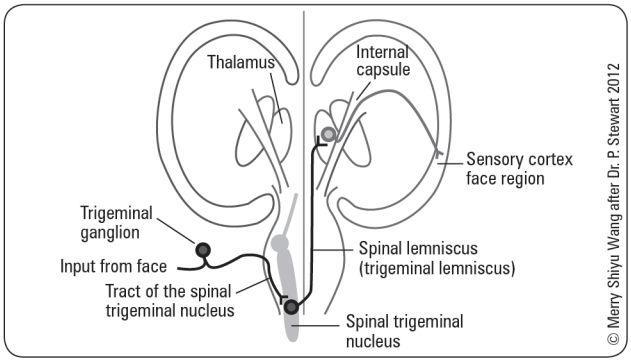


Figure 6. Spinothalamic tract pathway from face

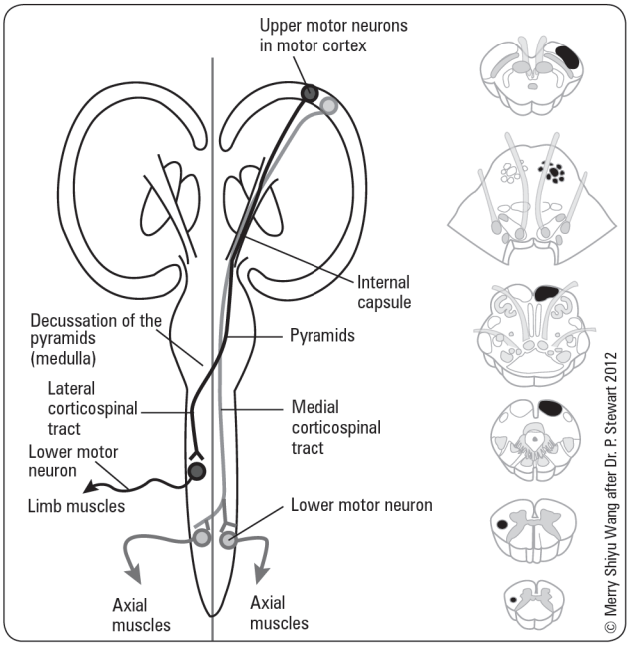


Figure 7. Corticospinal motor pathway

www.regentstudies.com

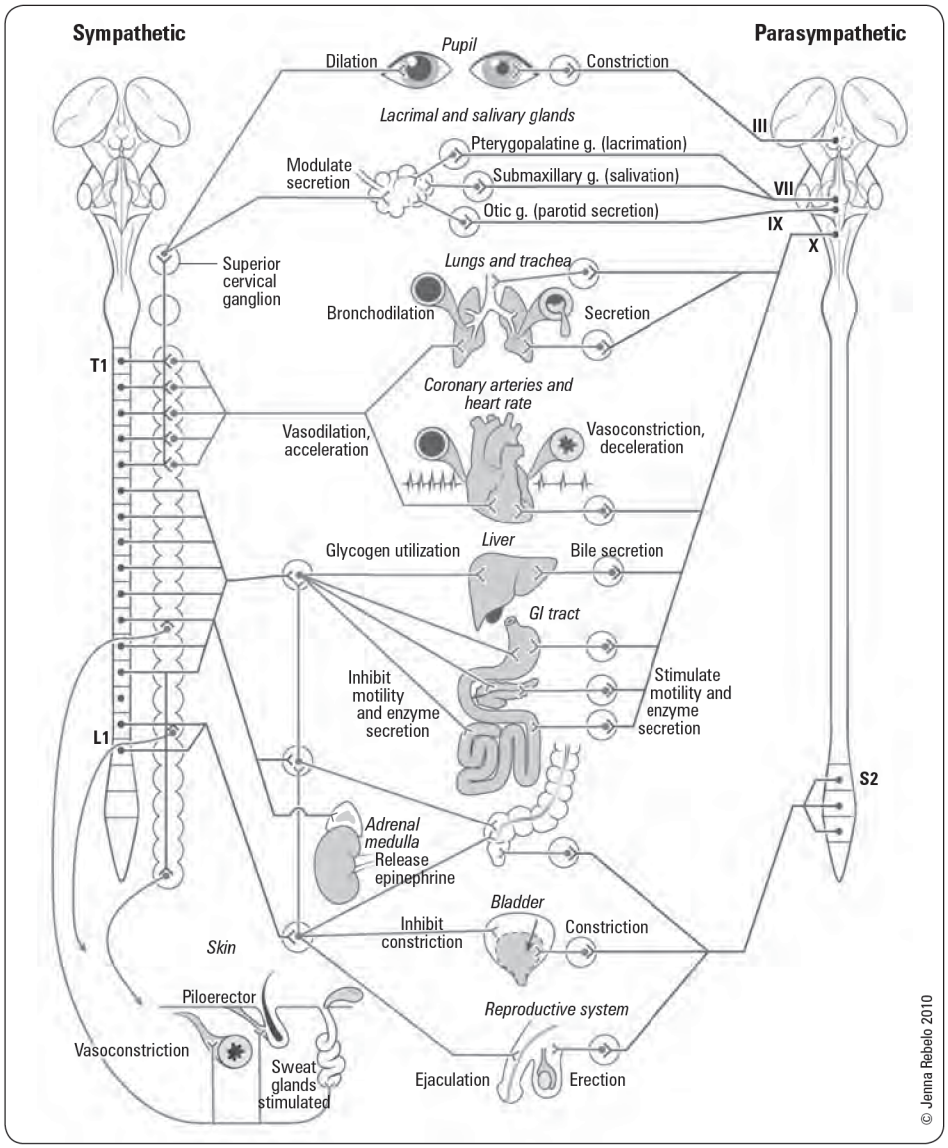


Figure 8. Sympathetic and parasympathetic pathway

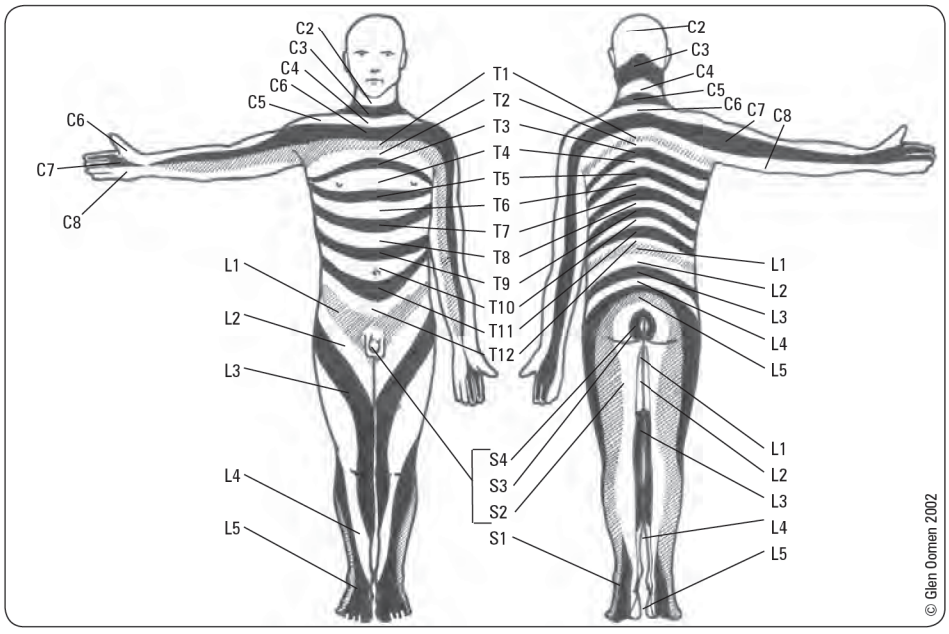


Figure 9. Dermatome map

Myotomes
C5 – Shoulder abduction/elbow flexion
C6 – Wrist extensors
C7 – Elbow extension
C8 – Squeeze hand
T1 – Finger abduction
T2-9 – Intercostal (abdominal reflexes)
T9-10 – Upper abdominals
T11-12 – Lower abdominals
L2 – Hip flexion
L3 – Hip adduction
L4 – Knee extension and ankle dorsiflexion
L5 – Ankle dorsiflexion and big toe extension
S1 – Plantarflexion

www.regentstudies.com

Lumbar Puncture

Indications
- diagnostic: CNS infection (meningitis, encephalitis), inflammatory disorder (MS, Guillain-Barré, vasculitis), subarachnoid hemorrhage (if CT negative), CNS neoplasm (neoplastic meningitis)
- therapeutic: to administer anesthesia, chemotherapy, contrast media; to decrease ICP (pseudotumor cerebri, NPH)

Contraindications
- mass lesion causing increased ICP, could lead to cerebral herniation; CT first if suspect mass lesion
- infection over LP site/suspected epidural abscess
- low platelets (<50,000) or treatment with anticoagulation (high INR or aPTT)
- uncooperative patient

The needle for a LP is inserted into one of L3-4, L4-5, or L5-S1 interspaces

Complications
- tonsillar herniation (rare)
- SDH
- transient 6th nerve palsy
- post-LP headache (5-40%): worse when upright, better supine; generally onset within 24 h
  - prevention: smaller gauge (i.e. 22) needle, reinsert stylet prior to needle removal, blunt-ended needle
  - symptomatic treatment: caffeine and sodium benzoate injection
  - corrective treatment: blood patch (autologous)
- spinal epidural hematoma
- infection

Do not delay antibiotics while waiting for a LP if infection is suspected

LP Tubes
- **tube #1: cell count and differential:** RBCs, WBCs, and differential
  - xanthochromia (yellow bilirubin pigmentation implies recent bleed into CSF, diagnostic of SAH)
- **tube #2: chemistry:** glucose (compare to serum glucose) and protein
- **tube #3: microbiology:** Gram stain and C&S
  - specific tests depending on clinical situation/suspicion
    - viral: PCR for herpes simplex virus (HSV) and other viruses
    - bacterial: polysaccharide antigens of *H. influenzae, N. meningitidis, S. pneumoniae*
    - fungal: cryptococcal antigen, culture
    - TB: acid-fast stain, TB culture, TB PCR
- **tube #4: cytology:** for evidence of malignant cells
- **tube #5: cell count:** compare RBC count to that of tube #1
  - **note:** tube 4 or 5 can be sent for repeat cell count

RBCs in tube #1 >> #5 → traumatic tap

RBCs in tube #1 = #5 → SAH

Table 4. Lumbar Puncture Interpretation (Normal vs. Various Infectious Causes)

Condition	Colour	Protein	Glucose	Cells
NORMAL	Clear	<0.45 g/L	60% of serum glucose or >3.0 mmol/L	0-5 x 10^6/L
INFECTIOUS				
Viral Infection	Clear or opalescent	Normal or slightly increased <0.45-1 g/L	Normal	<1,000 x 10^6/L Lymphocytes mostly, some PMNs
Bacterial Infection	Opalescent yellow, may clot	>1 g/L	Decreased (<25% serum glucose or <2.0 mmol/L)	>1,000 x 10^6/L PMNs
Granulomatous Infection (tuberculosis, fungal)	Clear or opalescent	Increased but usually <5 g/L	Decreased (usually <2.0-4.0 mmol/L)	<1,000 x 10^6/L Lymphocytes

Approach to Common Presentations

Weakness

Approach
- **mode of onset:** abrupt (vascular, toxic, metabolic), subacute (neoplastic, infective, inflammatory), insidious (hereditary, degenerative, endocrine, neoplastic)
- **course:** worse at onset (vascular), progressive (neoplastic, degenerative, infective), episodic (vascular, inflammatory), activity dependent (NMJ, muscular)
- **pattern:** objective vs. subjective, generalized vs. localized, asymmetric vs. symmetric, proximal vs. distal, UMN vs. LMN, peripheral vs. myotomal
- **associated symptoms:** sensory symptoms, cortical symptoms, spinal symptoms (i.e. bowel/bladder dysfunction), signs/symptoms specific to various etiologies
- **history:** family history, developmental history, medications, risk factors, recent/preceding exposures
- **investigations for LMN:** NCS/EMG
- **investigations for UMN:** imaging (brain and/or spinal cord)

www.regentstudies.com

Differential Diagnosis

- objective muscle weakness; also, differentiate between true muscle weakness vs. fatigue
  - generalized
    - myopathy (proximal > distal weakness)
      - endocrine: hypothyroidism, hyperthyroidism, Cushing's syndrome
      - rheumatologic: polymyositis, vasculitis
      - infectious: HIV, CMV, influenza
      - other: collagen vascular disorders, steroids, statins, alcohol, electrolyte disorders
    - NMJ (MG, botulism, LEMS, organophosphate poisoning)
    - cachexia
  - localized
    - UMN (leukodystrophy, vasculitis, abscess, brain tumour, vitamin B_{12} deficiency, MS, stroke)
    - radicular pain (i.e. nerve root)
    - anterior horn cell (spinal muscular atrophy, ALS, polio, paraneoplastic, lead toxicity)
    - peripheral neuropathy (peroneal muscle atrophy, GBS, leprosy, amyloid, myeloma, DM, lead toxicity)
- no objective muscle weakness
  - chronic illness (cardiac, pulmonary, anemia, infection, malignancy)
  - depression, deconditioning
- if loss of passive motion, consider intra-articular, peri-articular, or extra-articular causes

Numbness/Altered Sensation

Approach

- positive sensory symptoms: paresthesia/dysesthesia = tingling, pins and needles, prickling, burning, stabbing
- negative sensory symptoms: hypoesthesia/anesthesia = numbness, diminution, or absence of feeling
- determine distribution of sensory loss:
  - nerve root vs. peripheral nerve?
  - symmetric stocking-glove pattern? (indicative of distal symmetric polyneuropathy)
  - anterior-posterior spinal cord dissociation
- investigations: NCS, vitamin B_{12} levels, imaging based on associated findings

Differential Diagnosis

- cerebral: stroke, demyelination, tumour
  - associated symptoms: hemiplegia, aphasia, apraxia
- brainstem: stroke, demyelination, tumour
  - associated symptoms: diplopia, vertigo, dysarthria, dysphagia
- spinal cord/radiculopathy: cord infarction, tumour, MS, syringomyelia, vitamin B_{12} deficiency, disc lesion
  - associated symptoms: back/neck pain, weakness (paraparesis or Brown-Séquard pattern)
- neuropathy: focal compressive neuropathy (based on location and distribution), DM, uremia, vasculitis, vitamin B_{12} deficiency, HIV, Lyme disease, alcohol, paraneoplastic, amyloid

Cranial Nerve Deficits

CN I: Olfactory Nerve

Clinical Features

- absence of sense of smell associated with a loss of taste

Differential Diagnosis

- **nasal:** physical obstruction
  - heavy smoking, chronic rhinitis, sinusitis, neoplasms, septal deformity, choanal atresia, vestibular stenosis, foreign body
- **olfactory neuroepithelial:** destruction of receptors or their axon filaments
  - influenza, herpes simplex, interferon treatment of hepatitis C virus, atrophic rhinitis (leprosy)
- **central:** lesion of olfactory pathway
  - Kallmann syndrome, albinism, head injury, cranial surgery, SAH, chronic meningeal inflammation, meningioma, aneurysm, PD, stroke, MS
- **endocrine/metabolic**
  - DM, adrenal hypo/hyperfunction, pseudohypoparathyroidism, hypothyroidism, renal/liver failure, vitamin deficiency

If anosmia is not associated with loss of taste, consider malingering

Kallmann syndrome is a congenital disorder of anosmia and hypogonadotropic hypogonadism

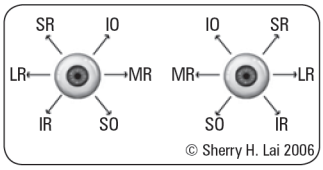


Figure 10. Diagnostic positions of gaze to isolate primary action of each muscle

www.regentstudies.com

CN II: Optic Nerve

- see *Neuro-Ophthalmology*, N14

CN III: Oculomotor Nerve

Clinical Features
- ptosis, resting eye position is "down and out" (depressed and abducted), pupil dilated (mydriasis)
- vertical and horizontal diplopia; paralysis of adduction, elevation, and depression

Differential Diagnosis
- **PComm aneurysm:** early mydriasis, then CN III palsy
- **cavernous sinus** (internal carotid aneurysm, meningioma, sinus thrombosis): associated with deficits in other CNs near the cavernous sinus
- **ischemia of CN III** (DM, temporal arteritis, HTN, atherosclerosis): pupil sparing CN III palsy
- **midbrain lesion:** complete unilateral CN III palsy with bilateral weakness of the superior rectus and ptosis with contralateral pyramidal signs ± mydriasis
- **orbital lesion:** associated with optic neuropathy, chemosis, proptosis
- **other** (inflammatory, infection, neoplasia, uncal herniation, trauma)

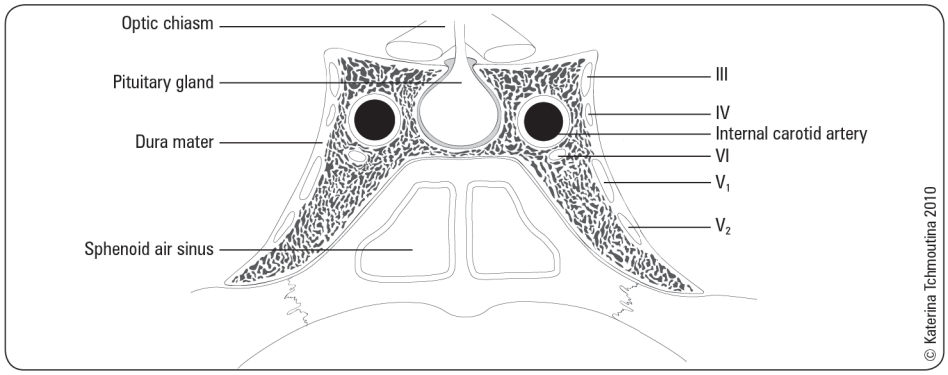


Figure 11. Cavernous sinus (coronal view)

Pupillary constrictor fibres run along outside of nerve, whereas vasculature is contained within nerve

For CN III palsy with a reactive pupil, always think ischemic cause ("pupil sparing")

For CN III palsy with mydriasis, think compressive lesion

DDx of CN III Palsy

iCAM
ischemic
Cavernous sinus
Aneurysm (PComm, internal carotid)
Midbrain lesion

Lesions involving the cavernous sinus can lead to cranial nerve palsies of III, IV, VI, V1, and V2 as well as orbital pain and proptosis

CN IV: Trochlear Nerve

Clinical Features
- vertical and torsional diplopia; defect of intorsion and depression
- patient may complain of difficulty going down stairs or reading

Differential Diagnosis
- common: ischemic (DM, HTN), idiopathic, trauma (TBI or surgical), congenital
- other: cavernous sinus lesion, superior orbital fissure (tumour, granuloma)

CN IV is the only cranial nerve that crosses the midline and exits posteriorly

A CN IV lesion may cause a contralateral deficit

CN IV is at risk of trauma during neurosurgical procedures involving the midbrain because of its long intracranial course

CN V: Trigeminal Nerve

Clinical Features
- ipsilateral facial numbness, weakness of muscles of mastication (V3 only) with pterygoid deviation towards the side of the lesion

Differential Diagnosis
- **brainstem** (ischemia, tumour, syringobulbia, demyelination)
- **peripheral** (tumour, aneurysm, chronic meningitis, metastatic infiltration of nerve)
- **trigeminal ganglion** (acoustic neuroma, meningioma, fracture of middle fossa)
- **cavernous sinus** (carotid aneurysm, meningioma, sinus thrombosis)
- **trauma**
- note: other CN V lesions that cause facial pain = trigeminal neuralgia, herpes zoster

Distinguishing CN III, IV, and VI Lesions

	III	IV	VI
Diplopia	Oblique	Vertical	Horizontal
Exacerbating	Near target	Looking down	Far target
Head Tilt	Up and rotated away	Down and flexed away	Rotated towards

Jaw deviation is towards the side of a LMN CN V lesion

CN VI: Abducens Nerve

Clinical Features
- resting inward deviation (esotropia)
- horizontal diplopia; defect of lateral gaze

CN VI has the longest intracranial course and is vulnerable to increased ICP, creating a false localizing sign

www.regentstudies.com

Differential Diagnosis
- **pons** (infarction, hemorrhage, demyelination, tumour): associated with facial weakness and contralateral pyramidal signs
- **tentorial orifice** (compression, meningioma, trauma): false localizing sign of increased ICP
- **cavernous sinus** (carotid aneurysm, meningioma, sinus thrombosis)
- **ischemia of CN VI** (DM, temporal arteritis, HTN, atherosclerosis)
- **congenital** (Duane's syndrome)

CN VII: Facial Nerve

Clinical Features
- LMN lesion: ipsilateral facial weakness (facial droop, flattening of forehead, inability to close eyes, flattening of nasolabial fold)
- UMN lesion: contralateral facial weakness with forehead sparing (due to bilateral frontalis innervation)
- impaired lacrimation, decreased salivation, numbness behind auricle, hyperacusis, taste dysfunction of anterior 2/3 of tongue

Forehead is spared in a UMN CN VII lesion due to bilateral innervation of CN VII nuclei from cerebral hemispheres for the frontalis

Differential Diagnosis
- **idiopathic** = Bell's palsy, 80-90% of cases (see Otolaryngology, OT23)
  - most often related to HSV, but other viruses may be implicated (CMV, herpes zoster, EBV)
- **other:** temporal bone fracture, EBV, Ramsay Hunt (HSV), otitis media/mastoiditis, sarcoidosis, DM mononeuropathy, parotid gland disease, Lyme meningitis, HIV

Facial Nerve Branch Memory Aid

To Zanzibar By Motor Car
Temporal
Zygomatic
Buccal
Mandibular
Cervical

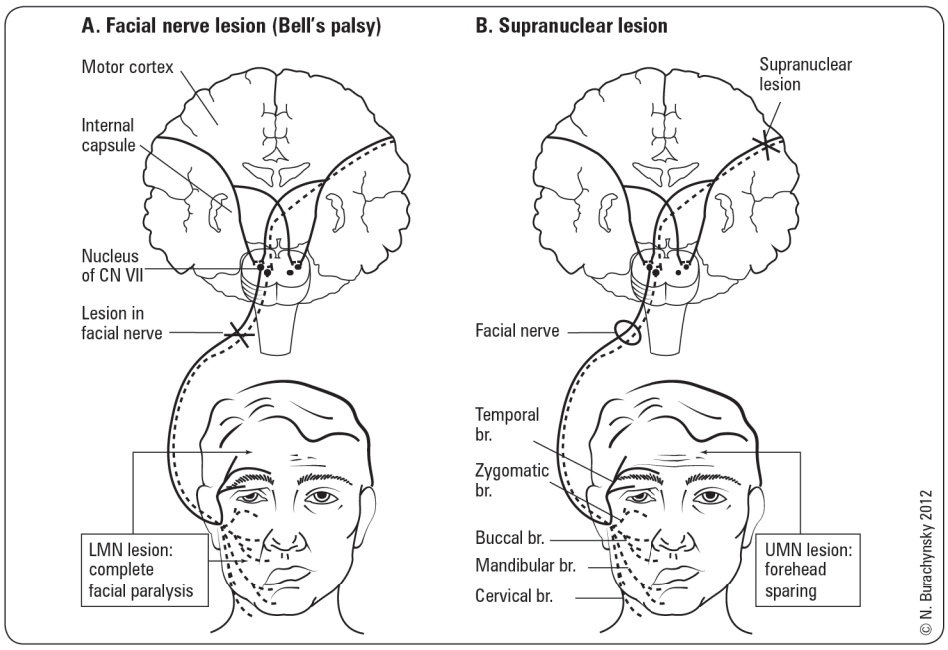


Figure 12. UMN vs. LMN facial nerve palsy

When screening for dysphagia and assessing aspiration risk, the presence of a gag reflex is insufficient; the correct screening test is to observe the patient drinking water from a cup while observing for any coughing, choking, or "wetness" of voice

Differential Diagnosis of Lower Cranial Nerve Deficits (CN IX, X, XI, XII)
Intracranial/Skull Base: meningioma, neurofibroma, metastases, osteomyelitis, meningitis
Brainstem: stroke, demyelination, syringobulbia, poliomyelitis, astrocytoma
Neck: trauma, surgery, tumours

CN VIII: Vestibulocochlear Nerve
- see Otolaryngology, OT9

CN IX: Glossopharyngeal Nerve

Clinical Features
- unilateral lesion is rare
- taste dysfunction in posterior 1/3 of tongue
- absent gag reflex and dysphagia

Disorders
- **glossopharyngeal neuralgia:** sharp paroxysmal pain of posterior pharynx radiating to ear, triggered by swallowing
  - treated with carbamazepine or surgical ablation of CN IX

Normal swallowing is initiated when the tongue moves a bolus back into the palatal archway. Tongue movements are innervated exclusively by CN XII. The bolus stimulates the soft palate to elevate and the bolus is deflected into the oropharynx. Next the pharyngeal constrictors contract, the larynx elevates, and the vocal cords close. Swallowing depends on afferent information via CN V, IX, and X and motor action via CN V, VII, IX, X, and XII.

Connections in the nucleus of the tractus solitarius in the medulla (in proximity to the respiratory centre) act as the swallowing centre. Swallowing and breathing are coordinated to prevent aspiration.

www.regentstudies.com

CN X: Vagus Nerve

Clinical Features

- oropharyngeal dysphagia (transfer dysphagia) due to palatal and pharyngeal weakness
  - neuromuscular causes of dysphagia
    - CNS: stroke, cerebral palsy, tumour, trauma, PD, AD, MS
    - CN: DM, laryngeal nerve palsy, polio, ALS
    - myopathic/NMJ: dermatomyositis, polymyositis, MG, sarcoidosis
  - other causes of dysphagia: see Gastroenterology, G8
- dysarthria: inability to produce understandable speech due to impaired phonation and/or resonance

Uvula deviation is **away from** the side of a LMN CN X lesion due to impaired ipsilateral palatal elevation

CN XI: Accessory Nerve

Clinical Features

- LMN lesion: paralysis of ipsilateral trapezius and sternocleidomastoid (ipsilateral shoulder drop, weakness on turning head to contralateral side)
- UMN lesion: paralysis of ipsilateral sternocleidomastoid and contralateral trapezius

CN XI is vulnerable to damage during neck surgery

CN XII: Hypoglossal Nerve

Clinical Features

- LMN lesion: tongue deviation towards lesion; ipsilateral tongue atrophy and fasciculations (if chronic)
- UMN lesion: tongue deviation away from lesion; absence of atrophy and fasciculations

Ipsilateral tongue paralysis with contralateral hemiparesis/sensory symptoms is pathognomonic for a medial medullary infarction

Table 5. Cranial Nerve Examination and Associated Deficits

Cranial Nerve	Recommended Physical Exams	Signs/Symptoms of Deficit
Olfactory (CN I)	Odor sensation: test each nostril separately	Anosmia (should be associated with loss of taste)
Optic (CN II)	Visual acuity: test each eye individually; best corrected vision Test visual fields Assess pupils: direct and consensual pupillary reaction (afferent), RAPD (swinging flashlight test) Fundoscopy: optic disc edema and pallor, venous pulsations, hemorrhages	Blindness Absence of light reflexes
Oculomotor (CN III)	Assess extraocular movements and nystagmus Test efferent limb of pupillary light response Assess size and shape of pupils; accommodation and saccadic eye movements	Eyes deviated down and out; can demonstrate mydriasis
Trochlear (CN IV)	Test movement of superior oblique	Vertical diplopia; may tilt head towards unaffected side; affected eye cannot turn inward and downward
Trigeminal (CN V)	Test sensation above supraorbital ridge (V1), buccal area (V2), mandible (V3) Test corneal reflex (afferent limb) Assess motor function: temporalis, masseter, pterygoids, jaw jerk reflex	Loss of facial sensations and corneal reflex on stimulation ipsilaterally Weakness and wasting of muscles of mastication; deviation of open jaw to ipsilateral side; trigeminal neuralgia
Abducens (CN VI)	Test movement of lateral rectus	Horizontal diplopia, esotropia (convergent strabismus) and abductor paralysis of ipsilateral eye
Facial (CN VII)	Sensorimotor nerve function: to muscles of facial expression Test efferent limb of corneal reflex Visceral sensory nerve function: to anterior 2/3 of the tongue Visceral motor nerve function: to salivary and lacrimal glands	Paralysis of ipsilateral upper and lower facial muscles Loss of lacrimation Decreased salivation, dry mouth Loss of taste to anterior 2/3 of the tongue ipsilaterally LMN lesion = ipsilateral facial weakness UMN lesion = contralateral facial weakness, sparing the brow bilaterally
Vestibulocochlear (CN VIII)	Vestibular function (nystagmus, calorics) Cochlear function (Rinne, Weber)	Vertigo, disequilibrium, and nystagmus Neural deafness
Glossopharyngeal (CN IX)	Assess vocal cord function and gag reflex Assess taste to posterior third of the tongue (bitter and sour taste)	Loss of taste in posterior third of ipsilateral tongue Loss of gag reflex and dysphasia Unilateral lesion is rare
Vagus (CN X)	Assess vocal cord function and gag reflex Observe uvula deviation and palatal elevation Assess swallowing	Loss of gag reflex, dysphagia, hoarse voice Paralysis of soft palate (failed elevation) Deviation of uvula to contralateral side of lesion; anesthesia of pharynx and larynx ipsilaterally
Accessory (CN XI)	Assess strength of trapezius (shoulder shrug) and sternocleidomastoid muscles (head turn)	Ipsilateral shoulder weakness and turning head to opposite side
Hypoglossal (CN XII)	Inspect tongue for signs of lateral deviation, atrophy, fasciculations, asymmetry of movement and strength	Wasting of ipsilateral tongue muscles and deviation to ipsilateral side on protrusion

www.regentstudies.com

NEURO-OPHTHALMOLOGY

Abnormalities of Vision

- see Ophthalmology, OP4

Acute Visual Loss

- see Ophthalmology, OP4

Optic Neuritis

- see *Optic Disc Edema* below, *Multiple Sclerosis*, N54

Anterior Ischemic Optic Neuropathy

- see *Optic Disc Edema*, below
- **non-arteritic (NAION):** due to atherosclerosis
- **arteritic (AION):** due to giant cell arteritis (see Rheumatology, RH20)

NAION can be caused by use of sildenafil (Viagra®) in rare cases

If you suspect the diagnosis of giant cell arteritis do not wait for biopsy results. Begin treatment immediately

Amaurosis Fugax

- see Ophthalmology, OP37 and *Stroke*, N50

Central Retinal Vein Occlusion

- see Ophthalmology, OP24

Optic Disc Edema

Table 6. Common Causes of Optic Disc Edema

	Optic Neuritis	Papilledema	AION	CRVO
Age	<50 yr	Any	>50 yr but usually >70 yr	>50 yr
Vision	Rapidly progressive monocular central vision loss with ↓ acuity and colour vision with recovery	Late visual loss	Painless unilateral acute field defect over hours to days with ↓ colour vision	Painless unilateral variable vision loss
Symptoms	Pain (especially with eye movement)	H/A, N/V, local neurological deficits	If GCA: H/A, scalp tenderness, jaw claudication, weight loss, fatigue	Cardiovascular risk factors
Pupil	RAPD	No RAPD	RAPD	± RAPD
Fundus	Disc swelling if anterior Normal disc if retrobulbar	Bilateral disc swelling, retinal hemorrhage, no venous pulsations	Pale segmental disc edema, retinal dot, flame hemorrhages	Swollen disc, venous engorgement, retinal hemorrhage
Etiologies	MS, viral	Increased ICP	Giant cell arteritis Non-arteritic: atherosclerosis	Associated with vasculopathy, thrombus
Investigations	MRI with gadolinium	Emergent CT; LP if CT is normal to measure opening pressure	CBC, ESR, CRP, temporal artery biopsy	Fluorescein angiogram and coherence tomography
Treatment	IV methylprednisolone	Treat cause	Consider ASA if non-arteritic; steroids if arteritic	Optimize risk factors, reduce IOP, ± laser, ± VEGF inhibitors

www.regentstudies.com

Optic Disc Atrophy

- **etiologies:** glaucoma, AION, compressive tumour, optic neuritis, Leber's hereditary optic neuropathy, congenital
- **presentation:** disc pallor, low visual acuity, peripheral vision defect, decreased colour vision
- **treatment:** none (irreversible), aim to prevent

Abnormalities of Visual Field

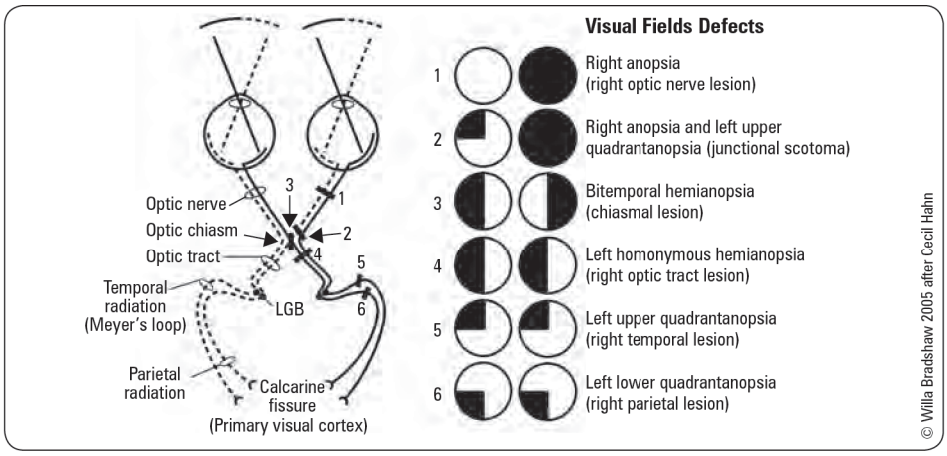


Figure 13. Characteristic visual field defects with lesions along the visual pathway

Bitemporal Hemianopsia DDx by Age
- Children: craniopharyngioma
- Middle aged (20s to 50s): pituitary mass
- Elderly (>60 yr): meningioma

In homonymous hemianopsia, more congruent deficits are caused by more posterior lesions; macular sparing may occur with occipital lesions

Check all hemiplegic patients for homonymous hemianopsia (ipsilateral to side of hemiplegia)

A lesion in a cerebral hemisphere causes eyes to "look away" from the hemiplegia, and to look towards the lesion

A lesion in the brainstem causes the eyes to "look toward" the side of the hemiplegia, and to look away from the lesion

Abnormalities of Eye Movements

Disorders of Gaze

Pathophysiology
- horizontal gaze: FEF → contralateral PPRF (midbrain/pons) → eyes saccade away from FEF
- vertical gaze: cortex → rostral interstitial nucleus in the MLF (midbrain)

Clinical Features
- unilateral lesion in one FEF → eyes deviate toward the side of the lesion
  - can be overcome with doll's eye maneuver
- unilateral lesion in the PPRF → eyes deviate away from the lesion
  - cannot be overcome with doll's eye maneuver if CN VI nucleus lesion as well
- seizure involving a FEF: eyes deviate away from the focus

Etiology
- common: infarcts (frontal or brainstem), MS, tumours

Internuclear Ophthalmoplegia

Pathophysiology
- results from a lesion in MLF which disrupts coordination between CN VI nucleus in pons and the contralateral CN III nucleus in midbrain → disrupts conjugate horizontal gaze

Clinical Features
- horizontal diplopia on lateral gaze, oscillopsia
- on gaze away from the side of the lesion
  - ipsilateral adduction defect
  - contralateral abduction nystagmus
- cannot be overcome by caloric testing
- accommodation reflex intact
- may be bilateral (especially in MS)

Etiology
- common: MS, brain stem infarct

Investigations
- MRI

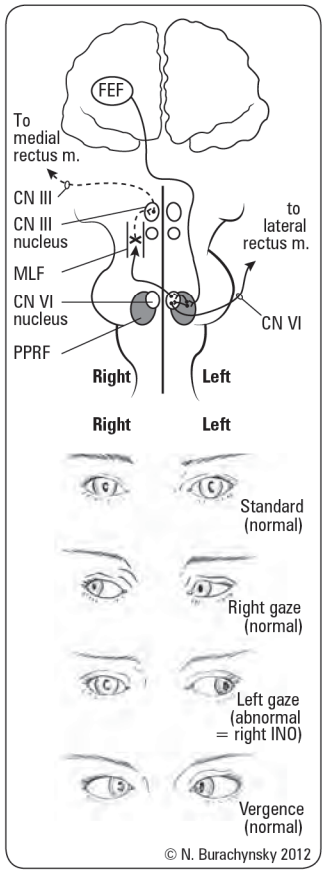


Figure 14. Internuclear ophthalmoplegia

www.regentstudies.com

Diplopia

Etiology – Monocular (see Ophthalmology, OP7)
- mostly due to relatively benign optical problems (refractive error, cataract) or functional

Etiology – Binocular (due to ocular misalignment)
- muscle
  - Graves' ophthalmopathy
  - EOM restriction/entrapment
- neuromuscular junction
  - MG (see *Myasthenia Gravis*, N40)
- cranial nerve palsy (see *Cranial Nerve Deficits*, N10)
- INO (see *Internuclear Ophthalmoplegia*, N15)
- other
  - orbital trauma (orbital floor fracture), tumour, infection, inflammation
  - Miller-Fisher variant of GBS
  - Wernicke's encephalopathy
  - leptomeningeal disease

Approach to Diplopia
- monocular vs. binocular
- horizontal vs. vertical vs. oblique diplopia
- direction of gaze that exacerbates diplopia
- corrective head movements

Workup
- may observe isolated 4th or 6th nerve palsy for a few weeks, but workup if persistent or other symptoms develop
- indications for neuroimaging
  - bilateral or multiple nerve involvement
  - severe sudden onset headache (rule out aneurysm)

Diplopia worse at the end of the day suggests myasthenia gravis (e.g. fatigable)

If diplopia is only on extremes of gaze, cover each eye in isolation during extremes of gaze

The covered eye that makes the lateral image disappear is the pathological one

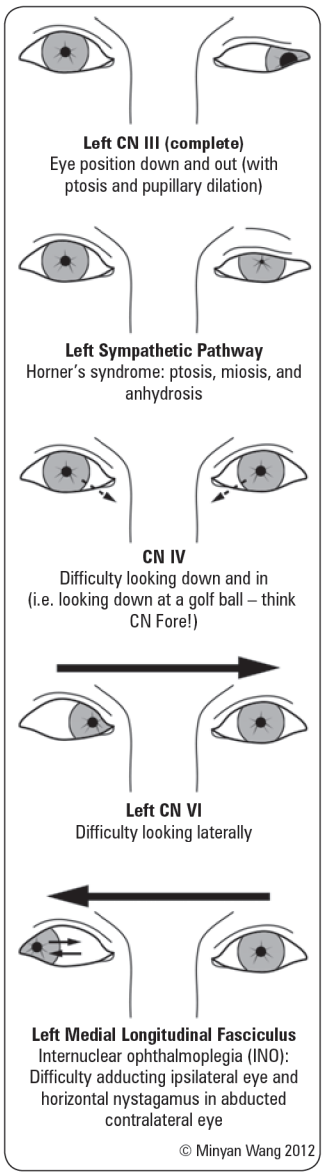


Figure 15. Abnormal eye movements

Nystagmus

- **definition:** rapid, involuntary, small amplitude movements of the eyes that are rhythmic in nature
- direction of nystagmus is labelled by the **rapid** component of the eye movement
- can be categorized by movement type (pendular, jerking, rotatory, coarse) or as physiological vs. pathological

Table 7. Nystagmus Features

	Peripheral (Vestibular)	Central (Brainstem)
Direction	Unidirectional, fast phase away from the lesion	May be bilateral/unidirectional
Vertical Nystagmus	–	±
Gaze Fixation	Relieves nystagmus	Does not relieve nystagmus
Vertigo	Severe	Mild
Auditory Symptoms	Common	Extremely rare
Other Neurological Signs	Absent	Often present
DDx	Benign paroxysmal positional vertigo, vestibular neuritis, Ménière's disease, toxicity, trauma, Ramsay Hunt syndrome	MS, vascular (brainstem/cerebellar), neoplastic/ paraneoplastic

Abnormalities of Pupils

- see Ophthalmology, OP30

www.regentstudies.com

Nutritional Deficiencies and Toxic Injuries

- sufficient nutritional intake is required for optimal nervous system functioning; deficiencies in the following key nutrients, among others, may impair central and peripheral nervous system function (potential neurological symptoms are provided)

Table 8. Nutritional Deficiency Features and Management

Vitamin Deficiency	Neurological Clinical Manifestation	Investigation	Treatment*
Vitamin B_{12}	Paresthesias and a sensory ataxia are the most common initial symptoms Myelopathy; may be accompanied by peripheral neuropathy Neuropsychiatric manifestations: memory impairment, change in personality, delirium, and psychosis Optic neuropathy	Serum cobalamin Serum methylmalonic acid Serum homocysteine	IM Vitamin B12 1,000 µg for 5 d, then once per month or oral B12 1,000 µg/d
Folate	Myelopathy, peripheral neuropathy May be clinically indistinguishable from Vitamin B12 deficiency	Serum folate Homocysteine	Oral folate 1 mg tid initially; 1 mg daily thereafter
Copper	Myelopathy, pyramidal signs (e.g. brisk muscle stretch reflexes at the knees and extensor plantar responses) Severe sensory loss	Serum copper and ceruloplasmin; urinary copper	Discontinue zinc; oral copper 8 mg/d for 1 wk; 6 mg/d for 1 wk; 4 mg/d for 1 wk; 2 mg/d thereafter
Vitamin E	Ophthalmoplegia, retinopathy, spinocerebellar syndrome with peripheral neuropathy (with signs of cerebellar ataxia)	Serum vitamin E; ratio serum vitamin E to sum of cholesterol and triglycerides	Vitamin E 2,200 mg/kg/d oral or IM
Thiamine	Three well-described manifestations include: beriberi (dry and wet), infantile beriberi, Wernicke's encephalopathy with Korsakoff's syndrome Alcoholism is a cause of reduced intake of thiamine, leading to deficiency	Clinical diagnosis; brain MRI	Thiamine 100 mg IV followed by 50-100 mg IV or IM until nutritional status stable
Pyridoxine (Vitamin B6)	Painful sensorimotor peripheral neuropathy	Serum pyridoxal phosphate	Pyridoxine 50-100 mg daily
Niacin	Encephalopathy, coma, and peripheral neuropathy	Urinary excretion niacin metabolites	Nicotinic acid 25-50 mg daily oral or IM

*IM = intramuscular; IV = intravenous

- it is also important to consider occupational neurotoxic syndromes secondary to exposure to pesticides, solvents, and metals. Encephalopathy, extrapyramidal features, neurodegenerative diseases, and peripheral neuropathy are commonly encountered. Onset and progression of neurological diseases should be temporally related to neurotoxin exposure. Main toxins associated with neurotoxicity are listed below

Table 9. Selected Occupational Neurotoxic Syndromes

Toxin	Associated Occupations	Characteristic Neurological Findings
Organic solvents	Printer, spray painters, industrial cleaners, paint or glue manufacturers, graphic industry, electronic industry, plastic industry	Nausea, H/A, concentration difficulty Long-term exposure may lead to "chronic solvent-induced encephalopathy", characterized by mild-to-severe cognitive impairment
Pesticides (e.g. insecticides, fungicides, rodenticides, fumigants, herbicides)	Agricultural work, pesticide manufacturing and formulating employees, highway and railway workers, green house, forestry and nursery workers	Parkinson's disease risk increased by ~70% following pesticide exposure
Metals (e.g. lead, mercury, manganese, aluminum, arsenic)	Battery and metal production (e.g. solder, pipes), chemical and electronic application industries, steel manufacturing, welders, alloy workers, transportation, packaging, construction	**Lead**: delayed or reversed development, permanent learning disabilities, seizures, coma, death from encephalopathy (rare) **Mercury**: psychiatric disturbances, ataxia, visual loss, hearing loss, tiredness, memory disturbances **Manganese**: psychiatric symptoms, hallucinations ("manganese madness"), extrapyramidal features, dystonia, parkinsonism (manganism) **Aluminum**: implicated in Alzheimer's pathogenesis **Arsenic**: sleeplessness/sleepiness, irritability, H/A, spasms in muscle extremities and muscle fatigue
Gases (e.g. carbon dioxide, nitrous oxide, formaldehyde)	Anesthesia, disinfection, manufacture of illuminating gas and water-gas	Cognitive/behavioural and emotional symptoms, parkinsonian syndromes

Neurologic Complications due to Toxic Injuries Related to Bariatric Surgery

- deficiencies of both fat- and water-soluble vitamins may occur following malabsorptive bariatric surgery
- patients who have undergone malabsorptive surgery should be monitored for late metabolic complications and neurological manifestations

www.regentstudies.com

Seizure Disorders and Epilepsy

Seizure

Definitions

- **seizure:** transient neurological dysfunction caused by excessive activity of cortical neurons, resulting in paroxysmal alteration of behaviour and/or EEG changes
- **epilepsy:** chronic condition characterized by two or more unprovoked seizures

Stroke is the most common cause of late-onset (>50 yr) seizures, accounting for 50-80% of cases

Classification

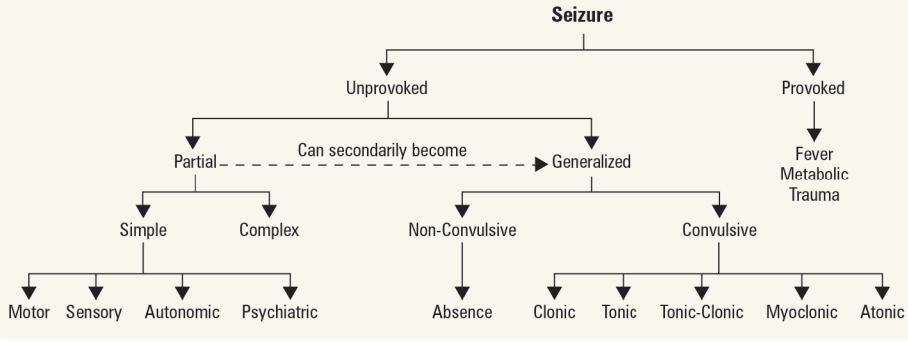


Figure 16. Classification of seizures

NOTE: seizures can also be classified using age of onset (childhood/adolescence, adulthood/late [i.e. >age 30]), setting (sleep, upon awakening), EEG (focal, generalized)

Seizures and Dementia
Neurodegenerative diseases can underlie seizures; conversely, seizures can be a cause of dementia

Signs and Symptoms

- **partial seizures**
  - simple or complex can secondarily generalize, or simple → complex → generalized seizures
  - **simple (preserved LOC)**
    - motor: postural, phonatory, forceful turning of eyes and/or head, focal muscle rigidity/jerking ± Jacksonian march (spreading to adjacent muscle groups)
    - sensory: unusual sensations affecting vision, hearing, smell, taste, or touch
    - autonomic: epigastric discomfort, pallor, sweating, flushing, piloerection, pupillary dilatation
    - psychiatric: symptoms rarely occur without impairment of consciousness and are more commonly complex partial
  - **complex (altered LOC)**
    - patient may appear to be awake but with impairment of awareness
    - classic complex seizure is characterized by automatisms such as chewing, swallowing, lip-smacking, scratching, fumbling, running, disrobing, and other stereotypic movements
    - other forms: dysphasic, dysmnesic (déjà vu), cognitive (disorientation of time sense), affective (fear, anger), illusions, structured hallucinations (music, scenes, taste, smells), epigastric fullness
- **generalized seizures (decreased LOC)**
  - **absence (petit mal):** usually only seen in children, unresponsive for 5-10 s with arrest of activity, staring, blinking or eye-rolling, no post-ictal confusion; 3 Hz spike and slow wave activity on EEG
  - **clonic:** repetitive rhythmic jerking movements
  - **tonic:** muscle rigidity in flexion or extension
  - **tonic-clonic** (grand mal, generalized tonic-clonic [GTC])
    - prodrome of unease or irritability hours to days before the episode
    - tonic ictal phase: muscle rigidity
    - clonic ictal phase: repetitive violent jerking of face and limbs, tongue biting, cyanosis, frothing, incontinence
    - post-ictal phase: flaccid limbs, extensor plantar reflexes, headache, confusion, aching muscles, sore tongue, amnesia, elevated serum CK lasting hours
  - **myoclonic:** sporadic contractions localized to muscle groups of one or more extremities
  - **atonic:** loss of muscle tone leading to drop attack

Temporal lobe epilepsy is suggested by an aura of fear, olfactory or gustatory hallucinations, and visceral or déjà vu sensations

Frontoparietal cortex seizures are suggested by contralateral focal sensory or motor phenomena

www.regentstudies.com

Table 10. Classic Factors Differentiating Seizure vs. Syncope

Characteristic	Seizure	Syncope
Time of Onset	Day or night	Day
Position	Any	Upright, not recumbent
Onset	Sudden or brief	Gradual
Aura	Possible specific aura	Lightheaded sensation
Colour	Normal or cyanotic	Pallor
Autonomic	Uncommon outside of ictal phase	Common; diaphoresis
Duration	Brief or prolonged	Brief
Incontinence	Common	Possible but rare
Post-Ictal	Occurs in tonic-clonic or complex partial	No
Motor Activity	Common	Occasional brief jerks
Injury	Common, tongue biting	Rare unless from fall
Automatisms	Common in absence or complex partial	None
EEG	Usually abnormal	Normal

DDx of Convulsions
Syncope, pseudoseizure, hyperventilation, panic disorder, TIA, hypoglycemia, movement disorder, alcoholic blackouts, migraines (confusional, vertebrobasilar), narcolepsy (cataplexy)

Note that frontal seizures (rare) can look like a pseudoseizure due to odd motor activity that may occur

Table 11. Classic Factors Differentiating Seizure vs. Pseudoseizure (Conversion Disorder)

Characteristic	Seizure	Pseudoseizure*
Triggers	Uncommon	Emotional disturbance
Duration	Brief or prolonged	May be prolonged
Motor Activity	Synchronous, stereotypic, automatisms, lateral tongue biting, eyes rolled back	Opisthotonos, rigidity, forced eye closure, irregular extremity movements, shaking head, pelvic thrust, crying, geotropic eye movements, tongue biting at the tip
Timing	Day or night	Day; other people present
Physical Injury	May occur	Rare
Incontinence	May occur	Rare
Reproduction of Attack	Spontaneous	Suggestion ± stimulus
EEG	Often inter-ictal discharges	Normal
Prolactin	Increased	Normal

*Pseudoseizures do **not** rule out seizures (not uncommon to present with both)

By law, the Ministry of Transportation must be contacted for all patients who have had a seizure; patients will have their license suspended until seizure free for 6 mo; commercial drivers face a longer wait

- alcoholic withdrawal seizures may occur up to 2 days from the last exposure to alcohol (see Emergency Medicine, ER54)

Investigations
- CBC, electrolytes, fasting blood glucose, Ca^{2+}, Mg^{2+}, ESR, Cr, liver enzymes, CK, prolactin
- also consider toxicology screen, EtOH level, AED level (if applicable)
- CT/MRI (if new seizure without identified cause or known seizure history with new neurologic signs/symptoms)
- LP (if fever or meningismus)
- EEG

EEG findings suggestive of epilepsy: abnormal spikes, polyspike discharges, spike-wave complexes

20-59% of first EEG are positive in epilepsy; 59-92% of epilepsy is picked up with repeated EEGs; normal interictal EEGs do not rule out epilepsy

Treatment
- avoid precipitating factors
- indications for medical therapy (anticonvulsants): 2 or more unprovoked seizures, known organic brain disease, EEG with epileptiform activity, first episode of status epilepticus, abnormal neurologic examination or findings on neuroimaging
- psychosocial issues: stigma of seizures, education of patient and family, status of driver's license, pregnancy issues
- safety issues: driving, operating heavy machinery, bathing, swimming alone
- consider surgical treatment if focal and refractory

Status Epilepticus

- **definition:** unremitting seizure or successive seizures without return to a baseline state of greater than 5 min
- **complications:** anoxia, cerebral ischemia and cerebral edema, MI, arrhythmias, cardiac arrest, rhabdomyolysis and renal failure, aspiration pneumonia/pneumonitis, death (20%)

Medical Emergency: Status epilepticus can cause irreversible brain damage without treatment

www.regentstudies.com

Pregnancy Issues
Teratogenicity of anticonvulsants includes neural tube defects, cleft palate, urogenital malformations, and heart defects. Advise patient planning pregnancy to take 5 mg/d of folic acid. Optimize AEDs with lowest possible dose associated with good seizure control, preferably monotherapy if possible. Risk of fetal malformations with AEDs is 2x general population; highest risk associated with valproic acid and/or 2+ concurrent AEDs. Consider pre-conception AED levels if patient is well-controlled, monthly serum levels during pregnancy, and titrate AED to maintain pre-conception serum levels. Refer to high risk OB for intrapartum fetal screening

The most common causes of status epilepticus are failure to take AEDs and first presentation of epilepsy

Status epilepticus as a result of EtOH withdrawal is rare, despite it being a very common cause of seizures

Rule out non-convulsive status epilepticus in any patient who is still unconscious >20 min post-ictal; order a stat EEG if unsure

Complex partial status epilepticus can resemble schizophrenia or psychotic depression

- **initial measures:** ABCs, vitals, monitors, capillary glucose (STAT), ECG, nasal O_2, IV NS, IV glucose, IV thiamine, ABGs (if respiratory distress/cyanotic)
- **blood work:** electrolytes, Ca^{2+}, Mg^{2+}, PO_4^{3-}, glucose, CBC, toxicology screen, EtOH level, AED levels
- **focused history:** onset, past history of seizures, drug and alcohol ingestion, past medical history, associated symptoms, witnesses/collateral history
- **physical exam** (once seizures controlled): LOC, vitals, HEENT (nuchal rigidity, head trauma, tongue biting, papilledema), complete neurological exam, signs of neurocutaneous disorders, decreased breath sounds, cardiac murmurs or arrhythmias, urinary incontinence, MSK exam (rule out injuries)
- **post-treatment stabilization:** CT head, EEG, Foley catheter to monitor urine output, urine toxicology screen, monitor for rhabdomyolysis, and IV fluids to maintain normal cerebral perfusion pressure

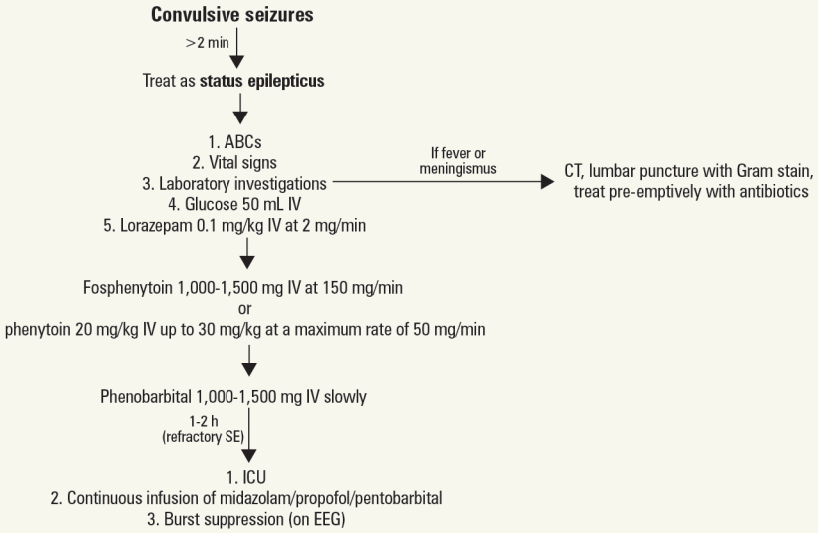


Figure 17. Status epilepticus treatment algorithm

Antiepileptic Drugs

- **generalized-onset and partial-onset seizures:** lamotrigine (Lamictal®), levetiracetam (Keppra®), rufinamide (Banzel®), topiramate (Topamax®), valproic acid (Depakene®, Apo-Valproic®), divalproex sodium (Epival®), zonisamide
- **partial seizures** (simple partial, complex partial, and secondarily generalized seizures): carbamazepine (Tegretol®), gabapentin (Neurontin®), lacosamide (Vimpat®), oxcarbazepine (Trileptal®), phenobarbital (Phenobarb®), phenytoin (Dilantin®), pregabalin (Lyrica®), primidone, tiagabine (Gabitril®), vigabatrin (Sabril®) note: these drugs may exacerbate generalized seizures)
- **absence seizures:** ethosuximide (Zarontin®)

www.regentstudies.com

Behavioural Neurology

- see Psychiatry, PS20

Acute Confusional State/Delirium

Table 12. Selected Intracranial Causes of Acute Confusion

	Etiology	Key Clinical Features	Investigations
Vascular	Subarachnoid hemorrhage	Thunderclap H/A Increased ICP Meningismus	CT (non-contrast) LP Angiography if CT and LP negative
	Stroke/TIA	Focal neurological signs	CT (non-contrast)
Infectious	Meningitis	Fever, H/A, nausea, photophobia Meningismus	CT, LP
	Encephalitis	Focal neurological signs Fever, H/A, ± seizure	CT, LP MRI
	Abscess	Increased ICP Focal neurological signs	CT with contrast (often ring enhancing lesion)
Traumatic	Diffuse axonal shear, epidural hematoma, SDH	Trauma Hx Increased ICP Focal neurological signs	CT (non-contrast) MRI
Autoimmune	Acute CNS vasculitis	Skin rash, active joints	ANA, ANCA, RF MRI Angiography
	Paraneoplastic encephalitis (anti-NMDA-R)	Onset: Psychiatric features, memory loss, seizures Delayed: Movement disorder, and changes in blood pressure, heart rate, and temperature	CSF (test for presence of antibodies)
Neoplastic	Mass effect/edema, hemorrhage, seizure	Increased ICP Focal neurological signs Papilledema	CT (non-contrast) MRI
Seizure	Status epilepticus	See *Seizure Disorders and Epilepsy*, N16	EEG
Primary Psychiatric	Psychotic disorder, mood disorder, anxiety disorder	No organic signs or symptoms	No specific tests
Other	Drugs (e.g. cocaine)	Chest pain, cough with black sputum, new-onset seizure, HTN, increased ICP, dyspnea	Vital signs Serum chemistry and electrolyte analysis
	Medications (with anticholinergic side effects)	Flushing, dry skin and mucous membranes, mydriasis with loss of accommodation	Serum chemistry and electrolyte analysis

Mild Neurocognitive Disorder (Mild Cognitive Impairment)

Definition

- cognitive impairment not meeting criteria of Major Neurocognitive Disorder
- several criteria proposed with considerable overlap
- in general, criteria include a measurable cognitive deficit in at least one domain reported by patient or others without impairment in ADLs and in the absence of Major Neurocognitive Disorder
- amnestic (precursor to AD) vs. Non-amnestic MCI

Pathophysiology

- genetic factors
  - minority (<7%) of AD cases are familial (autosomal dominant)
  - 3 major genes for autosomal dominant AD have been identified:
    - amyloid precursor protein (chromosome 21), presenilin 1 (chromosome 14), presenilin 2 (chromosome 1)
  - the E4 polymorphism of apolipoprotein E (ApoEAPOEApoE) is a susceptibility genotype (E2 is protective)
  - note: ApoEAPOEApoE cannot serve as a diagnostic marker because it is only a risk factor and neither necessary nor sufficient for disease occurrence
- pathology (not necessarily specific for AD)
  - gross pathology
    - diffuse cortical atrophy, especially frontal, parietal, and temporal lobes (hippocampi)
  - microscopic pathology
    - senile plaques (extracellular deposits of amyloid in the grey matter of the brain)
    - loss of synapses
    - neurofibrillary tangles (intracytoplasmic paired helical filaments with amyloid and hyperphosphorylated Tau protein)
    - loss of cholinergic neurons in nucleus basalis of Meynert which normally project diffusely throughout the cortex

Delirium is a medical emergency carrying significant risk of morbidity and mortality; it is characterized by acute onset, disorientation, fluctuating level of consciousness, poor attention, and marked psychomotor changes

Visual hallucinations more commonly indicate organic disease

www.regentstudies.com

- biochemical pathology
  - 50-90% reduction in action of choline acetyltransferase

Epidemiology
- published prevalence rates vary from 2-4 percent to more than 20 percent due to different diagnostic criteria and measuring instruments

Risk Factors
- elevated blood pressure, obesity, cardiac disease, and apolipoprotein E epsilon 4 genotype associated with increased risk of mild NCD

Signs and Symptoms
- cognitive impairment
  - particularly in amnestic subtype
  - important to ascertain that memory complaints represent change from baseline
  - patients with mild NCD are often troubled by memory symptoms in comparison to patients with dementia
- neuropsychiatric symptoms
  - depression (50%), irritability, anxiety, aggression, and apathy

Investigations
- establish a baseline for follow-up
- office evaluation
  - clinical interview is the cornerstone of mild NCD evaluation
  - ideally informants should be involved in the interview
  - consider drop-off in personal care and ADLs at later stage
- neuropsychological testing
  - MMSE or MoCA
  - should not be used in isolation
  - if abnormal, follow-up in one year to monitor for cognitive and functional decline
- neuroimaging
  - role uncertain
  - most advocate for a non-contrast brain CT to evaluate for structural abnormalities (CVD, SDH, NPH, or mass lesion)
- other testing
  - exclude treatable conditions and underlying psychiatric conditions

Treatment
- watch and wait
- no evidence for cholinesterase inhibitors, anti-inflammatory agents, vascular risk factor modification, exercise, cognitive interventions

Prognosis
- 10% progress to dementia per yr
- typically progress to dementia over a period of 2-3 yr

Major Neurocognitive Disorder (formerly Dementia)

- see Psychiatry, PS21 and Geriatric Medicine, GM4

Definition
- an acquired, generalized, and (usually) progressive impairment of cognitive function (i.e. memory, recall, orientation, language, abstraction) associated with impairment in activities of daily living (i.e. planning, shopping, food preparation, difficulties with finances)
- affects comprehension, but not level of consciousness
- diagnosis of major NCD requires presence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:
  A) concern of the individual or a knowledgeable informant AND
  B) a substantial impairment in cognitive performance either documented by standardized neuropsychological testing, or quantified clinical assessment
- see Psychiatry, PS21 for DSM-5 diagnostic criteria
- differentiated from mild NCD (formerly mild cognitive impairment) by the extent to which the impairment affects ADLs
  - mild NCD represents an intermediate stage between dementia and normal aging
  - by definition, IADLs are not affected in mild NCD

Epidemiology
- major NCD (dementia): 1-2% at age 65 yr and reaching as high as 30% by age 85 yr
- mild NCD: 2-10% at age 65 yr and 5-25% by age 85 yr

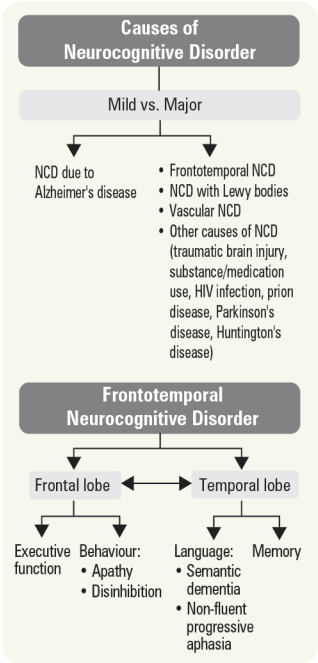


Figure 18. Dementia classification

www.regentstudies.com

- note
  - major NCD due to Alzheimer's disease is uncommon before age 60 yr
  - major NCD due to frontotemporal lobar degeneration has an earlier onset and represents a progressively smaller fraction of all NCDs with age

Etiology
- see Table 13 for common causes of dementia
- see Table 14 for acquired causes of dementia
- reversible causes: alcohol (intoxication or withdrawal, Wernicke's encephalopathy), medication (benzodiazepines, anticholinergics), heavy metal toxicity, hepatic or renal failure, B_{12} deficiency, glucose, cortisol, thyroid dysfunction, NPH, depression (pseudodementia), intracranial tumour, SDH, hypercalcemia (secondary to elevated PTH)
- must rule out delirium

History
- "geriatric giants"
  - confusion/incontinence/falls/polypharmacy
  - memory and safety (wandering, leaving doors unlocked, leaving stove on, losing objects)
  - behavioural (mood, anxiety, psychosis, suicidal ideation, personality changes, aggression)
- ADLs and IADLs
- cardiovascular, endocrine, neoplastic, renal ROS
- alcohol, smoking
- OTCs, herbal remedies, medications (sedative hypnotics, antipsychotics, antidepressants, anticholinergics), compliance, accessibility
- history of vascular disease or head trauma
- collateral history

Physical Exam
- blood pressure
- hearing and vision
- neurological exam with attention to signs of parkinsonism, UMN findings, CVD
- general physical exam depending on risk factors and history
- MMSE or MoCA, clock drawing, frontal lobe testing (go/no-go, word lists, similarities, proverb)

Investigations
- depends on suspected etiologies (see Tables 13 and 14)
  - CBC (note MCV for evidence of alcohol use and B_{12} deficiency), glucose, TSH, B_{12}, RBC folate
  - electrolytes, LFTs, renal function, lipids, serum calcium
  - CT head, MRI as indicated (MRI preferred), SPECT (optional)
  - as clinically indicated: VDRL, HIV, ANA, anti-dsDNA, ANCA, ceruloplasmin, copper, cortisol, toxicology, heavy metals
- issues to consider
  - failure to cope, fitness to drive, caregiver education and stress, power of attorney, legal will, advanced medical directives, patient and caregiver safety

Table 13. Common Causes of Major NCD (Dementia)

Etiology	Key Clinical Features	Investigations
PRIMARY DEGENERATIVE		
Alzheimer's disease	Memory impairment Aphasia, apraxia, agnosia	CT or MRI, SPECT
Dementia with Lewy bodies	Visual hallucinations Parkinsonism Fluctuating cognition	CT or MRI, SPECT
Frontotemporal dementia (e.g. Pick's disease)	Behavioural presentation: Disinhibition, perseveration, decreased social awareness, mental rigidity, memory relatively spared Language presentation: Progressive non-fluent aphasia, semantic dementia	CT or MRI, SPECT
Huntington's disease	Chorea	Genetic testing
VASCULAR		
Vascular cognitive impairment (previously Multi-infarct dementia)	Bradyphrenia without features of parkinsonism (slow thinking, slow rate of learning, slow gait) Dysexecutive syndrome May be abrupt onset Stepwise deterioration is classic but progressive deterioration is most common	CT or MRI, SPECT
CNS vasculitis	Systemic S&S of vasculitis	ANA; ANCA; RF CT or MRI Angiography

Sensitivity and Specificity

Tool	Sensitivity	Specificity
MMSE	87%	82%
Clinical Judgment	85%	82%
DSM IV	76%	80%

Vitamin B_{12} Deficiency Symptoms
- Macrocytic anemia, pallor, SOB, fatigue, chest pain, palpitations
- Confusion or change in mental status (if advanced)
- Decreased vibration sense
- Distal numbness and paresthesia
- Weakness with UMN findings
- Diarrhea, anorexia

Dementia DDx

VITAMIN D VEST
Vitamin deficiency (B_{12}, folate, thiamine)
Intracranial tumour
Trauma (head injury)
Anoxia
Metabolic (DM)
Infection (postencephalitis, HIV)
NPH
Degenerative (Alzheimer's, Huntington's, CJD)
Vascular (multi-infarct dementia)
Endocrine (hypothyroid)
Space occupying lesion (chronic SDH)
Toxic (alcohol)

Dementia Considerations for Management

ABCDs
Affective disorders, **A**DLs
Behavioural problems
Caretaker, **C**ognitive medications and stimulation
Directives, **D**riving
Sensory enhancement (glasses/hearing aids)

Cholinesterase Inhibitors for Dementia with Lewy Bodies (DLB), Parkinson's Disease Dementia (PDD) and Cognitive Impairment in Parkinson's Disease (CIND-PD)
Cochrane DB Syst Rev 2012;3:CD006504
Study: Meta-analysis of RCTs assessing efficacy of treatment with cholinesterase inhibitors in DLB, PDD, and CIND-PD.
Results: The six trials (n=1,236) included demonstrated therapeutic benefit of cholinesterase inhibitors for global assessment, cognitive function, behavioural disturbance, and activities of daily living. Cholinesterase inhibitors were associated with increased adverse events (OR 1.64) and drop out (OR 1.94). Adverse events were more common with rivastigmine but not with donepezil. Fewer deaths occurred in the treatment group (OR 0.28).
Conclusion: Current evidence supports use of cholinesterase inhibitors for patients with PDD but its role in DLB and CIND-PD is still unclear.

www.regentstudies.com

Table 14. Acquired Causes of Major NCD (Dementia)

Etiology	Key Clinical Features	Investigations
INFECTIOUS		
Chronic meningitis	Fever, H/A, nausea Meningismus Localizing neurological deficits	CT, LP
Chronic encephalitis	Fever, headache	CT or MRI
Chronic abscess	Increased ICP Localizing neurological deficits	CT with contrast
HIV	See Infectious Diseases, ID28	HIV serology
Creutzfeldt-Jakob disease	Rapidly progressive, myoclonus	EEG, CT or MRI, LP
Syphilis	Ataxia, myoclonus, tabes dorsalis	LP, CT, or MRI VDRL
TRAUMATIC		
Diffuse axonal shear, epidural hematoma, subdural hematoma, SDH	Trauma Hx Increased ICP, papilledema Localizing neurological signs	CT (non-contrast)
RHEUMATOLOGIC		
SLE	See Rheumatology, RH11	MRI ANA, anti-dsDNA
NEOPLASTIC		
Mass effect/edema, hemorrhage, seizure	Increased ICP Localizing neurological signs	CT with contrast MRI
Paraneoplastic encephalitis	Systemic symptoms of cancer	Anti-Hu antibodies

Most common causes of rapidly progressive neurodegenerative dementia (less than 4 yr survival): CJD, frontal temporal lobar dementia, tauopathies, diffuse Lewy body disease, and AD
Arch Neurol 2009;66:201-207

Early Signs of Dementia/Major NCD	Normal Aging
Forgetting the names of close relations	Forgetting the names of acquaintances
Increased frequency of forgetting	Briefly forgetting part of an experience
Repeating phrases/stories in the same conversation	Not putting away things properly
Unpredictable mood changes	Mood changes in response to appropriate causes
Decreased interest in activities and difficulty making choices	Changes in usual interests

Major or Mild NCD due to Alzheimer's Disease

- see Psychiatry, PS22

Definition

- beyond criterion for NCD, the core features of major or mild NCD due to Alzheimer's disease include an insidious onset and gradual progression of cognitive and behavioural symptoms
- typical presentation: amnestic (i.e. impairment in memory and learning - impaired ability to learn new information)
  - mild phase: impairment in memory and learning sometimes accompanied with deficits in executive function
  - moderate-severe phase: visuoconstructional/perceptual-motor ability and language may also be impaired
  - social cognition tends to be preserved until late in the course of the disease
- atypical nonamnestic presentation (one of the following)
  1. aphasia: language disturbance
  2. apraxia: impaired ability to carry out motor activities despite intact motor function
  3. agnosia: failure to recognize or identify objects despite intact sensory function
- note: there may be no evidence of mixed etiology (i.e. absence of other neurodegenerative or CVD)

4 As and one D of AD

Anterograde amnesia
Aphasia
Apraxia
Agnosia
Disturbance in executive function

(Anterograde amnesia plus at least one of the other features is required for AD diagnosis)

Pathophysiology

- genetic factors
  - minority (<7%) of AD cases are familial (autosomal dominant)
  - 3 major genes for autosomal dominant AD have been identified:
    - amyloid precursor protein (chromosome 21), presenilin 1 (chromosome 14), presenilin 2 (chromosome 1)
  - the E4 polymorphism of apolipoprotein E (APOE) is a susceptibility genotype (E2 is protective)
  - note: APOE cannot serve as a diagnostic marker because it is only a risk factor and neither necessary nor sufficient for disease occurrence
- pathology (although not necessarily specific for AD)
  - gross pathology
    - diffuse cortical atrophy, especially frontal, parietal, and temporal lobes (hippocampi)
  - microscopic pathology
    - senile plaques (extracellular deposits of amyloid in the grey matter of the brain)
    - loss of synapses
    - neurofibrillary tangles (intracytoplasmic paired helical filaments with amyloid and hyperphosphorylated Tau protein)
    - loss of cholinergic neurons in nucleus basalis of Meynert that project diffusely throughout the cortex
  - biochemical pathology
    - 50-90% reduction in action of choline acetyltransferase

Down syndrome predisposes to early onset of Alzheimer's (i.e. age of ~40) due to three copies of the amyloid gene (APP)

www.regentstudies.com

Epidemiology
- 1/12 of population 65-75 yr of age
- up to 1/3 population >85 yr of age
- accounts for 60-90% of all dementias (depending on setting and diagnostic criteria)

Risk Factors
- age is the largest risk factor
- genetic susceptibility polymorphism: apolipoprotein E4 increases risk and decreases age of onset
- other factors include: traumatic brain injury, family history, Down syndrome, low education, and presence of multiple vascular risk factors (e.g. smoking, HTN, hypercholesterolemia, DM)

Signs and Symptoms
- cognitive impairment
  - memory impairment for newly acquired information (early)
  - deficits in language, abstract reasoning, and executive function
- behavioural and psychiatric manifestations (80% of those with major NCD)
  - mild NCD: major depressive disorder and/or apathy
  - major NCD: psychosis, irritability, agitation, combativeness, and wandering
- motor manifestations (late)
  - gait disturbance, dysphagia, incontinence, myoclonus, and seizures
  - parkinsonism (if present consider DLB)

Investigations
- perform investigations to rule out other potentially reversible causes of dementia
- EEG: usually normal, may observe generalized slowing (nonspecific)
- MRI: preferential atrophy of the hippocampi and precuneus of the parietal lobe; dilatation of lateral ventricles; widening of cortical sulci
- SPECT: hypoperfusion in temporal and parietal lobes
- PET imaging using Pittsburgh compound B (PIB) as a tracer enables imaging of beta-amyloid plaque in neuronal tissue

Treatment
- acetylcholinesterase inhibitors have been shown to slow decline in cognitive function
  - donepezil, rivastigmine, galantamine
  - relative contraindications: bradycardia, heart block, arrhythmia, CHF, CAD, asthma, COPD, ulcers, or risk factors for ulcers and/or GI bleeding
  - galantamine is contraindicated in patients with hepatic/renal impairment
- memantine is an NMDA-receptor antagonist that has some benefits in later stage AD (i.e. when MMSE <17)
- symptomatic management
  1. pharmacologic
     - low dose neuroleptics for agitation (neuroleptics may worsen cognitive decline)
     - trazodone for sleep disturbance
     - antidepressants (SSRIs)
  2. non-pharmacologic
     - redirection
     - explore inciting factors for behaviour and modify behaviour of patient or caregiver
     - family support and day care facilities

Cognitive Effects of Atypical Antipsychotic Medications in Patients with Alzheimer's Disease: Outcomes from CATIE-AD
Am J Psychiatry 2011;168:831-839
Study: 421 outpatients with Alzheimer's disease and psychosis or agitated/aggressive behaviour were randomized to receive olanzapine, quetiapine, risperidone, or placebo in a multicentre double-blinded RCT. MMSE and Alzheimer's Disease Assessment Scale (ADAS) scores were measured at 36 wk.
Results: Patients receiving atypical antipsychotics exhibited a faster rate of cognitive decline as measured by MMSE scores (– 0.067/wk vs. -0.007/wk). They also had a significantly faster decline compared to placebo on a composite measure of ADAS, MMSE, and various other cognitive tests (-0.011/wk vs. -0.001/wk).
Conclusions: Long-term use of atypical antipsychotics for behavioural symptoms and psychosis in dementia patients is associated with greater rates of cognitive decline.

Prognosis
- mean duration of survival after diagnosis is approximately 10 yr, reflecting the advanced age of the majority of individuals rather than the course of the disease
- in those who survive the full course, death commonly results from aspiration

Major or Mild NCD with Lewy Bodies
(formerly Dementia with Lewy Bodies)

Definition
- A NCD that includes not only progressive cognitive impairment (with early changes in complex attention and executive function rather than learning and memory), but also recurrent complex visual hallucinations
- core diagnostic features
  - fluctuating cognition with pronounced variations in attention and alertness
  - recurrent visual hallucinations that are well formed and detailed
  - spontaneous features of parkinsonism, with onset subsequent to development of cognitive decline (rest tremor may be absent in DLB, but otherwise same classic features of Parkinson's disease)
- suggestive/supportive features
  - meets criteria for rapid eye movement (REM) sleep behaviour disorder
  - severe sensitivity to neuroleptic medications (rigidity, neuroleptic malignant syndrome, extrapyramidal symptoms)

www.regentstudies.com

- repeated falls, syncope, or transient episodes of unexplained loss of consciousness
- auditory or other nonvisual hallucinations, systematic delusions, and depression may also be present

Etiology and Pathogenesis
- Lewy bodies (eosinophilic cytoplasmic inclusions) found in both cortical and subcortical structures
- mixed DLB and AD pathology is common

Diagnostically Suggestive Markers
- low striatal dopamine transporter uptake on SPECT or PET
- relative preservation of medial temporal structures on CT/MRI

Epidemiology
- 0.1-5% of the general elderly population
- Lewy bodies are present in 20-35% of all dementia cases (more common in males)

Treatment
- acetylcholinesterase inhibitors (e.g. donepezil)

Prognosis
- average duration of survival 5-7 yr

Major or Mild Frontotemporal NCD
(formerly Frontotemporal Dementia)

Definition
- refers to a group of disorders caused by progressive cell degeneration in the brain's frontal or temporal lobes
- there are several variants of FTD each with specific core symptoms
- nevertheless, there is overlap between variants (i.e. NCD criteria along with relative sparing of learning and memory and perceptual-motor function)
- common neurocognitive symptoms include deficits in executive function (e.g. poor mental flexibility, abstract reasoning, response inhibition, planning/organization, and increased distractibility)
- "probable" is distinguished from "possible" frontotemporal NCD by:
  - evidence of causative frontotemporal NCD genetic mutation, from either family history or genetic testing
  - evidence of disproportionate frontal and/or anterior temporal atrophy on MRI or CT
  - evidence of frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT

Behavioural Variant FTD
- most common variant; disinhibition and apathy are common symptoms
- insidious onset: must show progressive deterioration of behaviour and/or cognition by observation or history
- prominent decline in social cognition and/or executive abilities
- typically early symptom presentation (i.e. within the first 3 yr)
- three out of the following symptoms must be present and persistent/recurrent:
  - behavioural disinhibition (socially inappropriate behaviour, impulsive, careless)
  - apathy or inertia
  - loss of sympathy or empathy (diminished response to others' needs/feelings, social interest)
  - preservative, stereotyped, or compulsive/ritualistic behaviour
  - hyperorality and dietary changes (binge eating, increased consumption of alcohol/cigarettes or inedible objects)

Language Variants (Primary Progressive Aphasia)
- prominent decline in language ability, in the form of speech production, word finding, object naming, grammar, or word comprehension
- three subtypes
  - nonfluent/agrammatic variant PPA (NFAV-PPA) or progressive nonfluent aphasia (PNFA): non-fluent, laboured articulation/speech, anomia, preserved single word comprehension, word-finding deficit, impaired repetition
  - semantic variant PPA (SV-PPA) or semantic dementia (SD): fluent, normal rate, anomia, impaired single word comprehension, intact repetition, use words of generalization ("thing") or supraordinate categories ("animal" for "dog")
  - logopenic progressive aphasia (LPA): naming difficulty and impaired repetition

www.regentstudies.com

FTD Movement Disorders
- corticobasal degeneration (CBD): shakiness, lack of coordination, muscle rigidity and spasms
- progressive supranuclear palsy (PSP): walking and balance problems; frequent falls and muscle stiffness

Etiology and Pathogenesis
- unknown, however there is likely a genetic/familial component (40% have family history of early onset NCD)
- genetic variants: MAPT gene (Tau), PGRN gene (progranulin), VCP gene, TARDBP gene (TDP-43), CHMP2D gene
- unlike AD, FTD does not show amyloid plaques or neurofibrillary tangles, instead it is characterized by severe atrophy and specific neuronal inclusion bodies
- gross changes: atrophy in the frontal and anterior temporal lobes; cortical thinning; possible ventricular enlargement
- histological changes: gliosis, swollen neurons, microvacuolation, inclusion bodies in neurons/glia (Tau or TDP-43)

Epidemiology
- fourth most common cause of dementia (5% of all dementia cases)
- common cause of early-onset NCD in individuals younger than 65 yr

Prognosis
- median survival being 6-11 yr after symptoms onset and 3-4 yr after diagnosis
- survival is shorter and decline is faster than in typical Alzheimer's disease

Major or Mild Vascular NCD

Definition
- diagnosis of major or mild NCD with determination of CVD as the dominant if not exclusive pathology that accounts for the cognitive deficits
- vascular etiology suggested by one of the following:
  - onset of cognitive deficits is temporally related to one or more cerebrovascular events
  - evidence for decline is prominent in complex attention (including processing speed) and frontal-executive function
- evidence of the presence of CVD from history, physical exam, and/or neuroimaging that is sufficient to account for the neurocognitive deficits
- neuroimaging evidence of cerbrovascular disease comprises one or more of the following:
  - one or more large vessel infarct or hemorrhage
  - a strategically placed single infarct or hemorrhage (e.g. angular gyrus, thalamus, basal forebrain)
  - two or more lacunar infarcts outside the brainstem
  - extensive and confluent white matter lesions
- for mild vascular NCD: history of a single stroke or extensive white matter disease is sufficient
- for major vascular NCD: history of two or more strokes, a strategically placed stroke, or a combination of white matter disease and one or more lacunae is generally necessary
- associated features supporting diagnosis: personality and mood changes, abulia, depression, emotional lability, and psychomotor slowing

Etiology and Pathogenesis
- major risk factors are the same as those for CVD (i.e. HTN, DM, smoking, obesity, high cholesterol levels, high homocysteine levels, other risk factors for atherosclerosis, atrial fibrillation, and conditions increasing risk of cerebral emboli)
- major or mild vascular NCD with gradual onset and slow progression is generally due to small vessel disease leading to lesions in white matter, basal ganglia, and/or thalamus
- cognitive deficits can be attributed to disruption of cortical-subcortical circuits

Epidemiology
- second most common cause of NCD
- prevalence estimates for vascular dementia/NCD range from 0.2-13% (by age 70), 16% (ages 80+) to 44.6% (ages 90+)
- higher prevalence in African Americans compared to Caucasians and East Asians
- prevalence higher in males than in females

Creutzfeldt-Jakob Disease

- rare degenerative fatal brain disorder caused by prion proteins causing spongiform changes, astrocytosis, and neuronal loss
- most common forms are sporadic (85%), hereditary (5-10%), and acquired (<1%)
- investigations: CSF analysis, MRI brain (cortical and/or subcortical FLAIR changes), EEG (periodic complexes)
- definitive diagnosis is by brain biopsy
- no treatments currently exist

Prion proteins have a normal form and an infectious form, which results from conversion of the protein from alpha-helix (normal) to beta-pleated sheet (abnormal); these abnormally folded proteins aggregate leading to neuronal loss

www.regentstudies.com

Normal Pressure Hydrocephalus

- see Neurosurgery, NS8

Aphasia

Definition

- an acquired disturbance of language characterized by errors in speech production, writing, comprehension, or reading

Neuroanatomy of Aphasia

- Broca's area (posterior inferior frontal lobe) involved in speech production (expressive)
- Wernicke's area (posterior superior temporal lobe) involved in comprehension of language (receptive)
- angular gyrus is responsible for relaying written visual stimuli to Wernicke's area for reading comprehension
- arcuate fasciculus association bundle connects Wernicke's and Broca's areas

Assessment of Language

- assessment of context
  - handedness (writing, drawing, toothbrush, scissors), education level, native language, learning difficulties
- assessment of aphasia
  - spontaneous speech (fluency, paraphasias, repetition, naming, comprehension – auditory and reading, writing, neologisms)

- >99% of right-handed people have left hemisphere language representation
- 70% of left-handed people have left hemisphere language representation, 15% have right hemisphere representation, and 15% have bilateral representation

Types of Paraphasias
- Semantic ("chair" for "table")
- Phonemic ("clable" for "table")

Aphasia localizes the lesion to the dominant cerebral hemisphere

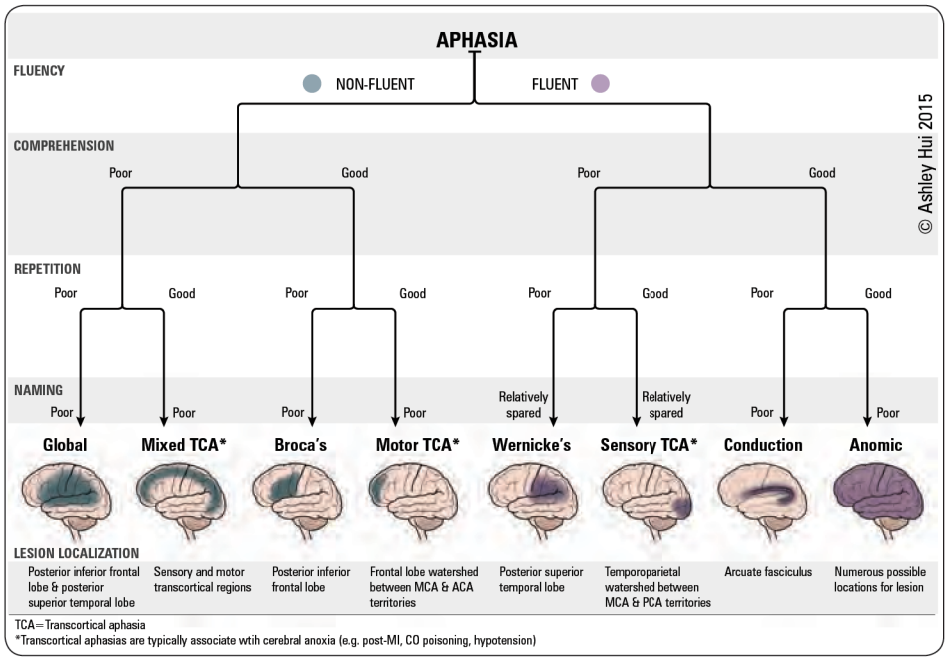


Figure 19. Aphasia classification

Apraxia

Definition

- inability to perform skilled voluntary motor sequences that cannot be accounted for by weakness, ataxia, sensory loss, impaired comprehension, or inattention

www.regentstudies.com

Clinicopathological Correlations

Table 15. Apraxia

	Description	Tests	Hemispheres
Ideomotor	Inability to perform skilled learned motor sequences	Blowing out a match; combing one's hair	Left
Ideational	Inability to sequence actions	Preparing and mailing an envelope	Right and left
Constructional*	Inability to draw or construct	Copying a figure	Right and left
Dressing*	Inability to dress	Dressing	Right

*Refers specifically to the inability to carry out the learned movements involved in construction, drawing, or dressing; not merely the inability to construct, draw, or dress. Many skills aside from praxis are needed to carry out these tasks

Agnosia

Definition
- disorder in the recognition of the significance of sensory stimuli in the presence of intact sensation and naming

Clinicopathological Correlations

Table 16. Agnosias

	Description	Lesion
Apperceptive Visual Agnosia	Inability to name or demonstrate the use of an object presented visually 2° to distorted visual perception Recognition by touch remains intact	Bilateral temporo-occipital cortex
Associative Visual Agnosia	Inability to name an object presented visually 2° to disconnect between visual cortex and language areas Visual perception is intact as demonstrated by visual matching	Bilateral inferior temporo-occipital junction
Prosopagnosia	Inability to recognize familiar faces in the presence of intact visual perception and intact auditory recognition	Bilateral temporo-occipital areas or right inferior temporo-occipital region
Colour Agnosia	Inability to perceive colour	Bilateral inferior temporo-occipital lesions
Impaired Stereognosis	Inability to identify objects by touch	Anterior parietal lobe in the hemisphere opposite the affected hand
Finger Agnosia	Inability to recognize, name, and point to individual fingers	Dominant hemisphere parietal-occipital lesions

Parietal Lobe Lesions
- Lesions of the dominant parietal lobe are characterized by Gerstmann's syndrome: acalculia, agraphia, finger agnosia, and left-right disorientation
- Lesions of the non-dominant parietal lobe are characterized by neglect, anosognosia, and asomatognosia
- Cortical sensory loss (graphesthesia, astereognosis, impaired 2 point discrimination and extinction) can be seen with left or right parietal lesions

Mild Traumatic Brain Injury

Definition
- mild TBI = concussion
- trauma induced transient alteration in mental status that may involve loss of consciousness
- hallmarks of concussion: confusion and amnesia, which may occur within minutes
- loss of consciousness (if present) must be less than 30 min, initial GCS must be between 13-15, and post-traumatic amnesia must be less than 24 h

- Extent of retrograde amnesia correlates with severity of injury
- Regained from most distant to recent memories

Epidemiology
- 75% of TBIs are estimated to be mild; remainder are moderate or severe (see Neurosurgery, NS31 and Emergency Medicine, ER9)
- highest rates in children 0-4 yr, adolescents 15-19 yr, and elderly >65 yr

Clinical Features
- impairments following mild TBI
  - somatic: headache, sleep disturbance, nausea, vomiting, blurred vision
  - cognitive dysfunction: attentional impairment, reduced processing speed, drowsiness, amnesia
  - emotion and behaviour: impulsivity, irritability, depression
- severe concussion: may precipitate seizure, bradycardia, hypotension, sluggish pupils
- associated conditions: brain contusion, diffuse axonal injury, C-spine injury

Investigations
- neurological exam to identify focal neurologic deficits
- neurocognitive assessment
  - simple orientation questions are inadequate to detect cognitive changes
  - initial assessment of severity is determined by
    - Glasgow Coma Scale: mild: 13-15, moderate: 9-12, severe: 3-8
  - sideline evaluation: Standardized Assessment of Concussion, Westmead Post-Traumatic Amnesia Scale, Sport Concussion Assessment Tool

www.regentstudies.com

- neuroimaging
  - x-ray of skull: not indicated for routine evaluation of MTBI
  - CT head as indicated by Canadian CT Head Rules (see Emergency Medicine, ER8)
  - MRI not indicated in initial evaluation – indicated in presence of continued or worsening symptoms despite normal CT

Treatment

- observation for first 24 h after mild TBI in all patients because of risk of intracranial complications
- emergency department for assessment if any loss of consciousness or persistent symptoms
- hospitalization with normal CT if GCS <15, seizures, or bleeding diathesis; or abnormal CT scan
- early rehabilitation to maximize outcomes
  - OT, PT, SLP, vestibular therapy, driving, therapeutic recreation
- pharmacological management of headaches, pain, depression
- CBT, relaxation therapy
- follow Return to Play guidelines (www.thinkfirst.ca)

Prognosis

- most recover from mild TBI with minimal treatment, but some experience long-term consequences
- athletes with a previous concussion are at increased risk of subsequent concussion and cumulative brain injury
- repeat TBI can lead to life threatening cerebral edema (controversially known as second impact syndrome) or permanent impairment
- sequelae include
  - post-concussion syndrome: dizziness, headache, neuropsychiatric symptoms, cognitive impairment (usually resolves within weeks to months)
  - post-traumatic headaches: begin within 7 d of injury
  - post-traumatic epilepsy: two-fold increase in risk of epilepsy in 5 yr post-TBI, prophylactic anticonvulsants not effective
  - post-traumatic vertigo

Neuro-Oncology

Paraneoplastic Syndromes

- see Endocrinology, E51

Tumours of the Nervous System

- see Neurosurgery, NS10

Movement Disorders

Overview of Movement Disorders

Table 17. Movement Disorder Definitions

Akathisia	Subjective restlessness relieved by stereotypic movements (e.g. squirming)
Asterixis	Loss of muscle contraction (negative myoclonus)
Athetosis	Slow writhing movements, especially distally
Bradykinesia	Slow and/or small amplitude movements
Chorea	Brief, abrupt, irregular movements; can appear purposeful in milder forms
Dyskinesia	Any sudden involuntary movement, but the term is often used to describe the stereotypical movements that come with long-term neuroleptic or dopaminergic use
Dystonia	Co-contraction of agonist and antagonists causing sustained twisting movements
Freezing	Episodes of halted motor action, especially during walking
Hemiballismus	Unilateral violent flinging movement
Myoclonus	Brief muscle group contraction that is either focal, segmental, or generalized
Myokymia	Spontaneous, fine, fascicular contraction of muscle
Tachykinesia	Acceleration of movements
Tics	Stereotyped repetitive actions due to inner urge; can be suppressed
Tremor	Rhythmic alternating muscle contraction and relaxation

In some cases, dystonias may only occur during voluntary movement and sometimes only during specific activities such as writing, chewing, or speaking

Hemiballismus is most often due to a vascular lesion of the contralateral subthalamic nucleus

Some myoclonus is stimulus sensitive and can be induced by noise, movement, light, visual threat, or pinprick

www.regentstudies.com

Function of the Basal Ganglia

- the cerebral cortex initiates movement via excitatory (glutamatergic) projections to the striatum, which then activate two pathways: direct and indirect
- direct: cortex → striatum → GPi/SNr → thalamus → motor cortex
  - activation of this pathway removes the inhibitory effect of the GPi on the thalamus, letting the thalamus activate the cortex and ultimately allowing movement
- indirect: cortex → striatum → GPe → STN → GPi/SNr → thalamus → motor cortex
  - activation of this pathway causes inhibition of the thalamus and ultimately prevents movement

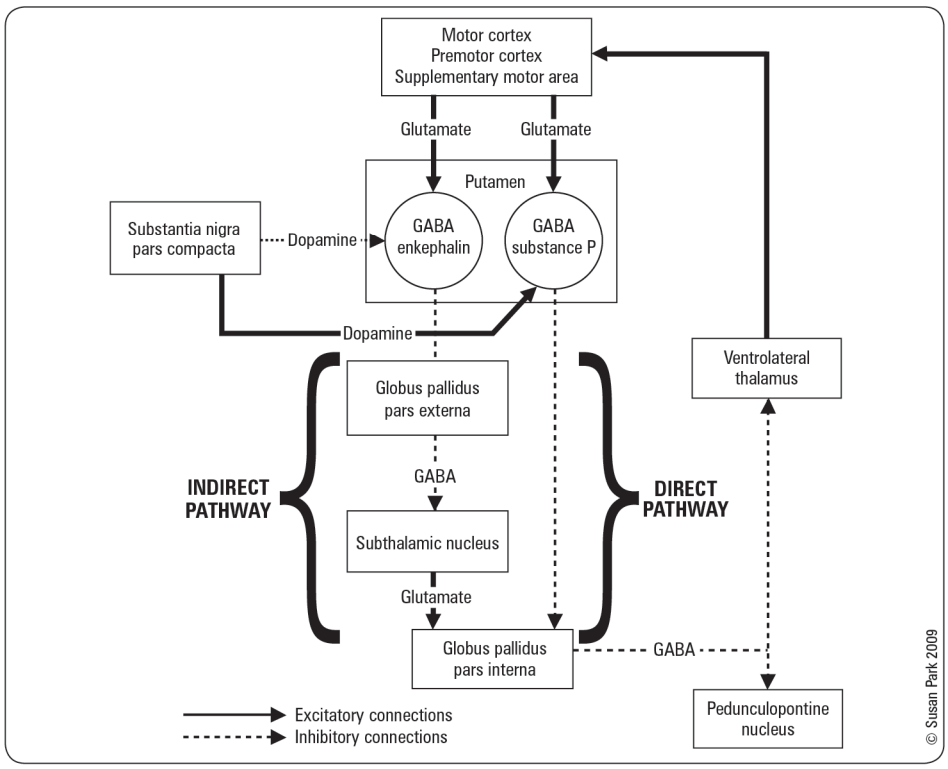


Figure 20. Neural connections of the basal ganglia

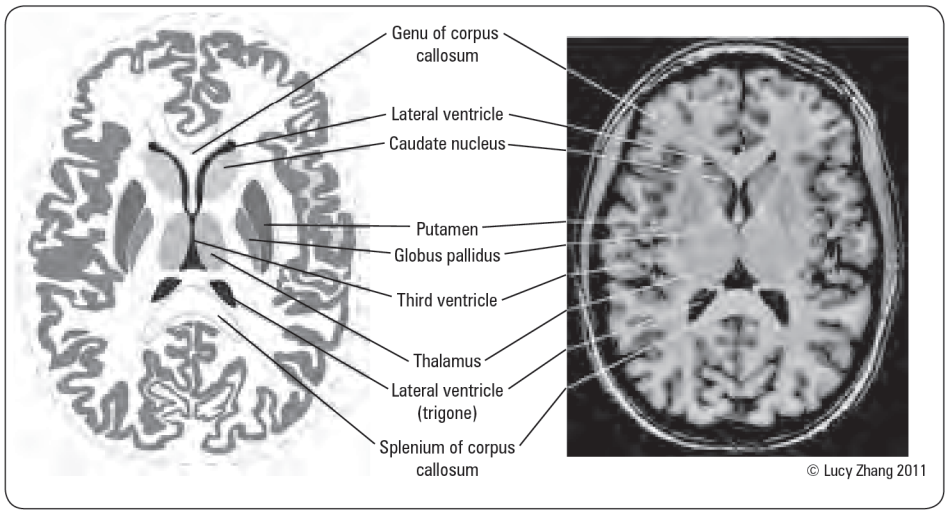


Figure 21. Horizontal section of basal ganglia

www.regentstudies.com

Movement Disorders

Differential Diagnoses

1. **Tremor**
   - **postural:** physiologic, anxiety, sedative/alcohol withdrawal, drug toxicity, heavy metal poisoning, carbon monoxide poisoning, thyrotoxicosis, benign essential tremor, cerebellar, Wilson's disease
     - benign essential tremor is a common autosomal dominant trait that presents as a bilateral postural tremor of the vertical axis, especially in the upper extremities
   - **intention:** brainstem lesion, cerebellar lesion, alcohol, anticonvulsants, sedatives, Wilson's disease
   - **resting:** Parkinsonism, Wilson's disease, mercury poisoning

In a young patient (<45) must do TSH (thyroid disease), ceruloplasmin (Wilson's disease), and CT/MRI (cerebellar disease) as indicated by type of tremor

Alcohol
- Dampens essential tremor
- Potentiates intention tremor
- Does not improve resting tremor of PD

Table 18. Approach to Tremors

	Resting	Postural	Intention
Body Part	Distal UE	UE/head/voice	Anywhere
Characteristics	3-7 Hz pill rolling	6-12 Hz fine tremor	<5 Hz coarse tremor
Worse with Associated Sx	Rest while concentrating "TRAP"	Sustained posture (outstretched arms) ± Autosomal dominant FHx	Finger to nose Cerebellar findings
DDx	PD, Parkinsonism, Wilson's disease	Physiologic, benign essential, drugs, hyperthyroid, hyperglycemic	Cerebellar disorders, Wilson's disease, alcohol, MS
Treatment	Carbidopa-levodopa (Sinemet®), surgery, DBS	Propranolol, anticonvulsants, primidone	Treat underlying cause

>90% of essential tremor does not need treatment

2. **Chorea:** Huntington's disease, neuroacanthocytosis, SLE, APLA syndrome, Wilson's disease, CVD, tardive dyskinesia, senile chorea, Sydenham's chorea, pregnancy chorea

Most common cause of chorea is drug therapy for PD

3. **Dystonia**
- **primary dystonia:** familial, sporadic (torticollis, blepharospasm, writer's cramp)
- **dystonia-plus syndromes:** dopa-responsive dystonia, myoclonus-dystonia
- **secondary dystonia:** thalamotomy, stroke, CNS tumour, demyelination, PNS injury, drugs/toxins (L-dopa, neuroleptics, anticonvulsants, Mn, CO, cyanide, methanol)
- **heredodegenerative dystonias:** Parkinsonian disorders, Wilson's disease, Huntington's disease

4. **Myoclonus**
- **physiologic myoclonus:** hiccups, nocturnal myoclonus
- **essential myoclonus**
- **epileptic myoclonus**
- **symptomatic myoclonus**
  - degenerative disorders (Wilson's disease, Huntington's disease, Corticobasal degeneration)
  - infectious disorders (CJD, viral encephalitis, AIDS-dementia complex)
  - metabolic disorders (drug intoxication/withdrawal, hypoglycemia, hyponatremia, HONK, hepatic encephalopathy, uremia, hypoxia)
  - focal brain damage (head injury, stroke, mass)

Palatal myoclonus can result from lesion to the Dentato-Rubro-Olivary tract, and is associated with an audible clicking

5. **Tics**
- **primary tic disorders:** transient tic disorder, chronic tic disorder, Gilles de la Tourette, adult onset or senile
- **secondary tic disorders:** encephalitis, CJD, Sydenham's chorea, head trauma, drugs, mental retardation syndromes
- association with OCD and ADHD

Key Parkinsonian Features

TRAP
Tremor (resting)
Rigidity
Akinesia/bradykinesia
Postural instability

Parkinson's Disease

Etiology

- **sporadic:** combination of oxidative stress to dopaminergic neurons, environmental toxins (e.g. pesticides), accelerated aging, genetics
- **familial** (10%): autosomal dominant α-synuclein mutations, autosomal recessive parkin gene or DJ-1 gene mutation (juvenile onset)
- **MPTP** (neurotoxin)

Diagnostic Criteria
- Bradykinesia, plus one of: resting tremor, muscle rigidity, postural instability not caused by other factors, OR
- 3 or more of the following features:
  - Resting tremor
  - Unilateral onset
  - Persistent asymmetry, with side of onset most affected
  - Progressive disorder
  - Excellent response (70-100%) to levodopa
  - Severe levodopa-induced chorea
  - Response to levodopa for 5 yr or more
  - Clinical course lasting 10 yr or more

Epidemiology

- prevalence of 0.3% in industrialized countries, but rises with increased age
- second most common neuro-degenerative disorder, after Alzheimer's
- mean age of onset is 60 yr

www.regentstudies.com

Risk Factors
- family history, male, head injury, rural living, exposure to certain neurotoxins
- protective: coffee drinking, smoking, NSAID use, estrogen replacement in post-menopausal women

Pathophysiology
- loss of dopaminergic neurons in pars compacta of substantia nigra, thus reduced dopamine in striatum leading to disinhibition of the indirect pathway and decreased activation of the direct pathway causing increased inhibition of cortical motor areas
- α-synucleinopathy: α-synuclein accumulates in Lewy bodies and causes neurotoxicity in substantia nigra

Toronto Notes 2016

Signs and Symptoms
- positive motor
  - resting tremor: asymmetric 4-5 Hz "pill-rolling" tremor, especially in hands
  - rigidity: lead-pipe rigidity with cogwheeling due to superimposed tremor
- negative motor
  - bradykinesia: slow, small amplitude movements, fatiguing of rapid alternating movements, difficulty initiating movement
- related findings: masked facies, hypophonia, aprosody (monotonous speech), dysarthria, micrographia, shuffling gait with decreased arm swing
- freezing: occurs with walking triggered by initiating stride or barriers/destinations, lasting seconds
- postural instability: late finding presenting as falls, festinating gait
- cognition: bradyphrenia (slow to think/respond), dementia (late finding)
- behavioural: decreased spontaneous speech, depression, sleep disturbances, anxiety
- autonomic: constipation, urinary retention, sexual dysfunction, later findings of orthostatic hypotension

Treatment
- pharmacologic
  - mainstay of treatment: levodopa/carbidopa (Sinemet®). Levodopa is a dopamine precursor; carbidopa decreases peripheral metabolism of levodopa, decreasing side effects and increasing half-life of levodopa
    - levodopa-related fluctuation: delayed onset of response (affected by mealtime), end-of-dose deterioration ("wearing-off"), random oscillations of on-off symptoms
    - major complication of levodopa is dyskinesia
  - treatment of early PD: dopamine agonists, amantadine, MAOI
  - adjuncts: dopamine agonists, MAOI, anticholinergics (especially if prominent tremors), COMT inhibitors
- surgical: thalamotomy, pallidotomy, deep brain stimulation (thalamic, pallidal, subthalamic)
- psychiatric

Juvenile Onset (Westphal Variant)
Begins in adolescence with bradykinesia and rigidity with a severe progressive course spanning 5-10 yr

Consider an Alternative Diagnosis if Atypical Parkinsonism
- Poor response to levodopa
- Abrupt onset of symptoms
- Rapid progression
- Early falls
- Early autonomic dysfunction
- Symmetric symptoms at onset
- Early age of onset (<50 yr)
- Early cognitive impairment
- FHx of psychiatric/dementing disorders
- Recent diagnosis of psychiatric disease
- History of encephalitis
- Unusual toxin exposure
- Extensive travel history

Other Parkinsonian Disorders
- **dementia/NCD with Lewy bodies** (see *Behavioural Neurology*, N21)
- **progressive supranuclear palsy**: tauopathy with limited vertical gaze (classically downgaze), early falls, axial rigidity and akinesia, dysarthia, and dysphagia
- **corticobasal degeneration**: tauopathy with varied presentations but classically presents with unilateral parkinsonism, dystonia/myoclonus, apraxia ± "alien limbs" phenomenon; may also present as progressive non-fluent aphasia
- **multiple system atrophy**: synucleinopathy presenting as either cerebellar predominant (previously olivopontocerebellar atrophy or OPCA) or parkinsonism predominant (previously nigrostriatal degeneration); both are associated with early autonomic dysfunction (previously Shy-Drager syndrome)
- **vascular parkinsonism**: multi-infarct presentation with lower body parkinsonism

Dopamine Agonist Therapy in Early Parkinson's Disease
Cochrane DB Syst Rev 2009;2:CD006564
Study: Meta-analysis of trials of dopamine agonists in early Parkinson's disease.
Results: Twenty-nine trials were included (n=5,247). Dopamine agonists were found to have decreased motor side effects (dyskinesia [OR 0.51], dystonia [OR 0.64], motor fluctuations [OR 0.75]) compared to levodopa, but provided poorer symptom control compared to levodopa. Also, other side effects were increased (constipation [OR 1.59], hallucinations [OR 1.69], dizziness [OR 1.45]).
Conclusion: Dopamine agonists have fewer motor side effects than levodopa, but provide worse symptom control and increased rate of other side effects.

Huntington's Disease
Etiology and Pathogenesis
- genetics: autosomal dominant CAG repeats (with anticipation) in Huntington's gene on Chromosome 4, which leads to accumulation of defective protein in neurons
- pathology: global cerebral atrophy, especially affecting the striatum, leading to increased activity of the direct pathway, and decreased activity of the indirect pathway

www.regentstudies.com

Epidemiology
- North American prevalence 4-8/100,000
- mean age of onset 35-44 yr; but varies with degree of anticipation from 5-70 yr

Signs and Symptoms
- typical progression: insidious onset with clumsiness, fidgetiness, and irritability, progressing over 15 yr to frank dementia, psychosis, and chorea
  - dementia: progressive memory impairment and loss of intellectual capacity
  - chorea: begins as movement of eyebrows and forehead, shrugging of shoulders, and parakinesia (pseudo-purposeful movement to mask involuntary limb jerking)
  - progresses to dance-like or ballism, and in late stage is replaced by dystonia and rigidity
  - mood changes: irritability, depression, anhedonia, impulsivity, bouts of violence

Investigations
- MRI: enlarged ventricles, atrophy of cerebral cortex and caudate nucleus
- genetic testing
  - expansion of the cytosine-adenine-guanine (CAG) trinucleotide repeats in the HTT gene
  - CAG repeats on chromosome 4p16.3 that encodes the protein huntingtin

Treatment
- no disease altering treatment
- psychiatric symptoms: antidepressants and antipsychotics
- chorea: neuroleptics and benzodiazepines
- dystonia: botulinum toxin

Botulinum toxin (BOTOX®) acts by preventing ACh release at the neuromuscular junction

Dystonia

Epidemiology
- third most common movement disorder after Parkinson's disease and essential tremor

Clinical Features
- symptoms exacerbated by fatigue, stress, emotions; relieved by sleep or specific tactile/proprioceptive stimuli ('geste antagoniste', e.g. place hand on face for cervical dystonia)
- more likely to be progressive and generalize if younger onset or leg dystonia

Treatment
- local medical: botulinum toxin
- systemic medical: anticholinergics (benztropine), muscle relaxants (baclofen), benzodiazepines, dopamine antagonists (reserpine, neuroleptics); dopamine for dopa-responsive dystonia
- surgical: surgical denervation of affected muscle, stereotactic thalamotomy (unilateral dystonia), posteroventral pallidotomy

Tic Disorders

Definition
- a tic is a sudden, rapid, recurrent, nonrhythmic, stereotyped motor movement or vocalization
- common criteria
  - tics may wax and wane in frequency but have persisted for an extended period of time
  - onset before age 18 yr
  - disturbance is not attributable to the physiological effects of a substance or another medical condition

Clinical Classification
- **Tourette's disorder**: multiple motor and one or more vocal tics that have persisted for more than 1 yr since onset
- **persistent (chronic) motor or vocal tic disorder**: single or multiple motor or vocal tics (but not both motor and vocal) that have persisted for more than 1 yr since onset
- **provisional tic disorder**: single or multiple motor and/or vocal tics present for <1 yr since first tic onset
- **other specified or unspecified tic disorder**: symptoms characteristic of a tic disorder but do not meet full criteria

Motor vs. Vocal Tics
- simple tics tend to be of short duration (milliseconds)
- complex tics tend to be longer (seconds) and often include a combination of simple tics
- complex tics may often appear to be purposeful

www.regentstudies.com

- motor tics
  - simple: blinking, head jerking, shoulder shrugging, extension of the extremities
  - dystonic: bruxism (grinding teeth), abdominal tension, sustained mouth opening
  - complex: copropraxia (obscene gestures), echopraxia (imitate gestures), throwing, touching
- vocal tics
  - simple: blowing, coughing, grunting, throat clearing
  - complex: coprolalia (shout obscenities), echolalia (repeat others' phrases), palilalia (repeat own phrases)

Treatment
- dopamine blocker

Tourette's Syndrome (Gilles de la Tourette's Syndrome)

Definition According to DSM 5
1. presence of both multiple motor and one or more vocal tics at some point during the illness, although not necessarily concurrently
2. tics may wax and wane in frequency but have persisted for more than 1 yr since first tic onset (with no tic-free periods greater than 3 mo)
3. onset is before age 18 yr
4. not due to effect of a substance or another medical condition

Less than 15% of people with Tourette's have coprolalia

Epidemiology
- estimated prevalence among adolescents 3-8 per 1,000 school-age children; M:F = 2:1 to 4:1

Signs and Symptoms
- **tics**: wide variety that wax and wane in type and severity; can be voluntarily suppressed for some time but are preceded by unpleasant sensation that is relieved once tic is carried out
  - can be worsened by anxiety, excitement, and exhaustion; better during calm focused activities
- **psychiatric**: compulsive behaviour (associated with OCD and ADHD), hyperactive behaviour, 'rages', sleep-wake disturbances, learning disabilities

Treatment
- clonidine, clonazepam

Prognosis
- typically begins between ages 4-6
- peak severity occurs between ages 10-12, with a decline in severity during adolescence (50% are tic-free by 18 yr of age)
- tic symptoms, however, can manifest similarly in all age groups and across the lifespan

Cerebellar Disorders

Clinico-Anatomic Correlations
- **vermis:** trunk/gait ataxia
- **cerebellar lobe (i.e. lateral):** rebound phenomenon, scanning dysarthria, dysdiadochokinesia, dysmetria, nystagmus

Symptoms and Signs of Cerebellar Dysfunction
- nystagmus: observe during extraocular movement testing (most common is gaze-evoked nystagmus)
- dysarthria (ataxic): abnormal modulation of speech velocity and volume – elicit scanning/telegraphic/slurred speech on spontaneous speech (see *CN X Vagus Nerve*, N13)
- ataxia: broad-based, uncoordinated, lurching gait
- dysmetria: irregular placement of voluntary limb or ocular movement
- dysdiadochokinesia: impairment of rapid alternating movements (e.g. pronation – supination task)
- postural instability: truncal ataxia on sitting, titubation (rhythmic rocking of trunk and head), difficulty with tandem and broad-based gait
- intention tremor: typically orthogonal to intended movement, and increases as target is approached
- hypotonia: decreased resistance to passive muscular extension (occurs shortly after injury to lateral cerebellum)
- pendular patellar reflex: knee reflex causes pendular motion of leg (occurs after injury to cerebellar hemispheres)
- rebound phenomenon: overcorrection after displacement of a limb
- hypometric and hypermetric saccades
  - pendular reflexes at triceps

Differentiating Ataxia

	Vestibular	Cerebellar	Sensory
Nystagmus/ Vertigo	+	±	–
Dysarthria	–	±	–
Limb Ataxia	–	+	+ (especially legs)
Stance	Worse with eyes closed	Poor with eyes open or closed	Positive Romberg
Vibration/ Proprioception	Normal	Normal	Impaired (especially distal)
Ankle Reflexes	Normal	Normal	Decreased/ absent

www.regentstudies.com

Wernicke-Korsakoff Syndrome

- see Psychiatry, PS25
- note that alcohol can also cause a cerebellar ataxia separate from thiamine deficiency; this ataxia can be due to cerebellar atrophy or alcohol polyneuropathy

Cerebellar Ataxias

Congenital Ataxias
- early onset non-progressive ataxias associated with various syndromes as well as developmental abnormalities (e.g. Arnold-Chiari malformation, Dandy-Walker cysts)

Hereditary Ataxias
- **autosomal recessive:** includes Friedrich's ataxia, ataxia telangiectasia, vitamin E deficiency
  - Friedrich's ataxia: prevalence 2/100,000; onset between 8 and 15 yr
    - signs: gait and limb ataxia, weakness, areflexia, extensor plantar reflex, impaired proprioception and vibration, dysarthria
    - death in 10-20 yr from cardiomyopathy or kyphoscoliotic pulmonary restriction
- **autosomal dominant:** most commonly spinocerebellar ataxias (30 types, most due to CAG repeats)
  - signs: ataxia and dysarthria; ± myoclonus, chorea, polyneuropathy, pyramidal or extrapyramidal features, hyporeflexia, seizures, dementia

Acquired Ataxias
- **neurodegeneration** (e.g. multiple system atrophy)
- **systemic:** alcohol, celiac sprue, hypothyroidism, Wilson's, thiamine deficiency
- **toxins:** carbon monoxide, heavy metals, lithium, anticonvulsants, solvents
- **vascular:** infarct, bleed, basilar migraine
- **autoimmune:** MS, Miller-Fischer (GBS)

Vertigo

- see Otolaryngology, OT12

Gait Disturbances

Approach to Gait Disturbances

1. **Characterization of the gait disturbance**
   - posture, stride length, width between feet, height of step, stability of pelvis, symmetry, arm swing, elaborate/inconsistent movements, standing from sitting
2. **Identification of accompanying neurologic signs**
   - full neurological exam required (diagnosis often can be made by P/E alone)
3. **Identify red flags**
   - sudden onset, cerebellar ataxia, paresis (hemi-, para- or quadri-), bowel/bladder incontinence
4. **Workup**
   - based on etiology – requires blood work, neuroimaging, and urgent neurologist referral

Central Motor Systems
3 components to the control of gait:
- Pyramidal: main outflow from cortex to spinal cord
- Extrapyramidal: basal ganglia inhibits excess movements
- Cerebellum: affects coordination of gait

Table 19. Types of Gait Disturbance

Location	Description	Disorder
Visual Loss	Broad based gait with tentative steps	Cataract surgery without lens replacement
Proprioceptive Loss	Sensory ataxia: wide-based with high stepping posture and positive Romberg	Demyelinating neuropathies, paraneoplastic syndrome, tabes dorsalis, MS, compressive myelopathy, B_{12} deficiency
Peripheral Vestibular Lesion 1. Acute 2. Bilateral	1. Vestibular ataxia 2. Disequilibrium	1. Tumour, trauma, infectious, Ménière's disease 2. Ototoxic drugs
Peripheral Nerve Disorder 1. Foot drop 2. Lumbosacral radiculopathy	Steppage gait	Acquired/hereditary peripheral neuropathy, compressive peroneal neuropathy, L4-5 radiculopathy
Myopathies	Waddling gait: broad based, short stepped gait with pronounced lumbar lordosis, rotation of pelvis	Progressive muscular dystrophy

www.regentstudies.com

Table 19. Types of Gait Disturbance (continued)

Location	Description	Disorder
Pyramidal/Corticospinal Tract Lesion 1. Unilateral 2. Bilateral	Spastic gait: spastic foot drop, circumduction, scissoring of legs or toe walking with bilateral circumduction	Unilateral: stroke (ischemic/hemorrhagic) Bilateral: cervical spondylosis, cerebral palsy, spinal cord tumour, combined spinal cord degeneration, MS, motor neuron disease
Basal Ganglia	1. Parkinsonian gait: small paces, stooped posture, reduced armswing 2. Choreic/hemiballistic/dystonic gait	Infarct, Huntington's, Sydenham's chorea, Wilson's disease, SLE, neuroleptic medications, polycythemia vera, genetic dystonia
Cerebellar Disorder	Cerebellar ataxic gait: wide-based without high stepping; veers to side of lesion Alcoholic gait	Primary and secondary neoplasm, toxins (alcohol), vitamin E deficiency, hypothyroid, hypoxia, hypoglycemia, paraneoplastic syndrome

Motor Neuron Disease

Amyotrophic Lateral Sclerosis (Lou Gehrig's Disease)

Definition
- progressive neurodegenerative disease that causes UMN and LMN symptoms and is ultimately fatal

Etiology
- idiopathic (most), genetic (5-10% familial, especially SOD1 mutation, other: C9orf72, TARDBP)

Pathology
- disorder of anterior horn cells of spinal cord, cranial nerve nuclei, and corticospinal tract

Epidemiology
- 5/100,000; incidence increases with age

Signs and Symptoms
- limb motor symptoms: segmental and asymmetrical UMN and LMN symptoms
- bulbar findings: dysarthria (flaccid or spastic), dysphagia, tongue atrophy and fasciculations, facial weakness and atrophy
- pseudobulbar affect, frontotemporal dementia (up to 10%)
- sparing of sensation, ocular muscles, and sphincters

Investigations
- EMG: chronic denervation and reinnervation, fasciculations
- NCS: to rule out peripheral neuropathy (i.e. multifocal motor neuropathy with conduction block)
- CT/MRI: to rule out cord disease/compression

Treatment
- riluzole (modestly slows disease progression)
- symptomatic relief
  - spasticity/cramping: baclofen, tizanidine (Zanaflex®), regular exercise, and physical therapy
  - sialorrhea: TCA (i.e. amitriptyline), sublingual atropine drops, parotid/submandibular Botox® (rare)
  - pseudobulbar affect: dextromethorphan/quinidine, TCA, SSRI
  - non-pharmacologic: high caloric diet, ventilatory support (especially BiPAP), early nutritional support (i.e. PEG tube), rehabilitation (PT, OT, SLP), psychosocial support

Prognosis
- median survival 3 yr; death due to respiratory failure

Red Flags Inconsistent with ALS
Sensory sx, predominant pain, bowel or bladder incontinence, cognitive impairment, ocular muscle weakness

Denervation on EMG
Fibrillations, positive sharp waves, complex repetitive discharges; reinnervation – increased amplitude and duration of motor units

The only interventions that have been shown to extend survival in ALS are riluzole and use of BiPAP

Other Motor Neuron Diseases

- **degenerative**
  - **progressive muscular atrophy (progressive bulbar palsy):** only LMN symptoms with asymmetric weakness, later onset than ALS, 5-10% of patients in ALS centres
  - **primary lateral sclerosis (progressive pseudobulbar palsy):** UMN symptoms, later onset, not fatal with variable disability; 5-10% of patients in ALS centres
  - **spinal muscular atrophy:** pediatric disease with symmetric LMN symptoms
- **infectious**
  - **post-polio syndrome:** residual asymmetric muscle weakness, atrophy
- **acquired**
  - **multifocal motor neuropathy:** conduction block on NCS, asymmetric LMN symptoms, ± anti-GM1, treatable with IVIG

www.regentstudies.com

Peripheral Neuropathies

Diagnostic Approach to Peripheral Neuropathies

1. differentiate: motor vs. sensory vs. autonomic vs. mixed
2. pattern of deficit: symmetry; focal vs. diffuse; upper vs. lower limb; cranial nerve involvement
3. temporal pattern: acute vs. chronic; relapsing/remitting vs. constant vs. progressive
4. history: PMH, detailed FHx, exposures (e.g. insects, toxins, sexual, travel), systemic symptoms
5. detailed peripheral neuro exam: LMN findings, differentiate between root and peripheral nerves, cranial nerves, respiratory status

Classification

- **monoradiculopathy:** dermatomal deficit due to single nerve root lesion
  - due to disc herniation or root compression causing radicular pain
  - little tactile anesthesia, as dermatomes overlap
- **polyradiculopathy:** multiple dermatome deficits due to multiple nerve root lesions
  - one type is cauda equina syndrome (lumbosacral roots)
- **plexopathy:** deficit matching distribution of a nerve plexus
  - **brachial plexopathy**
    - upper (C5-C7): LMN sx of shoulder and upper arm muscles (Erb's palsy)
    - lower (C8-T1): LMN sx and sensory sx of forearm and hand (Klumpke's palsy)
    - DDx: trauma, idiopathic neuritis, tumour infiltration, radiation, thoracic outlet syndrome (i.e. cervical rib)
  - **lumbosacral plexopathy** (rare, especially unilateral)
    - DDx: idiopathic neuritis, infarction (i.e. DM), compression
- **mononeuropathy:** single nerve deficit
  - **carpal tunnel syndrome** (most common): compression of median nerve at wrist
    - symptoms: wrist pain, paresthesia first 3 and ½ digits, ± radiation to elbow, worse at night
    - signs: Tinel's sign, Phalen's test, thenar muscle wasting, sensory deficit
    - EMG and NCS: slowing at wrist (both motor and sensory)
    - etiology: entrapment, pregnancy, DM, gammopathy, rheumatoid arthritis, thyroid disease
  - **Bell's palsy** (most common cranial neuropathy): see Otolaryngology, OT23
  - other less common mononeuropathies due to entrapment/compression: ulnar (compression at elbow), median (at pronator teres), radial (at spiral groove of humerus), obturator (from childbirth), peroneal (due to crossing legs or surgical positioning), posterior tibial (tarsal canal)
- **mononeuropathy multiplex:** deficit affecting multiple discrete nerves (asymmetric)
  - must rule out vasculitis or collagen vascular disease
- **polyneuropathy:** symmetrical distal stocking-glove pattern
  - symmetrical distal sensorimotor deficit affecting longest fibres first (stocking-glove distribution), hypotonia; progression of dysesthesia early and weakness later
  - etiology: DM (most common), renal disease, substances, toxins, genetics, SLE, HIV, leprosy, alcohol, B_{12} deficiency, uremia
  - **chronic inflammatory demyelinating polyneuropathy (CIDP)**
    - chronic relapsing sensorimotor polyneuropathy with increase protein in CSF and demyelination (shown on EMG/NCS)
    - course is fluctuating, in contrast with the acute onset of GBS
    - treatment: first-line is prednisone; alternatives are plasmapheresis, IVIG, and azathioprine

Table 20. Differential Diagnosis of Symmetric Polyneuropathy

	Etiology	Mechanism	Course	Modalities	Investigations
Vascular	PAN	Ischemic	Chronic	S/M	see Rheumatology, RH19
	SLE	Ischemic	Chronic	S/M	see Rheumatology, RH11
	RA	Ischemic	Chronic	S/M	see Rheumatology, RH8
Infectious	HIV	Axonal/demyelination	Chronic	S/A	HIV serology
	Leprosy	Infiltrative	Chronic	S/A	Leprosy serology Nerve biopsy
	Lyme	Axonal/demyelination	Chronic	M	Lyme serology
Immune	GBS	Demyelination	Acute	M	LP (↑ protein; no ↑ cells)
	CIDP	Demyelination	Chronic	S/M	LP (↑ protein)
Hereditary	HMSN	Axonal/demyelination	Chronic	S/M	Genetic testing
Neoplastic	Paraneoplastic	Axonal/demyelination	Chronic	S/M	Paraneoplastic antibodies
	Myeloma	Axonal/demyelination	Chronic	S/M	SPEP Skeletal bone survey
	Lymphoma	Axonal	Chronic	M	SPEP Bone marrow biopsy
	Monoclonal gammopathy	Demyelination	Chronic	S/M	SPEP Bone marrow biopsy

Diabetic Neuropathies
- Peripheral neuropathy: pain or loss of sensation in a glove and stocking distribution (hands and feet affected before arms and legs)
- Autonomic: anhidrosis, orthostatic hypotension, impotence, gastroparesis, bowel and bladder dysfunction
- Mononeuropathy multiplex: nerve infarct or compression
- Cranial neuropathy: CN III (pupil sparing) > IV > VI
- Lumbosacral plexopathy

Tinel's Sign: Tap lightly over the median nerve at the wrist, the patient's symptoms of carpal tunnel will be elicited in a positive test

Phalen's Test: Hold both wrists in forced flexion (with the dorsal surfaces of the hands pressed against each other) for 30-60 s; test is positive if symptoms of carpal tunnel are elicited

DDx of Demyelinating Neuropathy
GBS, CIDP, paraproteinemia, diphtheria, amiodarone, Charcot-Marie-Tooth, storage diseases, pressure palsy predisposition, paraneoplastic

www.regentstudies.com

Table 20. Differential Diagnosis of Symmetric Polyneuropathy (continued)

	Etiology	Mechanism	Course	Modalities	Investigations
Toxin	EtOH	Axonal	Sub-acute	S/M	GGT, MCV
	Heavy metals	Axonal	Sub-acute	S/M	Urine heavy metals
	Medications	Axonal	Sub-acute	S/M	Drug levels
Metabolic	DM	Ischemic/axonal	Chronic	S/A	Fasting glucose, HbA1c, 2 h OGTT
	Hypothyroidism	Axonal	Chronic	S/M	TSH, T_3, T_4
	Renal failure	Axonal	Chronic	S/A	Electrolytes, Cr, BUN
Nutritional	B_{12} deficiency	Axonal	Sub-acute	S/M	Vitamin B_{12}
Other	Porphyria	Axonal	Sub-acute	M	Urine porphyrins
	Amyloid	Axonal	Sub-acute	S	Nerve biopsy

A = autonomic; CIDP = chronic inflammatory demyelinating polyneuropathy; GGT = gamma-glutamyl transferase; HMSN = hereditary motor sensory neuropathy; M = motor; OGTT = oral glucose tolerance test; PAN = polyarteritis nodosa; RA = rheumatoid arthritis; S = sensory; SLE = systemic lupus erythematosus; SPEP = serum protein electrophoresis

Axonal neuropathies have decreased amplitude on NCS; demyelinating neuropathies have decreased velocity on NCS

Ototoxic drugs (e.g. aminoglycosides) should not be given to diabetics

Sensory neuropathy of the feet prevent them from adequately compensating for loss of vestibular function

Guillain-Barré Syndrome

- **definition:** acute rapidly evolving demyelinating inflammatory polyneuropathy that often starts in the distal lower limbs and ascends
- **etiology**
  - autoimmune attack and damage to peripheral nerve myelin
  - sometimes preceded by viral/bacterial infections
- **signs and symptoms**
  - sensory: distal and symmetric paresthesias, loss of proprioception and vibration sense, neuropathic pain
  - motor: weakness starting distally in legs, areflexia
  - autonomic: blood pressure dysregulation, arrhythmias, bladder dysfunction
- **investigations**
  - CSF: albuminocytologic dissociation (high protein, normal WBC)
  - EMG/NCS: conduction block, differential or focal (motor > sensory) slowing, decreased F-wave, sural sparing
- **subtypes**
  1. acute inflammatory demyelinating polyneuropathy (AIDP)
  2. acute motor-sensory axonal neuropathy (AMSAN)
  3. acute motor axonal neuropathy (AMAN)
- **treatment**
  - IVIG or plasmapheresis, ± pain management, monitor vitals and vital capacity
- **prognosis**
  - peak of symptoms at 2-3 wk, resolution at 4-6 wk
  - 5% mortality (higher if require ICU); up to 15% have permanent deficits

Evaluation of Distal Symmetric Polyneuropathy: Role of Laboratory and Genetic Testing
Neurology 2009;72:185-192
Screening Lab Tests: Blood glucose, serum B12 with metabolites, serum protein immunofixation electrophoresis.
Genetic Testing: Indicated for cryptogenic polyneuropathy exhibiting classic hereditary neuropathy phenotype. Screen for CMT1A duplication/deletion and Cx32 mutations.

GBS is a neurological emergency due to risk of imminent respiratory failure

The most common antecedent infection in GBS is *Campylobacter jejuni*

Miller-Fischer Variant of GBS – Triad
- Ophthalmoplegia
- Ataxia
- Areflexia

IVIG and plasmapheresis lead to more rapid improvement, less intensive care and less ventilation, but do not change mortality or relapse rate

Neuromuscular Junction Diseases

Clinical Approach to Disorders of the Neuromuscular Junction

Table 21. Common Disorders of the Neuromuscular Junction

	Myasthenia Gravis	Lambert-Eaton	Botulism
Ocular/Bulbar Paresis	+	–	++ (early)
Limb Weakness	+	+	+
Fatigability	+	+	+
Post-Exercise Enhancement	–	+	+
Reflexes	N	↓	↓
Anticholinergic Sx	–	+	++
Sensory Sx	–	–	–
Associated Conditions	Thymoma	Small cell carcinoma	GI S&S
Repetitive EMG Stimulation	Decremental response	Incremental response	↑ (rapid stimulation) ↓ (slow stimulation)

www.regentstudies.com

Myasthenia Gravis

- Diseases of the neuromuscular junction typically feature prominent fatigability
- Fatigability can be tested by holding the arms out or by holding the gaze in the upward position (especially in MG)
- Muscle weakness due to fatigability will improve with rest or ice

Etiology and Pathophysiology
- progressive autoimmune disorder due to anti-AChR antibodies, resulting in early saturation at the NMJ and inadequate muscle activation with increasing nerve stimulation
- 15% of patients with MG have associated thymic neoplasia, 85% have thymic hyperplasia

Epidemiology
- bimodal age of onset – 20s (mostly women) and 60s (mostly men)

Signs and Symptoms
- see Table 21
- fatigable, symmetric or asymmetric weakness without reflex changes, sensory changes, or coordination abnormalities
- ocular (diplopia/ptosis), bulbar (dysarthria/dysphagia), and/or proximal limb weakness
- symptoms may be exacerbated by infection, pregnancy, menses, and various drugs
- respiratory muscle weakness may lead to respiratory failure

Investigations
- edrophonium (Tensilon®) test
  - assess for improvement over 2 min following edrophonium injection
- EMG
  - repetitive stimulation → decremental response
  - single fibre electromyography shows increased jitter (80-100% sensitivity)
- spirometry – forced vital capacity may be used to monitor adequacy of respiratory effort over time
- anti-acetylcholine receptor antibody assay (70-80% sensitivity)
- MUSK antibody may be used if seronegative for AChR antibody
- CT/MRI to screen for thymoma/thymic hyperplasia

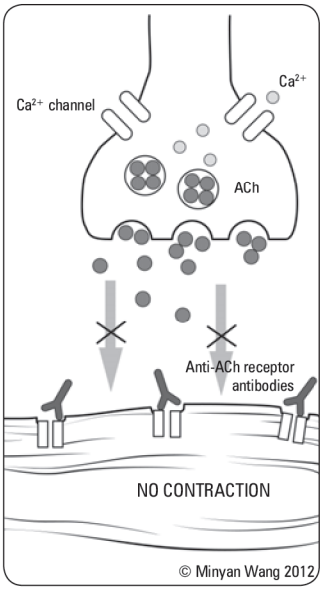


Figure 22. Myasthenia gravis

Treatment
- thymectomy
  - 85% of patients show improvement or remission
- symptomatic relief
  - acetylcholinesterase inhibitors (e.g. pyridostigmine)
  - does not affect primary pathologic process so rarely results in control of disease when used alone
- immunosuppression
  - steroids are mainstay of treatment (70-80% remission rate)
  - azathioprine, cyclophosphamide, and mycophenolate as adjuncts or as steroid sparing therapy
- short-term immunomodulation (for crises)
  - IVIG and plasmapheresis

Tensilon® is a drug that inhibits acetylcholinesterase. It improves muscle function immediately in myasthenia gravis, but not in a cholinergic crisis This test is infrequently used; when performed, a crash cart should be nearby as respiratory difficulty and/or bradycardia may occur

Prognosis
- 30% eventual spontaneous remission
- with treatment, life expectancy is equal to that of a person without MG, but quality of life may vary

Lambert-Eaton Myasthenic Syndrome

Etiology and Pathophysiology
- autoimmune disorder due to antibodies against presynaptic voltage-gated calcium channels, causing decreased ACh release at the NMJ
- 50-66% are associated with small cell carcinoma of the lung

Signs and Symptoms
- see Table 21
- weakness of skeletal muscles without sensory or coordination abnormalities
- reflexes are diminished or absent, but increase after active muscle contraction
- bulbar and ocular muscles affected in 25% (vs. 90% in MG)
- prominent anticholinergic autonomic symptoms (dry mouth > impotence > constipation > blurred vision)

Investigations
- edrophonium test (see *Myasthenia Gravis*, N40) → no response
- EMG
  - rapid (>10 Hz) repetitive stimulation → incremental response
  - post-exercise facilitation → an incremental response with exercise
- screen for malignancy, especially small cell lung cancer

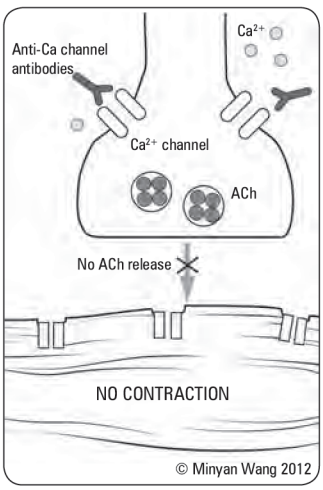


Figure 23. Lambert-Eaton myasthenic syndrome (LEMS)

www.regentstudies.com

Treatment
- tumour removal
- acetylcholine modulation
  - increased acetylcholine release (3,4-diaminopyridine)
  - decreased acetylcholine degradation (pyridostigmine)
- immunomodulation
  - steroids, plasmapheresis, IVIG

Botulism

Etiology and Pathophysiology
- caused by a toxin produced by spores of *Clostridium botulinum* bacteria, which is found in soil and water throughout the world
- bacteria can enter the body through wounds or by ingesting improperly preserved foods
- infantile botulism is the most common form, and is usually from ingestion of honey or corn syrup

Signs and Symptoms
- occur 6-48 h after ingestion
- difficulty with convergence, ptosis, paralysis of extraocular muscles
- dilated, poorly reactive pupils
- other autonomic dysfunction: jaw weakness, dysarthria, dysphagia
- spreads to trunk and limbs
  - abdominal cramps with nausea and vomiting
  - symmetric weakness with paralysis and absent/decreased deep tendon reflexes
  - anticholinergic symptoms: dry mouth, constipation, urinary retention
- rarely respiratory distress, potentially advancing to respiratory failure
  - pattern of paresis often starts with GI symptoms (constipation, early satiety), then paresis of extraocular muscles, then dysphagia, then limbs/respiratory involvement; all associated with dry mouth

Investigations
- blood test for toxin
- stool culture

Treatment
- botulinum anti-toxin – good prognosis with prompt treatment
- supportive therapy as required

Myopathies

Clinical Approach to Muscle Diseases

Table 22. Myopathies

	Etiology	Key Clinical Features	Key Investigations
Inflammatory	Polymyositis	Myalgias Pharyngeal involvement	↑ CK Biopsy: endomysial infiltrates; necrosis
	Dermatomyositis	Myalgias Characteristic rashes Can be paraneoplastic	↑ CK Biopsy: perifascicular atrophy
	Sarcoidosis	See Respirology, R14	ACE level Biopsy: granulomas
	Inclusion body myositis	Weak quadriceps and deep finger flexors	↑ CK Biopsy: inclusion bodies
Endocrine	Thyroid (↑ or ↓) Cushing's syndrome Parathyroid (↑ or ↓)	See Endocrinology, E20	TSH, serum cortisol, calcium panel
Toxic	Medication	Medication or toxin history	Toxicology screen
	Critical illness myopathy	ICU patient Hx steroids and nondepolarizing paralyzing agents Failure to wean from ventilation	Biopsy: selective loss of thick myosin filaments
Infectious	Parasitic, bacterial, or viral	Myalgias Inflammatory myopathy	↑ myoglobin

Myopathies are characterized by prominent symmetric proximal weakness and absent sensory changes

Good Questions to Assess Proximal Weakness
- Legs: climbing stairs, stand from sit
- Arms: reach above head, wash hair

www.regentstudies.com

Table 22. Myopathies (continued)

	Etiology	Key Clinical Features	Key Investigations
Hereditary Dystrophy	Duchenne	Early onset (Duchenne and Becker)	Dystrophin analysis: absent
	Becker	Progressive proximal muscle weakness Calf pseudohypertrophy	Dystrophin analysis: abnormal
	Myotonic dystrophy	Distal myopathy Myotonia Genetic anticipation	Genetic testing
Hereditary Metabolic	McArdle's	Exercise-related myalgias, cramping, and myoglobuminuria	↑ lactate ↑ serum/urinary myoglobin post-exercise
Hereditary Periodic Paralysis	"Channelopathy"	Episodic weakness Normal between attacks	Normal, ↑ or ↓ K^+
Hereditary Mitochondrial	MERRF	Myoclonus, generalized seizures, dementia, myopathy	Biopsy: ragged red fibres Increased lactate
	MELAS	Pediatric onset, stroke-like symptoms, episodic vomiting, dementia	
	Kearns Sayre	Progressive ophthalmoplegia, retinal pigment degeneration, cardiac conduction abnormalities	

MELAS = mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERRF = mitochondrial encephalomyopathy with ragged red fibres

Common Medications that Cause Myopathy: steroids, statins, anti-retrovirals, thyroxine, fibrates, cyclosporine, ipecac

Common Drugs that Cause Myopathy: ethanol, cocaine, heroin

Polymyositis/Dermatomyositis

- see Rheumatology, RH15

Myotonic Dystrophy

Etiology and Pathophysiology
- unstable trinucleotide (CTG) repeat in DMK gene (protein kinase) at 19q13.3, number of repeats correlates with severity of symptoms
- autosomal dominant

Epidemiology
- most common adult muscular dystrophy
- prevalence 3-5/100,000

Signs and Symptoms
- appearance: ptosis, bifacial weakness, frontal baldness (including women), triangular face giving a drooping/dull appearance
- physical exam
  - distribution of weakness: distal weaker than proximal (in contrast to other myopathies), steppage gait
  - myotonia: delayed relaxation of muscles after exertion (elicit by tapping on thenar muscles with hammer)
  - cardiac: 90% have conduction defects (1° heart block; atrial arrhythmias)
  - respiratory: hypoventilation 2° to muscle weakness
  - ocular: subcapsular cataracts, retinal degeneration, decreased intraocular pressure
  - other: DM, infertility, testicular atrophy
- EMG: subclinical myotonia – long runs with declining frequency and amplitude

Treatment and Prognosis
- no cure, progressive, death usually around 50 yr
- management of myotonia: phenytoin

Duchenne and Becker Muscular Dystrophy

- see Pediatrics, P45

www.regentstudies.com

Pain Syndromes

Approach to Pain Syndromes

Definitions
- **nociceptive pain:** pain arising from normal activation of peripheral nociceptors
- **neuropathic pain:** pain arising from direct injury to neural tissue, bypassing nociceptive pathways
- **spontaneous pain:** unprovoked burning, shooting, or lancinating pain
- **paresthesia:** spontaneous abnormal non-painful sensation (e.g. tingling)
- **dysesthesia:** evoked pain with inappropriate quality or excessive quantity
- **allodynia:** a dysesthetic response to a non-noxious stimulus
- **hyperalgesia:** an exaggerated pain response to a noxious stimulus

Non-Pharmacological Management
- physical (PT, acupuncture, chiropractic manipulation, massage)
- psychoeducational (CBT, family therapy, education, psychotherapy)

Medical Pain Control
- combination multi-modal therapy is important
- primary analgesics: acetaminophen, NSAIDs (often used for soft tissue injuries, strains, sprains, headaches, and arthritis), opiates
- adjuvants: antidepressants (TCAs, SSRIs), anticonvulsants (gabapentin, carbamazepine, pregabalin), baclofen, sympatholytics (phenoxybenzamine), α2-adrenergic agonists (clonidine)

Surgical Pain Control
- peripheral ablation: nerve blocks, facet joint denervation
- direct delivery: implantable morphine pump
- central ablation: stereotactic thalamotomy, spinal tractotomy, or dorsal root entry lesion
- DBS or dorsal column stimulation

- Pinprick sensation mediated by Aδ fibres
- Pain due to tissue damage is mediated by C fibres

WHO Pain Ladder
- **Mild Pain:** Non-opioid (acetaminophen and/or NSAID) ± adjuvant
- **Moderate Pain:** Opioid for mild to moderate pain (codeine/oxycodone) + non-opioid ± adjuvant
- **Severe Pain:** Opioid for moderate to severe pain (morphine/hydromorphone) + non-opioid ± adjuvant

Axonal regeneration is directed by intact nerve sheaths; if the nerve sheath is damaged, axons grow without direction, become tangled and form a neuroma, which can result in ectopic electrical impulses and neuropathic pain

Neuropathic Pain

Definition
- pain resulting from a disturbance of the central or peripheral nervous system

Symptoms and Signs
- hyperalgesia/allodynia
- subjectively described as burning, heat/cold, pricking, electric shock, perception of swelling, numbness (i.e. stocking/sock distribution)
- can be spontaneous or stimulus evoked
- distribution may not fall along classical neuro-anatomical lines
- associated issues: sleep difficulty, anxiety/stress/mood alteration

Causes of Neuropathic Pain
- **sympathetic**
  - complex regional pain syndrome
- **central:** abnormal CNS activity
  - phantom limb, post spinal cord injury, post stroke, MS
- **non-sympathetic:** damage to peripheral nerves
  - **systemic disease:** DM, thyroid disease, renal disease, rheumatoid arthritis
  - **nutritional/toxicity:** alcoholism, pernicious anemia, chemotherapy
  - **infectious:** post-herpetic, HIV
  - **trauma/compression:** nerve entrapment, trigeminal neuralgia, post-surgical, nerve injury, cervical/lumbar radiculopathy, plexopathy

Treatment
- identify/treat underlying cause
- **pharmacotherapy**
  - Stepwise approach (*Canadian Pain Society*, 2007): TCA, anticonvulsant, SNRI, topical lidocaine, long acting opiate (caution), tramadol
  - other: capsaicin cream, intrathecal opioid, or clonidine, botulinum toxin injection, nerve block
- **common non-pharmacologic therapies**
  - neuropsychiatry: CBT, psychotherapy
  - rehabilitation: physiotherapy
  - complementary and alternative medicine: acupuncture, meditation, massage therapy, traditional Chinese medicine
- **surgical therapies:** dorsal column neurostimulator, DBS (thalamus)

www.regentstudies.com

Trigeminal Neuralgia

Clinical Features
- recurrent episodes of sudden onset, excruciating unilateral paroxysmal shooting "electric" pain in trigeminal root territory (V3>V2>>V1)
- may have normal sensory exam
- pain lasts seconds/minutes over days/weeks; may remit for wk/mo
- triggers: touching face, eating, talking, cold wind, shaving, applying make-up

Etiology
- **classic TN:** idiopathic
- **secondary TN:** compression by tortuous blood vessel (superior cerebellar artery), cerebellopontine angle tumour (5%), MS (5%)

Epidemiology
- F>M; usually middle-aged and elderly

Diagnosis
- clinical diagnosis
- investigate for secondary causes, which are more likely if bilateral TN or associated sensory loss
  - MRI to rule out structural lesion, MS, or vascular lesion

Treatment
- first line: carbamazepine or oxcarbazepine
- second line: baclofen or lamotrigine
- narcotics not generally recommended
- if medical treatment fails: trigeminal ganglion percutaneous technique, gamma knife, invasive percutaneous denervation (radiofrequency/glycerol), percutaneous balloon microcompression, microvascular decompression

Postherpetic Neuralgia

Herpes Zoster of Trigeminal Nerve
Typically involves V1 (ophthalmic division)

Hutchinson's Sign: Tip of nose involvement predicts corneal involvement

Clinical Features
- pain persisting in the region of a cutaneous outbreak of herpes zoster
- constant deep ache or burning, intermittent spontaneous lancinating/jabbing pain, allodynia
- distribution: thoracic, trigeminal, cervical > lumbar > sacral
- associated impaired sleep, decreased appetite, decreased libido

Etiology and Pathogenesis
- destruction of the sensory ganglion neurons (e.g. dorsal root, trigeminal, or geniculate ganglia) secondary to reactivation of herpes zoster infection

Epidemiology
- incidence in those with zoster increases with age (2% in <60 yr, 19% in >70 yr)
- risk factors: older age, greater acute pain, greater rash severity

Prevention
- varicella zoster vaccine (Varivax®) in childhood reduces incidence of varicella zoster
- herpes zoster vaccine (Zostavax®) reduces incidences of shingles, PHN, and other herpetic sequel (currently recommended in Canada for those >60 yr old)

Treatment
- medical: TCA (i.e. amitriptyline), anti-convulsants (i.e. pregabalin, gabapentin), analgesia (i.e. opiates, lidocaine patch), intrathecal methylprednisolone, topical capsaicin
  - early treatment of acute herpes zoster with antivirals (acyclovir; longer-acting famciclovir and valacyclovir more effective)
  - treatment of herpes zoster with corticosteroids DOES NOT decrease PHN
- surgical: spinal tractotomy, dorsal root entry zone lesion, DBS of thalamus

Painful Diabetic Neuropathy

- see Endocrinology, E13

Approach
- determine if pain is neuropathic or vascular
- more likely neuropathic if
  - feet > calves
  - sharp/tingling pain
  - pain present at rest and improves with walking

www.regentstudies.com

Treatment
- Level A: pregabalin
- Level B: venlafaxine, duloxetine, amitriptyline, gabapentin, valproate, rarely opioids, capsaicin

Complex Regional Pain Syndromes

Clinical Features
- presence of an initiating noxious event (MI, stroke)
- continuing pain, allodynia, or hyperalgesia with pain disproportionate to inciting event
- evidence during the course of symptoms of edema, changes in skin blood flow or abnormal vasomotor activity
- absence of conditions that would otherwise account for degree of pain and dysfunction
- other features can include edema, osteoporosis, hyperhidrosis, hair loss, fascial thickening

Classification
- **CRPS type I (reflex sympathetic dystrophy):** minor injuries of limb or lesions in remote body areas precede onset of symptoms
- **CRPS type II (causalgia):** injury of peripheral nerves precedes the onset of symptoms

Investigations
- trial of differential neural blockade may be helpful in diagnosis
- autonomic testing (evidence of sympathetic dysfunction)
- bone scan, plain radiography, MRI

Prevention
- early mobilization after injury/infarction

Treatment
- goal of treatment: to facilitate function
- conservative treatment: education, support groups, PT/OT, smoking cessation
- medical: topical capsaicin, TCA, NSAID, tender point injections with corticosteroid/lidocaine, gabapentin/pregabalin/lamotrigine, calcitonin or bisphosphonates, oral corticosteroids
- surgical: paravertebral sympathetic ganglion blockade
- refer to pain management clinic

If CT is negative but clinically there is suspicion of SAH or meningitis, perform a LP

Headache DDx

ER VISIT
Eye (acute angle closure glaucoma, sinusitis)
Recurrent/Chronic (migraine, tension, cluster, TMJ disease, cervical OA)
Vascular (SAH, ICH, temporal arteritis)
Infectious (meningitis, encephalitis)
Systemic (anemia, anoxia, CO, pre-eclampsia)
ICP (mass/abscess, HTN encephalopathy, pseudotumour cerebri)
Trauma (concussion, SDH, EDH)

Headache

- see Emergency Medicine, ER23 and Family Medicine, FM33

Clinical Approach
- **history**
  - pain characteristics: onset, frequency, duration, intensity, location, radiation, other specific features (e.g. worse in AM, worse with bending/cough/Valsalva)
  - associated symptoms: visual changes, change in mental status, nausea/vomiting, fever, meningismus, photophobia, phonophobia, TMJ popping/clicking, jaw claudication, neurological symptoms
  - precipitating/alleviating factors (triggering factors, analgesics), medications (especially nitrates, CCBs, NSAIDs, anticoagulants), PMH, FHx
  - red flags (possible indications for CT scan/further investigation): new-onset headache (especially if age <5 or >50), quality worse/different than previous headaches, sudden and severe ('thunderclap'), immunocompromised, fever, focal neurological deficits, trauma
- **physical exam**
  - vitals (including BP and temp), Kernig's/Brudzinski's, MSK examination of head and neck
  - HEENT: fundi (papilledema, retinal hemorrhages), red eye, temporal artery tenderness, sinus palpation, TMJ
  - full neurological exam (including LOC, orientation, pupils (symmetry), and focal neurological deficits)
  - **red flags:** papilledema, altered LOC, fever, meningismus, focal neurological deficits, signs of head trauma

Classification
- **primary**
  - tension, migraine, cluster, other autonomic cephalgias
- **secondary**
  - cervical OA, TMJ syndrome, SAH, ICH, stroke, venous sinus thrombosis, meningitis/encephalitis, trauma, increased ICP (space-occupying lesion, malignant HTN or pseudotumour cerebri), temporal arteritis, sinusitis, acute-angle closure glaucoma, pre-eclampsia, post LP, drugs/toxins (e.g. nitroglycerin use and analgesia withdrawal); all can be associated with serious morbidity or mortality

www.regentstudies.com

Table 23. Headaches – Selected Primary Types

	Tension-Type	Migraine	Cluster
Prevalence	70%	~10-20%	<1%
Age of Onset	15-40	10-30	20-40
Sex Bias	F>M	F>M	M>F
Family History	None	+++	+
Location	Bilateral frontal Nuchal-occipital	Unilateral > bilateral Fronto-temporal	Retro-orbital
Duration	Minutes – days	Hours – days	10 min-2 h
Onset/Course	Gradual; worse in PM	Gradual; worse in PM	Daily attacks for weeks to months; more common early AM or late PM
Quality	Band-like; constant	Throbbing	Constant, aching, stabbing
Severity	Mild-moderate	Moderate-severe	Severe (wakes from sleep)
Triggers/Provoking	Depression Anxiety Noise Hunger Sleep deprivation	Noise/light Caffeine/alcohol Hunger Stress Sleep deprivation	Light EtOH
Palliating	Rest	Rest	Walking around
Associated Sx	No vomiting No photophobia	Nausea/vomiting Photo/phonophobia Aura	Red watery eye Nasal congestion or rhinorrhea Unilateral Horner's
Management	Non-pharmacological • Psychological counseling • Physical modalities (e.g. heat, massage) Pharmacological • Simple analgesics • Tricyclic antidepressants	Acute Rx • ASA • NSAIDs • Triptans • Ergotamine Prophylaxis 1. TCA 2. Anticonvulsants 3. Propranolol	Acute Rx • O_2 • Sumatriptan (nasal or injection) Prophylaxis • Verapamil • Lithium • Methysergide • Prednisolone

Table 24. Prophylactic Management of Migraine Headaches

Class	Drug	Evidence	Contraindications	Side Effects
Beta-blockers	Propranolol Timolol Metoprolol	A A B	Asthma, DM (mask hypoglycemia) CHF	Fatigue Depression Light-headedness
TCA	Amitriptyline Nortriptyline	A C	Heart disease, glaucoma *Avoid in elderly	Sedation Dry mouth Weight gain Light-headedness
CCBs	Flunarizine	A	Depression, obesity	Weight gain, depression, PD (rare)
	Verapamil	B	Heart disease	Weight gain (4.5-9 kg), constipation
AED	Valproate	A	Liver, renal, pancreatic disease	Weight gain, tremor, alopecia, teratogenic: neural tube defect
	Topiramate + folic acid supplement	A	Renal disease	Paresthesia, weight loss, cognitive: memory loss, difficulty concentrating, renal stone (rare)

Table 25. Headaches – Selected Serious but Rare Secondary Types

	Meningeal Irritation	Increased ICP	Temporal Arteritis
Age of Onset	Any age	Any age	>60 yr
Location	Generalized	Any location	Temporal
Onset/Course	Meningitis: hours-days SAH: thunderclap onset	Gradual; worse in AM	Variable
Severity	Severe	Severe	Variable; can be severe
Provoking	Head movement	Lying down Valsalva Head low Exertion	Jaw claudication
Associated Sx	Neck stiffness Photophobia Focal deficits (e.g. CN palsies)	N/V Focal neuro symptoms Decreased level of consciousness	Polymyalgia rheumatica Visual loss

Acute and Preventive Pharmacologic Treatment of Cluster Headache
Neurology 2010;75:463-473
Study: Meta-analysis of prospective, double-blind, RCTs of pharmacologic agents for prevention or treatment of CH.
Results: 27 trials were included. Sumatriptan 6 mg SC, zolmitriptan nasal spray 5-10 mg, and 100% oxygen 6-12 L/min received Level A recommendation for acute treatment. For prevention, Level B recommendations were given for intranasal civamide 100 µg daily and suboccipital steroid injections.
Conclusion: Sumatriptan, zolmitriptan, and mid flow oxygen are effective acute treatments for CH.

Anticonvulsants in Migraine Prophylaxis
Cochrane DB Syst Rev 2009;3:CD003226
Study: Meta-analysis of prospective, controlled trials of anticonvulsant drugs in migraine headache prophylaxis.
Results: Twenty-three studies (n=2,927) were included. Anticonvulsants reduce migraine frequency by 1.3 attacks per 28 d compared to placebo and double the number of patients for whom migraine frequency is reduced by 50% (RR=2.25, NNT=3.9). Valproate and topiramate are better than placebo, while clonazepam, acetazolamide, lamotrigine, and vigabatrin are not. Clinically important adverse events were associated with valproate and topiramate with NNH 7.0-18.8 and 2.4-31.2, respectively.
Conclusion: Anti-convulsants are effective in reducing migraine frequency and reasonably well-tolerated. Valproate and topiramate are the two most studied but further studies of head-to-head comparisons between agents is needed.

The Rational Clinical Examination: Does this Patient with Headache have a Migraine or Need Neuroimaging?
JAMA 2006;296:1274-1283
Does this patient with headache have a migraine?
The most useful panel of questions for diagnosing migraine is summarized by the POUNDing mnemonic:
P – **P**ulsatile quality
O – duration of 4-72 h
U – **U**nilateral location
N – **N**ausea or vomiting
D – **D**isabling intensity
The LR for definite or possible migraine diagnosis varies with the number of features present: with ≥4, 3 and ≥2 features, the LRs are 24 (1.5-388), 3.5 (1.3-9.2), and 0.41 (0.32-0.52), respectively.

Does this patient with headache need neuroimaging?
In patients with new or changed headache the prevalence of significant intracranial pathology is 32% (24-42%), and in those presenting with thunderclap headache the prevalence is 43% (20-68%).
Several individual clinical features were found to be predictive of significant intracranial pathology:

Symptom	*OR*
Cluster-type headache	10.7 (2.2-52)
Abnormal neurological exam	5.3 (2.4-12)
Undefined-type headache (non-tension/migraine/cluster-type)	3.8 (2.0-7.1)
Headache with aura	3.2 (1.6-6.6)
Aggravated by exertion/Valsalva	2.3 (1.4-3.8)
Headache with vomiting	1.8 (1.2-2.6)

www.regentstudies.com

Table 25. Headaches – Selected Serious but Rare Secondary Types (continued)

	Meningeal Irritation	Increased ICP	Temporal Arteritis
Physical Signs	Kernig's sign Brudzinski's sign Meningismus	Focal neuro symptoms Papilledema	Temporal artery changes: • Firm, nodular, incompressible • Tender
Management	CT/MRI with gadolinium LP, antibiotics for bacterial meningitis	CT/MRI and treatment to reduce pressure See Neurosurgery, NS7	Prednisone See Rheumatology, RH21
Etiology	Meningitis, SAH	Tumour, IIH, malignant HTN	Vasculitis (GCA)

IIH = idiopathic intracranial HTN

Migraine Headaches

Definition (Common Migraine)

- ≥5 attacks fulfilling each of the following criteria
  - 4-72 h duration
  - 2 of the following: unilateral, pulsating, moderate-severe (interferes with daily activity), aggravated by routine physical activity
  - 1 of the following: nausea/vomiting, photophobia/phonophobia/osmophobia

Epidemiology

- 18% females, 6% males; frequency decreases with age (especially at menopause)

Etiology and Pathophysiology

- theories of migraine etiology
  - depolarizing wave of "cortical spreading depression" across the cerebral cortex that may cause an aura (e.g. visual symptoms due to wave through occipital cortex) and also activate trigeminal nerve afferent fibres
  - possible association with vasoconstriction/dilation
- significant genetic contribution
- **triggers:** stress, sleep excess/deprivation, drugs (estrogen, nitroglycerin), hormonal changes, caffeine withdrawal, chocolate, tyramines (e.g. red wine), nitrites (e.g. processed meats)

Signs and Symptoms

- stages of uncomplicated migraine
  i. prodrome (hours to days before headache onset)
  ii. aura
  iii. headache (see Table 23 for description of typical headache)
  iv. postdrome
- aura
  - fully reversible symptom of focal cerebral dysfunction lasting <60 min
  - examples: visual disturbance (fortification spectra – zigzags; scintillating scotomata – spots), unilateral paresthesia and numbness or weakness, aphasia
- prodrome/postdrome: appetite change, autonomic symptoms, altered mood, psychomotor agitation/retardation
- classification of migraines
  - common migraine: no aura
  - classic migraine: with aura (headache follows reversible aura within 60 min)
  - complicated migraine: with severe/persistent sensorimotor deficits
    - examples
      - basilar-type migraine (occipital headache with diplopia, vertigo, ataxia, and altered level of consciousness)
      - hemiplegic/hemisensory migraine
      - ophthalmoplegic migraine
  - acephalgic migraine (i.e. migraine equivalent): aura without headache

Treatment

- avoid triggers
- mild to moderate migraine
  - 1st line: NSAIDs (ibuprofen, naproxen)
- moderate to severe migraine
  - triptans (most effective), ergots (dihydroergotamine, DHE)
- migraine prophylaxis: anticonvulsants (divalproex, topiramate, gabapentin), TCA (amitriptyline, nortriptyline), propranolol, calcium channel blocker (verapamil)

The oral contraceptive pill is contraindicated with complicated migraine due to risk of stroke

Migraine auras can mimic other causes of transient neurological deficits (e.g. TIAs and seizures)

"Menstrual Migraine" Subtype
Migraine headache that is associated with the onset of menstruation – usually 2 d before to 3 d after the onset of menstrual bleeding

If patient presents to ED with severe migraine and N/V – consider treating with IV anti-emetics (chlorpromazine, prochlorperazine)

Pharmacological Treatments for Acute Migraine
Pain 2002;97:247-257
Study: Meta-analysis of 54 double-blind, placebo-controlled RCTs of pharmacologic treatment of acute migraine of moderate to severe intensity (21,022 patients in total).
Data Extraction: Number of patients, dosing regimens, details of study design, and timing or type of rescue medication. Outcomes include headache relief at 1 and 2 h, freedom from pain at 2 h, sustained relief for 24 h, and adverse effects within 24 h.
Main Results: Data were available for 9 oral medications, 2 intranasal medications, and subcutaneous sumatriptan. For H/A relief at 2 h, all interventions were effective except Cafergot®, with NNTs ranging from 2.0 for sumatriptan 6 mg SC to 5.4 for naratriptan 2.5 mg. The lowest NNT for oral medication was 2.6 for eletriptan 80 mg. For patients pain free at 2 h, the lowest NNT was 2.1 for sumatriptan 6 mg SC, with the lowest NNT for oral medication being 3.1 for rizatriptan 10 mg. For sustained relief over 24 h NNT ranged from 2.8 for eletriptan 80 mg to 8.3 for rizatriptan 5 mg. Side effects could not be analyzed systematically. There were no drug-to-drug comparisons.
Conclusion: Overall, most treatments were effective. Subcutaneous sumatriptan and oral triptans were most effective.

A prophylactic agent is recommended only if migraine attacks are severe enough to cause impairment of a patient's quality of life or if a patient has >3 migraines/mo that have not responded adequately to treatment

Neurology 2000;55:754-763

www.regentstudies.com

Sleep Disorders

Overview of Sleep

Definition
- newborn: 18 h sleep (50% REM), adolescents: 10 h, adults: 7-9 h but most get insufficient amounts
- many elderly have reduced sleep as a consequence of underlying sleep disorders

Sleep Architecture
- **polysomnogram (PSG) measures:** EEG, eye movements (electro-oculogram – EOG), EMG, respiratory effort, oxygenation, ECG

Table 26. Sleep Stage Characteristics

	EEG	EOG	Muscle Tone	Other Characteristics
Waking State	Alpha waves: high frequency (8-13 Hz), low voltage	Rapid, blinking	High	
Stage N1 (~5%)	Alpha waves: high frequency (8-13 Hz), low voltage	Slow, roving eye movements	High, but gradually dropping	Marker for very light quality sleep or sleep disruption
Stage N2 (~50%)	K complexes (high voltage negative and positive discharges) with sleep spindles (11-16 Hz)	Still	High	
Stage N3 (previously 3 and 4)/Slow Wave/ Delta Sleep (~20%)	Delta waves: low frequency (<2 Hz), high voltage (>75 μV)	Still	Low	Homeostatic sleep Reduced BP, HR, cardiac output, RR Growth hormone release
Rapid Eye Movement (REM) Sleep (~25%)	Sawtooth waves, mixed frequency, low voltage	Rapid eye movements	Very low	Irregular respiration Arrhythmias, heart rate variation Classical dreaming state

Elements of Sleep History
- Initiation of sleep
  - Events prior to bed
  - Lights
  - Latency (estimated)
  - Restless legs
  - Hallucinations
- Maintaining sleep
  - Number of wakeups/night
  - Sleep walking/talking
  - Snoring/gasping
  - Dreams/nightmares
- Consequences of sleep
  - Restorative
  - Morning headache
  - Falling asleep in inappropriate setting

Disturbances of Alertness and Sleep

Coma
- see Neurosurgery, NS34

Insomnia
- **definition/criteria**
  - difficulty initiating or maintaining sleep, or waking up earlier than desired (leading to sleep that is chronically non-restorative/poor quality) despite adequate opportunity and circumstances for sleep
- **types**
  - sleep state misperception, psychophysiologic insomnia (learned sleep-preventing associations – i.e. clock watching), fatal familial insomnia (rare prion protein mutation causing autonomic dysfunction), idiopathic (lifelong difficulty)
  - **secondary causes**
    - psychiatric disorders (80% of psychiatric patients): anxiety and depression (see Psychiatry, PS10)
    - neurologic disorders: neurodegenerative disease, epilepsy, neuromuscular disorders, many others
    - sleep disorders: restless legs syndrome (sleep initiation difficulties), sleep apnea (sleep maintenance difficulties)
    - medical conditions: pregnancy, cardiorespiratory (COPD/HF), GERD, pain (arthritis, fibromyalgia, cancer)
    - drugs/toxins: caffeine, alcohol, stimulants, antidepressants, glucocorticoids, sedative withdrawal
- **treatment**
  - sleep log, sleep hygiene, stimulus control, sleep restriction, relaxation response, CBT

Drug Effects on Wakefulness and Sleep
- Antihistamines associated with increased sleepiness
- Stimulants increase arousal
- Caffeine (an adenosine antagonist) increases wakefulness
- Benzodiazepines reduce slow wave sleep
- Antidepressants (TCA/MAOI/SSRI) reduce REM, prolong REM latency
- Alcohol may hasten sleep onset but associated with increased arousals

www.regentstudies.com

Sleep Apnea

- **definition**
  - disorder of breathing in sleep associated with sleep disruption and consequent excessive somnolence (or drowsiness)
- **epidemiology**
  - >2-4% of the population
  - increasing obesity
  - significant morbidity: HTN, stroke, heart failure, sleepiness, mortality (accidents)
- **types**
  - obstructive sleep apnea: see Respirology, R31
  - central sleep apnea: no effort to breath over 10 s
  - mixed apnea: starts as central, but eventually becomes obstructive
- **etiology of central apnea:** heart failure, opiates, brainstem pathology, myotonic dystrophy
- **diagnosis:** apnea hypopnea index (AHI) or respiratory disturbance index (RDI) should be <5 in the normal state
- **treatment:** conservative measures, dental devices, CPAP (common), surgery (rare), ensure driving safety

Avoid sleep medications (especially in elderly patients) due to increased risk of falls, pseudodepression, and memory loss

Restless Leg Syndrome and Periodic Limb Movement in Sleep

- **definition**
  - urge to move accompanied by uncomfortable sensations that begin or worsen with rest, are partially or totally relieved with movement, and are worse in evening/night
  - RLS refers to sensation
  - PLMS refers to the manifestation
- **epidemiology:** 10% North Americans, 90% of RLS have PLMS, 50% of patients with PLMS have RLS
- **etiology:** central (spasticity), peripheral nervous system (radiculopathy, neuropathy), pregnancy, iron deficiency, alcohol use
- **treatment**
  - underlying contributors (iron and B_{12} supplementation), dopaminergic agonists (first line), clonazepam (causes tachyphylaxis), opioids (only exceptional circumstances)
  - NOT recommended: Sinemet®, causes augmentation

Narcolepsy

- **definition/clinical features:** excessive daytime sleepiness (all narcolepsy), cataplexy = loss of muscle tone with emotional stimuli (pathognomonic), sleep paralysis (unable to move upon wakening), hypnagogic hallucinations (vivid dreams or hallucinations at sleep onset)
- **epidemiology:** prevalence 1:2,000, onset in adolescence/early adulthood; life-long disorder
- **etiology:** presumed autoimmune attack on orexin/hypocretin system, post head injury, MS, hypothalamic tumours; rarely familial
- **diagnosis:** based on clinical history + multiple sleep latency test findings of short sleep latency <8 min and REM within 15 min of sleep onset on 2/4 naps
- **treatment**
  - sleep hygiene and scheduled brief naps, restricted driving
  - alerting agents: modafinil (non-amphetamine stimulant), stimulant (i.e. methylphenidate)
  - anticataplectic: TCAs, SSRIs, sodium oxybate

Parasomnias

- **definition/clinical features:** unusual behaviours in sleep with clinical features appropriate to stage of sleep
- **etiology:** in elderly, REM sleep behaviour disorder may be associated with PD; in children, slow wave sleep arousals (sleep walking) may be associated with sleep disordered breathing
- **diagnosis:** clinical history in children, polysomnography in adults to exclude nocturnal seizures
- **treatment:** behavioural management (safety, adequate sleep); clonazepam for REM sleep behaviour, tonsillectomy if appropriate in children

Circadian Rhythm

- **definition/clinical features:** abnormalities based on time of day rather than sleep (i.e. jet lag, shift work)
- **diagnosis:** clinical history

CNS Infections

- see Infectious Diseases, ID18

Spinal Cord Syndromes

- see Neurosurgery, NS27

www.regentstudies.com

Stroke

Terminology

- **stroke:** sudden onset of neurological deficits of a vascular basis with infarction of CNS tissue
  - infarction is permanent tissue injury (confirmed by neuroimaging)
- **TIA:** sudden onset of neurological deficits of a vascular basis without infarction (i.e. no imaging evidence of stroke)

Pathophysiology

- two major types: ischemic (~80%) and hemorrhagic (~20%)

1. Ischemic
- **arterial thrombosis:** thrombus formation in artery (local/*in situ*)
  - **large vessel:** stenosis or occlusion of the internal carotid artery, vertebral, or intracranial arteries
    - mechanisms
      - insufficient blood flow beyond lesion (hemodynamic stroke)
      - underlying processes: atherosclerosis (most common cause), dissection, and vasculitis
  - **small vessel/lacunar**
    - mechanism: chronic HTN and DM cause vessel wall thickening and decreased luminal diameter
      - affects mainly small penetrating arteries (primarily basal ganglia, internal capsule, and thalamus)
- **cardioembolic:** blockage of cerebral arterial blood flow due to particles originating from a cardiac source
  - atrial fibrillation (most common), rheumatic valve disease, prosthetic heart valves, recent MI, fibrous and infectious endocarditis
- **systemic hypoperfusion** (global cerebral ischemia)
  - inadequate blood flow to brain, usually secondary to cardiac pump failure (e.g. cardiac arrest, arrhythmia, or MI)
  - primarily affects watershed areas (between the major cerebral arterial territories)

2. Hemorrhagic
- **intracerebral hemorrhage**
  - mechanisms
    - hypertensive (most common): rupture of small microaneurysms (Charcot-Bouchard aneurysms) causing intraparenchymal hemorrhage
      - most common sites: putamen, thalamus, cerebellum, and pons
    - other: trauma, amyloid angiopathy (associated with lobar hemorrhage), vascular malformations, vasculitis, drug use (cocaine or amphetamines)
- **subarachnoid hemorrhage** see Neurosurgery, NS18

Stroke Syndromes According to Vascular Territory

- **ACA:** contralateral leg paresis, sensory loss, cognitive deficits (e.g. apathy, confusion, and poor judgment)
- **MCA:** proximal occlusion involves
  1. contralateral weakness and sensory loss of face and arm
  2. cortical sensory loss
  3. may have contralateral homonymous hemianopia or quadrantanopia
  4. if dominant (usually left) hemisphere: aphasia
  5. if non-dominant (usually right) hemisphere: neglect
  6. eye deviation towards the side of the lesion and away from the weak side
- **PCA**
  1. contralateral hemianopia or quadrantanopia
  2. midbrain findings: CN III and IV palsy/pupillary changes, hemiparesis
  3. thalamic findings: sensory loss, amnesia, decreased level of consciousness
  4. if bilateral: cortical blindness or prosopagnosia
- **basilar artery** (locked-in syndrome):
  1. quadriparesis
  2. dysarthria
  3. impaired eye movements
- **PICA (lateral medullary or Wallenberg syndrome):** ipsilateral ataxia, ipsilateral Horner's, ipsilateral facial sensory loss, contralateral limb impairment of pain and temperature sensation, nystagmus, vertigo, nausea/vomiting, dysphagia, dysarthria, hiccups

Hypertension Encephalopathy
Acute severe HTN (typically dBP >130 or sBP >200) can cause hypertensive encephalopathy – abnormal fundoscopic exam (papilledema, hemorrhages, exudates, cotton-wool spots), focal neurologic symptoms, N/V, visual disturbances, and change in LOC

Consider transfer of acute stroke patient to a designated stroke centre for neuroprotective or thrombolytic therapy if the patient is seen in first few hours

Early seizure activity occurs in 5-25% of patients after ICH

Cerebral venous sinus thrombosis should be considered in the differential diagnosis of stroke and headache. It is an uncommon cause of either, but is associated with high morbidity and mortality. Patients often present with headache alone, but can also have seizures, focal neurological deficits, or cranial nerve palsies. This is diagnosed with MRV or CTV. Treatment is typically anticoagulation with heparin initially, then transition to warfarin

20-40% of patients with ischemic stroke may develop hemorrhagic transformation within 1 wk after the initial infarction

Blood work should only delay treatment if: patient is on anticoagulants, low platelet count suspected, abnormal electrolytes suspected, or any bleeding abnormality suspected

Suspect an alternate diagnosis if: fever, decreased LOC, fluctuating symptoms, gradual onset, no focal neurological symptoms, and/or positive symptoms

Infarcted area of brain tissue can often appear normal on CT during the first several hours after the onset of stroke

www.regentstudies.com

- **medial medullary infarct** (anterior spinal artery, which can be associated with anterior cord infarct): contralateral hemiparesis (facial sparing), contralateral impaired proprioception and vibration sensation, ipsilateral tongue weakness
- **lacunar infarcts (deep hemispheric white matter)**
  - pure motor hemiparesis (posterior limb of internal capsule): contralateral arm, leg, and face
  - pure sensory loss (thalamic): hemisensory loss
  - ataxic hemiparesis: ipsilateral ataxia and leg paresis
  - dysarthria-clumsy hand syndrome: dysarthria, facial weakness, dysphagia, mild hand weakness and clumsiness

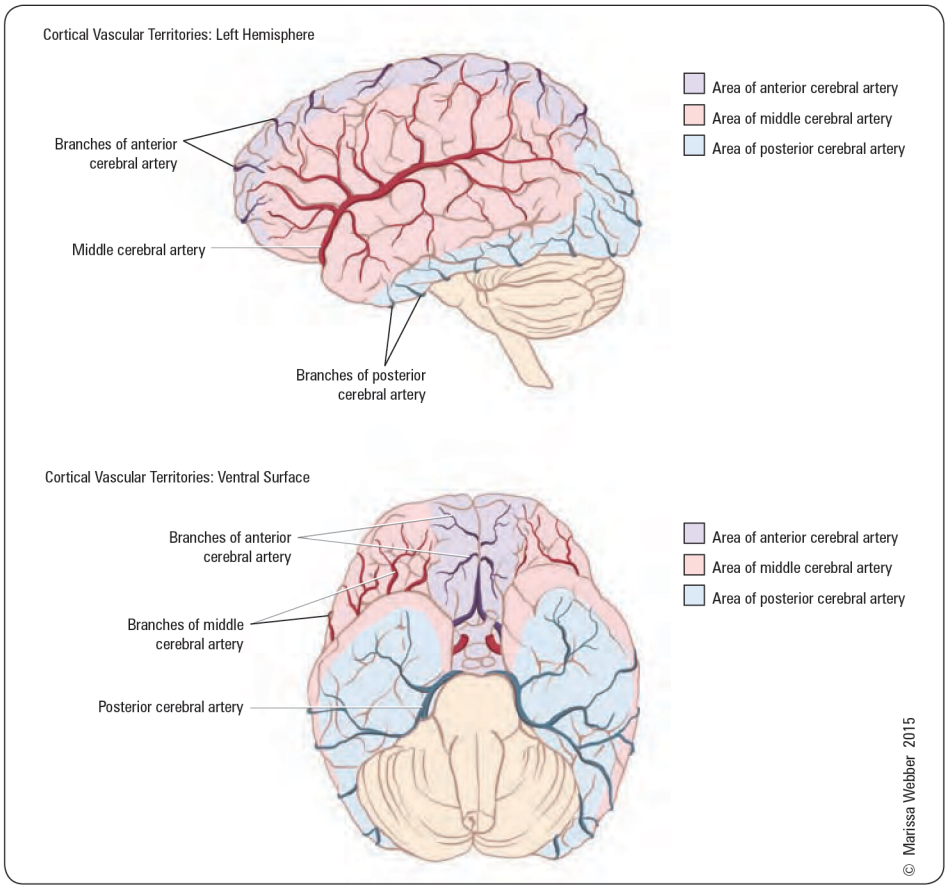


Figure 24. Vascular territories

Assessment and Treatment of Ischemic Stroke

General Assessment

- ABCs, full vital sign monitoring, capillary glucose, (Accu-Chek®), urgent CODE STROKE if <4.5 h from symptom onset (for possible thrombolysis)
- level of consciousness (knows age, month, obeys commands), dysarthria, anomiadysnomiaanomia (cannot name objects),
- gaze preference, visual fields, facial palsy
- arm drift, leg weakness, ataxia
- sensation to pinprick, extinction/neglect
- history
  - onset: time when last known to be awake and symptom free
  - mimics to rule out: seizure/post-ictal, hypoglycemia, migraine, conversion disorder
- investigations
  - non-contrast CT head (STAT): to rule out hemorrhage and assess extent of infarct
  - ECG: to rule out atrial fibrillation (cardioembolic cause)
  - CBC, electrolytes, creatinine, PTT/INR, blood glucose
- imaging (i.e. CT) signs of stroke
  - loss of cortical white-grey differentiation
  - sulcal effacement (i.e. mass effect decreases visualization of sulci)
  - hypodensity of parenchyma
  - insular ribbon sign
  - hyperdense MCA sign

The **National Institute of Health Stroke Scale (NIHSS)** is a standardized clinical examination that determines the severity of an acute stroke; it can also be used to monitor response to treatment over time
The scale uses 11 items that evaluate:
- Level of consciousness
- Visual system
- Motor system
- Sensory system
- Language abilities

Scoring (x/42):
0=no stroke
1-4=mild stroke
5-15=moderate stroke
15-20=moderate to severe stroke
21-42=severe stroke

rtPA is typically considered if score ≥6, but some stroke neurologists will administer rtPA with lower NIH stroke scale scores

Aspect Score: 10-point quantitative score to assess ischemic changes on CT scan
- 10/10 is normal and <4/10 signifies high risk of bleed with rtPA
- Subtract 1 point for each of following structures if abnormal within the ischemic hemisphere: caudate, lentiform, insula, internal capsule, MCA 1, 2, 3, 4, 5, 6 regions

www.regentstudies.com

ACUTE STROKE MANAGEMENT

1. Thrombolysis
- **rtPA** (recombinant tissue plasminogen activator)
- given **within 4.5 h** of acute ischemic stroke onset provided there are clinical indications and no contraindications to use:
- indications: based on NIH Stroke Scale (NIHSS – see sidebar)
- contraindications: see sidebar

If rtPA given at stroke onset, delay acute antiplatelet/anticoagulation treatment by 24 h

Absolute Contraindications to rtPA
Hx: improving sx, minor sx, seizure at stroke onset, recent major surgery (within 14 d) or trauma, recent GI or urinary hemorrhage (within 21 d), recent LP or arterial puncture at noncompressible site, PMHx ICH, sx of SAH/pericarditis/MI, pregnancy

P/E: sBP ≥185, dBP ≥110, aggressive treatment to decrease BP, uncontrolled serum glucose, thrombocytopenia

Ix: hemorrhage or mass on CT, high INR or aPTT

2. Anti-Platelet Therapy
- give at presentation of TIA or stroke if rtPA not received
- antiplatelet agents
  - ASA: recommended dose 81 mg chewed
  - if patient intolerant to ASA, use other antiplatelet agent (i.e. clopidogrel)

3. Acute Anti-Coagulant Therapy
- for patients with TIA or stroke and atrial fibrillation if rtPA not received
  - recommend IV heparin (or ensuring INR between 2-3 if already anticoagulated on warfarin)

4. Intra-arterial Thrombectomy by Interventional Radiology

Other Acute Management Issues
- avoid hyperglycemia which can increase the infarct size
- lower temperature if febrile (febrile stroke: think septic emboli from endocarditis)
- prevent complications
  - NPO if dysphagia (to be reassessed by SLP)
  - DVT prophylaxis if bed-bound
  - initiate rehabilitation early

Blood Pressure Control
- do **NOT** lower the blood pressure unless the HTN is severe
  - antihypertensive therapy is withheld for at least 5 d after thromboembolic stroke unless sBP >220 mmHg or dBP >120 mmHg, or in the setting of acute MI, renal failure, aortic dissection
- acutely elevated BP is necessary to maintain brain perfusion to the ischemic penumbra
- most patients with an acute cerebral infarct are initially hypertensive and their BP will fall spontaneously within 1-2 d
- IV labetalol first-line if needed

Etiological Diagnosis
- further investigations
  - additional neuroimaging (MRI)
  - vascular imaging: CTA/MRA/carotid dopplers
  - cardiac tests: echocardiogram, Holter monitoring
  - correct etiological diagnosis is critical for appropriate secondary prevention strategies

Dabigatran vs. Warfarin in Patients with Atrial Fibrillation (The RE-LY Trial)
NEJM 2011; 365:883-891
Study Type: Prospective, multicentre RCT. Double-blinded between different doses of dabigatran, unblinded comparison between dabigatran and warfarin.
Population: 18,113 patients with atrial fibrillation and a risk of stroke followed over 2 yr.
Primary Outcome: Stroke or systemic embolism.
Results: Rates of outcome were 1.69% per yr in warfarin group and 1.53% per yr in dabigatran group (RR 0.91, p<0.001 for non-inferiority). Minor bleeds were slightly increased in warfarin group (3.36% versus 2.71% with dabigatran; p=0.003). Risk of hemorrhagic stroke was lower with dabigatran (0.12% vs. 0.38 %; p<0.001).
Conclusions: Dabigatran at 110 mg PO bid was associated with similar rates of stroke and systemic embolism and lower rates of major hemorrhage compared to warfarin in patients with atrial fibrillation. The 150 mg PO bid dose of dabigatran was more effective at stroke prevention and had a similar bleeding risk to warfarin.

Primary and Secondary Prevention of Ischemic Stroke

Anti-Platelet Therapy
- primary prevention
  - current evidence has not firmly established a protective role for antiplatelet agents for low-risk patients without a prior stroke/TIA
- secondary prevention
  - ASA is the initial antiplatelet of choice for stroke prevention
  - other agents (generally reserved for those who suffer cerebrovascular symptoms while on ASA or if unable to tolerate ASA)
    - Aggrenox® (ESPRIT trial)
    - clopidogrel (CAPRIE trial)

High-Dose Atorvastatin after Stroke or Transient Ischemic Attack (SPARCL Trial)
NEJM 2006;355:549-559
Method: Multicentre double-blind RCT.
Population: 4,731 patients with stroke or TIA within 1-6 mo before study entry, LDL 100-190 mg/dL, no coronary heart disease.
Intervention: 80 mg atorvastatin PO OD or placebo.
Outcome: First non-fatal or fatal stroke over 5 yr.
Results: Patients receiving atorvastatin had a lower rate of stroke (ARI 2.2%, hazard ratio 0.84; p=0.03). There was a five yr absolute reduction in risk of 3.5% (p=0.002). There was no significant change in mortality rate, but a small significant increase in the risk of hemorrhagic stroke.
Conclusions: High-dose atorvastatin decreases overall incidence of strokes and cardiovascular events in patients with a history of recent stroke or TIA.

Carotid Stenosis
- primary prevention (asymptomatic)
  - carotid endarterectomy is controversial: if stenosis >60%, risk of stroke is 2% per yr; carotid endarterectomy reduces the risk of stroke by 1% per yr (but 5% risk of complications)
- secondary prevention (previous stroke/TIA in carotid territory)
  - carotid endarterectomy clearly benefits those with symptomatic severe stenosis (70-99%), and is less beneficial for those with symptomatic moderate stenosis (50-69%) (NASCET trial), see Vascular Surgery, VS8

www.regentstudies.com

- according to the CREST trial, endarterectomy and carotid stenting have similar benefits in a composite endpoint of reduction of stroke, MI, and death; however, in the periprocedural period, stenting results in a higher rate of stroke, while endarterectomy results in a higher rate of MI

Atrial Fibrillation
- primary and secondary prevention with anticoagulation
  - classically risk stratification used CHADS^2 score, but Stroke 2014 guidelines recommend that virtually all patients with atrial fibrillation without contraindication be anticoagulated
    - 0 (very low risk): antiplatelet
    - 1 (low risk): anticoagulant or antiplatelet – patient specific decision
    - >2 (mod-high risk): anticoagulant
  - anticoagulation therapy
    - warfarin (titrate to INR 2-3)
    - dabigatran (110 or 150 mg PO bid), apixaban (2.5 or 5 mg PO bid) or rivaroxaban (15 or 20 mg PO daily) may be alternatives to warfarin, but should be used cautiously due to lack of a reversal agent should bleeding occur

Hypertension
- primary prevention
  - targets: BP <140/90 (or <130/80 for diabetics or renal disease)
  - ramipril 10 mg PO OD is effective in patients at high risk for cardiovascular disease (HOPE trial)
    - ACEI reduce the risk of stroke beyond their antihypertensive effect
- secondary prevention
  - ACEI and thiazide diuretics are recommended in patients with previous stroke/TIA (PROGRESS trial)

Hypercholesterolemia
- primary prevention
  - statins reduce the risk of stroke in patients with CAD or at high risk for cardiovascular events, even with normal cholesterol (CARE trial)
- secondary prevention
  - statins reduce risk of subsequent stroke – best evidence is for high dose atorvastatin (SPARCL trial) but lower doses may be more appropriate if patient cannot tolerate high dose

Diabetes
- ideal management: HbA1c <7%, fasting blood glucose between 4 and 7

Smoking
- primary prevention
  - smoking increases risk of stroke in a dose-dependent manner
- secondary prevention
  - after smoking cessation, the risk of stroke decreases to baseline within 2-5 yr

Physical Activity
- regular physical activity is an important lifestyle measure in stroke prevention and its beneficial effect has a dose-related response in terms of intensity and duration of activity

Stroke Rehabilitation
- individualized based on severity and nature of impairment; may require inpatient program and continuation through home care or outpatient services
- multidisciplinary approach includes dysphagia assessment and dietary modifications, communication rehabilitation, cognitive and psychological assessments including screen for depression, therapeutic exercise programs, assessment of ambulation and evaluation of need for assistive devices, splints or braces, vocational rehabilitation

Cerebral Hemorrhage

Investigations
- general investigations, see *Assessment and Treatment of Ischemic Stroke*, N51
- further investigations
  - LP (if suspect subarachnoid hemorrhage despite negative CT)
  - may require cerebral angiogram if suspect aneurysm or AVM
  - if typical location for hypertensive hemorrhage, repeat CT head in 4-6 wk after hemorrhage has resolved to rule out an underlying lesion

CHADS^2
Stroke risk stratification for patients with atrial fibrillation

CHF (1 point)
HTN sBP >160 mmHg/treated HTN (1 point)
Age >75 yr (1 point)
DM (1 point)
Prior **S**troke or TIA (2 points)

Carotid endarterectomy needs to be done within 2 wk of the ischemic event for the most benefit

ABCD^2 Score
To predict/identify individuals at high risk of stroke following TIA

Age: 1 point for age >60 yr
Blood pressure (at presentation): 1 point for HTN (>140/90 mmHg at initial evaluation)
Clinical features: 2 points for unilateral weakness, 1 point for speech disturbance without weakness
Duration of symptoms: 1 point for 10-59 min, 2 points for >60 min
DM: 1 point

Stroke risk: 0-3: low risk, 4-5: moderate risk, 6-7: high risk

Evaluating for occult atrial fibrillation – CRYSTAL AF Trial
NEJM 2014: 370:2478-2486.

Patients with a cryptogenic ischemic stroke or TIA and no evidence of atrial fibrillation on ECG and Holter monitoring may benefit from ambulatory cardiac monitoring with subcutaneous implantable loop recorder or external loop recorder for several weeks.

ACE Inhibitor in Stroke Prevention – HOPE Trial
NEJM 2000;342:145-153
Study: Randomized, blinded, placebo-controlled trial. Mean follow-up 5 yr.
Patients: 9,297 patients ≥55 yr (mean age 66 yr, 73% men) who had evidence of vascular disease or DM plus one other cardiovascular risk factor and who were not known to have a low ejection fraction or heart failure.
Intervention: Ramipril 10 mg daily orally vs. matching placebo.
Main Outcomes: Stroke, MI, or death from cardiovascular causes.
Results:

Outcome	RRR (95%CI)	NNT (CI)
Stroke	32% (16-44)	67 (43-145)
MI, stroke, or CV mortality	22% (14-30)	26 (19-43)
All-cause mortality	16% (5-25)	56 (32-195)

Treatment with ramipril reduced the risk of stroke (3.4% vs. 4.9%; RR 0.68; p<0.001).
Conclusions: In adults at high risk for cardiovascular events, ramipril reduced the risk of stroke, as well as other vascular events and overall mortality.

www.regentstudies.com

Treatment
- medical
  - anti-hypertensives: no conclusive BP target ranges for managing ICH exist; 2010 AHA/ASA guidelines suggest that reducing sBP to as low as 140 mmHg with IV anti-hypertensives is safe and appropriate management (target sBP 140-160 systolic)
  - ICP lowering medical management (if necessary): see Neurosurgery, NS7
- surgical: see Neurosurgery, NS20

Neurocutaneous Syndromes

- see Pediatrics, P86

Multiple Sclerosis

Definition
- a chronic inflammatory disease of the CNS characterized by relapsing remitting, or progressive neurologic symptoms due to inflammation, demyelination, and axonal degeneration

Clinical Patterns of MS
- relapsing remitting (RRMS) 85%, primary progressive (PPMS) 10%, progressive relapsing (PRMS) 5%, secondary progressive (SPMS)
- benign MS (BMS): retrospective diagnosis made after 15 years of mild disease, with no evidence of worsening (in functional ability and MRI)
- most RRMS goes on to become SPMS

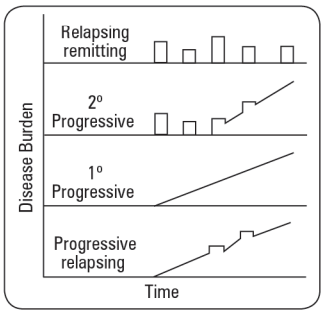


Figure 25. Clinical patterns of MS

MS Variants
- **Devic's = neuromyelitis optica (NMO):** severe optic neuritis and extensive transverse myelitis extending >3 vertebral segments (NMO antibody positive)
- **clinically isolated syndrome (CIS):** single MS-like episode, which may progress to MS
- **tumefactive MS:** solitary lesion >2 cm mimicking neoplasms on MRI
- **fulminant MS (Marburg)**: rapidly progressive and fatal MS associated with severe axonal damage, inflammation, and necrosis
- **pediatric MS:** onset of MS before the age of 18
  - epidemiology: rare (1.35-2.5 per 100,000 children)
  - presentation: more likely to present with isolated optic neuritis, isolated brainstem syndrome or symptoms of encephalopathy compared to adults
  - course: 98% have RRMS
  - diagnosis and treatment similar to adult MS
  - differential diagnosis: in the setting of nonspecific CSF abnormalities and MRI evidence of white matter lesion, rule out ADEM, optic neuritis, transverse myelitis, neuromyelitis optica, CNS malignancies, leukodystrophies, and mitochondrial disease
- **acute disseminated encephalomyelitis (ADEM):** monophasic demyelinating disorder with multifocal neurologic symptoms seen mainly in children often following infection or vaccination

Most symptoms in MS are due to cord, brainstem, and optic nerve lesions

Etiology
- genetic
  - polygenetic: the HLA-DRB1 gene has been demonstrated to be a genetically susceptible area
  - 30% concordance for monozygotic twins, 2-4% risk in offspring of affected mother or father
- environmental
  - MS is more common in regions with less sun exposure and lower stores of vitamin D (Europe, Canada, US, New Zealand, SE Australia)
  - MS has also been linked to certain viruses (EBV is associated with MS)

Epidemiology
- onset 17-35 yr; F:M = 3:1
- PPMS occurs in an older population with F=M

Diagnosis
- dissemination in space and in time as based on the revised McDonald criteria
  - dissemination in time: 2 or more attacks, new gadolinium enhancing lesion 3 mo later, or new T2 lesions >1 mo after first attack
  - dissemination in space: clinical evidence of 2 or more lesions; or three of (1 gadolinium enhancing or 9 T2 lesions), (1 infratentorial lesion), (1 juxtacortical lesion), (3 periventricular lesions)

www.regentstudies.com

Clinical Features

- symptoms include numbness, visual disturbance (optic neuritis), weakness, spasticity, diplopia (e.g. INO), impaired gait, vertigo, bladder dysfunction
- **Lhermitte's sign**: flexion of neck causes electric shock sensation down back into limbs indicating cervical cord lesion
- **Uhthoff's phenomenon**: worsening of symptoms (classically optic neuritis) in heat
- SPMS: classically weakness of legs in pyramidal distribution paired with cerebellar findings of arms (i.e. intention tremor)
- symptoms not commonly found in MS: visual field defects, aphasia, apraxia, progressive hemiparesis
- relapse: acute/subacute onset of clinical dysfunction that peaks from days to weeks, followed by remission with variable symptom resolution (symptoms must last at least 24 h)
- in RRMS, average 0.4 to 0.6 relapses/yr, but higher disease activity in 1st yr of disease

Chronic Cerebrospinal Venous Insufficiency (CCSVI)
A theory proposed in 2008 describing abnormal venous blood flow in patients with MS; while some RCTs are still underway, recent studies have largely discredited this highly controversial theory. That is, studies indicate no connection between CCSVI and MS

Investigations

- **MRI:** demyelinating plaques appear as hyperintense lesions on T2 weighted MRI, with active lesions showing enhancement with gadolinium
  - typical locations: periventricular, corpus callosum, cerebellar peduncles, brainstem, juxtacortical region, and dorsolateral spinal cord
  - Dawson's fingers: periventricular lesions extending into corpus callosum
  - cranial MRI is more sensitive than spinal MRI
- **CSF:** oligoclonal bands in 90%, increased IgG concentration
- **evoked potentials (visual/auditory/somatosensory):** delayed but well-preserved wave forms

The Expanded Disability Status Scale (EDSS) is used as a measure of disability progression and is scored from 0 to 10 based on the neurologic exam and ambulation

Treatment

- **acute treatment:** methylprednisolone 1,000 mg IV daily x 3-7 d (no taper required); if poor response to corticosteroids may consider plasma exchange
- **disease modifying therapy (DMT)**
  - goals: decrease relapse rate, decrease progression of disability, slow accumulation of MRI lesions
  - first line: interferon-β (injection: Betaseron®, Avonex®, Rebif®), glatiramer acetate (injection: Copaxone®)
  - second line: natalizumab (Tysabri®) (monthly IV infusion)
  - new oral agents: fingolimod (Gilenya®)
    - indications for fingolimod: newly diagnosed patients with active RRMS who prefer oral treatment despite increased risks or those intolerant of first line therapies
  - CIS: early treatment with interferons may delay potential second attack
  - RRMS: DMT reduces rate of relapse by about 30%
  - PPMS/SPMS: no proven efficacy of DMTs
- **symptomatic treatment**
  - spasticity: baclofen, tizanidine, dantrolene, benzodiazepine, botulinum toxin
  - bladder dysfunction: oxybutynin
  - pain: TCA, carbamazepine, gabapentin
  - fatigue: amantadine, modafinil, methylphenidate
  - depression: antidepressant, lithium
  - constipation: high fibre intake, stool softener, laxatives
  - sexual dysfunction: sildenafil (Viagra®), tadalafil (Cialis®), vardenafil (Levitra®, Staxyn®)
- **education and counseling:** MS Society, support groups, psychosocial issues

Oral Fingolimod or Intramuscular Interferon for Relapsing Multiple Sclerosis
NEJM 2010;362:402-415
Method: Multicentre double-blind RCT.
Population: 1,292 patients with relapsing-remitting MS and at least one relapse.
Intervention: Oral fingolimod at 0.5-1.25 mg or 30 μg IM interferon-β.
Outcomes: Annualized relapse rate over 1 yr; lesions on T2-weighted MRI.
Results: Annualized relapse rate was lower in both groups receiving fingolimod compared to interferon: 0.20 (95% CI 0.16-0.26) with 1.25 mg fingolimod, 0.16 (95% CI 0.12-0.21) with 0.5 mg fingolimod, 0.33 with interferon (95% CI 0.26-0.42; p<0.001). MRI findings also showed greater reduction of lesions in fingolimod-treated patients. Progression of disability was unchanged. Side effects included severe infections like HSV encephalitis, disseminated VZV, other HSV infections, and skin cancer.
Conclusions: Oral fingolimod is superior to interferon-β injections in reducing relapses and MRI lesion load in patients with MS.

Recombinant Interferon Beta or Glatiramer Acetate for Delaying Conversion of the First Demyelinating Event to Multiple Sclerosis
Cochrane DB Syst Rev 2008;2:CD005278
Study: Meta-analysis of RCTs of clinically isolated syndrome (CIS) patients treated with immunomodulatory drugs.
Primary Outcomes: Proportion of patients converting to clinically definite MS and adverse effects.
Results: Three trials (n=1,160) tested the efficacy of interferon (IFN-β) and no trial tested glatiramer acetate (GA). A pooled odds ratio (OR) of 0.53 (95% CI 0.40-0.71, p<0.0001) for patients on IFN vs. placebo at 1 yr. Two year follow-up odds ratio was 0.52 (95% CI 0.38-0.70, p<0.0001). There was no significant increase in adverse events for those on IFN-β.
Conclusions: IFN-β treatment can delay progression to clinically definite MS in patients with CIS over 2 yr.

Prognosis

- good prognostic indicators: female, young, RRMS, presenting with optic neuritis, low burden of disease on initial MRI, low rate of relapse early in disease
- PPMS: poor prognosis, higher rates of disability, poor response to therapy

www.regentstudies.com

Common Medications

Table 27. Common Medications – Major Issues

Indications	Mechanism of Action/Class	Generic Name	Trade Name	Dosing	Contraindications	Side Effects
Parkinson's Disease	Dopamine precursor	levodopa + carbidopa	Sinemet®	Carbidopa 25 mg/levodopa 100 mg PO tid Maximum 200 mg carbidopa and 2,000 mg levodopa per day	Narrow-angle glaucoma, use of MAO inhibitor in last 14 d, history of melanoma or undiagnosed skin lesions	Nausea, hypotension, hallucinations, dyskinesias in last 14 d, history of melanoma or undiagnosed skin lesions
	Dopamine agonist	bromocriptine	Parlodel®	1.25 mg PO bid, increase by 2.5 mg/d q2-4wk, up to 10-30 mg PO tid	Concomitant use of potent inhibitors of CYP3A4, uncontrolled HTN, ischemic heart disease, peripheral vascular disease; caution with renal or hepatic disease	Hypotension, N/V, dizziness, constipation, diarrhea, abdominal cramps, H/A, nasal congestion, drowsiness, hallucinations
	MAO B inhibitor	selegiline	Eldepryl®	5 mg PO bid	Concomitant use of meperidine or tricyclic antidepressants	H/A, insomnia, dizziness, nausea, dry mouth, hallucinations, confusion, orthostatic hypotension, increased akinesia, risk of hypertensive crisis with tyramine-containing foods
Myasthenia Gravis	Acetylcholinesterase inhibitor	pyridostigmine	Mestinon®	600 mg/d PO divided in 5-6 doses Range 60-1,500 mg/d	GI or GU obstruction	Nausea, vomiting, diarrhea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis, diaphoresis, muscle cramps, fasciculations, muscle weakness
Acute Migraine	Triptan (selective 5-hydroxytryptamine receptor agonist)	sumatriptan	Imitrex®	25-100 mg PO prn, maximum 200 mg/d	Hemiplegic/basilar migraine, ischemic heart disease, CVD, uncontrolled HTN, use of ergotamine/5-HT1 agonist in past 24 h, use of MAO inhibitor in last 14 d, severe hepatic disease	Vertigo, chest pain, flushing, sensation of heat, hypertensive crisis, peripheral vascular disease, coronary artery vasospasm, cardiac arrest, nausea, vomiting, H/A, hyposalivation, fatigue
	Ergot (5-HT1D receptor agonist)	dihydroergotamine	Migranal®	Nasal spray 0.5 mg/spray, maximum 4 sprays/d	Hemiplegic/basilar migraine, high-dose ASA therapy, uncontrolled HTN, ischemic heart disease, peripheral vascular disease, severe hepatic or renal dysfunction, use of triptans in last 24 h, use of MAO inhibitors in last 14 d	Coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, ventricular fibrillation; may cause significant rebound H/A
Migraine Prophylaxis	Anticonvulsant	topiramate	Topamax®	25 mg OD PO (in evening); may increase weekly by 25 mg/d to a max 50 mg bid		Sedation, mood disturbance, cognitive dysfunction, anorexia, nausea, diarrhea, paresthesias, metabolic acidosis, glaucoma, SJS/TEN
	β-blocker	propranolol	Inderal®	80 mg/d divided every 6-8 h; increase by 20-40 mg/dose every 3-4 wk to max 160-240 mg/d in divided doses q6-8h	Uncompensated CHF, severe bradycardia or heart block, severe COPD or asthma	Fatigue, cognitive dysfunction, disturbed sleep, rashes, dyspepsia, dry eyes, heart failure, bronchospasm, risk of acute tachycardia and HTN if withdrawal
Epilepsy	Anticonvulsant for partial ± 2° generalization, generalized tonic-clonic	carbamazepine	Tegretol®	Start at 100-200 mg PO OD-tid, increase by 200 mg/d up to 800-1,200 mg/d	History of bone marrow depression, hepatic disease, hypersensitivity to the drug, use of MAO inhibitor in last 14 d	Drowsiness, H/A, unsteadiness, dizziness, N/V, skin rash, agranulocytosis/aplastic anemia (rare)
	Anticonvulsant for partial, tonic-clonic, status epilepticus	phenytoin	Dilantin®	100 mg PO tid, maintenance dose up to 200 mg PO tid SE: 10-15 mg/kg IV loading dose then maintenance doses of 100 mg PO or IV q6-8h	Hypersensitivity, pregnancy, breastfeeding; caution with P-450 interactions	Hypotension, SJS/TEN, SLE-type symptoms, gingival hypertrophy, peripheral neuropathy, H/A, blood dyscrasias, nystagmus, N/V, constipation, sedation, teratogenic
	Anticonvulsant for partial or generalized, absence seizures	valproic acid	Depakene® Apo-Valproic®	10-15 mg/kg/d PO in divided doses, increase incrementally until therapeutic dose to max of 60 mg/kg/d	Hypersensitivity, hepatic disease, urea cycle disorders	Hepatic failure, H/A, somnolence, alopecia, N/V, diarrhea, tremor, diplopia, thrombocytopenia, hypothermia, pancreatitis, encephalopathy
	Anticonvulsant for absence seizures	ethosuximide	Zarontin®	500 mg/d PO, increase by 250 mg every 4-7 d to max 1.5 g/d in divided doses	Hypersensitivity (succinimides)	CNS depression, blood dyscrasias, SLE, SJS, GI symptoms

www.regentstudies.com

Table 27. Common Medications – Major Issues (continued)

Indications	Mechanism of Action/Class	Generic Name	Trade Name	Dosing	Contraindications	Side Effects
Stroke Prevention in AF	Anticoagulant (direct thrombin inhibitor)	dabigatran	Pradaxa®	110 mg PO bid or 150 mg PO bid	CrCl <30 mL/min, significant hemostatic impairment or CNS lesions within 6 mo with high risk of bleeding	Dyspepsia, gastritis, bleeding
	Anticoagulant (Factor Xa inhibitor)	rivaroxaban	Xarelto®	15 mg PO daily or 20 mg PO daily	Concomitant anticoagulant, hepatic disease, pregnancy, strong CYP3A4 and P-gp inhibitors e.g. itraconazole, ritonavir	Bleeding
	Anticoagulant (Factor Xa inhibitor)	apixaban	Eliquis®	2.5 mg PO bid or 5 mg PO bid	Active bleeding, gastrointestinal bleeding, recent cerebral infarction, active peptic ulcer disease with recent bleeding, hepatic disease with coagulopathy	Bleeding (conjunctival, gastrointestinal, gingival, contusion, hematoma, epistaxis, hematuria)
Mild to Moderate AD or DLB	Cholinesterase Inhibitor	donepezil	Aricept®	5 mg PO OD, may increase to 10 mg PO OD after 4-6 wk	Hypersensitivity to donepezil or to piperidine derivatives	Diarrhea, N/V, insomnia, muscle cramps, fatigue, anorexia, HTN, syncope, AV block
Multiple Sclerosis	MS Disease Modifying Therapy	interferon-β-1b interferon-β-1a SC interferon-β-1a IM	Betaseron® Rebif® Avonex®	0.25 mg (8 MU) SC every other day 44 μg SC 3 times/wk 30 μg IM once weekly	Pregnancy, hypersensitivity to natural or recombinant interferon-β	Injection site reactions, injection site necrosis, flu-like symptoms (fever, chills, myalgia; tend to decrease over time)
	MS Disease Modifying Therapy	glatiramer acetate	Copaxone®	20 mg SC OD	Hypersensitivity to glatiramer or mannitol	Injection site reactions, nausea, transient chest pain, vasodilation
	MS Disease Modifying Therapy	natalizumab	Tysabri®	300 mg IV given over 1 h, every 4 wk	Hypersensitivity to natalizumab, progressive multifocal leukoencephalopathy (PML)	Rash, nausea, arthralgia, H/A, infections, rare risk of PML and melanoma
	MS Disease Modifying Therapy	fingolimod	Gilenya®	0.5 mg PO OD	Not available	Diarrhea, transaminitis, H/A, bradyarrhythmia, lymphopenia
Spasticity (i.e. MS)	Muscle Relaxant – Antispastic	baclofen	Lioresal®	5 mg PO tid, increase by 15 mg/d q3d to max dose 80 mg/d in three divided doses	Hypersensitivity to baclofen	Transient drowsiness, daytime sedation, dizziness, weakness, fatigue, convulsions, constipation, nausea

www.regentstudies.com

Landmark Neurology Trials

Trial	Reference	Results
NASCET	*NEJM* 1991;7:445-53	Patients with symptomatic carotid stenosis of 70-99% benefited more from carotid endarterectomy than best medical therapy
Interferon-β Multiple Sclerosis Study Group Trial	*Neurology* 1993;43:655-61	Interferon-β-1b reduces relapse rate and severity of relapses in RRMS
NINDS rtPA	*NEJM* 1995;333:1581-7	rtPA reduces mortality and long-term disability when administered within 3 h of acute stroke
SPARCL	*NEJM* 2006;355:549-59	The observed benefit of statins in cardiovascular disease is also extended to patients with a recent stroke or TIA
ECASS 3	*NEJM* 2008;359:1317-29	rtPA improved clinical outcomes when administered within 3 to 4.5 h of acute ischemic stroke
PROFESS	*NEJM* 2008;359:1238-51	ASA + dipyridamole and clopidogrel showed similar benefits in secondary stroke prevention
RELY	*NEJM* 2009;361:1139	Dabigatran superior to warfarin for stroke prevention in patients with atrial fibrillation
CREST	*NEJM* 2010;363:11-23	Carotid stenting and endarterectomy had similar benefits in reduction of stroke, MI, and death in carotid stenosis, but in the periprocedural period, stenting had a higher rate of stroke, while endarterectomy had a higher rate of MI
INTERACT2	*NEJM* 2013;368:2355-65	Intensive lowering of blood pressure (sBP$<$140) in spontaneous intracerebral hemorrhage did not improve mortality or severe disability but improved functional outcomes (odds ratio for greater disability, 0.87; 95% CI, 0.77 to 1.00; P=0.04)
MR CLEAN	*NEJM* 2015;372:11-20	Intra-arterial treatment (intra-arterial thrombolysis, mechanical treatment, or both) for emergency revascularization administered within 6 h after stroke onset was effective and safe for acute ischemic stroke caused by proximal intracranial occlusion of the anterior circulation

www.regentstudies.com

References

Coma
Bhidayasiri R, Waters MF, Giza CC. Neurological differential diagnosis: a prioritized approach. Massachusetts: Blackwell Publishing, 2005. 71-72.
Kasper DL, Braunwald E, Fauci AS, et al. (editors). Harrison's principles of internal medicine, 16th ed. Toronto: McGraw-Hill Companies, 2005. 1629-1630.

Common Presenting Complaints
Bhidayasiri R, Waters MF, Giza CC. Neurological differential diagnosis: a prioritized approach. Massachusetts: Blackwell Publishing, 2005. 12-13, 305-314.

Drug Information
Compendium of Pharmaceuticals and Specialties 2010. Ottawa: Canadian Pharmacists Association, 2010.
Lexi-Comp Online™. Hudson: Lexi-Comp, 2011.

Epilepsy
Ambati BK, Smith WT, Azer-Bentsianov MT. Residents' manual of medicine. Hamilton: BC Decker, 2001. 203-205.
Ferri FF. Practical guide to the care of the medical patient. St. Louis: Mobsy, 2001. 617-619.
Lowenstein DH, Alldredge BK. Status epilepticus. NEJM 1998;338:970-976.

General
Aminoff MJ, Greenberg DA, Simon RP. Lange: clinical neurology, 6th ed. Toronto: McGraw-Hill, 2009.
Ettinger AB, Weisbrot DM. Neurologic Differential Diagnosis: a Case-Based Approach. Cambridge: Cambridge University Press, 2014.
Mumenthaler M, Mattle H. Fundamentals of neurology. Thieme: Stuttgart and New York, 2006.
Scherokman B, Selwa L, Alguire PC. Approach to common neurological symptoms in internal medicine: AAN core curricula. 2011.
Yamada KA, Awadalla S. The Washington manual of medical therapeutics, 31st ed. New York: Lippincott Williams & Wilkins. 531-534.

Headache
Chronicle EP, Mulleners WM. Anticonvulsant drugs for migraine prophylaxis. Cochrane DB Syst Rev 2009:CD003226.
Detsky ME, McDonald DR, Baerlocher MO, et al. Does this patient with headache have a migraine or need neuroimaging? JAMA 2006;296:1274-1283.
Francis GJ, Becker WJ, Pringsheim TM. Acute and preventive pharmacologic treatment of cluster headache. Neurology 2010;75:463-473.
Headache Classification Subcommittee of the International Headache Society. The international classification of headache disorders, 2nd ed. Cephalalgia 2004;24(S1):9-160.
Oldman AD, Smith LA, McQuay HJ, et al. Pharmacological treatments for acute migraine: quantitative systematic review. Pain 2002;97:247-257.

Movement Disorders
Bayard M, Avonda T, Wadzinski J. Restless legs syndrome. Am Fam Physician 2008; 78:235-40.
Centers for Disease Control and Prevention (CDC). Diagnosis and management of foodborne illnesses: a primer for physicians and other health care professionals. MMWR Recomm Rep 2004;53(RR-4):1-33.
England JD, Gronseth G, Franklin G, et al. Practice Parameter: evaluation of distal symmetric polyneuropathy: role of laboratory and genetic testing (an evidence-based review). Neurology 2009;72:185-192.
Hughes AJ, Daniel SE, Kilford L, et al. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181-184.
Stowe RL, Ives NJ, Clarke CE, et al. Dopamine agonist therapy in early Parkinson's disease. Cochrane DB Syst Rev 2008:CD006564.
Walkup JT, Ferrao Y, Leckman JF, et al. Tic disorders: some key issues for DSM-V. Depression and Anxiety 2010:600-610.

Multiple Sclerosis
Ambati BK, Smith WT, Azer-Bentsianov MT. Residents' manual of medicine. Hamilton: BC Decker, 2001. 211-213.
Carpenter CCJ, Griggs RC, Loscalzo J (editors). Cecil essentials of medicine, 5th ed. Philadelphia: WB Saunders, 2001. 973-976.
Clerico M, Faggiano F, Palace J, et al. Recombinant interferon beta or glatiramer acetate for delaying conversion of the first demyelinating event to multiple sclerosis. Cochrane DB Syst Rev 2009:CD005278.
Ferri FF. Practical guide to the care of the medical patient. St. Louis: Mosby, 2001. 654-656.
Noseworthy JH, Lucchinetti C, Rodriguez M, et al. Multiple sclerosis. NEJM 2000;343:938-952.
Olek MJ (editor). Multiple sclerosis: etiology, diagnosis, and new treatment strategies. New Jersey: Humana Press, 2005. 36-40, 57, 131, 222-223.
Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". Ann Neurol 2005;58:840-846.
Samuels MA, Feske SK (editors). Office practice of neurology, 2nd ed. Philadelphia: Elsevier Science, 2003. 410-411.
The TRANSFORMS Study Group. Oral fingolimod or intramuscular interferon for relapsing MS. NEJM 2010;362:402-415.
Vosoughi R, Freedman MS. Therapy of MS. Clin Neurol Neurosurg 2010;112:365-385.

Neurocognitive Disorders (Dementia)
Feldman HH, Jacova C, Robillard A, et al. Diagnosis and treatment of dementia: diagnosis. CMAJ 2008;178:825-836.
Josephs KA, Ahlskog JE, Parisi JE, et al. Rapidly progressive neurodegenerative dementias. Arch Neurol 2009;66:201-207.
McKeith IG, Dickson DW, Lowe J, et al. Consortium on DLB. Diagnosis and management of dementia with Lewy bodies: third report of the DLB consortium. Neurology 2005;65:1863-1872.
Neary D, Snowden JS, Gustafson L, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 1998;51:1546-1554.
Patterson C, Feightner JW, Garcia A, et al. Diagnosis and treatment of dementia: risk assessment and primary prevention of Alzheimer disease. CMAJ 2008;178:548-556.
Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain 2011;134:2456-2477.
Rolinski M, Fox C, Maidment I, et al. Cholinesterase inhibitors for dementia with Lewy bodies, Parkinson's disease dementia and cognitive impairment In Parkinson's disease. Cochrane DB Syst Rev 2012:CD006504.
Vigen CL, Mack WJ, Keefe RS, et al. Cognitive effects of atypical antipsychotic medications in patients with Alzheimer's disease: outcomes from CATIE-AD. Am J Psychiatry 2011;168:831-839.
Zerr I, Pocchiari M, Collins S, et al. Analysis of EEG and CSF 14-3-3 proteins as aids to the diagnosis of Creutzfeldt-Jakob disease. Neurology 2000;55:811-815.
Zerr I, Kallenberg K, Summers DM, et al. Updated clinical diagnostic criteria for sporadic Creutzfeldt-Jakob disease. Brain 2009;132:2659-2668.

Pain
Chen N, Li Q, Zhang Y, et al. Vaccination for preventing postherpetic neuralgia. Cochrane DB Syst Rev 2011:CD007795.
Coen PG, Scott F, Leedham-Green M, et al. European Journal of Pain 2006;10:695-700.
Marcus D. Chronic pain - a primary guide to practical management. New Jersey: Humana Press, 2005. 111-128.
Salinas RA, Alvarez G, Daly F, et al. Corticosteroids for Bell's palsy (idiopathic facial paralysis). Cochrane DB Syst Rev 2010:CD001942.
Vargas-Schaffer G. Is the WHO analgesic ladder still valid? Twenty-four yr of experience. Can Fam Phys 2010;56:514-517.

Spinal Cord Syndrome
Wagner R, Jagoda A. Neurologic emergencies: spinal cord syndromes. Emerg Med Clinic N Am 1997;15:699-711.

www.regentstudies.com

Stroke
Adams HP Jr., Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. Stroke 1993;24:35-41.
Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and Aspirin® versus Aspirin® alone for the prevention of atherothrombotic events. NEJM 2006;354:1706-1717.
Brott TG, Hobson RW, George H, et al. Stenting versus endarterectomy for treatment of carotid stenosis. NEJM 2010;363:11-23.
CAPRIE Steering Committee. A randomized, blinded, trial of clopidogrel versus Aspirin® in patients at risk of ischaemic events (CAPRIE). Lancet 1996;348:1329-1339.
Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. NEJM 2009;361:1139-1151.
Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin® and clopidogrel compared with clopidogrel alone after recen: ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomized, double-blind, placebo-controlled trial Lancet 2004;364:331-337.
Frontera W, Silver J. Essentials of physical medicine and rehabilitation. Philadelphia: Hanley and Belfus, 2002. 778-782.
Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001;285:2864-2870.
Johnston SC, Rothwell PM, Nguyen-Huynh MN, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet 2007;369:283-292.
Lindsay K, Bone I. Neurology and neurosurgery illustrated. Philadelphia: Churchill Livingstone, 2003. 244.
Mullins ME, Lev MH, Scheillingerhout D, et al. Intracranial hemorrhage complicating acute stroke: how common is hemorrhagic stroke on initial head CT scan and how often is initial clinical diagnosis of acute stroke eventually confirmed? Am J Neuroradiol 2005;26:2207-2212.
Stroke Unit Trialists' Collaboration. Organized inpatient (stroke unit) care for stroke. Cochrane DB Syst Rev 2009:CD000197.
Passero S, Rocchi R, Rossi S, et al. Seizures after spontaneous supratentorial intracerebral hemorrhage. Epilepsia 2002;43:1175-1180.
Pexman JH, Barber PA, Hill MD, et al. Use of the Alberta Stroke Program Early CT Score (ASPECTS) for assessing CT scans in patients with acute stroke. Am J Neuroradiol 2001;22:1534-1542.
Program early CT score (ASPECTS) for assessing CT scans in patients with acute strokes. AMJ Neuroradiol 2001;22:1534-1542.
The ESPRIT Study Group. Aspirin® plus dipyridamole versus Aspirin® alone after cerebral ischaemia of arterial origin (ESPRIT): randomized controlled trial. Lancet 2006;367:1665-1673.
The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an ACEI, ramipril, on cardiovascular events in high-risk patients. NEJM 2000;342:145-153.
The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. NEJM 1995;333:1581-1588.
The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Effects of tissue plasminogen activator for acute ischemic stroke at one year. NEJM 1999;340:1781-1787.

Traumatic Brain Injury
Anderson-Barnes VC, Weeks SR, Tsao JW. Mild traumatic brain injury update. Continuum 2010;16(6):17-23.

www.regentstudies.com

NS Neurosurgery

Oliver Ayling and **Holly Yeo Jin Lee,** chapter editors
Hasaan Chaudhry and **Nardin Samuel,** associate editors
Alex Cressman and **Shany Gertzbein,** EBM editor
Dr. Todd Mainprize and **Dr. Eric Massicotte,** staff editors

www.regentstudies.com

Acronyms

AVF	arteriovenous fistula	GPi	globus pallidus pars interna	PAG	periaqueductal grey matter
AVM	arteriovenous malformation	H/A	headache	PET	positron emission tomography
CBF	cerebral blood flow	IC	internal capsule	PLL	posterior longitudinal ligament
CSF	cerebral spinal fluid	ICF	intracellular fluid	PNET	primitive neuroectodermal tumour
CPA	cerebellar pontine angle	ICH	intracerebral hemorrhage	PVG	periventricular grey matter
CPP	cerebral perfusion pressure	ICP	intracranial pressure	SAH	subarachnoid hemorrhage
CVR	cerebral vascular resistance	IVH	intraventricular hemorrhage	SDH	subdural hemorrhage
DBS	deep brain stimulation	LMN	lower motor neuron	SIADH	syndrome of inappropriate antidiuretic hormone
DI	diabetes insipidus	LOC	loss of consciousness	SPECT	single photon emission computed tomography
ECF	extracellular fluid	LP	lumbar puncture	SRS	stereotactic radiosurgery
ECT	electroconvulsive therapy	MAP	mean arterial pressure	STN	subthalamic nucleus
EEG	electroencephalography	MLS	midline shift	UMN	upper motor neuron
EMG	electromyography	NC	neurogenic claudication	VPL	ventral posterolateral
EVD	external ventricular drain	NPH	normal pressure hydrocephalus	VPM	ventral posteromedial
GCS	Glasgow coma scale	OPLL	ossification of posterior longitudinal ligament	WBRT	whole brain radiation therapy

Basic Anatomy Review

See Functional Neuroanatomy Software

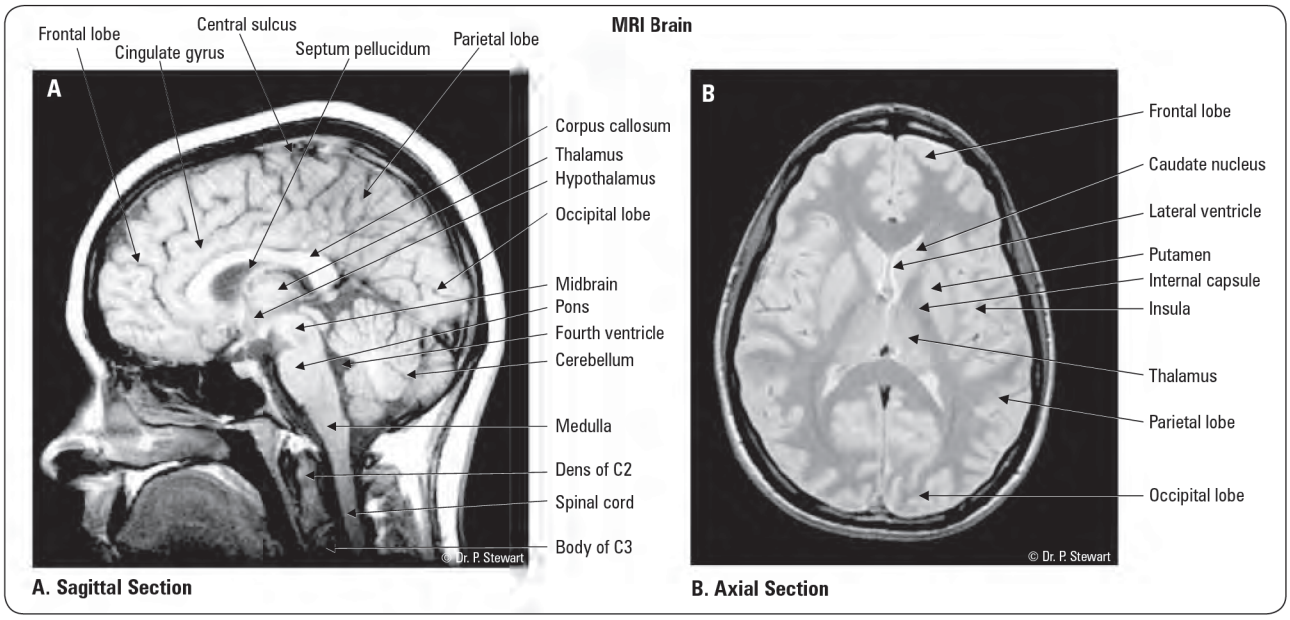


Figure 1. Magnetic resonance imaging (MRI) neuroanatomy
Stewart P, et al. Functional Neuroanatomy (Version 2.1). Health Education Assets Library 2005

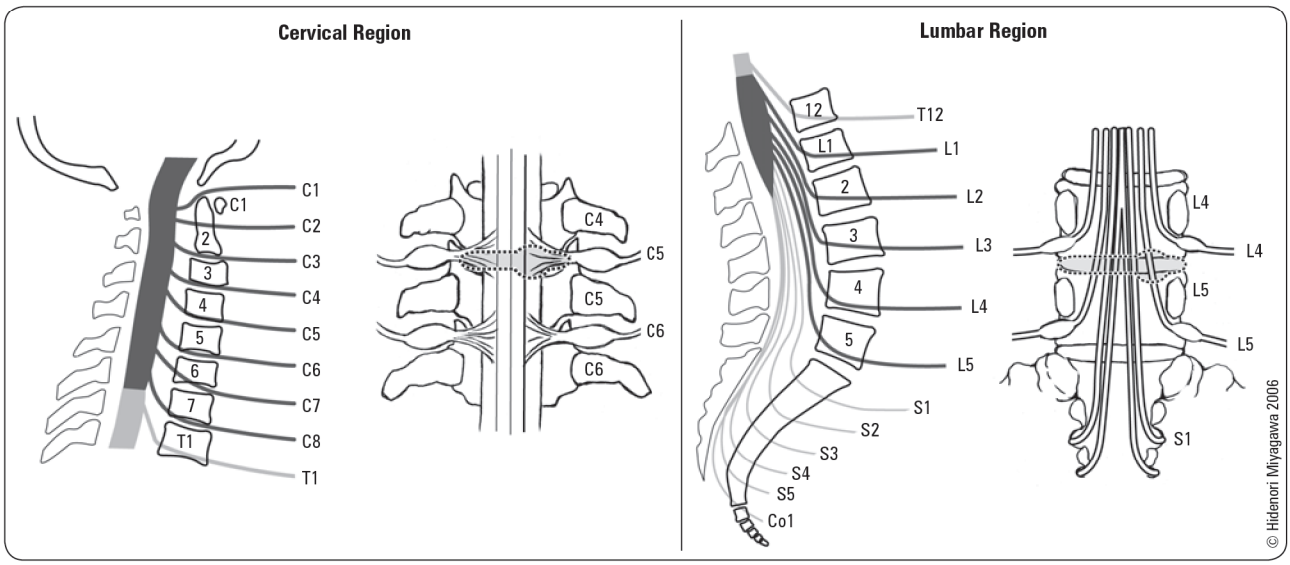


Figure 2. Relationship of nerve roots to vertebral level in the cervical and lumbar spine
Note: AP views depict left-sided C4-5 and L4-5 disc herniation, and correlating nerve root impingement

www.regentstudies.com

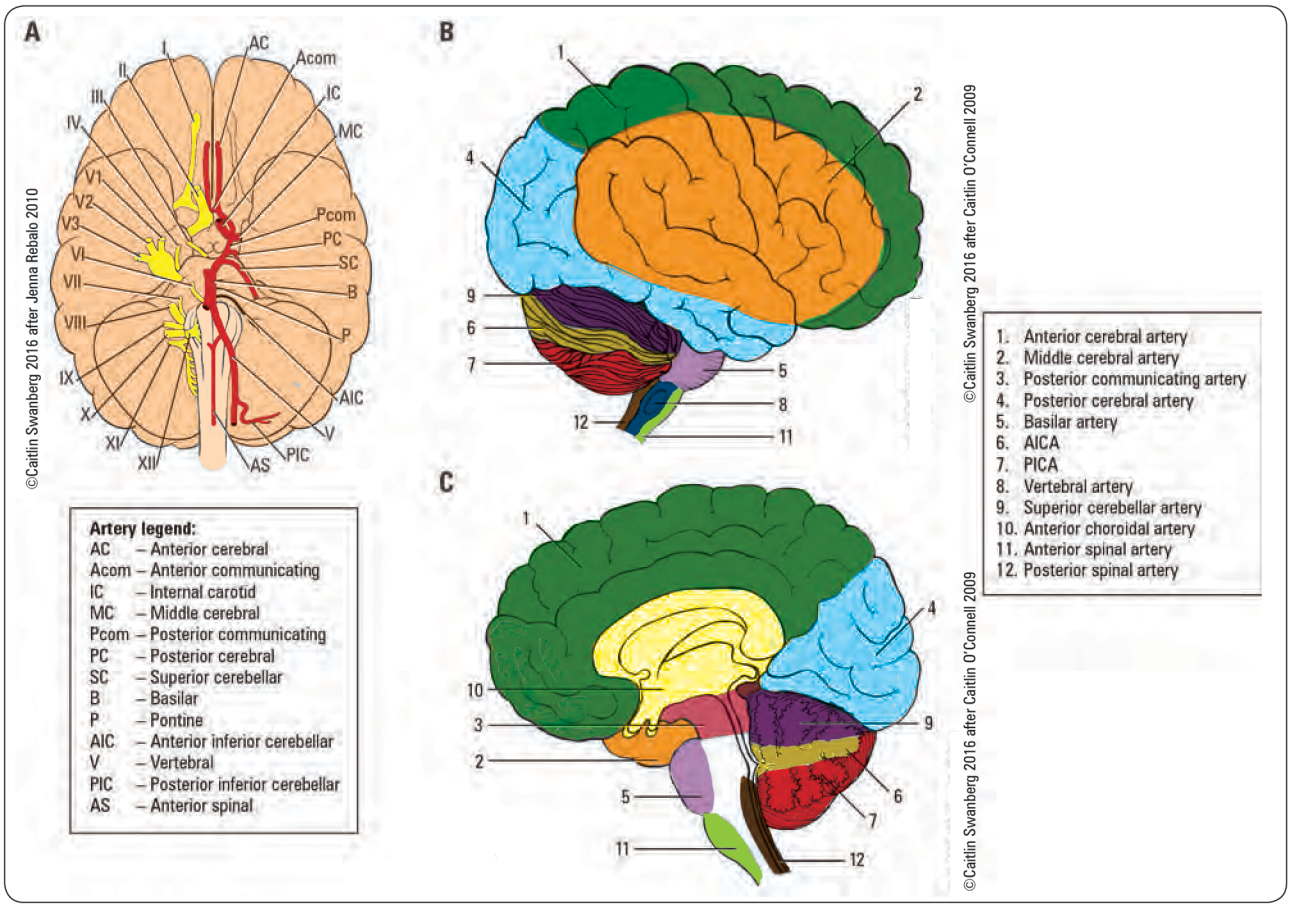


Figure 3. Vascular supply of the brain. Please see legend for artery names. 3A. Circle of Willis, most common variant. 3B. Vascular territories of the brain and brainstem, saggital view, seen laterally. 3C. Vascular territories of the brain and brainstem, saggital view, seen medially

Differential Diagnoses of Common Neurosurgical Presentations

Intracranial Mass Lesions	Disorders of the Spine	Peripheral Nerve Lesions
Tumour Metastasis Astrocytoma Meningioma Vestibular schwannoma (acoustic neuroma) Pituitary adenoma Primary CNS lymphoma Pus/inflammation Cerebral abscess, extradural abscess, subdural empyema Encephalitis (see Infectious Diseases, ID18) Tumefactive MS Blood Extradural (epidural) hematoma Subdural hematoma Ischemic stroke Hemorrhage: SAH, ICH, IVH Cyst Arachnoid cyst Dermoid cyst Epidermoid cyst Colloid cyst (3rd ventricle)	Extradural Degenerative: disc herniation, canal stenosis, spondylolisthesis/spondylolysis Infection/inflammation: osteomyelitis, discitis Ligamentous: ossification of posterior longitudinal ligament (OPLL) Trauma: mechanical compression/instability, hematoma Tumours (55% of all spinal tumours): lymphoma, metastases (lymphoma, lung, breast, prostate), neurofibroma Intradural extramedullary Vascular: dural arteriovenous fistula, subdural hematoma (especially if on anticoagulants) Tumours (40% of all spinal tumours): meningioma, schwannoma, neurofibroma Intradural intramedullary Tumours (5% of all spinal tumours): astrocytomas and ependymomas most common; also hemangioblastomas and dermoids Syringomyelia (common causes: trauma, congenital, idiopathic) Infectious/inflammatory: TB, sarcoid, transverse myelitis Vascular: AVM, ischemia	Neuropathies Traumatic Entrapments Iatrogenic Inflammatory Tumours

www.regentstudies.com

INTRACRANIAL PATHOLOGY

Intracranial Pressure Dynamics

Table 1. Approach to Intracranial Pathology

Issue	Time Frame	Features
Vascular	Sudden	No H/A = occlusive H/A = hemorrhagic
Metabolic	Hours to days	Affects entire CNS
Infectious	Days to weeks	Often a source of infection on history
Tumor	Months	Increased ICP: Initially → H/A • Constant • Progressive • Severe • Worse in morning As ICP increases: • Blurry vision • Projectile vomiting Severely raised ICP: • Cushing's reflex • Bradycardia • HTN • Respiratory changes

Table 2. Consequences of Common Brain Lesions

Location of Lesion	Consequence
Frontal lobe	1. Disinhibition 2. Concentration deficits 3. Orientation deficits 4. Judgment deficits 5. ± Primitive reflex re-emergence 6. ± Contralateral motor deficits if motor cortex involved
Broca's area (inferior frontal gyrus of dominant hemisphere)	1. Non-fluent aphasia 2. Repetition impaired 3. Comprehension relatively spared
Wernicke's area (superior temporal gyrus of dominant hemisphere)	1. Fluent aphasia 2. Repetition impaired 3. Comprehension markedly impaired
Occipital lobe	Contralateral visual field deficits
Right parietal lobe	Hemispatial neglect syndrome • Contralateral agnosia
Basal ganglia	1. Rest tremor 2. Chorea 3. Athetosis
Subthalamic nucleus	Contralateral hemiballismus
Mammillary bodies (bilateral)	Wernicke-Korsakoff syndrome 1. Wernicke • Confusion • Ophthalmoplegia • Ataxia 2. Korsakoff • Anterograde amnesia • Confabulation • Personality changes
Hippocampus	Anterograde amnesia
Reticular activating system (midbrain)	Reduced levels of arousal and wakefulness
Paramedian pontine reticular formation	Gaze deviation away from side of lesion
Frontal eye fields	Gaze deviation toward side of lesion
Cerebellar hemisphere	1. Intention tremor 2. Limb ataxia 3. Fall towards side of lesion
Cerebellar vermis	1. Truncal ataxia 2. Dysarthria

www.regentstudies.com

ICP/Volume Relationship

- adult skull is rigid with a constant intracranial volume
- contents (CSF, blood, brain) are incompressible (Monro-Kellie doctrine)
- increase in one constituent/space-occupying lesion = 1) increase in ICP, 2) require redistribution of CSF, blood, or brain
- however, ICP does not rise initially due to compensatory mechanisms
  - **immediate**: displacement of CSF to lumbar theca, displacement of blood from venous sinuses
  - **delayed**: displacement of ECF or ICF, displacement of brain tissue into compartments under less pressure (herniation)
- once compensation is exhausted, ICP rises exponentially

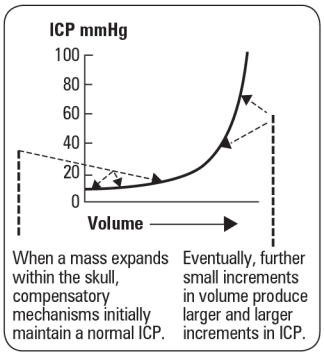


Figure 4. ICP-volume curve
Adapted from: Lindsay KW, et al. Neurology and neurosurgery illustrated. © 2004. With permission from Elsevier

Cerebral Blood Flow

- brain receives about 15% of cardiac output (~750 mL/min)
- CBF depends on cerebral perfusion pressure (CPP) and cerebral vascular resistance (CVR)
- normal CPP >50 mmHg in adults
- cerebral autoregulation maintains constant CBF by compensating for changes in CPP, unless:
  - high ICP such that CPP <60 mmHg
  - MAP >150 mmHg or MAP <50 mmHg
  - brain injury: e.g. SAH, severe trauma

CBF = CPP / CVR
CPP = MAP – ICP

ICP Measurement

- normal ICP <15 mmHg (8-18 cmH_2O) for adult, 3-7 mmHg (4-9.5 cmH_2O) for child; varies with patient position
  - moderate elevation: increase in mean pressure >20 mmHg
  - severe elevation: increase in mean pressure >40 mmHg
- waveform: comprised of respiratory and cardiac pulsations (Traube-Hering waves); the amplitude increases with ICP
  - β-waves: coarse, variably increased amplitude, frequency ½-2/min, often related to respiration
  - plateau waves: elevation of ICP over 50 mmHg lasting 5-20 min, precursor of further deterioration

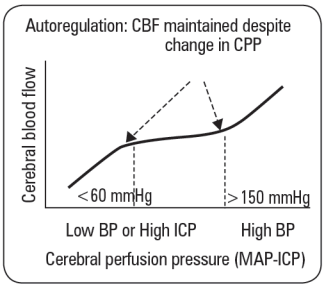


Figure 5. Cerebral autoregulation curve
Adapted from: Lindsay KW, et al. Neurology and neurosurgery illustrated. © 2004. With permission from Elsevier

Acute Monitoring

- lumbar puncture (LP)
- intraventricular catheter/ventriculostomy/external ventricular drain (EVD) ("gold standard", also permits therapeutic drainage of CSF to decrease ICP)

Chronic Monitoring

- fibreoptic monitor (intraventricular, intraparenchymal, subdural), subarachnoid bolt (Richmond screw), and epidural monitor

Lumbar puncture is contraindicated with known/suspected intracranial mass

Elevated ICP

Etiology

- intracranial space-occupying lesion
  - tumour
  - pus
  - blood (trauma → hematoma [most common], subarachnoid hemorrhage)
  - depressed skull fracture
  - foreign body
- increased intracranial blood volume
  - vasodilatation (increased pCO_2/decreased pO_2/decreased extracellular pH, e.g. hypoventilation)
  - venous outflow obstruction (venous sinus thrombosis, superior vena cava syndrome, space-occupying lesion)
  - cranial dependency
- cerebral edema
  - vasogenic (vessel damage, e.g. hypertensive encephalopathy, tumour)
  - cytotoxic (tissue/cell death, e.g. hypoxia, brain injury)
  - osmotic (acute hyponatremia, hepatic encephalopathy)

Consider Monitoring of ICP in the Following Situations
- Patients with an abnormal head CT and GCS score of 3-8 after cardiopulmonary resuscitation

Or
- Patients with a normal head CT and GCS score of 3 to 8 AND the presence of two or more of the following:
  - >40 yr
  - Unilateral or bilateral motor posturing
  - sBP <90mmHg
- Post-operative monitoring
- Investigation of NPH

www.regentstudies.com

- hydrocephalus
  - obstructive: acquired acqueductal stenosis
  - non-obstructive: decreased CSF absorption with SAH
- pseudotumour cerebri (idiopathic intracranial HTN)
- impaired autoregulation (hypotension, HTN, brain injury)
- status epilepticus (chronic seizure resulting in brain edema)

Blood Brain Barrier
Glucose and amino acids cross slowly
Non-polar/lipids cross fast

Clinical Features

1. Acute Elevated ICP

- H/A: worse in the morning, aggravated by stooping, and bending
- N/V
- decreased LOC if ICP = dBP, or midbrain compressed
- drop in GCS = best index to monitor progress and predict outcome of acute intracranial process (see *Neurotrauma*, NS29)
- papilledema ± retinal hemorrhages (may take 24-48 h to develop)
- abnormal extra-ocular movements (EOM)
  - CN VI palsy: often falsely localizing (causative mass may be remote from nerve)
  - upward gaze palsy (especially in children with obstructive hydrocephalus)
- herniation syndromes
- focal signs/symptoms due to lesion

Blood Brain Barrier
Infarction/neoplasm → destroy tight junctions → vasogenic edema

Cushing's Triad of Acute Raised ICP (full triad seen in 1/3 of cases)
- HTN
- Bradycardia (late finding)
- Irregular respiratory pattern

2. Chronic Elevated ICP

- H/A
  - postural: worsened by coughing, straining, and bending over
  - morning/evening H/A → vasodilatation due to increased CO_2 with recumbency
- visual changes
  - due to papilledema
  - enlarged blind spot, if advanced → episodic constrictions of visual fields ("grey-outs")
  - optic atrophy/blindness
  - differentiate from papillitis (usually unilateral with decreased visual acuity)
- decreased level of consciousness

Papilledema
- Optic disc swelling with blurred margins (most commonly bilateral)
- Larger blind spot

Investigations

- patients with suspected elevated ICP require an urgent CT/MRI
- ICP monitoring where appropriate

Herniation Syndromes

Table 3. Herniation Syndromes

Herniation Syndrome	Definition	Etiology	Clinical Features
1. Subfalcine	Cingulate gyrus herniates under falx	• Lateral supratentorial lesion	• Usually asymptomatic • Warns of impending transtentorial herniation • Risk of ACA compression
2. Central Tentorial (Axial)	Displacement of diencephalon through tentorial notch	• Supratentorial midline lesion • Diffuse cerebral swelling • Late uncal herniation	• Small pupils, moderately dilated, fixed (rostral to caudal deterioration), sequential failure of diencephalon, medulla • Decreased LOC (midbrain compression), EOM/upward gaze impairment ("sunset eyes"): compression of pretectum and superior colliculi • Brainstem hemorrhage ("Duret's" – secondary to shearing of basilar artery perforating vessels) • Diabetes insipidus (traction on pituitary stalk and hypothalamus), end-stage sign
3. Lateral Tentorial (Uncal)	Uncus of temporal lobe herniates down through tentorial notch	• Lateral supratentorial lesion (often rapidly expanding traumatic hematoma)	• Ipsilateral non-reactive dilated pupil (earliest, most reliable sign) + ipsilateral EOM paralysis, ptosis (CN III compression) • Decreased LOC (midbrain compression) • Contralateral hemiplegia ± extensor (upgoing) plantar response ± ipsilateral hemiplegia ("Kernohan's notch" – a false localizing sign resulting from pressure from the edge of the tentorium on the contralateral cerebral peduncle)
4. Upward	Cerebellar vermis herniates through tentorial incisura	• Large posterior fossa mass (common after VP shunting)	• Cerebellar infarct (superior cerebellar artery [SCA] compression) • Hydrocephalus (cerebral aqueduct compression)
5. Tonsillar	Cerebellar tonsils herniate through foramen magnum	• Infratentorial lesion • Following central tentorial herniation • Following LP in presence of intracranial mass lesion	• Neck stiffness and head tilt (tonsillar impaction) • Decreased LOC (midbrain compression) • Flaccid paralysis • Respiratory irregularities, respiratory arrest (compression of medullary respiratory centres) • Blood pressure instability (compression of medullary cardiovascular centres)

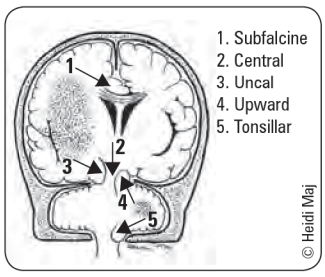


Figure 6. Herniation types

www.regentstudies.com

Treatment of Elevated ICP

- CT or MRI to identify etiology, assess for midline shift/herniation
- treat primary cause (i.e. remove mass lesions, ensure adequate ventilation)
- if elevated ICP persists following treatment of primary cause, consider therapy when ICP >20 mmHg
- goals: keep ICP <20 mmHg, CPP >65 mmHg, MAP >90 mmHg

Conservative Measures

- elevate head of bed at 30°, maintain neck in neutral position → increases intracranial venous outflow with minimal effect on arterial pressure
- prevent hypotension with fluid and vasopressors, dopamine, norepinephrine prn
- ventilate to normocarbia (pCO_2 35-40 mmHg) → prevents vasodilatation
- oxygen to maintain pO_2 >60 mmHg → prevents hypoxic brain injury
- osmolar diuresis (mannitol 20% IV solution 1-1.5 g/kg, then 0.25 g/kg q6h to serum osmolarity of 315-320)
  - can give rapidly, acts in 15-30 min, must maintain sBP >90 mmHg
- corticosteroids → decrease edema over subsequent days around brain tumour, abscess, blood
  - no proven value in head injury or stroke

Treatment of Elevated ICP

ICP HEAD
Intubate
Calm (sedate)/**C**oma
Place drain/**P**aralysis

Hyperventilate
Elevate head
Adequate BP
Diuretic (mannitol)

Aggressive Measures

- sedation ("light" e.g. barbiturates/codeine → "heavy" e.g. fentanyl/$MgSO_4$)
- paralysis with vecuronium → reduces sympathetic tone, reduces HTN induced by muscle contraction
- hyperventilate to pCO_2 30-35 mmHg
  - use for brief periods only – also results in decreased cerebral blood flow
- drain 3-5 mL CSF via ventricles, assess each situation independently
- insert EVD (if acute) or shunt
- barbiturate-induced coma induced with pentobarbital to reduce cerebral blood flow and metabolism (10 mg/kg over 30 min, then 1 mg/kg q1h continuous infusion)
  - decreases mortality, but no improvement in neurological outcome
- decompressive craniectomy is a last resort
- no role for the use of hypothermia in head injury

Hydrocephalus

- hydrocephalus in children, see *Pediatric Neurosurgery,* NS35

Definition

- accumulation of excess CSF in the brain
- CSF: produced by choroid plexus lateral ventricles
- total volume ~120 mL, including 30 cc within ventricular system, remainder in SA space
- flow: lateral ventricle → 3rd ventricle → cerebral acqueduct → 4th ventricle → subarachnoid space
- re-absorbed by arachnoid villi into dural venous sinuses

CSF produced by choroid plexus, flows to: ventricles → foramina of Luschka (lateral) and Magendie (medial) → subarachnoid space → absorbed by arachnoid villi/granulations into venous sinuses

CSF production = CSF reabsorption = ~500 mL/d in normal adults
Normal CSF volume ~150 mL (50% spinal, 50% intracranial → 25 mL intraventricular, 50 mL subarachnoid)

Etiology

- congenital versus acquired
- obstruction to CSF flow
- decreased CSF absorption
- increased CSF production (rarely) – e.g. choroid plexus papilloma (0.4-1% of intracranial tumours)

Epidemiology

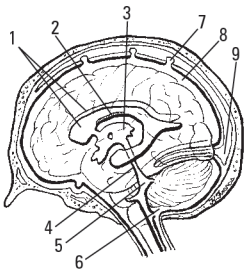
- estimated prevalence 1-1.5%; incidence of congenital hydrocephalus ~1-2/1,000 live births

www.regentstudies.com

Classification

Table 4. Classification of Hydrocephalus

Disorder	Definition	Etiology	Findings on CT/MRI
Obstructive (Non-Communicating) Hydrocephalus	Circulation blocked within ventricular system proximal to the arachnoid granulations	**Acquired** • Aqueductal stenosis (adhesions following infection, hemorrhage) • Intraventricular lesions (tumours e.g. 3rd ventricle colloid cyst, hematoma) • Mass causing tentorial herniation, aqueduct/4th ventricle compression • Others: neurosarcoidosis, abscess/granulomas, arachnoid cysts **Congenital** • Aqueductal stenosis, Dandy-Walker malformation, Chiari malformation (see *Pediatric Neurosurgery*, NS34)	• Ventricular enlargement proximal to block • Periventricular hypodensity (transependymal migration of CSF forced into extracellular space) • Sulcal effacement
Non-Obstructive (Communicating) Hydrocephalus	CSF absorption blocked at extraventricular site = arachnoid granulations	• Post-infectious (#1 cause) meningitis, cysticercosis • Post-hemorrhagic (#2 cause) → SAH, IVH, traumatic • Choroid plexus papilloma (rare, causes increased CSF production) • Idiopathic → normal pressure hydrocephalus	• All ventricles dilated
Normal Pressure Hydrocephalus (NPH)	Persistent ventricular dilatation in the context of normal CSF pressure	• Idiopathic (50%) • Others: subarachnoid hemorrhage, meningitis, trauma, radiation-induced	• Enlarged ventricles without increased prominence of cerebral sulci
Hydrocephalus *Ex Vacuo*	Ventricular enlargement resulting from atrophy of surrounding brain tissue	• Normal aging • Alzheimer's, Creutzfeldt-Jacob Disease	• Enlarged ventricles and sulci • Cerebral atrophy



1. Lateral ventricles
2. Choroid plexus
3. Third ventricle
4. Cerebral aqueduct (of Sylvius)
5. Fourth ventricle
6. Foramina of Luschka and Magendie
7. Arachnoid granulations
8. Subarachnoid space
9. Superior sagittal sinus

© Kari Francis 2004

Figure 7. The flow of CSF

Clinical Features

- acute hydrocephalus
  - signs and symptoms of acute elevated ICP (see *Elevated ICP*, NS5)
  - impaired upward gaze ("sunset eyes") and/or CN VI palsy
- chronic/gradual onset hydrocephalus (i.e. NPH)
  - gradual onset of classic triad developing over weeks or months
    - pressure of ventricle on lower extremity motor fibres → gait disturbance (ataxia and apraxia usually initial symptoms)
    - pressure on cortical bowel/bladder centre → urinary incontinence
    - pressure on frontal lobes → dementia
  - CSF pressure can be measured within clinically "normal" range

Classic Triad of NPH Progression

AID
Ataxia/**A**praxia of gait
Incontinence
Dementia

Investigations

- CT/MRI (periventricular lucency suggests raised CSF pressure)
- ultrasound (through anterior fontanelle in infants)
- ICP monitoring (e.g. LP) may be used to investigate NPH, test response to shunting (lumbar tap test)
- radionuclide cisternography can test CSF flow and absorption rate (unreliable)
- β-2 transferrin assay to test for the presence of CSF leak

Treatment

- ventricular drainage
- surgical removal of obstruction (if possible) or excision of choroid plexus papilloma
- shunts
  - ventriculoperitoneal (VP): most common
  - ventriculopleural
  - ventriculo-atrial (VA): relatively increased risk of infections, shunt emboli
  - lumboperitoneal: for communicating hydrocephalus and pseudotumour cerebri
- third ventriculostomy (for obstructive hydrocephalus) via ventriculoscopy
- LPs for transient hydrocephalus (e.g. SAH), IVH in premature infants, etc.

www.regentstudies.com

Shunt Complications

Table 5. Shunt Complications

Complication	Etiology	Clinical Features	Investigations
Obstruction (most common)	• Obstruction by choroid plexus • Buildup of proteinaceous accretions, blood, cells (inflammatory or tumour) • Infection • Disconnection or damage	• Acute hydrocephalus • Increased ICP	• "Shunt series" (plain x-rays of entire shunt that only rule-out disconnection, break, tip migration) • CT • Radionuclide "shuntogram"
Infection (3-6%)	• *S. epidermidis* • *S. aureus* • *P. acnes* • Gram-negative bacilli	• Fever, N/V, anorexia, irritability • Meningitis • Peritonitis • Signs and symptoms of shunt obstruction • Shunt nephritis (VA shunt)	• CBC • Blood culture • Tap shunt for C&S (LP usually NOT recommended)
Overshunting (10% over 6.5 yr)	• Slit ventricle syndrome, collapse of ventricles leading to occlusion of shunt ports by ependymal lining	• Chronic or recurring headaches often relieved when lying down	• CT/MRI • Slit-like ventricles on imaging
	• Subdural hematoma • Collapsing brain tears bridging veins (especially common in NPH patients)	• Asymptomatic • Headaches, vomiting, somnolence	• CT
	• Secondary craniosynostosis (children): apposition and overlapping of the cranial sutures in an infant following decompression of hydrocephalus	• Abnormal head shape	• Clinical • CT
Seizures (5.5% risk in 1st yr, 1.1% after 3rd yr)			• EEG
Inguinal Hernia (17% incidence with VP shunt inserted in infancy) ± skin breakdown over hardware	• Increased intraperitoneal pressure/fluid results in hernia becoming apparent	• Inguinal swelling, discomfort	• U/S

Idiopathic Intracranial Hypertension (Pseudotumour Cerebri)

Definition

- raised intracranial pressure and papilledema without evidence of any mass lesion, hydrocephalus, infection, or hypertensive encephalopathy (diagnosis of exclusion)

Etiology

- unknown (majority), but associated with
  - lateral venous sinus thrombosis
  - habitus/diet: obesity, hyper/hypovitaminosis A
  - endocrine: reproductive age, menstrual irregularities, Addison's/Cushing's disease, thyroid irregularities
  - hematological: iron deficiency anemia, polycythemia vera
  - drugs: steroid administration or withdrawal, tetracycline, nalidixic acid, etc.
- risk factors overlap with those of venous sinus thrombosis; similar to those for gallstones ("fat, female, fertile, forties")

Epidemiology

- incidence ~0.5/100,000 per year
- usually in 3rd and 4th decade (F>M)

Clinical Features

- symptoms and signs of raised ICP (H/A in >90%, pulsatile intracranial noise), but no LOC or diplopia
- decreased visual acuity, papilledema, visual field defect, optic atrophy (key morbidity)
- usually self-limited, recurrence is common, chronic in some patients
- risk of blindness is not reliably correlated to symptoms or clinical course

www.regentstudies.com

Investigations
- CT: normal
- CSF studies: normal
- MRI: must look for venous sinus thrombosis

Important Features to Note on CT and MRI (± contrast enhancement)
- Lesions (± edema, necrosis, hemorrhage)
- Midline shifts and herniations
- Effacement of ventricles and sulci (often ipsilateral), basal cisterns
- Single or multiple (multiple implies metastasis)

Treatment
- rule out conditions that cause intracranial HTN (especially sinus thrombosis)
- discontinue offending medications, encourage weight loss, fluid/salt restriction
- pharmacotherapy: acetazolamide (decreases CSF production), thiazide diuretic, or furosemide
- if above fail: serial LPs, shunt
- optic nerve sheath decompression (if progressive impairment of visual acuity)
- 2 yr follow-up with imaging to rule out occult tumour, ophthalmology follow-up

Tumours

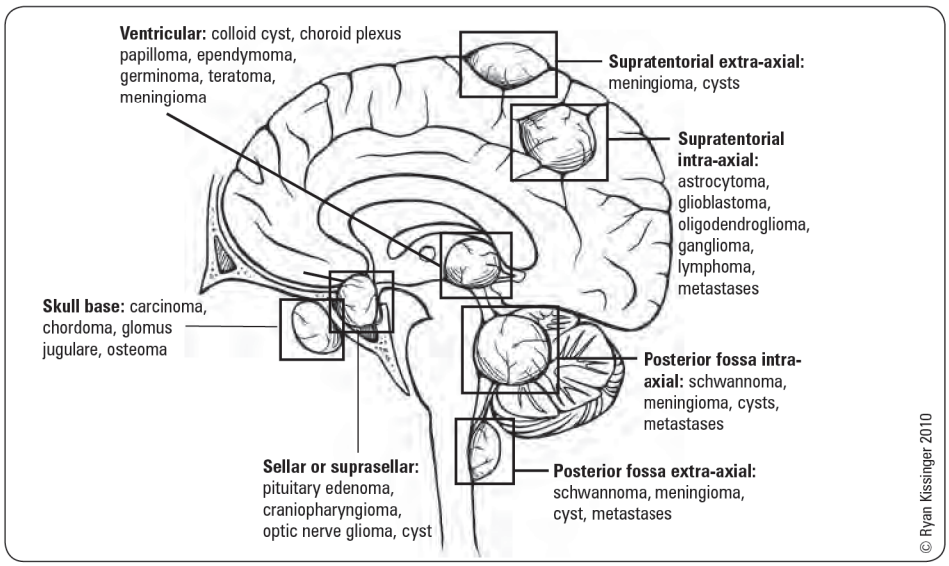


Figure 8. Tumours

DDx for Ring Enhancing Lesion on CT with Contrast

MAGICAL DR
Metastases*
Abscess*
Glioblastoma (high grade astrocytoma)*
Infarct
Contusion
AIDS (toxoplasmosis)
Lymphoma
Demyelination
Resolving hematoma
(*3 most common diagnoses)

Classification
- primary vs. metastatic, intra-axial (parenchymal) vs. extra-axial, supratentorial vs. infratentorial, adult vs. pediatric
- benign: non-invasive, but can be devastating due to expansion of mass in fixed volume of skull (mass effect)
- malignant: implies rapid growth, invasiveness, but rarely extracranial metastasis
- types of intracranial tumours (* = most common)
  - neuroepithelial tissue
    - astrocytic tumours: astrocytoma, glioblastoma
    - oligodendroglial tumours
    - oligoastrocytic tumours
    - neuronal and mixed neuronal-glial tumours: ganglion cell tumours, cerebral neurocytomas/neuroblastomas
    - embryonal tumours: medulloblastoma, neuroectodermal
    - other: pineal, ependymal, and choroid plexus tumours
  - meningeal: meningiomas*, mesenchymal, hemangioblastomas
  - cranial and paraspinal nerves: schwannoma, neurofibroma
  - lymphomas and hematopoietic neoplasms
  - germ cell: germinomas, teratomas
  - pituitary adenomas*
  - sellar region: craniopharyngiomas, spindle cell oncocytoma
  - cysts: epidermoid/dermoid cysts, colloid cysts
  - local extension: chordomas, glomus jugulare tumours
  - metastatic tumours

Primary Sources of Metastatic Brain Tumours

Lung	44%
Breast	10%
Kidney (RCC)	7%
GI	6%
Melanoma	3%

Primary CNS lymphoma reported in 6-20% of HIV infected patients

Brain Metastasis
~1/3 of all adult brain tumours
Well circumscribed, often at grey-white matter junction

Clinical Features
- **supratentorial lesions**
  - progressive neurological deficit (70%)
    - frontal lobe: hemiparesis, dysphasia, personality changes, cognitive changes
    - temporal lobe: auditory/olfactory hallucinations, memory deficits, contralateral superior quadrantanopsia

www.regentstudies.com

- symptoms suggestive of TIA (occlusion of vessel by tumour cells or 2° to "steal phenomenon" where blood is shunted from ischemic regions to non-ischemic regions and manifested as neurological changes)
- endocrine disturbances with pituitary tumours (e.g. Cushing's disease, prolactinoma)
- rarely presents with hemorrhage
- **infratentorial lesions**
  - •most commonly presents with signs of elevated ICP
    - headache
    - nausea and vomiting
    - papilledema
  - diplopia (direct compression CN VI versus indirect compression from increased ICP)
  - vertigo
  - ataxia (due to cerebellar lesions)
- **familial syndromes associated with CNS tumours**
  - von Hippel-Lindau (hemangioblastoma of brain, spinal cord, and eye)
  - tuberous sclerosis (giant cell astrocytoma, cortical tubers, and supependymal nodules)
  - neurofibromatosis type 1 and 2 (astrocytoma, bilateral acoustic neuroma respectively)
  - Li-Fraumeni (astrocytoma)
  - Turcot syndrome (glioblastoma multiforme)
  - multiple endocrine neoplasia type 1 (MEN-1) (pituitary adenoma)

Investigations
- CT, MRI, stereotactic biopsy (tissue diagnosis), metastatic workup

Treatment
- conservative: serial Hx, Px, imaging for slow growing/benign lesions
- medical: corticosteroids to reduce cytotoxic cerebral edema, pharmacological (see *Pituitary Adenoma*, NS13)
- surgical: total or partial excision (decompressive, palliative), shunt if hydrocephalus
- radiotherapy: conventional fractionated radiotherapy (XRT), stereotactic radiosurgery (e.g. Gamma Knife®)
- chemotherapy: e.g. alkylating agents (temozolomide)

Table 6. Tumour Types: Age, Location

Age	Supratentorial	Infratentorial (posterior fossa)
<15 yr • Incidence: 2-5/100,000/yr • 60% infratentorial	Astrocytoma (all grades) (50%) Craniopharyngioma (2-5%) Others: pineal region tumours, choroid plexus tumours, ganglioglioma, DNET	Medulloblastoma (15-20%) Cerebellar astrocytoma (15%) Ependymoma (9%) Brainstem astrocytoma
>15 yr • 80% supratentorial	High grade astrocytoma (12-15%, e.g. GBM) Metastasis (15-30%, includes infratentorial) Meningioma (15-20%) Low grade astrocytoma (8%) Pituitary adenoma (5-8%) Oligodendroglioma (5%) Other: colloid cyst, CNS lymphoma, dermoid/epidermoid cysts	Metastasis Acoustic neuroma (schwannoma) (5-10%) Hemangioblastoma (2%) Meningioma

Primary Brain Tumours
- Rarely undergo metastasis
- Adults = mostly supratentorial
- Children = mostly infratentorial

Guideline on the Management of Newly Diagnosed Brain Metastasis(es) (American Society for Radiation Oncology)
Pract Radiat Oncol 2012;2:210-225

Prognostic Factors
Three prognostic groups based on 1,200 patients:
Class I – Karnofsky performance status (KPS) ≥70 yr, <65 yr with controlled primary (3 mo stability on imaging or newly diagnosed), no extracranial metastases (median survival 7.1 mo).
Class II – everything else (median survival 4.2 mo).
Class III – KPS <70 (median survival 2.3 mo).

Summary of Evidence for Single and Multiple Brain Metastasis(es)
1) For patients with good performance status (e.g. KPS ≥70), limited extracranial disease and resectable metastasis, complete resection improves the probability of extended survival. WBRT in addition to resection improves local and overall brain control but does not affect overall survival or duration of functional independence.
2) For patients with a good prognosis (>3 mo expected survival), single brain metastases <4 cm in size, good performance status, and controlled extracranial disease, the addition of radiosurgery to WBRT improves survival when compared with WBRT alone.
3) In patients with a good prognosis and up to 4 brain metastases <4 cm in size, radiosurgery added to WBRT improves lesion site and overall brain control compared with WBRT alone, but does not influence survival. Therefore, WBRT alone may be considered in these patients.
4) The use of radiosurgery boost to WBRT may improve KPS and decrease the need for steroids at 6 mo in patients with up to 3 brain metastases.
5) For selected patients with poor life expectancy (<3 mo), the use of WBRT may or may not significantly improve symptoms from brain metastases. Comfort measures, or short course (20 Gy in 5 daily fractions) WBRT are reasonable options.
6) There is no evidence of a survival benefit with the combined use of radiosensitizers with WBRT.
7) Although chemotherapy trials have reported improved response rates with combined chemotherapy and WBRT, the addition of chemotherapy leads to increased toxicity and does not improve survival. The routine use of chemotherapy in the management of brain metastases is not generally recommended.

Metastatic Tumours

- most common brain tumour seen clinically
- 15-30% of cancer patients present with cerebral metastatic tumours
  - most common sources: lungs, breast
  - other sources: kidney, thyroid, stomach, prostate, testis, melanoma
- hematogenous spread most common

Location
- 80% are hemispheric, often at grey-white matter junction or junction of temporal-parietal-occipital lobes (likely emboli spreading to terminal MCA branches)

Investigations
- identify primary tumour
  - metastatic workup (CXR, CT chest/abdo, abdominal U/S, bone scan, mammogram)
- CT with contrast → round, well-circumscribed, often ring enhancing, ++ edema, often multiple
- MRI more sensitive, especially for posterior fossa
- consider biopsy in unusual cases, or if no primary identified

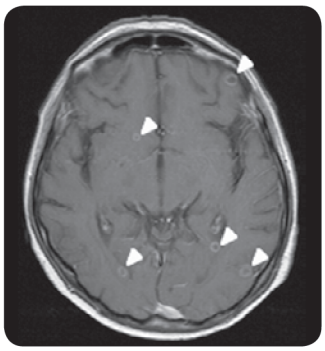


Figure 9. Multiple brain metastases (see arrows)

www.regentstudies.com

Treatment
- medical
  - phenytoin (or levetiracetam) for seizure prophylaxis if patient presents with seizure
  - dexamethasone to reduce edema given with ranitidine
  - chemotherapy (e.g. small cell lung cancer)
- radiation
  - stereotactic radiosurgery: for discrete, deep-seated/inoperable tumours
  - multiple lesions: use WBRT; consider stereotactic radiosurgery if <3 lesions
  - post-operative WBRT is commonly used
- surgical
  - single/solitary lesions: use surgery and radiation

Prognosis
- median survival without treatment once symptomatic is ~1 mo, with optimal treatment 6-9 mo but varies depending on primary tumour type

Astrocytoma
- most common primary intra-axial brain tumour, common in 4th-6th decades

Table 7. Astrocytoma Grading System

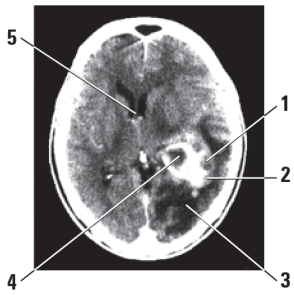
World Health Organization (WHO)	Typical CT/MRI Findings	Survival
I – Pilocytic astrocytoma	± mass effect, ± enhancement	>10 yr, cure if gross total resection
II – Low grade/diffuse	Mass effect, no enhancement	5 yr
III – Anaplastic	Complex enhancement	1.5-2 yr
IV – Glioblastoma multiforme (GBM)	Necrosis (ring enhancement)	12 mo, 10% at 2 yr

Clinical Features
- sites: cerebral hemispheres >> cerebellum, brainstem, spinal cord
- symptoms: recent onset of new/worsening H/A, N/V, seizure, ± focal deficits or symptoms of increased ICP

Investigations
- CT/MRI with contrast: variable appearance depending on grade
  - hypodense on CT, hypointense on T1 MRI, hyperintense on T2 MRI
  - low grade: most do not enhance and have calcification on CT
  - high grade: most enhance with CT contrast dye/gadolinium

Treatment
- low grade diffuse astrocytoma
  - close follow-up, radiation, chemotherapy, and surgery all valid options
  - surgery: not curative, trend towards better outcomes
  - radiotherapy alone or post-operative prolongs survival (retrospective evidence)
  - chemotherapy: usually reserved for tumour progression
- high grade astrocytomas (anaplastic astrocytoma and GBM)
  - surgery
    - gross total resection: maximal safe resection + fractionated radiation with 2 cm margin + concomitant and adjuvant temozolomide
      - except: extensive dominant lobe GBM, significant bilateral involvement, end-of-life near, extensive brainstem involvement
    - stereotactic biopsy if resection not possible, followed by fractioned radiation with 2 cm margin
  - expectant (based on functional impairment – Karnofsky score <70; patient's/family's wishes)
  - aim to prolong "quality" survival
  - chemotherapy: ~20% response rate, temozolomide (agent of choice); better response to temozolomide predicted by MGMT gene hypermethylation
- multiple gliomas: WBRT ± chemotherapy

Meningioma
- most common *primary* intracranial tumour, arise from arachnoid membrane
- often calcified, cause hyperostosis of adjacent bone
- classically see Psammoma bodies on histology
- common locations: parasagittal convexity or falx (70%), sphenoid wing, tuberculum sellae, foramen magnum, olfactory groove



1. Heterogenous contrast enhancement
2. Ill-defined borders (infiltrative)
3. Peritumoural edema
4. Central necrosis
5. Compression of ventricles, midline shift

Figure 10. High grade astrocytoma on CT

Comparison of a Strategy Favouring Early Surgical Resection vs. a Strategy Favouring Watchful Waiting in Low-gGade Gliomas
JAMA (2012) 308(18): 1881-8

Purpose: To examine "watchful waiting" vs. early surgical resection of low grade gliomas.
Study: A population-based parallel cohort study was undertaken between two hospitals that each favoured different management approaches for low grade gliomas (biopsy and watchful waiting vs. early surgical resection).
Results: 66 patients were included from the watchful waiting hospital and 87 patients from the early resection centre. Median follow-up was 7.0 and 7.1 years at each centre. The two groups were equivalent in terms of baseline parameters. Overall, survival was significantly better with early surgical resection (watchful waiting: median survival of 5.9 years 95% CI, 4.5-7.3 vs. early resection: median survival was not reached due to prolonged length of life, p<0.01).
Conclusions: Early surgical resection of low grade-gliomas is associated with better overall survival as compared to watchful waiting.

Bevacizumab Plus Radiotherapy-Temozolamide for Newly Diagnosed Glioblastoma
NEJM 2014;370:709-722

Purpose: To evaluate the effect of combined bevacizumab and radiotherapy-temozolamide in the treatment of newly diagnosed glioblastoma.
Study: Patients with supratentorial glioblastoma randomly assigned to receive intravenous bevacizumab or placebo plus radiotherapy and oral temozolamide for 30 wk total in cycles, followed by bevacizumab or placebo monotherapy. Outcomes were progression-free survival and overall survival.
Results: 458 patients in bevacizumab group, 463 patients in placebo. The median progression-free survival was longer in the bevacizumab group compared with placebo (10.6 mo vs. 6.2 mo, HR 0.64, 95% CI 0.55-0.74), although overall survival did not differ significantly between groups (HR 0.88, 95% CI 0.76-1.02). Baseline health-related QOL and performance status were maintained longer in the bevacizumab group although there was a higher frequency of adverse events.
Conclusions: The addition of bevacizumab to radiotherapy-temozolamide improves progression-free survival but not overall survival in patients with glioblastoma.

WHO Classification of Meningioma (by histology)
Grade 1: low risk of recurrence
Grade 2: intermediate risk of recurrence
Grade 3: high risk of recurrence

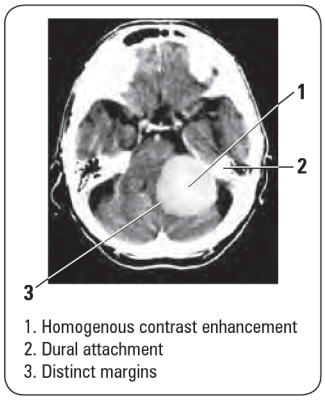
www.regentstudies.com

Clinical Features
- middle aged, slight female preponderance (M:F = 2:3), high progesterone receptors (increase in size with pregnancy), symptoms of increased ICP, focal deficits, usually solitary (10% multiple, likely with loss of NF2 gene/22q12 deletion)

Investigations
- CT with contrast: homogeneous, densely enhancing, along dural border ("dural tail"), well circumscribed
- contrast enhanced MRI provides better detail
- angiography
  - most are supplied by external carotid feeders (meningeal vessels)
  - also assesses venous sinus involvement, "tumour blush" commonly seen (prolonged contrast image)
- octreotide scintigraphy: to establish if expression of somatostatin receptor

Treatment
- conservative management for non-progressive, asymptomatic lesions
- surgery is treatment of choice if symptomatic or progression on sequential imaging (curative if complete resection)
- SRS may be an option for lesions <3 cm
- endovascular embolization to facilitate surgery
- SRS or XRT for recurrent atypical/malignant meningiomas

Prognosis
- >90% 5-yr survival, recurrence rate variable (often ~10-20%)
- depends on extent of resection (Simpson's classification)



1. Homogenous contrast enhancement
2. Dural attachment
3. Distinct margins

Figure 11. Meningioma on CT

Vestibular Schwannoma (Acoustic Neuroma)

- slow-growing (average of 1-10 mm/yr), benign posterior fossa tumour
- arises from vestibular component of CN VIII in internal auditory canal, expanding into bony canal and cerebello-pontine angle (CPA)
- if bilateral, diagnostic of neurofibromatosis type II
- epidemiology: all age groups affected, peaks at 4th-6th decades

Progressive unilateral or asymmetrical sensorineural hearing loss = acoustic neuroma until proven otherwise

Clinical Features
- compression of structures in CPA, often CN VIII (unilateral hearing loss 98%, tinnitus, disequilibrium), followed by CN V and VII
- ataxia and raised ICP are late features

Investigations
- MRI with gadolinium or T2 FIESTA sequence (>98% sensitive/specific), CT with contrast 2nd choice
- audiogram, brainstem auditory evoked potentials, caloric tests

Treatment
- conservative: serial imaging (CT/MRI q6mo) and audiometry
- radiation: stereotactic radiosurgery or fractionated radiotherapy
- surgery if: lesion >3 cm, brainstem compression, edema, hydrocephalus
  - curable if complete resection (almost always possible)
  - operative complications: CN VII, VIII dysfunction (only significant disability if bilateral), CSF leak

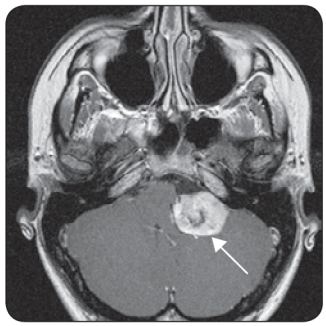


Figure 12. Vestibular schwannoma (tumour in cerebello-pontine angle)

Pituitary Adenoma

- primarily from anterior pituitary, 3rd-4th decades, M=F
- incidence in autopsy studies approximately 20%
- classification
  - microadenoma <1 cm; macroadenoma ≥1 cm
  - endocrine active (functional/secretory) vs. inactive (non-functional)
    - most common functional: prolactinomas, adrenocorticotropic, growth-hormone producing
- differential: parasellar tumours (e.g. craniopharyngioma, tuberculum sellae meningioma), carotid aneurysm

www.regentstudies.com

Clinical Features
- mass effects
  - H/A
  - bitemporal hemianopsia (compression of optic chiasm)
  - CN III, IV, V_1, V_2, VI palsy (compression of cavernous sinus)
- endocrine effects
  - hyperprolactinemia (prolactinoma): infertility, amenorrhea, galactorrhea, decreased libido
  - ACTH production: Cushing's disease, hyperpigmentation
  - GH production: acromegaly/gigantism
  - panhypopituitarism (hypothyroidism, hypoadrenalism, hypogonadism)
  - associated MEN-1 syndrome
  - diabetes insipidus
- pituitary apoplexy (sudden expansion of mass due to hemorrhage or necrosis)
  - abrupt onset H/A, visual disturbances, ophthalmoplegia, reduced mental status, and panhypopituitarism
  - CSF rhinorrhea and seizures (rare)
  - signs and symptoms of subarachnoid hemorrhage (rare)

Investigations
- formal visual fields, CN testing
- endocrine tests (prolactin level, TSH, 8 AM cortisol, fasting glucose, FSH/LH, IGF-1), electrolytes, urine electrolytes, and osmolarity
- imaging (MRI with and without contrast)

Go Look For The Adenoma Please – GH, LH, FSH, TSH, ACTH, Prolactin
A compressive adenoma in the pituitary will impair hormone production in this order (i.e. GH-secreting cells are most sensitive to compression)

Treatment
- medical
  - for apoplexy: rapid corticosteroid administration ± surgical decompression
  - for prolactinoma: dopamine agonists (e.g. bromocriptine)
  - for Cushing's: serotonin antagonist (cyproheptadine), inhibition of cortisol production (ketoconazole)
  - for acromegaly: somatostatin analogue (octreotide) ± bromocriptine
  - endocrine replacement therapy
- surgical
  - trans-sphenoidal, trans-ethmoidal, trans-cranial approaches for non-secreting adenomas causing mass effect and Cushing/acromegaly (50% cure rate)

Pus

Sources of Pus/Infection
- four routes of microbial access to CNS
  1. hematogenous spread (most common): arterial and retrograde venous
     - adults: chest is #1 source (lung abscess, bronchiectasis, empyema)
     - children: congenital cyanotic heart disease with R to L shunt
     - immunosuppression (AIDS – toxoplasmosis)
  2. direct implantation (dural disruption)
     - trauma
     - iatrogenic (e.g. following LP, post-operative)
     - congenital defect (e.g. dermal sinus)
  3. contiguous spread (adjacent infection): from air sinus, naso/oropharynx, surgical site (e.g. otitis media, mastoiditis, sinusitis, osteomyelitis, dental abscess)
  4. spread from PNS (e.g. viruses: rabies, herpes zoster)
- common examples
  - epidural abscess: in cranial and spinal epidural space, associated with osteomyelitis
    - treatment: immediate drainage and antibiotics, surgical emergency if cord compression
  - subdural empyema: bacterial/fungal infection, due to contiguous spread from bone or air sinus, progresses rapidly
    - treatment: surgical drainage and antibiotics, 20% mortality
  - meningitis, encephalitis (see Infectious Diseases, ID18)
  - cerebral abscess

Cerebral Abscess

Definition
- pus in brain substance, surrounded by tissue reaction (capsule formation)

Etiology
- modes of spread: 10-60% of patients have no cause identified
- pathogens
  - *Streptococcus* (most common), often anaerobic or microaerophilic
  - *Staphylococcus* (penetrating injury)
  - Gram-negatives, anaerobes (*Bacteroides, Fusobacterium*)
  - in neonates: *Proteus* and *Citrobacter* (exclusively)

www.regentstudies.com

- immunocompromised: fungi and protozoa (*Toxoplasma, Nocardia, Candida albicans, Listeria monocytogenes, Mycobacterium,* and *Aspergillus*)

Risk Factors
- lung abnormalities (infection, AV fistulas; especially Osler-Weber-Rendu syndrome [i.e. hereditary hemorrhagic telengiectasia])
- congenital coronary heart disease: R-to-L shunt bypasses pulmonary filtration of micro-organisms
- bacterial endocarditis
- penetrating head trauma
- immunosuppression (e.g. AIDS)
- dental abscess

Clinical Features
- focal neurological signs and symptoms
  - H/A, decreased LOC; hemiparesis and seizures in 50%
- mass effect, increased ICP and sequelae (cranial enlargement in children)
- hemiparesis and seizures in 50%
- ± signs and symptoms of systemic infection (low-grade fever, leukocytosis)

Complications
- with abscess rupture: ventriculitis, meningitis, venous sinus thrombosis
- CSF obstruction
- transtentorial herniation

Investigations
- CT scan often first test in emergency department
- MRI
  - imaging of choice
  - apparent diffusion coefficient (ADC) used to differentiate abscess (black) from tumour (white)
- WBC/ESR may be normal, blood cultures rarely helpful and LP contraindicated if large mass
- CSF: non-specific (high ICP, high WBC, high protein, normal carbohydrate), rarely helpful, usually negative culture

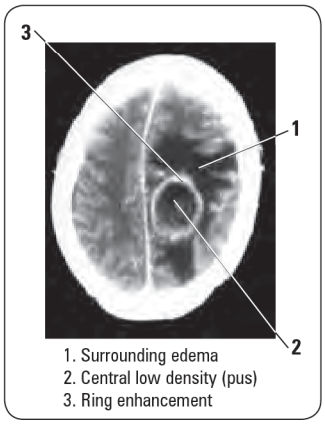


Figure 13. Cerebral abscess on CT

Treatment
- aspiration ± excision and send for Gram stain, acid fast bacillus (AFB), C&S, fungal culture
- excision preferable if location suitable
- antibiotics
  - empirically: vancomycin + ceftriaxone + metronidazole or chloramphenicol or rifampin (6-8 wk therapy)
  - revise antibiotics when C&S known
- anti-convulsants (1-2 yr)
- follow-up CT is critical (do weekly initially, more frequent if condition deteriorates)

Prognosis
- mortality with appropriate therapy ~10%, permanent deficits in ~50%

Blood

Table 8. Comparison of Epidemiology and Etiology of Intracranial Bleeds

Types of Hematoma/ Hemorrhage	Etiology	Epidemiology	Clinical Features	CT Features	Treatment	Prognosis
Epidural Hematoma	Skull fracture causing middle meningeal bleed	M>F (4:1), associated with trauma	Lucid interval before LOC	Hyperdense lenticular mass with sharp margins, usually limited by suture lines	Craniotomy	Good with prompt management (Note: respiratory arrest can occur from uncal herniation)
Acute SDH	Ruptured subarachnoid bridging vessels	Age >50, associated with trauma	No lucid interval, hemiparesis, pupillary changes	Hyperdense crescentic mass, crossing suture lines	Craniotomy if bleed >1 cm thick	Poor
Chronic SDH	Ruptured subarachnoid bridging vessels	Age >50, EtOH abusers, anti-coagulated	Often asymptomatic, minor H/A, confusion, signs of increased ICP	Hypodense crescentic mass, crossing suture lines	Burr hole to drain; craniotomy if recurs	Good
SAH	Trauma, spontaneous (aneurysms, idiopathic, AVM)	Age 55-60 20% cases under age 45	Sudden onset thunderclap H/A, signs of increased ICP	Hyperdense blood in cisterns/fissures (sensitivity decreases over time)	Conservative: NPO, IV NS, ECG, Foley, BP 120-150, vasospasm prophylaxis (nimodipine); open vs. endovascular surgery to repair if rebleed	Poor: 50% mortality 30% of survivors have moderate to severe disability
ICH	HTN, vascular abnormality, tumours, infections, coagulopathy	Age >55, male, drug use (cocaine, EtOH, amphetamine)	TIA-like symptoms, signs of increased ICP	Hyperdense intraparenchymal collection	Medical: decrease BP, control ICP Surgical: craniotomy	Poor: 44% mortality due to cerebral herniation

www.regentstudies.com

Extradural ("Epidural") Hematoma

Etiology
- temporal-parietal skull fracture: 85% are due to ruptured middle meningeal artery; remainder of cases are due to bleeding from middle meningeal vein, dural sinus, or bone/diploic veins

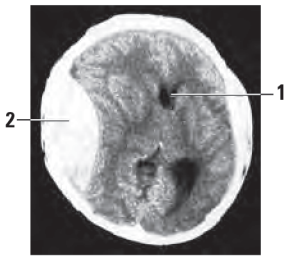
Epidemiology
- young adult, M>F = 4:1; rare before age 2 or after age 60
- 1-4% of traumatic head injuries

Clinical Features
- classic sequence (seen in <30%): post-traumatic reduced LOC, a lucid interval of several hours, then obtundation, hemiparesis, ipsilateral pupillary dilatation, and coma
- signs and symptoms depend on severity but can include H/A, N/V, amnesia, altered LOC, aphasia, seizures, HTN, and respiratory distress
- deterioration can take hours to days

Investigations
- CT without contrast: "lenticular-shaped" usually limited by suture lines but not limited by dural attachments

Treatment
- admission, close neurological observation with serial CT indicated if all of the following are present
  - small volume clot, minimal midline shift (MLS <5 mm), GCS >8, no focal deficit
- otherwise, craniotomy to evacuate clot, follow up CT
- mannitol pre-operative if elevated ICP or signs of brain herniation

Prognosis
- good with prompt management, as the brain is often not damaged
- worse prognosis if bilateral Babinski or decerebration pre-operative
- death is usually due to respiratory arrest from uncal herniation (injury to the midbrain)



1. Compression of ventricles (midline shift)
2. Blood

Figure 14. Extradural hematoma on CT

Poor Prognostic Indicators for Epidural Hematoma
- Older age
- Low GCS on admission
- Pupillary abnormalities (especially non-reactive)
- Longer delay in obtaining surgery (if needed)
- Post-operative elevated ICP

CT Density and MRI Appearance of Blood

Time	CT	MRI T1	MRI T2
Acute (<72 h)	Hyper.	**G**rey	**B**lack
Subacute (<3 wk)	Iso.	**W**hite	**W**hite
Chronic (>3 wk)	Hypo.	**B**lack	**B**lack

MRI-T1: "**G**eorge **W**ashington **B**ridge"
MRI-T2: "Oreo" cookie – **B**lack/**W**hite/**B**lack

Subdural Hematoma

ACUTE SUBDURAL HEMATOMA
- 1-2 d after bleeding onset

Etiology
- rupture of vessels that bridge the subarachnoid space (e.g. cortical artery, large vein, venous sinus) or cerebral laceration

Risk Factors
- trauma, acceleration-deceleration injury, anticoagulants, alcohol, cerebral atrophy, infant head trauma

Clinical Features
- no lucid period, signs and symptoms can include altered LOC, pupillary irregularity, hemiparesis

Investigations
- CT: hyperdense concave "crescentic" mass, crossing suture lines

Treatment
- craniotomy if clinically symptomatic, if hematoma >1 cm thick, or if MLS >5 mm (optimal if surgery <4 h from onset); otherwise observe with serial imaging

Prognosis
- poor overall since the brain parenchyma is often injured (mortality range is 50-90%, due largely to underlying brain injury)
- prognostic factors: initial GCS and neurologic status, post-operative ICP

Use of Drains vs. No Drains After Burr-Hole Evacuation of Chronic Subdural Hematoma: A Randomized Control Trial
Lancet 2009;374:1067-1073
Purpose: To examine the effect of drains on recurrence rates of chronic subdural hematoma (SDH) and clinical outcomes.
Study: RCT with 269 patients ≥18 yr of age with chronic SDH. Half of the patients were randomly assigned to receive a subdural drain and the other half no drain after evacuation.
Results: Recurrence occurred in 9.3% of people with a drain and 24% without (p=0.003; 95% CI 0.14-0.70). Although rates of complications were the same between the study groups, mortality at 6 mo was 8.6% in the group receiving a drain and 18.1% in the group not receiving a drain (p=0.042; 95% CI 0.1-0.99).
Conclusions: Use of drains after burr-hole drainage of chronic SDH is safe and associated with a reduced recurrence and mortality at 6 mo.

www.regentstudies.com

CHRONIC SUBDURAL HEMATOMA

- ≥15 d after bleeding onset

Etiology

- many start out as acute SDH
- blood within the subdural space evokes an inflammatory response:
  - fibroblast invasion of clot and formation of neomembranes within days → growth of neocapillaries → fibrinolysis and liquefaction of blood clot (forming a hygroma)
- course is determined by the balance of rebleeding from neomembranes and resorption of fluid

Risk Factors

- older, alcoholics, patients with CSF shunts, anticoagulants, coagulopathies

Clinical Features

- often due to minor injuries or no history of injury
- may present with minor H/A, confusion, language difficulties, TIA-like symptoms, symptoms of raised ICP ± seizures, progressive dementia, gait problem
- obtundation disproportionate to focal deficit; "the great imitator" of dementia, tumours

Investigations

- CT: hypodense (liquefied clot), crescentic mass

Treatment

- seizure prophylaxis only if post-traumatic seizure
- reverse coagulopathies
- burr hole drainage of liquefied clot indicated if symptomatic or thickness >1 cm; craniotomy if recurs more than twice

Prognosis

- good overall as brain usually undamaged, but may require repeat drainage

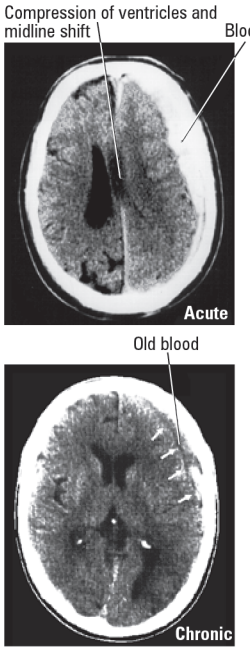


Figure 15. Subdural hematoma on CT

Cerebrovascular Disease

Ischemic Cerebral Infarction (80%)

- embolic, thrombosis of intracerebral arteries, vasculitis, hypercoagulability, etc. (see Neurology, N50)

Intracranial Hemorrhage (20%)

- SAH, spontaneous ICH, IVH

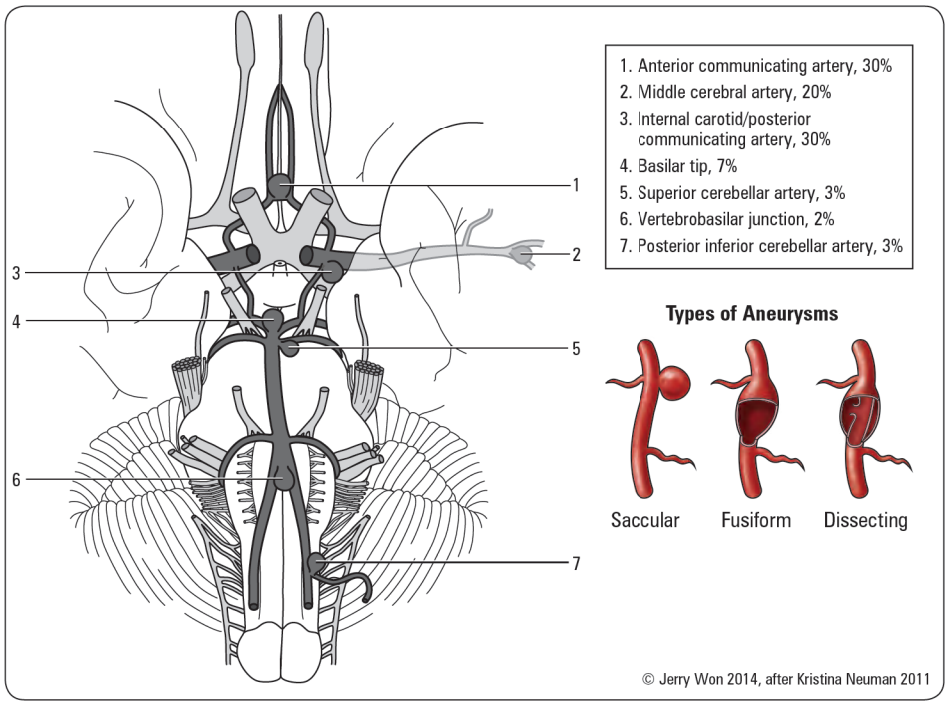


Figure 16. Aneurysms of the Circle of Willis

Hemicraniectomy in Older Patients with Extensive Middle-Cerebral-Artery Stroke
NEJM 2014;370:1091-1100
Purpose: To determine if early decompressive hemicraniectomy reduces mortality among patients >60 yr.
Study: 112 patients >60 yr (median age 70 yr) with malignant MCA infarction randomly assigned to conservative ICU treatment versus hemicraniectomy. Endpoint was survival without severe disability (modified Rankin scale score 0-4).
Results: The proportion of patients who survived without severe disability was 38% in the hemicraniectomy group and 18% in the control group (OR 2.91, 95% CI 1.06-7.49). Modified Rankin scale scores in hemicraniectomy versus control group in terms of percentages of patients: 0-2 (0%, 0%), 3 or moderate disability (7%, 3%), 4 or moderate severe disability (32%, 15%), 5 or severe disability (28%, 13%) and 6 or death (33%, 70%). Infections were more frequent in the hemicraniectomy group and herniation more frequent in the control group.
Conclusions: Hemicraniectomy increased survival without severe disability among patients >60 yr with a malignant MCA infarction.

www.regentstudies.com

Subarachnoid Hemorrhage

Definition
- bleeding into subarachnoid space (intracranial vessel between arachnoid and pia)

Etiology
- trauma (most common)
- spontaneous
  - ruptured aneurysms (75-80%)
  - idiopathic (14-22%)
  - AVMs (4-5%)
- coagulopathies (iatrogenic or primary), vasculitides, tumours, cerebral artery dissections (<5%)

Epidemiology
- ~10-28/100,000 population/yr
- peak age 55-60, 20% of cases occur under age 45

Risk Factors
- HTN
- pregnancy/parturition in patients with pre-existing AVMs, eclampsia
- oral contraceptive pill
- substance abuse (cigarette smoking, cocaine, alcohol)
- conditions associated with high incidence of aneurysms (see *Intracranial Aneurysms*, NS21)

Clinical Features of Spontaneous SAH
- sudden onset (seconds) of severe "thunderclap" H/A usually following exertion and described as the "worst headache of my life" (up to 97% sensitive, 12-25% specific)
- N/V, photophobia
- meningismus (neck pain/stiffness, positive Kernig's and Brudzinski's sign)
- decreased LOC (due to either raised ICP, ischemia, seizure)
- focal deficits: cranial nerve palsies (CN III, IV), hemiparesis
- ocular hemorrhage in 20-40% (due to sudden raised ICP compressing central retinal vein)
- reactive HTN
- sentinel bleeds
  - represents undiagnosed SAH
  - SAH-like symptoms lasting <1 d ("thunderclap H/A")
  - may have blood on CT or LP
  - ~30-60% of patients with full blown SAH give history suggestive of sentinel bleed within past 3 wk
- differential diagnosis: sentinel bleed, dissection/thrombosis of aneurysm, venous sinus thrombosis, benign cerebral vasculitis, benign exertional H/A

Hunt and Hess Grade (clinical grading scale for SAH)

Grade	Description
1	No Sx or mild H/A and/or mild meningismus
2	Grade 1 + CN palsy
3	Confusion/lethargy, mild hemiparesis, or aphasia
4	GCS <15 but >8, moderate-severe hemiparesis, mild rigidity
5	Coma (GCS <9), decerebrate, moribund appearance

Mortality of Grade 1-2 20%, increased with grade

Investigations
- non-contrast CT – for diagnosis of SAH
  - 98% sensitive within 12 h, 93% within 24 h; 100% specificity
  - may be negative if small bleed or presentation delayed several days
  - acute hydrocephalus, IVH, ICH, infarct or large aneurysm may be visible
- lumbar puncture (highly sensitive) – for diagnosis of SAH if CT negative but high suspicion:
  - elevated opening pressure (>18 cmH_2O)
  - bloody initially, xanthochromic supernatant with centrifugation ("yellow") by ~12 h, lasts 2 wk
  - RBC count usually >100,000/mm^3 without significant drop from first to last tube (in contrast to traumatic tap)
  - elevated protein due to blood breakdown products
- four vessel cerebral angiography ("gold standard" for aneurysms)
  - demonstrates source of SAH in 80-85% of cases
  - angiogram negative SAH: repeat angiogram in 7-14 d, if negative → "perimesencephalic SAH"
- MRA and CTA: sensitivity up to 95% for aneurysms, CTA>MRA for smaller aneurysms and delineating adjacent bony anatomy

World Federation of Neurological Surgeons Grading of SAH

WFNS Grade	GCS Score	Aphasia, Hemiparesis, or Hemiplegia
0 *		
1	15	–
2	13-14	–
3	13-14	+
4	7-12	+ or –
5	3-6	+ or –

*Intact aneurysm

www.regentstudies.com

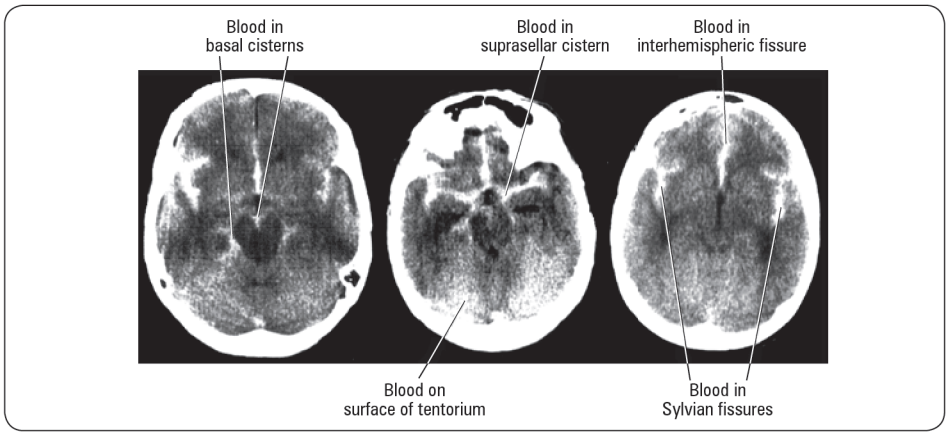


Figure 17. Diagnosis of SAH

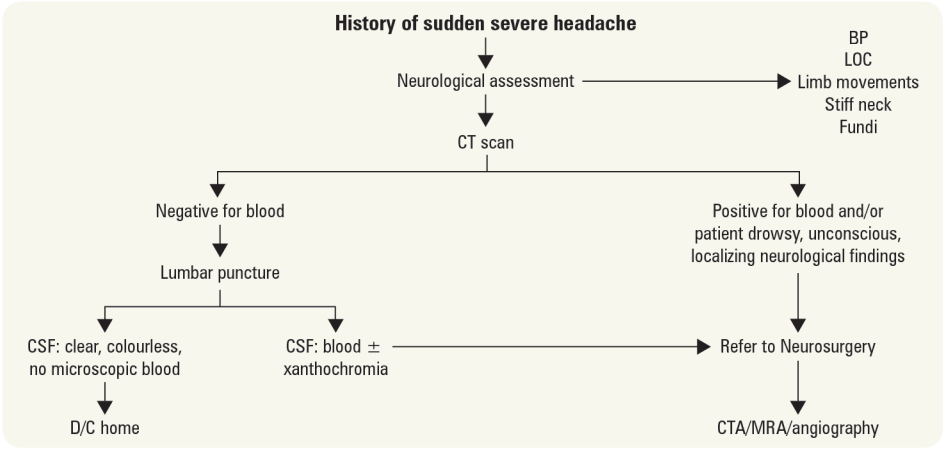


Figure 18. Approach to SAH

Treatment

- admit to ICU or NICU
  - oxygen/ventilation prn
  - NPO, bed rest, elevate head of bed 30°, minimal external stimulation, neurological vitals q1h
  - aim to maintain sBP = 120-150 (balance of vasospasm prophylaxis, risk of re-bleed, risk of hypotension since CBF autoregulation impaired by SAH)
  - cardiac rhythm monitor, Foley prn, strict monitoring of ins and outs
- medications
  - IV NS with 20 mmol KCl/L at 125-150 cc/h
  - nimodipine 60 mg PO/NG q4h x 21 d for delayed cerebral ischemia neuroprotection; may discontinue earlier if patient is clinically well
  - seizure prophylaxis: levetiracetam (Keppra®) 500 mg PO/IV q12h x 1 wk
  - mild sedation prn

Complications

- vasospasm: vasoconstriction and permanent pathological vascular changes in response to vessel irritation by blood – can lead to delayed cerebral ischemia and death
  - onset: 4-14 d post-SAH, peak at 6-8 d; most commonly due to SAH, rarely due to ICH/IVH
  - clinical features (new onset ischemic deficit): confusion, decreased LOC, focal deficit (speech or motor e.g. pronator drift)
  - risk factors: large amount of blood on CT (high Fisher grade), smoking, increased age, HTN
  - "symptomatic" vasospasm in 20-30% of SAH patients
  - "radiographic" vasospasm in 30-70% of arteriograms performed 7 d following SAH
  - diagnosed clinically, and/or with transcranial Doppler (increased velocity of blood flow)
  - risk of cerebral infarct and death
  - treatment
    - hyperdynamic ("triple H") therapy using fluids and pressors, usually after ruptured aneurysm has been clipped/coiled
    - direct vasodilation via angioplasty or intra-arterial verapamil for refractory cases
- hydrocephalus (15-20%): due to blood obstructing arachnoid granules
  - can be acute or chronic, requires extraventricular drain (EVD) or shunt, respectively
- neurogenic pulmonary edema

Nontraumatic Subarachnoid Hemorrhage in the Setting of Negative Cranial Computed Tomography Results: External Validation of a Clinical and Imaging Prediction Rule
Ann Emerg Med 2012;59:460-8.e1-7.doi:10.1016
Background: Two rules for SAH diagnosis exist. A clinical prediction rule states that patients with acute severe H/A but without the clinical variables age ≥40 yr, neck pain, loss of consciousness, or onset of H/A with exertion are at low risk for SAH. An imaging prediction rule bases diagnosis on non-contrast cranial CT for patients within 6 h of H/A onset.
Methods: Matched case-control study of 55 patients at 21 emergency departments between 2000 and 2011, and diagnoses were verified by lumbar puncture.
Results: The clinical prediction rule for diagnosis of SAH was 97.1% sensitive, 22.7% specific, and had a negative likelihood ratio of 0.13. Using the imaging prediction rule resulted in a false negative rate of 20%.
Conclusions: Performing the clinical and imaging rules together has the potential for maximizing sensitivity of prediction and reducing rates of lumbar puncture, but using imaging alone can result in missed cases.

Calcium Antagonists for Aneurysmal Subarachnoid Hemorrhage
Cochrane DB Syst Rev 2007;3:CD000277
Introduction: This study looked to review the evidence in regards to whether calcium antagonists improve the outcome in patients with aneurysmal subarachnoid hemorrhage.
Methods/Population: The review included 3,361 patients presenting with aneurysmal subarachnoid hemorrhage from 16 RCTs comparing treatment with calcium antagonists vs. control from 1980 to March 2006.
Results: The results were based mainly on one large trial of oral nimodipine, which showed a RR of 0.67 (95% CI 0.55-0.81) and the evidence for other calcium agonists was not statistically significant.
Conclusion: The authors endorse the use of oral nimodipine in patients with aneurysmal subarachnoid hemorrhage.

Fisher Grade (SAH on CT scan)

Grade	Finding
1	Normal scan
2	<1 mm thick blood
3	>1 mm thick blood
4	SAH + ICH or IVH

"Triple H" Therapy for Vasospasm

HTN
Hypervolemia
Hemodilution

www.regentstudies.com

- hyponatremia: due to cerebral salt wasting (increased renal sodium loss and ECFV loss), not SIADH
- diabetes insipidus
- cardiac: arrhythmia (>50% have ECG changes), MI, CHF

Prognosis
- 10-15% mortality before reaching hospital, overall 50% mortality (majority within first 2-3 wk)
- 30% of survivors have moderate to severe disability
- a major cause of mortality is rebleeding, for untreated aneurysms:
  - risk of rebleed: 4% on first day, 15-20% within 2 wk, 50% by 6 mo
  - if no rebleed by 6 mo, risk decreases to same incidence as unruptured aneurysm (2%)
  - only prevention is early clipping or coiling of "cold" aneurysm
  - rebleed risk for "perimesencephalic SAH" is approximately same as for general population

Intracerebral Hemorrhage

Definition
- hemorrhage within brain parenchyma, accounts for ~10% of strokes
- can dissect into ventricular system (IVH) or through cortical surface (SAH)

Etiology
- HTN (usually causes bleeds at putamen, thalamus, pons, and cerebellum)
- hemorrhagic transformation (reperfusion post stroke, surgery, strenuous exercise, etc.)
- vascular anomalies
  - aneurysm, AVMs, and other vascular malformations (see *Vascular Malformations*, NS22)
  - venous sinus thrombosis
  - arteriopathies (cerebral amyloid angiopathy, lipohyalinosis, vasculitis)
- tumours (1%): often malignant (e.g. GBM, lymphoma, metastases)
- drugs (amphetamines, cocaine, alcohol, anticoagulants, etc.)
- coagulopathy (iatrogenic, leukemia, TTP, aplastic anemia)
- CNS infections (fungal, granulomas, herpes simplex encephalitis)
- post trauma (immediate or delayed, frontal and temporal lobes most commonly injured via coup-contrecoup mechanism)
- eclampsia
- post-operative (post-carotid endarterectomy cerebral reperfusion, craniotomy)
- idiopathic

Commonest Locations of Saccular Aneurysms
- AComm: 30%
- PComm: 25%
- MCA: 20%
- Basilar tip: 7%

Epidemiology
- 12-15 cases/100,000 population/yr

Risk Factors
- increasing age (mainly >55 yr)
- male gender
- HTN
- Black/Asian > Caucasian
- previous CVA of any type (23x risk)
- both acute and chronic heavy alcohol use; cocaine, amphetamines
- liver disease
- anticoagulants

ICH Risk Factors

CALL HARM
CVA past histor**y**
Age (>55 yr)
Liver disease
Liquid blood (anticoagulated)
HTN
Alcohol, cocaine, amphetamines
Race (Black/Asian > Caucasian)
Male

Clinical Features
- TIA-like symptoms often precede ICH, can localize to site of impending hemorrhage
- gradual onset of symptoms over minutes-hours, usually during activity
- H/A, N/V, and decreased LOC are common
- specific symptoms/deficits depend on location of ICH

Location of ICH
Basal Ganglia/Internal Capsule (50%)
Thalamus (15%)
Cerebral White Matter (15%)
Cerebellum/Brainstem – usually pons (15%)
Other (5%)

Investigations
- hyperdense blood on non-contrast CT
- CTA routine, if spot sign demonstrated there is high likelihood of clot growth

Treatment
- medical
  - decrease MAP to pre-morbid level or by ~20% (target BP 140/90)
  - check PTT/INR, and correct coagulopathy
  - control raised ICP (see *Intracranial Pressure Dynamics*, NS4)
  - levetiracetam/phenytoin for seizure prophylaxis
  - follow electrolytes (SIADH common)
  - angiogram to rule out vascular lesion unless >45 yr, known HTN, and putamen/thalamic/posterior fossa ICH (yield ~0%)

www.regentstudies.com

- surgical
  - craniotomy with evacuation of clot, treatment of source of ICH (i.e. AVM, tumour, cavernoma), ventriculostomy to treat hydrocephalus
  - indications
    - symptoms of raised ICP or mass effect
    - rapid deterioration (especially if signs of brainstem compression)
    - favourable location (e.g. cerebellar, non-dominant hemisphere)
    - young patient (<50 yr)
    - if tumour, AVM, aneurysm, or cavernoma suspected (resection or clip to decrease risk of rebleed)
  - contraindications
    - small bleed: minimal symptoms, GCS >10
    - poor prognosis: massive hemorrhage (especially dominant lobe), low GCS/coma, lost brainstem function
    - medical reasons (e.g. very elderly, severe coagulopathy, difficult location [e.g. basal ganglia, thalamus])

Prognosis
- 30-d mortality rate 44%, mostly due to cerebral herniation
- rebleed rate 2-6%, higher if HTN poorly controlled

Intracranial Aneurysms

Epidemiology
- prevalence 1-4% (20% have multiple)
- F>M; age 35-65 yr

Risk Factors
- autosomal dominant polycystic kidney disease (15%)
- fibromuscular dysplasia (7-21%)
- AVMs
- connective tissue diseases (Ehlers-Danlos, Marfan)
- family history
- bacterial endocarditis
- Osler-Weber-Rendu syndrome (hereditary hemorrhagic telangiectasia)
- atherosclerosis and HTN
- trauma

Types
- saccular (berry)
  - most common type
  - located at branch points of major cerebral arteries (Circle of Willis)
  - 85-95% in carotid (anterior) system, 5-15% in vertebrobasilar (posterior) circulation
- fusiform
  - atherosclerotic
  - more common in vertebrobasilar system, rarely rupture
- infectious
  - secondary to any infection of vessel wall, 20% multiple
  - 60% *Streptococcus* and *Staphylococcus*
  - 3-15% of patients with bacterial endocarditis

Table 9. Five Year Cumulative Rupture Risk in Unruptured Aneurysms Based on Size and Location

	Cavernous Carotid	AC/MC/IC	Vertebrobasilar/PC/PComm
<7 mm	0%	0%	2.5%
7-12 mm	0%	2.6%	14.5%
13-24 mm	3%	14.5%	18.4%
≥24 mm	6.4%	40%	50%

AC = anterior cerebral/anterior communicating artery; IC = internal carotid artery; MC = middle cerebral artery; PC = posterior cerebral artery; PComm – posterior communicating artery
Lancet 2003;362:103-110

Clinical Presentation
- rupture (90%), most often SAH, but 30% ICH, 20% IVH, 3% subdural bleed
- sentinel hemorrhage ("thunderclap H/A") → requires urgent clipping/coiling to prevent catastrophic bleed
- mass effect (giant aneurysms)
  - internal carotid or anterior communicating aneurysm may compress:
    - the pituitary stalk or hypothalamus causing hypopituitarism
    - the optic nerve or chiasm producing a visual field defect
  - basilar artery aneurysm may compress midbrain, pons (limb weakness), or CN III
  - posterior communicating artery aneurysm may produce CN III palsy
  - intracavernous aneurysms (CN III, IV, V_1, V_2, VI)

Risk of Recurrent Subarachnoid Hemorrhage, Death, or Dependence and Standardized Mortality Ratios after Clipping or Coiling of an Intracranial Aneurysm in the International Subarachnoid Aneurysm Trial (ISAT): Long-Term Follow-Up
Lancet Neurol 2009;8:427-433
Objective: To assess the long-term risk of death, disability, and rebleeding in patients randomly assigned to clipping or endovascular coiling after rupture of an intracranial aneurysm in the follow-up of the ISAT trial.
Methods: Randomized controlled trial comparing endovascular coiling treatment with craniotomy and clipping for ruptured intracranial aneurysms in 2,143 patients who were considered eligible for either modality of therapy. Annual follow-up was done for a mean length of 9 yr to assess long-term survival and dependency.
Results: 10 patients in the coiled group and 3 patients in the clipped group had rebled from the original aneurysm. In patients with ruptured intracranial aneurysms suitable for both treatments, the survival rate at 5 yr after endovascular coiling was higher at 89% vs. 86% for neurosurgical clipping (relative risk 0.77, p=0.03). The likelihood of independence at 5 yr following treatment is the same for both groups (83% for coiling vs. 82% for clipping).
Conclusions: The risk of death at 5 yr was significantly lower in the coiled group than it was in the clipped group. There was a small increased risk of recurrent bleeding from a coiled aneurysm compared with a clipped aneurysm.

Long-Term, Serial Screening for Intracranial Aneurysms in Individuals with a Family History of Aneurysmal Subarachnoid Hemorrhage: A Cohort Study
Lancet Neurol 2014;13:385-392
Purpose: To examine the yield of long-term serial screening for intracranial aneurysms for individuals with a positive family history of aneurysmal subarachnoid hemorrhage (aSAH) (two or more first degree relatives who have had aSAH or unruptured intracranial aneurysms).
Study: Screening results from April 1 1993 to April 1 2013 were reviewed in a cohort study. MRA or CTA was done from age 16-18 to 65-70 yr. After a negative screen, individuals were advised to contact the clinic in 5 yr for follow up.
Results: Aneurysms were identified in 11% of individuals at first screening (n=458), 8% at second screening (n=261), 5% at third screening (n=128), and 5% at fourth screening (n=63). Smoking (OR 2.7, 95% CI 1.2-5.9), history of previous aneurysms (3.9, 1.2-12.7), and familial history of aneurysms (3.5, 1.6-8.1) were significant risk factors for aneurysm at first screening. History of previous aneurysms was the only significant risk factor for aneurysms at follow-up screening (HR 4.5, 95% CI 1.1-18.7).
Conclusions: The benefit of long-term screening in individuals with a family history of aSAH is substantial up to and after 10 yr of follow-up and two initial negative screens.

www.regentstudies.com

- distal embolization (e.g. amaurosis fugax)
- seizures
- H/A (without hemorrhage)
- incidental CT or angiography finding (asymptomatic)

Investigations
- CT angiogram (CTA), magnetic resonance angiography (MRA), cerebral angiogram

Treatment
- ruptured aneurysms
  - overall trend towards better outcome with early surgery or coiling (48-96 h after SAH)
  - treatment options: surgical placement of clip across aneurysm neck, trapping (clipping of proximal and distal vessels), thrombosing using Guglielmi detachable coils (coiling) or flow diversion stents, wrapping (last resort)
  - choice of surgery vs. coiling not yet well defined, consider location, size, shape, and tortuosity of the aneurysm, patient comorbidities, age, and neurological condition. In general:
    - coiling: posterior > anterior circulation, deep/eloquent location, basilar artery bifurcation/apex, older age, presence of comorbidities, presence of vasospasm
    - clipping: superficial > deep, broad aneurysmal base, branching arteries at the aneurysm base, tortuosity/atherosclerosis of afferent vessels, dissection, hematoma, acute brainstem compression
- unruptured aneurysms
  - average 1% annual risk of rupture: risk dependent on size and location of aneurysm
  - no clear evidence on when to operate: need to weigh life expectancy
  - risk of morbidity/mortality of SAH (20%-50%) vs. surgical risk (2%-5%)
  - generally treat unruptured aneurysms >10 mm
  - consider treating when aneurysm 7-9 mm in middle-aged, younger patients or patients with a family history of aneurysms
  - follow smaller aneurysms with serial angiography

Development of the PHASES Score for Prediction of Risk of Rupture of Intracranial Aneurysms: A Pooled Analysis of Six Prospective Cohort Studies
Lancet Neurol 2014;13:59-66
Purpose: The construction of an algorithm for estimating 5 yr aneurysm rupture risk.
Study: Systematic review and analysis of patient data. 8,382 patients, 6 prospective cohort studies. Outcome was SAH.
Results: Predictors of aneurysm rupture were age, HTN, history of subarachnoid hemorrhage, aneurysm size, aneurysm location, and geographical region. In North America and European populations, the 5 yr risk of rupture ranged from 0.25% in individuals <70 yr without vascular risk factors and with ICA aneurysm <7 mm to >15% in patients ≥70 yr with HTN, a history of SAH, and >20 mm posterior circulation aneurysm. Finnish and Japanese people had a 3.6- and 2.8-fold higher risk of rupture, respectively, compared with North American and European populations.
Conclusions: The PHASES score may help to predict risk of rupture for incidental intracranial aneurysms.

Vascular Malformations

Types
- arteriovenous malformations (AVMs)
- cavernous malformations (= cavernomas, cavernous hemangiomas/angiomas)
- venous angioma
- capillary telangiectasias
- arteriovenous fistula (AVF) (carotid-cavernous fistula, dural AVF, vein of Galen aneurysm)
- "angiographically occult vascular malformations" (any type, 10% of malformations)

Spetzler-Martin AVM Grading Scale

Item	Score
Size	
0-3 cm	1
3.1-6.0 cm	2
>6 cm	3
Location	
Noneloquent	0
Eloquent	1
Deep Venous Drainage	
Not present	0
Present	1

AVM grades calculated by adding the 3 individual Spetzler-Martin Scale scores from the above table. e.g. a 2 cm tumour in noneloquent location without deep venous drainage = Grade I

Arteriovenous Malformations

Definition
- tangle of abnormal vessels/arteriovenous shunts, with no intervening capillary beds or brain parenchyma; usually congenital

Epidemiology
- prevalence ~0.14%, M:F = 2:1, average age at diagnosis = 33 yr
- 15-20% of patients with hereditary hemorrhagic telengiectasia (Osler-Weber-Rendu syndrome) will have cerebral AVMs

Clinical Features
- hemorrhage (40-60%): small AVMs are more likely to bleed due to direct high pressure AV connections
- seizures (50%): more common with larger AVMs
- mass effect
- focal neurological signs secondary to ischemia (high flow → "steal phenomena")
- localized headache, increased ICP
- bruit (especially with dural AVMs)
- may be asymptomatic ("silent")

Investigations
- MRI (flow void), MRA
- angiography (7% will also have one or more associated aneurysms)

Treatment
- decreases risk of future hemorrhage and seizure
  - surgical excision is treatment of choice
  - SRS (stereotactic radiosurgery) is preferred for small (<3 cm) or very deep lesions
  - endovascular embolization (glue, balloon) can be curative (5%) or used as adjuvant to surgery or SRS in larger lesions
- conservative (e.g. palliative embolization, seizure control if necessary)

Untreated Clinical Course of Cerebral Cavernous Malformations: A Prospective, Population-Based Cohort Study
Lancet Neurol 2012;11:217-224
Purpose: To determine whether or not the risk of hemorrhage and focal neurological deficits from cerebral cavernous malformations (CCMs) is influenced by factors such as sex and CCM location.
Methods: Population-based study to identify CCM diagnoses in residents of Scotland from 1999-2003. Primary outcome was a composite of intracranial hemorrhage and focal neurological deficit related to CCM.
Results: 139 patients with at least one CCM. The 5 yr risk of a first hemorrhage was lower than the risk of recurrent hemorrhage (2.4% vs. 29.5%; p<0.0001) during 1,177 person-years of follow-up. For the primary outcome, the 5 yr risk of a first event was lower than the risk of recurrence (9.3% vs. 42.4%; p<0.0001). The annual risk of recurrence of the primary outcome declined from 19.8% in yr 1 to 5.0% in yr 5 and was higher for women than men.
Conclusions: The risk of recurrent hemorrhage or focal neurological deficit from a CCM is greater than the risk of a first event, is greater for women, and declines over 5 yr.

www.regentstudies.com

Prognosis
- 10% mortality, 30-50% morbidity (serious neurological deficit) per bleed
- risk of major bleed in untreated AVMs: 2-4% per year

Cavernous Malformations

- benign vascular hamartoma consisting of irregular sinusoidal vascular channels located within the brain without intervening neural tissue or associated large arteries/veins
- several genes now described: CCM1, CCM2, CCM3
- prevalence of 0.1-0.2%, both sporadic and hereditary forms described

Clinical Features
- seizures (60%), progressive neurological deficit (50%), hemorrhage (20%), H/A
- often an incidental finding
- hemorrhage risk less than AVM, usually minor bleeds

Investigations
- T2WI MRI (non-enhancing) gradient echo sequencing (best for diagnosis)

Treatment
- surgical excision
  - only appropriate for symptomatic lesions that are surgically accessible (supratentorial lesions are less likely to bleed than infratentorial lesions)

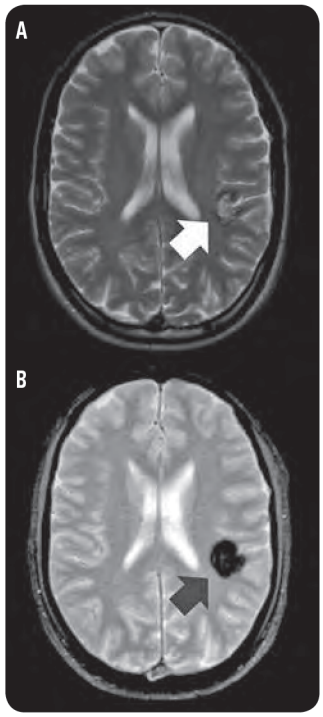


Figure 19. MRI of cavernous malformation
A. T2 weighted imaging MRI
B. Gradient echo sequencing MRI

EXTRACRANIAL PATHOLOGY

Approach to Limb/Back Pain

- see Orthopedics, OR4

Extradural Lesions

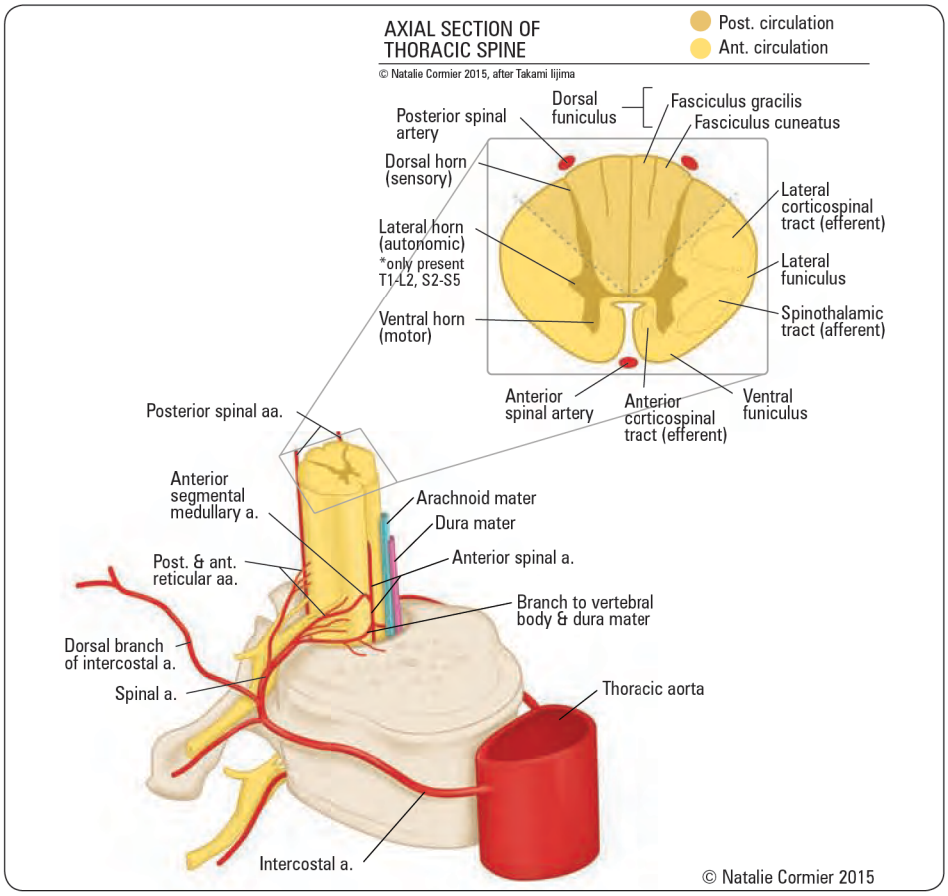


Figure 20. Vascular supply of spinal cord

Stereotactic Radiosurgery for Cavernous Malformations
J Neurosurg 2000;93:987-991
Introduction: The use of radiosurgery for treatment of cerebral cavernous malformations (CM) is controversial. The safety and efficacy of CM radiosurgery is described.
Methods: Retrospective review of 17 patients with CM who underwent radiosurgery over a 10 yr period. All patients had at least 2 documented hemorrhages prior to therapy.
Results: Annual hemorrhage rate 51 mo preceding surgery was 40.1% compared to 8.8% in first 2 yr after radiosurgery and 2.9% thereafter. However, 41% of patients developed a permanent radiation-related morbidity.
Conclusions: Impossible to conclude that radiosurgery protects patients with CMs against future hemorrhage.

RED FLAGS for Back Pain

BACK PAIN
Bowel/**B**ladder (retention or incontinence)
Anesthesia (saddle)
Constitutional symptoms
Khronic disease
Parasthesia
Age >50 yr or <20 yr
IV drug use
Neuromotor deficits

Cauda Equina
- Urinary retention or incontinence, fecal incontinence or loss of anal sphincter tone, saddle anesthesia, uni/bilateral, leg weakness/pain

Malignancy
- Age >50 yr, previous Hx of cancer, pain unrelieved by bed rest, constitutional symptoms

Infection
- Increased ESR, IV drug use, immunosuppressed, fever

Compression Fracture
- Age >50 yr, trauma, prolonged steroid use

www.regentstudies.com

Root Compression

Differential Diagnosis
- herniated disc
- neoplasm (neurofibroma, schwannoma)
- synovial cyst, abscess
- hypertrophic bone/spur

Sensory Fibres
Fasciculus gracilis/cuneatus: proprioception, fine touch, vibration
Spinothalamic tract: pain and temperature

Motor Fibres
Corticospinal tract: skilled movements

Cervical Disc Syndrome

Etiology
- nucleus pulposus herniates through annulus fibrosus and impinges upon nerve root, most commonly at C6-C7 (C7 root)

Disc herniations impinge the nerve root at the level below the interspace (i.e. C5-6 disc affects the C6 nerve root)

Clinical Features
- pain in arm follows nerve root distribution, worse with neck extension, ipsilateral rotation, and lateral flexion (all compress the ipsilateral neural foramen)
- LMN signs and symptoms
- central cervical disc protrusion causes myelopathy as well as nerve root deficits

Investigations
- if red flags: C-spine x-ray, CT, MRI (imaging of choice)
- only consider EMG, nerve conduction studies if diagnosis uncertain and presenting more as peripheral nerve issue

Treatment
- conservative
  - no bedrest unless severe radicular symptoms
  - activity modification, patient education (reduce sitting, lifting)
  - physiotherapy, exercise programs focus on strengthening core muscles
  - analgesics, NSAIDs are more efficacious
  - avoid cervical manipulation, like traction
- surgical indications
  - anterior cervical discectomy is usual approach
  - intractable pain despite adequate conservative treatment for >3 mo
  - progressive neurological deficit

Prognosis
- 95% improve spontaneously in 4-8 wk

Table 10. Lateral Cervical Disc Syndromes

	C4-5	C5-6	C6-7	C7-T1
Root Involved	C5	C6	C7	C8
Incidence	2%	19%	69%	10%
Sensory	Shoulder	Thumb	Middle finger	Ring finger, 5th finger
Motor	Deltoid, biceps, supraspinatus	Biceps	Triceps	Digital flexors, intrinsics
Reflex	No change	Biceps, brachioradialis	Triceps	Finger jerk (Hoffmann's sign)

Cervical Spondylosis

Definition
- progressive degenerative process of cervical spine leading to canal stenosis – congenital spinal stenosis, degeneration of intervertebral discs, hypertrophy of lamina, dura, or ligaments, subluxation, altered mobility, telescoping of the spine due to loss of height of vertebral bodies, alteration of normal lordotic curvature
- resultant syndromes include mechanical neck pain, radiculopathy (root compression), myelopathy (spinal cord compression) and combinations

Epidemiology
- typically begins at age 40-50, M>F, most commonly at the C5-C6 > C6-C7 levels

Pathogenesis
- any of: disc degeneration/herniation, osteophyte formation, ossification, and hypertrophy of ligaments
- pathophysiology includes static compression, dynamic compression, and vascular compromise

www.regentstudies.com

Clinical Features
- insidious onset of mechanical neck pain exacerbated by excess vertebral motion (particularly rotation and lateral bending with a vertical compressive force – Spurling's test)
- the earliest symptoms are gait disturbance and lower extremity weakness or stiffness
- occipital H/A is common
- radiculopathy may involve 1 or more roots, and symptoms include neck, shoulder and arm pain, paresthesias and numbness
- cervical myelopathy may be characterized by weakness (upper > lower extremity), decreased dexterity, and sensory changes
- UMN findings such as hyperreflexia, clonus, and Babinski reflex may be present
- most worrisome complaint is lower extremity weakness (corticospinal tracts)
- myelopathy may be associated with funicular pain, characterized by burning and stinging ± Lhermitte's sign (lightning-like sensation down the back with neck flexion)

Investigations
- x-ray of cervical spine ± flexion/extension (alignment, fractures)
- MRI most useful for determination of compression of the neural element
- CT is only used for better determination of bony anatomy (i.e. OPLL)
- EMG/nerve conduction studies reserved for peripheral nerve investigation

Treatment
- nonsurgical: prolonged immobilization with cervical bracing (limit movement to minimize cumulative trauma to spinal cord), bed rest, anti-inflammatory medications
- surgical: anterior approach (anterior cervical discectomy or corpectomy), posterior approach (decompressive cervical laminectomy)
- surgical indications: myelopathy with motor impairment, progressive neurologic impairment, intractable pain
- complete remission almost never occurs. Surgical decompression may stop progression of disease

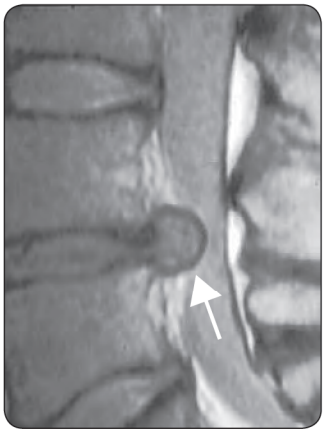


Figure 21. T2-weighted MRI of lumbar disc herniation

Lumbar Disc Syndrome

Etiology
- posteriolaterally herniated disc compressed nerve root exiting BELOW the level of the disc or the traversing nerve root
- far lateral disc herniation compressed nerve root AT the level of the disc or the exiting nerve root
- central herniation causes cauda equina or lumbar stenosis (neurogenic claudication)

Clinical Features
- initialy back pain, then leg pain > back pain
- limited back movement (especially forward flexion) due to pain
- motor weakness, dermatomal sensory changes, decreased reflexes
- exacerbation with valsalva; relief with flexing the knee or thigh
- nerve root tension signs
  - straight leg raise (SLR, Lasegue's test) or crossed SLR (pain should occur at less than 60°) suggests L5, S1 root involvement
  - femoral stretch test suggests L2, L3, or L4 root involvement

Investigations
- MRI is modality of choice
- x-ray spine (only to rule out other lesions), CT (bony anatomy)
- myelogram and post-myelogram CT (only if MRI is contraindicated)

Treatment
- conservative (same as cervical disc disease)
- surgical indications
  - same as cervical disc + cauda equina syndrome

Prognosis
- 95% improve spontaneously within 4-8 wk
- do not follow patients with serial MRIs; clinical status is more important at guiding management

Table 11. Lateral Lumbar Disc Syndromes

	L3-4	L4-5	L5-S1
Root Involved	L4	L5	S1
Incidence	<10%	45%	45%
Pain	Femoral pattern	Sciatic pattern	Sciatic pattern
Sensory	Medial leg	Dorsal foot to hallux Lateral leg	Lateral foot
Motor	Tibialis anterior (dorsiflexion)	Extensor hallucis longus (hallux extension)	Gastrocnemius, soleus (plantar flexion)
Reflex	Knee jerk	Medial hamstrings	Ankle jerk

Lumbar Disc Herniation: What are Reliable Criterions Indicative for Surgery?
Orthopedics 2009;32:589-597
1) The only clear indication for early surgery in LDH is cauda equina syndrome.
2) Pain may also be an indication for surgery. If conservative treatment is intended, it should be considered for at least 2 mo but not beyond 1 yr if the patient shows minimal improvement, since the beneficial effects of surgery will diminish after this period.
3) The type of herniation on MRI is not relevant to the decision of whether or not to operate on patients with LDH.
4) Although paresis is often a red flag symptom for patients with LDH, neither the magnitude nor the duration of paresis should be used as an indication for early surgery.

Magnetic Resonance Imaging in Follow-Up Assessment of Sciatica
NEJM 2013;368:999-1007
Background: Follow-up MRI is a controversial method for monitoring sciatica in patients with known lumbar-disc herniation.
Methods: Participants (n=283) were recruited from a simultaneous, parallel, randomized study comparing surgery and conservative care for sciatica (the Sciatica Trial). MRI and clinical assessment were undertaken pre-treatment and 1 yr post-treatment randomization to visualize disc herniation and evaluate outcome.
Results: At 1 yr, disc herniation was visible in 35% with a favourable outcome (complete, or nearly complete symptom resolution) and in 33% with an unfavourable outcome (p=0.70). A favourable outcome was reported in 85% of patients with disc herniation and 83% without disc herniation (p=0.70).
Conclusions: Anatomical abnormalities visible on repeated MRI 1 yr after treatment for sciatica due to lumbar-disc herniation could not distinguish patients with resolution of their symptoms from patients still experiencing symptoms.

www.regentstudies.com

Table 12. Differentiating Conus Medullaris Syndrome from Cauda Equina Syndrome

	Conus Medullaris Syndrome	Cauda Equina Syndrome
Onset	Sudden, bilateral	Gradual, unilateral
Spontaneous Pain	Rare, if present usually bilateral, symmetric in perineum or thighs	Severe, radicular type: in perineum, thighs, legs, back, or bladder
Sensory Deficit	Saddle; bilateral and symmetric; sensory dissociation	Saddle; no sensory dissociation; may be unilateral and asymmetric
Motor Deficit	Symmetric; paresis less marked; fasciculations may be present	Asymmetric; paresis more marked; atrophy may be present; fasciculations rare
Reflexes	Only ankle jerk absent (preserved knee jerk)	Knee and ankle jerk may be absent
Autonomic Symptoms (bladder dysfunction, impotence, etc.)	Urinary retention and atonic anal sphincter prominent early; impotence frequent	Sphincter dysfunction presents late; impotence less frequent

Cauda Equina Syndrome

Etiology
- compression or irritation of lumbosacral nerve roots below conus medullaris (below L2 level)
- decreased space in the vertebral canal below L2
- common causes: herniated disc ± spinal stenosis, vertebral fracture, and tumour

Clinical Features
- usually acute (develops in less than 24 h); rarely subacute or chronic
- motor (LMN signs)
  - weakness/paraparesis in multiple root distribution
  - reduced deep tendon reflexes (knee or ankle)
- autonomic
  - urinary retention (or overflow incontinence) and/or fecal incontinence due to loss of anal sphincter tone
- sensory
  - low back pain radiating to legs (sciatica) aggravated by Valsalva maneuver and by sitting; relieved by lying down
  - bilateral sensory loss or pain: depends on the level affected
  - saddle area (S2-S5) anesthesia
  - sexual dysfunction (late finding)

Investigations
- urgent MRI to confirm compression of S2-S3-S4 nerve root by a large disc herniation
- post-void residual very helpful to determine if true retention is present; volumes controversial but anything over 250 cc in a healthy individual is cause for concerns

Treatment
- surgical decompression (<48 h) to preserve bowel, bladder, and sexual function, and/or to prevent progression to paraplegia

Prognosis
- markedly improves with surgical decompression
- recovery correlates with function at initial presentation: if patient is ambulatory, likely to continue to be ambulatory; if unable to walk, unlikely to walk after surgery

Lumbar Spinal Stenosis

Etiology
- congenital narrowing of spinal canal combined with degenerative changes (herniated disc, hypertrophied facet joints, and ligamentum flavum)

Clinical Features
- gradually progressive back and leg pain with standing and walking that is relieved by sitting or lying down (neurogenic claudication – 60% sensitive)
- neurologic exam may be normal, including straight leg raise test

Investigations
- MRI is the optimal investigation to confirm and localize the level of stenosis (unlike nerve root compression which can be localized with clinical exam)

Treatment
- conservative: NSAIDs, analgesia
- surgical: laminectomy with root decompression (the role of fusion may need to be considered if the amount of bone removed with the laminectomy results in de-stabilization)

www.regentstudies.com

Neurogenic Claudication

Etiology
- ischemia of lumbosacral nerve roots secondary to vascular compromise and increased demand from exertion, often associated with lumbar stenosis

Clinical Features
- dermatomal pain/paresthesia/weakness of buttock, hip, thigh, or leg initiated by standing or walking
- slow relief with postural changes (sitting >30 min), NOT simply exertion cessation
- induced by variable degrees of exercise or standing
- may be elicited with lumbar extension, but may not have any other neurological findings, no signs of vascular compromise (e.g. ulcers, poor capillary refill, etc.)

Key Features of Neurogenic vs. Vascular Claudication

Neurogenic Claudication: dermatomal distribution with positional relief occurring over minutes

Vascular Claudication: sclerotomal distribution with relief occurring with rest over seconds

Investigations
- bicycle test may help distinguish neurogenic claudication (NC) from vascular claudication (the waist-flexed individuals on the bicycle with NC can last longer)

Treatment
- same as for lumbar spinal stenosis

Intradural Intramedullary Lesions

Syringomyelia (Syrinx)

Definition
- cystic cavitation of the spinal cord
- presentation is highly variable, usually progresses over months to years
- initially pain, weakness; later atrophy and loss of pain and temperature sensation

Etiology
- 70% are associated with Chiari I malformation, 10% with basilar invagination
- post-traumatic
- tumour
- tethered cord

Clinical Features
- nonspecific features for any intramedullary spinal cord pathology:
  - initially pain, weakness, atrophy, loss of pain and temperature in upper extremities (central syrinx) with progressive myelopathy over years
  - sensory loss with preserved touch and proprioception in a band-like distribution at the level of cervical syrinx
  - sensory loss with preserved touch and proprioception in a band-like distribution at the level of cervical syrinx
  - dysesthetic pain often occurs in the distribution of the sensory loss
  - LMN arm/hand weakness or wasting
  - painless neuropathic arthropathies (Charcot's joints), especially in the shoulder and neck due to loss of pain and temperature sensation

Figure 22. T1 Weighted MRI of syringomyelia

Investigations
- MRI is best method, myelogram with delayed CT

Treatment
- treat underlying cause (e.g. posterior fossa decompression for Chiari I, surgical removal of tumour if causing a syrinx)
- rarely does the syrinx need to be shunted, only when progressive and size allows for insertion of tube

Spinal Cord Syndromes

- spinal cord injury impairment classified according to ASIA score
- ASIA A: complete, no motor/sensory below neurological level including S4/5
- ASIA B: incomplete, sensory but not motor function preserved below neurological level including S4/5

www.regentstudies.com

- ASIA C: incomplete, motor function preserved below neurological level, and more than half of the key muscles below neurological level have a muscle grade <3
- ASIA D: incomplete, motor function preserved below neurological level, and more than half of the key muscles below neurological level have a muscle grade 3 or more
- ASIA E: normal motor and sensory function

Complete Spinal Cord Lesion
- bilateral loss of motor/sensory and autonomic function at ≥4 segments below lesion/injury, with UMN signs
- about 3% of patients with complete injuries will develop some recovery within 24 h, beyond 24 h, no distal function will recover

Incomplete Spinal Cord Lesion
- any residual function at ≥4 segments below lesion
- signs include sensory/motor function in lower limbs and "sacral sparing" (perianal sensation, voluntary rectal sphincter contraction)

Table 13. Comparison Between Incomplete Spinal Cord Lesion Syndromes

Syndrome	Etiology	Motor	Sensory
Brown-Séquard	Hemisection of cord	Ipsilateral LMN weakness at the lesion Ipsilateral UMN weakness below the lesion	Ipsilateral loss of vibration and proprioception Contralateral loss of pain and temperature Preserved light touch
Anterior Cord	Anterior spinal artery compression or occlusion	Bilateral LMN weakness at the lesion Bilateral UMN weakness below the lesion Urinary retention	Preserved vibration and proprioception Bilateral loss of pain and temperature Preserved light touch
Central Cord (most common)	Syringomyelia, tumours, spinal hyperextention injury	Bilateral motor weakness: Upper limb weakness (LMN lesion) > Lower limb weakness (UMN lesion) Urinary retention	Variable bilateral suspended sensory loss Loss of pain and temperature > loss of vibration and proprioception
Posterior Cord	Posterior spinal artery infarction, trauma	Preserved	Bilateral loss of vibration, proprioception, light touch at and below the lesion Preserved pain and temperature

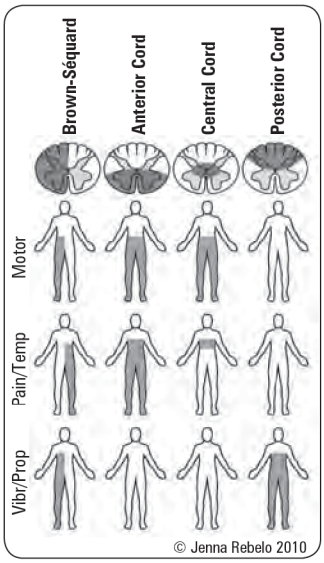


Figure 23. Spinal cord lesion syndromes

Peripheral Nerves

- see Neurology, N34

Seddon's Classification of Peripheral Nerve Injury
- class I: **neurapraxia** – axon structurally intact but fails to function; recovery within hours to months (average 6-8 wk)
- class II: **axonotmesis** – axon and myelin sheath disrupted but endoneurium and supporting structures intact → Wallerian degeneration of axon segment distal to injury → spontaneous axonal recovery at 1 mm/d, max at 1-2 yr
- class III: **neurotmesis** – nerve completely transected, need surgical repair for possibility of recovery
- etiologies: ischemia, nerve entrapment – nerve compressed by nearby anatomic structures, often secondary to localized, repetitive mechanical trauma with additional vascular injury to nerve

Investigations
- neurological exam (power, sensation, reflexes), localization via Tinel's sign (paresthesias elicited by tapping along the course of a nerve)
- electrophysiological studies (EMG, nerve conduction study) may be helpful in assessing nerve integrity and monitoring recovery, not helpful until 2-3 wk post-injury
- labs: blood work, CSF
- imaging: C-spine, chest/bone x-rays, myelogram, CT, magnetic resonance neurography
- angiogram if vascular damage is suspected

Treatment
- early neurosurgical consultation if injury is suspected
- entrapment
  - conservative: prevent repeated stress/injury, physiotherapy, NSAIDs, local anesthesia/steroid injection
  - surgical: nerve decompression ± transposition for progressive deficits, muscle weakness/atrophy, failure of medical management
- stretch/contusion
  - follow-up clinically for recovery; exploration if no recovery in 3 mo

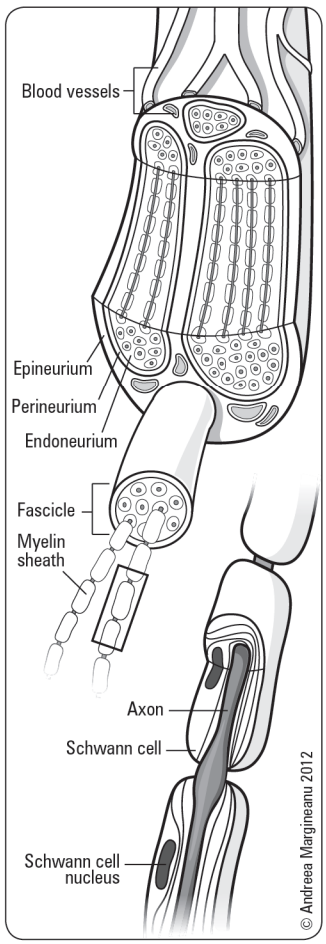


Figure 24. Peripheral nerve structure

www.regentstudies.com

- axonotmesis
  - if no evidence of recovery, resect damaged segment
  - prompt physical therapy and rehabilitation to increase muscle function, maintain joint range of motion, and maximize return of useful function
  - recovery usually incomplete
- neurotmesis
  - surgical repair of nerve sheath unless known to be intact (suture nerve sheaths directly if ends approximate or nerve graft [usually sural nerve])
  - clean laceration: early exploration and repair
  - contamination or associated injuries: tag initially with nonabsorbable suture, reapproach within 10 d

Complications
- neuropathic pain: with neuroma formation
- complex regional pain syndrome: with sympathetic nervous system involvement

SPECIALTY TOPICS

Neurotrauma

Trauma Management (see Emergency Medicine, ER7)

Indications for Intubation in Trauma
1. depressed LOC (patient cannot protect airway): usually GCS ≤8
2. need for hyperventilation
3. severe maxillofacial trauma: patency of airway is doubtful
4. need for pharmacologic paralysis for evaluation or management
   - if basal skull fracture suspected, avoid nasotracheal intubation as may inadvertently enter brain
   - note: intubation prevents patient's ability to verbalize for determining GCS

Glasgow Coma Scale

Eye Response	Verbal Response	Motor Response
4 spontaneous	5 oriented	6 obeys commands
3 opens eyes to voice	4 confused	5 localizes to pain
2 opens eyes to pain	3 inappropriate words	4 withdraws from pain
1 no eye opening	2 incomprehensible sounds	3 flexion to pain (decorticate posturing)
	1 no response	2 extension to pain (decerebrate posturing)
	T intubated	1 no response

Best response for each component recorded individually (e.g. E3V3M5)
≥13 is mild injury; 9-12 is moderate injury; ≤8 is severe injury

Trauma Assessment

INITIAL MANAGEMENT

ABCs of Trauma Management
- see Emergency Medicine, ER7

NEUROLOGICAL ASSESSMENT

Mini-History
- period of LOC, post-traumatic amnesia, loss of sensation/function, type of injury/accident

Neurological Exam
- GCS
- head and neck (lacerations, bruises, basal skull fracture signs, facial fractures, foreign bodies)
- spine (palpable deformity, midline pain/tenderness)
- eyes (pupillary size and reactivity)
- brainstem (breathing pattern, CN palsies)
- cranial nerve exam
- motor exam, sensory exam (only if GCS is 15), reflexes
- sphincter tone
- record and repeat neurological exam at regular intervals

Assessment of Spine CT/X-Ray (Parasagittal View)

ABCDS
Alignment (columns: anterior vertebral line, posterior vertebral line, spinolaminar line, posterior spinous line)
Bone (vertebral bodies, facets, spinous processes)
Cartilage
Disc (disc space and interspinous space)
Soft tissues

Investigations
- spinal injury precautions (cervical collar) are continued until C-spine is cleared
- C,T,L-spine x-rays
  - AP, lateral, odontoid views for C-spine (must see from C1 to T1; swimmer's view if necessary) or CT
  - rarely done: oblique views looking for pars interarticularis fracture ("Scottie dog" sign)
- CT head and upper C-spine (whole C-spine if patient unconscious) look for fractures, loss of mastoid or sinus air spaces, blood in cisterns, pneumocephalus
- cross and type, ABG, CBC, drug screen (especially alcohol)
- chest and pelvic x-ray as indicated

- Never do lumbar puncture in head injury unless increased ICP has been ruled out
- All patients with head injury have C-spine injury until proven otherwise
- Suspect hematoma in alcoholic-related injuries
- Low BP after head injury means injury elsewhere
- Must clear spine both radiologically AND clinically

TREATMENT

Treatment for Minor Head Injury
- observation over 24-48 h
- wake every hour
- judicious use of sedatives or pain killers during monitoring period

www.regentstudies.com

Treatment for Severe Head Injury (GCS ≤8)
- clear airway and ensure breathing (if GCS ≤8, intubate)
- secure C-spine
- maintain adequate BP
- monitor for clinical deterioration
- monitor and manage increased ICP if present (see *Herniation Syndromes,* NS6)

Admission required if:
- skull fracture (indirect signs of basal skull fracture, see *Head Injury*)
- confusion, impaired consciousness, concussion with >5 min amnesia
- focal neurological signs, extreme H/A, vomiting, seizures
- unstable spine
- use of alcohol
- poor social support

Head Injury

Epidemiology
- M:F = 2-3:1

Pathogenesis
- acceleration/deceleration: contusions, subdural hematoma, axon and vessel shearing/mesencephalic hematoma
- impact: skull fracture, concussion, epidural hematoma
- penetrating: worse with high velocity and/or high missile mass
  - low velocity: highest damage to structures on entry/exit path
  - high velocity: highest damage away from missile tract

Scalp Injury
- rich blood supply
- considerable blood loss (vessels contract poorly when ruptured)
- minimal risk of infection due to rich vascularity

Skull Fractures
- depressed fractures: double density on skull x-ray (outer table of depressed segment below inner table of skull), CT with bone window is gold standard
- simple fractures (closed injury): no need for antibiotics, no surgery
- compound fractures (open injury): increased risk of infection, surgical debridement within 24 h is necessary
  - internal fractures into sinus may lead to meningitis, pneumocephalus
  - risk of operative bleed may limit treatment to antibiotics
- basal skull fractures: not readily seen on x-ray, rely on clinical signs
  - retroauricular ecchymoses (Battle's sign)
  - periorbital ecchymoses (raccoon eyes)
  - hemotympanum
  - CSF rhinorrhea, otorrhea (suspect CSF if halo or target sign present); suspect with Lefort II/III midface fracture

Cranial Nerve Injury
- most traumatic causes of cranial nerve injury do not warrant surgical intervention
- surgical intervention
  - CN II: local eye/orbit injury
  - CN III, IV, VI: if herniation secondary to mass
  - CN VIII: repair of ossicles
- CN injuries that improve
  - CN I: recovery may occur in a few months; most do not improve
  - CN III, IV, VI: majority recover
  - CN VII: recovery with delayed lesions
  - CN VIII: vestibular symptoms improve over weeks, deafness usually permanent (except when resulting from hemotympanum)

Arterial Injury
- e.g. carotid-cavernous (C-C) fistula, carotid/vertebral artery dissection

Intracranial Bleeding
- see *Blood,* NS15 and *Cerebrovascular Disease,* NS17

Comparative Effectiveness of Using Computed Tomography Alone to Exclude Cervical Spine Injuries in Obtunded or Intubated Patients: Meta-Analysis of 14,327 Patients with Blunt Trauma
J Neurosurg 2011;115:541-549
Purpose: To determine the effectiveness of helical CT alone (vs. CT and adjuvant imaging such as MR) to diagnose acute unstable cervical spine injury following blunt trauma.
Results: 17 studies with 14,327 patients total. Sensitivity and specificity for modern CT were both >99.9% (95% CI 0.99 -1.00 for both). The negative predictive value of a normal CT scan was 100% (95% CI 0.96-1.00) and accuracy was not affected by the global severity of injury, CT slice thickness, or study quality.
Conclusions: CT alone is sufficient to detect unstable cervical spine injuries in trauma patients and adjuvant imaging is unnecessary with a negative CT scan result. Consequently, if a CT scan is negative for acute injury, the cervical collar may be removed from obtunded or intubated trauma patients.

The Canadian CT Head Rule for Patients with Minor Head Injury
Lancet 2001;357:1391-1396

CT Head is only required for patients with minor head injuries with any one of the following:

High Risk (for neurological intervention)
- GCS score <15 at 2 h after injury.
- Suspected open or depressed skull fracture.
- Any sign of basal skull fracture (hemotympanum, "raccoon" eyes, cerebrospinal fluid otorrhea/rhinorrhoea, Battle's sign).
- Vomiting ≥2 episodes.
- Age ≥65 yr.

Medium Risk (for brain injury on CT)
- Amnesia after impact >30 min.
- Dangerous mechanism (pedestrian struck by motor vehicle, occupant ejected from motor vehicle, fall from height >3 feet or five stairs).

Minor Head Injury is defined as witnessed loss of consciousness, definite amnesia, or witnessed disorientation in a patient with a GCS score of 13-15.

A Trial of Intracranial-Pressure Monitoring in Traumatic Brain Injury
NEJM 2012;367:2471-2481
Background: ICP monitoring is frequently used to monitor severe traumatic brain injury, but controversy exists over whether it is beneficial.
Methods: Study sample (n=324 patients, ≥13 yr) consisted of those who had severe traumatic brain injury and were being treated in ICU in Bolivia or Ecuador. Patients were randomly assigned to one management group:
1. ICP-monitoring based management.
2. Management based on imaging and clinical examination.
Primary outcome was a composite of survival time, impaired consciousness, functional status (at 3, 6 mo), and neuropsychological status (at 6 mo).
Results: No significant difference between management groups based on primary outcome, 6-mo mortality, median length of ICU stay, or occurrence of serious adverse events. However, duration of brain-specific treatments (e.g. use of hyperosmolar fluids or hyperventilation) higher in the imaging-clinical examination group (4.8 d vs. 3.4 d, p=0.002).
Conclusion: Maintaining monitored ICP at 20 mmHg or less is not superior to care based on imaging and clinical examination.

www.regentstudies.com

Brain Injury

Primary Impact Injury
- mechanism of injury determines pathology: penetrating injuries, direct impact
  - low velocity: local damage
  - high velocity: distant damage possible (due to wave of compression), concussion
- **concussion**: a trauma-induced alteration in mental status
  - American Academy of Neurology (AAN) Classification
  - no parenchymal abnormalities on CT
- **coup** (damage at site of blow) and **contrecoup** (damage at opposite site of blow)
  - acute decompression causes cavitation followed by a wave of acute compression
- **contusion** (hemorrhagic)
  - high density areas on CT ± mass effect
  - commonly occurs with brain impact on bony prominences (inferior frontal lobe, pole of temporal lobe)
- **diffuse axonal injury/shearing**
  - wide variety of damage results
  - may tear blood vessels (hemorrhagic foci)
  - often the cause of decreased LOC if no space-occupying lesion on CT

AAN Classification
Grade 1: altered mental status <15 min
Grade 2: altered mental status >15 min
Grade 3: any loss of consciousness

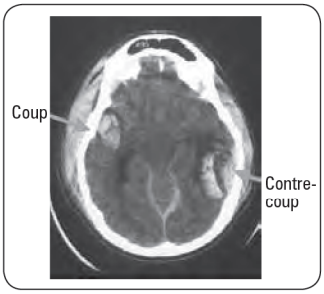


Figure 25. CT showing coup-contrecoup injury

Secondary Pathologic Processes
- same subsequent biochemical pathways for each traumatic etiology
- delayed and progressive injury to the brain due to
  - high glutamate release → NMDA receptor activation → cytotoxic cascade
  - cerebral edema
  - intracranial hemorrhages
  - ischemia/infarction
  - raised ICP, intracranial HTN
  - hydrocephalus

SIADH → hyponatremia
DI → hypernatremia

Extracranial Conditions
- hypoxemia
  - due to trauma to the chest, upper airway, brainstem
  - extremely damaging to vulnerable brain cells
  - leads to ischemia, raised ICP
- hypercarbia
  - leads to raised ICP (secondary to vasodilation)
- systemic hypotension
  - caused by blood loss (e.g. ruptured spleen)
  - loss of cerebral autoregulation leads to decreased CPP, ischemia
- hyperpyrexia
  - leads to increased brain metabolic demands → ischemia
- fluid and electrolyte imbalance
  - iatrogenic (most common)
  - SIADH caused by head injury
  - diabetes insipidus (DI)
  - may lead to cerebral edema and raised ICP
- coagulopathy

Concussion Grades

AAN Grade	Management Options
1	• Examine 15 min for amnesia and other symptoms • Return to normal activity if symptoms clear within 15 min
2	• Remove from activity for 1 d, then re-examine • CT or MRI if H/A or other symptoms worsen or last >1 wk • Return to normal activity after 1 wk without symptoms
3	• Emergent neurological exam + imaging; if initial exam is normal, may go home with close follow-up • Admit if any signs of pathology or persistent abnormal mental status • CT or MRI if H/A or other symptoms • If brief loss of consciousness (<1 min), return to normal activity after 1 wk without symptoms • If prolonged loss of consciousness (>1 min), return to normal activity only after 2 wk without symptoms

Intracranial Conditions
- raised ICP due to traumatic cerebral edema OR traumatic intracranial hemorrhage

Brain Injury Outcomes
- mildly traumatic (GCS 13-15): post-concussive symptoms: H/A, fatigue, dizziness nausea, blurred vision, diplopia, memory impairment, tinnitus, irritability, low concentration; 50% at 6 wk, 14% at 1 yr
- moderately traumatic (GCS 9-12): proportional to age (>40) and CT findings; 60% good recovery, 26% moderately disabled, 7% severely disabled, 7% vegetative/dead
- severe (GCS ≤8): difficult to predict, correlates with post-resuscitation GCS (especially motor) and age

Late Complications of Head/Brain Injury

- seizures: 5% of head injury patients develop seizures
  - incidence related to severity and location of injury (increased with local brain damage or intracranial hemorrhage)
  - post-traumatic seizure may be immediate, early, or late
  - presence of early (within first wk) post-traumatic seizure raises incidence of late seizures
- meningitis: associated with CSF leak from nose or ear
- hydrocephalus: acute hydrocephalus or delayed normal pressure hydrocephalus (NPH)

www.regentstudies.com

Spinal Cord Injury

- see Orthopedics, OR23 and Emergency Medicine, ER9

Neurogenic and Spinal Shock

1. neurogenic shock: hypotension that follows SCI (sBP usually ≤80 mmHg) caused by:
   - interruption of sympathetics (unopposed parasympathetics) below the level of injury
   - loss of muscle tone due to skeletal muscle paralysis below level of injury → venous pooling (relative hypovolemia)
   - blood loss from associated wounds (true hypovolemia)
2. spinal shock: transient loss of all neurologic function below the level of the spinal cord injury, causing flaccid paralysis and areflexia for variable periods

Whiplash-Associated Disorders

- definition: traumatic injury to the soft tissue structures in the region of the cervical spine due to hyperflexion, hyperextension, or rotational injury to the neck

Initial Management of SCI

- major causes of death in SCI are aspiration and shock
- the following patients should be treated as having a SCI until proven otherwise:
  - all victims of significant trauma
  - minor trauma patients with decreased LOC or complaints of neck or back pain, weakness, abdominal breathing, numbness/tingling, or priapism

Stabilization and Initial Evaluation in the Hospital

1. ABCs, immobilization (backboard/head strap), oxygenation, Foley catheter to urometer, temperature regulation
2. hypotension: maintain sBP >90 mmHg with pressors (dopamine), hydration, and atropine
   - DVT prophylaxis
3. monitor CBC/electrolytes
4. focused history (see *Trauma Assessment*, NS29)
5. spine palpation: point tenderness or deformity
6. motor level assessment (including rectal exam for voluntary anal sphincter contraction)
7. sensory level assessment: pinprick, light touch, and proprioception
8. evaluation of reflexes
9. signs of autonomic dysfunction: altered level of perspiration, bowel or bladder incontinence, priapism
10. radiographic evaluation
    - 3 views C-spine x-rays (AP, lateral, and odontoid) to adequately visualize C1 to C7-T1 junction
    - flexion-extension views to disclose occult instability
    - CT scan (bony injuries) typically most trauma centres use CT as the modality of choice for looking at fractures, very sensitive with the high resolution scanners
    - MRI mandatory if neurological deficits (soft tissue injuries)

Medical Management Specific to SCI

- option: methylprednisolone (given within 8 h of injury) this is controversial and you need to confer with Neurosurgery service
- ± decompression in acute, non-penetrating SCI

Pharmacological Therapy for Acute Spinal Cord Injury: Congress of Neurological Surgeons (CNS) and American Association of Neurological Surgeons (AANS) Guidelines
Neurosurgery 2013;72(Suppl 2):93-105
Level I Recommendations
- No Class I or Class II medical evidence supports the use of methylprednisone in the treatment of acute SCI. Several Class II and Class III studies have been published stating inconsistent effects of methylprednisone likely related to random chance or selection bias.
- Administration of GM-1 ganglioside (Sygen) for the treatment of acute SCI is not recommended.

Early vs. Delayed Decompression for Traumatic Cervical Spinal Cord Injury: Results of the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS)
PLoS ONE 2012;7:e32037. doi:10.1371/journal.pone.0032037
Introduction: This study sought to determine the relative effectiveness of early (<24 h after injury) versus late (≥24 h after injury) decompressive surgery following a traumatic cervical spinal cord injury (SCI).
Methods/Population: A prospective cohort study completed in 2002-2009 involving 6 North American institutions. Participants were 16-80 yr with a cervical SCI. Outcomes evaluated were changes in American Spinal Injury Association Impairment Scale (AIS) grade at 6 mo follow-up, complications, and mortality.
Results: Of 313 participants enrolled, 182 underwent early surgery and 131 underwent late surgery. 222 participants were available for follow-up at 6 mo. The odds of at least 2 grade AIS improvement were greater for those who had early surgery compared to those with late surgery (OR = 2.83, 95% CI 1.10, 7.28). Mortality was observed for each group during the first 30 d post injury. No statistically significant differences were observed for complications (p=0.21).
Conclusion: Early decompression surgery following a SCI is safe and associated with higher AIS improvement at 6 mo following injury.

Fractures of the Spine

FRACTURES AND FRACTURE-DISLOCATIONS OF THE THORACIC AND LUMBAR SPINE

- assess ligamentous instability using flexion/extension x-ray views of C-spine ± MRI
- thoracolumbar spine unstable if 4/6 segments disrupted (3 columns divided into left and right)
  - anterior column: anterior half of vertebral body, disc, and anterior longitudinal ligament
  - middle column: posterior half of vertebral body, disc, and posterior longitudinal ligament
  - posterior column: posterior arch, facet joints, pedicle, lamina and supraspinous, interspinous, and ligamentum ligaments

Types of Injury (Denis Classification)

- **compression fracture** (58%)
  - produced by flexion
  - posterior ligament complex (supraspinous and interspinous ligaments, ligamentum flavum, and intervertebral joint capsules) remain intact
  - fractures are stable but lead to kyphotic deformity

A New Classification of Thoracolumbar Injuries: The Importance of Injury Morphology, the Integrity of the Posterior Ligamentous Complex, and Neurological Status
Spine 2005;30:2325-2333
Introduction: To devise a practical and comprehensive classification system to assist in clinical decision of operative or non-operative thoracolumbar injuries.
Methods/Population: Spine trauma specialists contributed factors that were deemed important for clinical decisions regarding thoracolumbar trauma.
Results: A new classification system called the Thoracolumbar Injury Classification and Severity Score (TLICS) was devised based on three parameters: 1) morphology of the injury determined radiographically, 2) integrity of posterior ligamentous complex, and 3) neurological status.
Conclusion: An easy to apply and clinically relevant decision making tool regarding thoracolumbar trauma.

www.regentstudies.com

- **burst fracture** (17%)
  - stable: anterior and middle columns parted with bone retropulsed nearby
    - hallmark is pedicle widening on AP x-ray
    - spinal cord (seen on x-ray and CT); posterior column is uninjured
  - unstable: same as the stable but with posterior column disruption (usually ligamentous)
- **flexion distraction injury** (6%)
  - hyperflexion and distraction of posterior elements
    - middle and posterior columns fail in distraction
  - classic: Chance = horizontal fracture through posterior arch, pedicles, posterior vertebral body
  - can be purely ligamentous, i.e. through PLL and disc
- **fracture-dislocation** (6%)
  - anterior and cranial dislocation of superior vertebral body → 3 column failure
  - three types:
    - flexion-rotation
    - flexion-distraction
    - shear/hyperextension (rare)

Management of Thoracolumbar Injury
- severity and management based on TLICS classification

FRACTURES OF THE CERVICAL SPINE

Types of Injury
- C1 vertebral fracture (Jefferson fracture)
  - vertical compression forces the occipital condyles of the skull down on the C1 vertebra (atlas), pushing the lateral masses of the atlas outward and disrupting the ring of the atlas
  - also can cause an occipital condylar fracture
- odontoid process fracture
  - causes C1 and odontoid of C2 to move independently of C2 body
  - this occurs because
    - normally C1 vertebra and odontoid of C2 are a single functional unit
    - alar and transverse ligaments on posterior aspect of odontoid most commonly remain intact following injury
  - patients often report a feeling of instability and present holding their head with their hands
- C2 vertebral fracture (hangman fracture, traumatic spondylolisthesis of axis):
  - bilateral fracture through the pars interarticularis of C2 with subluxation of C2 on C3
  - usually neurologically intact
- Clay-Shoveler fracture
  - avulsion of spinous process, usually C6 or C7

Imaging
- AP spine x-ray (open-mouth and lateral view), CT

Treatment
- immobilization in cervical collar or halo vest until healing occurs (usually 2-3 mo)
- Type II and III odontoid fractures
  - consider surgical fixation for comminution, displacement, or inability to maintain alignment with external immobilization
  - confirm stability after recovery with flexion-extension x-rays

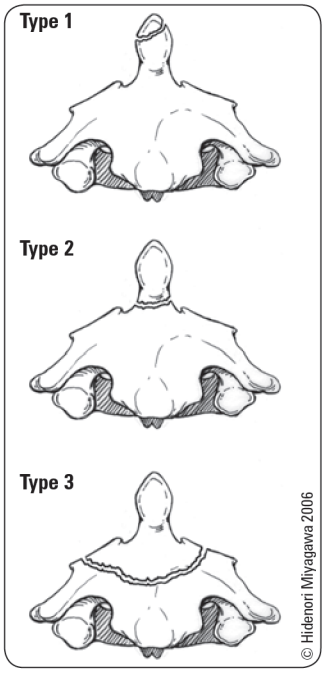


Figure 26. Odontoid fracture classification

TLICS Scoring

Parameter	Points
Morphology	
Compression fracture	1
Burst fracture	2
Translational/rotational fracture	3
Distraction	4
Neurologic Status	
Intact	0
Nerve root injury	2
Spinal Cord Status	
Incomplete	3
Complete	2
Cauda equine	3
Posterior Ligamentous Complex	
Intact	0
Injury suspected/indeterminate	2
Injured	3

- TLICS scoring based on morphology of injury, status of posterior ligamentous complex, and neurological status
- Non-operative management if TLICS = 0-3, operative management if TLICS = 5+, either operative or non-operative if TLICS = 4

Neurologically Determined Death

Definition
- irreversible and diffuse brain injury resulting in absence of clinical brain function
- cardiovascular activity may persist for up to 2 wk

Criteria of Diagnosis
- prerequisites: no CNS depressant drugs/neuromuscular blocking agents, no drug intoxication/poisoning, temperature >32°C, no electrolyte/acid-base/endocrine disturbance
- absent brainstem reflexes:
  - absent pupillary light reflex
  - absent corneal reflexes
  - absent oculocephalic response
  - absent caloric responses (e.g. no deviation of eyes to irrigation of each ear with 50 cc of ice water – allow 1 min after injection, 5 min between sides)
  - absent pharyngeal and tracheal reflexes
  - absent cough with tracheal suctioning
  - absent respiratory drive at $PaCO_2$ >60 mmHg or >20 mmHg above baseline (apnea test)
- 2 evaluations separated by time, usually performed by two specialists (e.g. anesthetist, neurologist, neurosurgeon)
- confirmatory testing: flat EEG, absent perfusion assessed with cerebral angiogram

www.regentstudies.com

Coma

Definition
- an unrousable state in which patients show no meaningful response to environmental stimuli

Pathophysiology
- lesions affecting the cerebral cortex bilaterally, the reticular activating system (RAS) or their connecting fibres
- focal supratentorial lesions do not alter consciousness except by herniation (compression on the brainstem or on the contralateral hemisphere) or by precipitating seizures

Classification
- structural lesions (tumour, pus, blood, infarction, CSF): 1/3 of comas
  - supratentorial mass lesion: leads to herniation
  - infratentorial lesion: compression of or direct damage to the RAS or its projections
- metabolic disorders/diffuse hemispheric damage: 2/3 of comas
  - deficiency of essential substrates (e.g. oxygen, glucose, vitamin B_{12})
  - exogenous toxins (e.g. drugs, heavy metals, solvents)
  - endogenous toxins/systemic metabolic diseases (e.g. uremia, hepatic encephalopathy, electrolyte imbalances, thyroid storm)
  - infections (meningitis, encephalitis)
  - trauma (concussion, diffuse shear axonal damage)

Investigations and Management
- ABCs
- labs: electrolytes, extended electrolytes, TSH, LFTs, Cr, BUN, toxin screen, glucose
- CT/MRI, LP, EEG

Persistent Vegetative State

Definition
- a condition of complete unawareness of the self and the environment accompanied by sleep-wake cycles with either complete or partial preservation of hypothalamic and brainstem autonomic function
- "awake but not aware"
- follows comatose state

Etiology/Prognosis
- most commonly caused by cardiac arrest or head injury
- due to irreversible loss of cerebral cortical function but intact brainstem function
- average life expectancy is 2-5 yr

Pediatric Neurosurgery

Spinal Dysraphism

SPINA BIFIDA OCCULTA

Definition
- congenital absence of a spinous process and a variable amount of lamina
- no visible exposure of meninges or neural tissue

Epidemiology
- 15-20% of the general population; most common at L5 or S1

Etiology
- failure of fusion of the posterior neural arch

Clinical Features
- no obvious clinical signs
- presence of lumbosacral cutaneous abnormalities (dimple, sinus, port-wine stain, or hair tuft) should increase suspicion of an underlying anomaly (lipoma, dermoid, diastematomyelia)

Investigations
- plain film: absence of the spinous process along with minor amounts of the neural arch
- U/S, MRI to exclude spinal anomalies

Treatment
- requires no treatment

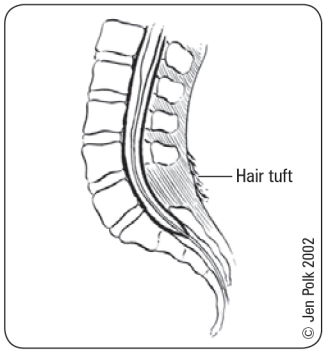


Figure 27. Spina bifida occulta

www.regentstudies.com

MENINGOCELE (SPINA BIFIDA APERTA)

Definition
- herniation of meningeal tissue and CSF through a defect in the spine, without associated herniation of neural tissue

Etiology
- primary failure of neural tube closure

Clinical Features
- most common in lumbosacral area
- usually no disability, low incidence of associated anomalies, and hydrocephalus

Investigations
- plain films, CT, MRI, U/S, echo, GU investigations

Treatment
- surgical excision and tissue repair (excellent results)

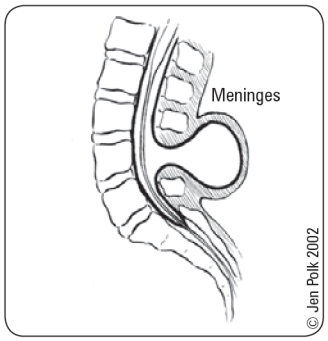


Figure 28. Meningocele

MYELOMENINGOCELE (SPINA BIFIDA APERTA)

Definition
- herniation of meningeal and CNS tissue through a defect in the spine

Etiology
- same as meningocele

Clinical Features
- sensory and motor changes distal to anatomic level producing varying degrees of weakness
- urinary and fecal incontinence
- 65-85% of patients with myelomeningocele have hydrocephalus
- most have Type II Chiari malformation (see *Chiari Malformations*, NS36)

Investigations
- plain films, CT, MRI, U/S, echo, GU investigations

Treatment
- surgical closure to preserve neurologic status and prevent CNS infections
- closure *in utero* shown to decrease hydrocephalus and improve post natal motor scores

Prognosis
- operative mortality close to 0%, 95% 2-yr survival
- 80% have IQ >80 (but most are 80-95), 40-85% ambulatory, 3-10% have normal urinary continence
- early mortality usually due to Chiari malformation complications (respiratory arrest and aspiration), whereas late mortality is due to shunt malfunction

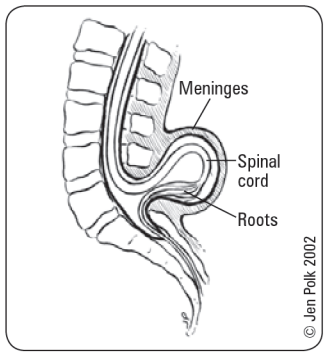


Figure 29. Myelomeningocele

Intraventricular Hemorrhage

- see Pediatrics, P70

Hydrocephalus in Pediatrics

Etiology
- congenital
  - aqueductal anomalies, primary aqueductal stenosis in infancy
  - secondary gliosis due to intrauterine viral infections (mumps, varicella, TORCH)
  - Dandy-Walker malformation (2-4%)
  - Chiari malformation, especially Type II
  - myelomeningocele
- acquired
  - post meningitis
  - post hemorrhage (SAH, IVH)
  - masses (vascular malformation, neoplastic)

Clinical Features
- symptoms and signs of hydrocephalus are age related in pediatrics
- increased head circumference (HC), bulging anterior fontanelle, widened cranial sutures
- irritability, lethargy, poor feeding, and vomiting
- "cracked pot" sound on cranial percussion
- scalp vein dilation (increased collateral venous drainage)
- sunset sign – forced downward deviation of eyes
- episodic bradycardia and apnea

www.regentstudies.com

Investigations
- skull x-ray, U/S, CT, MRI, ICP monitoring

Treatment
- similar to adults (see *Hydrocephalus*, NS7)

Dandy-Walker Malformation

Definition
- atresia of foramina of Magendie and Luschka, resulting in:
  - complete or incomplete agenesis of the cerebellar vermis with widely separated, hypoplastic cerebellar hemispheres
  - posterior fossa cyst, enlarged posterior fossa
  - dilatation of 4th ventricle (also 3rd and lateral ventricles)
- associated anomalies
  - hydrocephalus (90%)
  - agenesis of corpus callosum (17%)
  - occipital encephalocele (7%)

Epidemiology
- 2-4% of pediatric hydrocephalus

Clinical Features
- 20% are asymptomatic, seizures occur in 15%
- symptoms and signs of hydrocephalus combined with a prominent occiput in infancy
- ataxia, spasticity, poor fine motor control common in childhood

Investigations
- ultrasound, CT, MRI

Treatment
- asymptomatic patients require no treatment
- associated hydrocephalus requires surgical treatment
  - e.g. ventriculoperitoneal (VP) shunt, cystoperitoneal (CP) shunt, lumboperitoneal (LP) shunt, ventriculoatrial (VA) shunt, lumbar drain

Progosis
- 75-100% survival, 50% have normal IQ

Chiari Malformations

Definition
- malformations at the medullary-spinal junction

Etiology
- unclear, likely maldevelopment/dysgenesis during fetal life

Categories

Table 14. Categories of Chiari Malformations

	Type I	Type II
Definition	Cerebellar tonsils lie below the level of the foramen magnum	Part of cerebellar vermis, medulla, and 4th ventricle extend through the foramen magnum often to midcervical region
Epidemiology	Average age at presentation 15 yr	Present in infancy
Clinical Features	Many are aysmptomatic Pain (69%), weakness (56%), numbness (52%), loss of temperature sensation (40%) Central cord syndrome (65%) Foramen magnum compression syndrome (22%), Cerebellar syndrome (11%), Syringomyelia (50%), Hydrocephalus (10%)	Findings due to brainstem and lower cranial nerve dysfunction Neurogenic dysphagia (69%), apnea (58%), stridor (56%), aspiration (40%), arm weakness (27%), downbeat nystagmus Respiratory arrest is the most common cause of mortality Usually associated with myelomingocele and hydrocephalus
Investigations	MRI	MRI
Treatment	Symptomatic patients (early surgery recommended; <2 yr post symptom onset) → suboccipital craniectomy, duraplasty	Preserved When symptomatic, check the shunt first. Then consider surgical decompression (which does not reverse intrinsic brainstem abnormalities) → cervical laminectomy, duraplasty

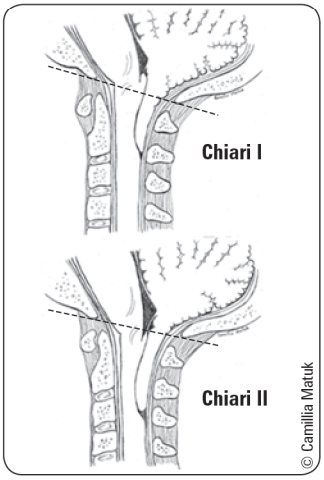


Figure 30. Chiari malformations

www.regentstudies.com

Craniosynostosis

Definition
- premature closure of the cranial suture(s)

Classification
- sagittal (most common): long narrow head with ridging sagittal suture (scaphocephaly)
- coronal: expansion in superior and lateral direction (brachiocephaly)
- metopic (trigonocephaly)
- lambdoid: least common

Epidemiology
- 0.6/1,000 live births, most cases are sporadic; familial incidence is 2% of sagittal and 8% of coronal synostosis

Clinical Features
- skull deformity, raised ICP ± hydrocephalus
- ophthalmologic problems due to increased ICP or bony abnormalities of the orbit
- must differentiate between positional plagiocephaly (secondary to back sleeping)

Investigations
- plain radiographs, CT scan

Treatment
- parental counseling about nature of deformity, associated neurological symptoms
- surgery for cosmetic purposes, except in cases of elevated ICP (≥2 sutures involved)

Pediatric Brain Tumours

- see *Tumours*, NS10

Epidemiology
- 20% of all pediatric cancers (second only to leukemia)
- 60% of pediatric brain tumours are infratentorial
- pediatric brain tumours arise from various cellular lineages
  - glia: low-grade astrocytoma (supra- or infratentorial), anaplastic astrocytoma, glioblastoma multiforme (largely supratentorial) (see *Astrocytoma*, NS12)
  - primitive nerve cells: supratentorial PNET
    - 90% of neonatal brain tumours, infratentorial (medulloblastoma), pineal gland (pineoblastoma)
  - non-neuronal cells: germ cell tumour, craniopharyngioma, dermoid, meningioma, neurinoma (schwanoma), pituitary adenoma, others

Most Common Pediatric Brain Tumors
Astrocytoma, low grade
  Supratentorial
  Infratentorial
Medulloblastoma
Ependymoma
Gliobastoma

Clinical Features
- vomiting, seizure, macrocrania, hydrocephalus
- developmental delay, poor feeding, failure to thrive
- often initially escapes diagnosis due to expansile cranium and neural plasticity in children

Table 15. Overview of Childhood Primary Brain Tumours

Pilocytic (low grade) Astrocytoma	• Usually in posterior fossa • Well circumscribed • Benign, good prognosis
Medulloblastoma	• A primitive neuroectodermal tumour (PNET) • In cerebellum → compresses 4th ventricle → hydrocephalus • Highly malignant
Ependymoma	• In 4th ventricle → hydrocephalus • Poor prognosis
Hemangioblastoma	• Often cerebellar • Associated with von Hippel-Lindau syndrome with retinal angiomas • Can produce EPO → secondary polycythemia
Craniopharyngioma	• Causes bitemporal hemianopsia (thus often confused with pituitary adenoma) • Most common supratentorial childhood tumour • Benign

www.regentstudies.com

Functional Neurosurgery

Movement Disorders

- see Neurology, *Tremor, Parkinson's Disease, Dystonia*, and *Multiple Sclerosis*, N32, N32, N34, N54, respectively

Table 16. Surgical Targets for Movement Disorders

Disorder	Indications	Procedures	Outcomes	Morbidity
Parkinson's Disease	Intractable contralateral bradykinesia/tremor Failure of medical management (advanced disease) Drug-induced dyskinesias (see dystonia, below)	Simultaneous, bilateral surgery/stimulation is most common Preferred target: anterodorsal subthalamic nucleus (STN) Other targets: stereotactic ablation (pallidotomy)/stimulation of posteroventral globus pallidus pars interna (GPi) Caudal zona incerta Parkinsonian tremor: stereotactic ablation (thalamotomy)/stimulation of ventral intermediate (Vim) nucleus of thalamus	39-48% improvement in Unified Parkinson's Disease Rating Scale (UPDRS) scores Reduced dosage of medications (STN) More effective than medical management in advanced PD Early intervention may reduce severity, course, and progression of disease Of little benefit for patients with atypical presentations	Intracerebral hemorrhage, infection, seizure (1%-4%) Paresthesias Involuntary movements Cognitive functioning: decreased lexical fluency, impaired executive function (STN > GPi) Psychiatric: depression, mania, anxiety, apathy (STN > GPi)
Dystonia	Contralateral primary (generalized) dystonias; cervical and tardive dystonias (GPi) Contralateral secondary dyskinesia (i.e. drug-induced: L-dopa, neuroleptics; STN)	Preferred target (primary dystonia): stereotactic ablation (pallidotomy/stimulation of posteroventral GPi Secondary dystonia: stimulation of anterodorsal STN Stimulation of ventral posterior lateral (VPL) thalamic nucleus	Primary dystonia: 51% reduction in Burke-Fahn-Marsden Dystonia Scale (BFMDS) score Secondary dystonia: 62-89% improvement in dystonias Delayed effects: weeks → months	Intracerebral hemorrhage, infection, seizure (1%-4%) Minor effects on cognitive functioning (especially decreased lexical fluency; STN > GPi)
Tremor	Contralateral appendicular ET (first disorder to be treated by DBS; DBS is viable alternative to Rx) Intention tremor (IT) resulting from demyelination of cerebellar outflow tracts (e.g. in multiple sclerosis) Brainstem tremor (Holmes tremor)	Preferred target: stereotactic ablation (thalamotomy)/stimulation of Vim nucleus of thalamus Other targets: stimulation of caudal zona incerta Parkinsonian tremor: stimulation of anterodorsal STN	Durable reductions in essential tremor rating scale (ETRS) scores Reduced dosage of medications Conflicting data on vocal/facial tremor	Intracerebral hemorrhage, infection, seizure (1%-4%) Paresthesias/pain Dysarthria Ataxia Minor effects on cognitive functioning (especially decreased lexical fluency) Tolerance may develop over time

Neuropsychiatric Disorders

- see Neurology, N35 and Psychiatry, PS17, PS9 for *Tourette's Syndrome, Obsessive Compulsive Disorder* and *Depression*

Table 17. Surgical Targets for Neuropsychiatric Disorders

Disorder	Indications	Procedures	Outcomes	Morbidity
Obsessive Compulsive Disorder (OCD)	Severe symptoms refractory to medical management	Anterior capsulotomy/stimulation of the anterior limb of the internal capsule (IC)	Currently under investigation Reportedly 25-75% response rate	Intracerebral hemorrhages (1-2%) Mild effects on cognitive functioning Anxiety ± panic disorder (case report)
Tourette's Syndrome	Severe symptoms refractory to medical management	Stimulation of midline intralaminar nuclei of the thalamus Stimulation of motor and limbic portions of GPi Stimulation of the anterior limb of the IC	Currently under investigation Reportedly >70% reduction in vocal or motor tics + urge	Intracerebral hemorrhages (1-2%) Mild sexual dysfunction
Major Depressive Disorder (MDD)	Severe depression refractory to medical management and ECT	Stimulation of the subgenual cingulate cortex	Currently under investigation Reportedly 60% response rate; 35% remission rate	Intracerebral hemorrhages (1-2%) Pain, H/A Worsening mood, irritability

www.regentstudies.com

Chronic Pain

Table 18. Surgical Targets for Chronic Pain

Disorder	Indications	Procedures	Outcomes	Morbidity
Neuropathic Pain	Severe, intractable, organic neuropathic pain (e.g. post-stroke pain, phantom limb pain, trigeminal neuralgia, chronic low-back pain, complex regional pain syndrome)	Preferred target: stimulation of the contralateral VPL VPM thalamic nuclei ± periventricular/ periaqueductal grey matter (PVG/PAG) Other targets: stimulation of the contralateral IC Stimulation of the contralateral motor cortex	47% improvement in perception of pain intensity Less favourable results in central pain syndromes and poorly localized pain	Intracerebral hemorrhages (1-2%) Paresthesia Anxiety ± panic disorder
Nociceptive Pain	Severe, intractable, organic nociceptive pain	Bilateral (most common) stimulation of the PVG/PAG	Reportedly 63% improvement in perception of pain intensity	Intracerebral hemorrhages (1-2%) Paresthesia Anxiety ± panic disorder

Surgical Management of Epilepsy

- see Neurology, N18 for the medical treatment of epilepsy

Indications
- medically refractory seizures, usually defined as seizures resistant to two first line anti-seizure medications used in succession
- identification of a distinct epileptogenic region through clinical history, EEG, MRI, and neuropsychological testing; other localizing investigations include magnetoencephalography, SPECT, and PET
- if a distinct epileptogenic region cannot be identified, the patient may be a candidate for a palliative procedure such as corpus callosotomy

Procedure
- adults: resection of the hippocampus and parahippocampal gyrus for mesial temporal lobe epilepsy arising from mesial temporal sclerosis
- children: resection of an epileptogenic space-occupying lesion
- hemispherectomy and corpus callosotomy are less common

Outcomes
- 41-79% of adult patients are seizure free for 5 yr after temporal lobe resection
- 58-78% of children are seizure free after surgery
- surgery is associated with improvements in preexisting psychiatric conditions such as depression and anxiety, as well as improvement in quality of life measures

Morbidity
- 0.4-4% of surgical patients will have partial hemianopsia, aphasia, motor deficit, sensory deficit, or cranial nerve palsy following anteromedial temporal lobectomies
- most patients will have some decline in verbal memory following dominant temporal lobectomy and in visuospatial memory in non-dominant temporal resection
- the degree of memory decline stabilizes after 1-2 yr

Predictors
- positive predictive factors for seizure freedom following anteromedial temporal lobectomy
  - hippocampal sclerosis (unilateral)
  - focal localization of interictal epileptiform discharges
  - absence of pre-operative generalized seizures
  - tumoural cause
  - complete resection of the lesion

A Randomized, Controlled Trial of Surgery for Temporal Lobe Epilepsy
NEJM 2001;345:311-318
Introduction: This RCT evaluates the efficacy and safety of neurosurgery for temporal lobe epilepsy.
Methods: 80 patients with poorly controlled temporal lobe epilepsy were randomized for surgery (n=40) or for continued treatment with antiepileptic drugs (n=40). The primary outcome was freedom from seizures that impair awareness of self and surroundings during the period of 1 yr. Secondary outcomes included frequency and severity of seizures, quality of life, disability and death.
Results: The surgical group had higher cumulative proportion of patients without seizures impairing awareness compared to the medical group ($p<0.01$). The surgical group also had lower seizure frequency ($p<0.001$) and better quality of life ($p<0.001$). 4 patients in the surgical group had adverse effects (thalamic infarct, n=1; wound infection, n=1; verbal memory decline impairment occupation, n=2). One patient in the medical group died; no patients died in the surgical group.
Conclusions: In patients with poorly controlled temporal-lobe epilepsy, surgery is superior to prolonged medical therapy.

Surgical Management for Trigeminal Neuralgia

- reserved for cases refractory to medical management; see Neurology, N44 for medical management

Surgical Options
- trigeminal nerve branch procedures
  - local blocks (phenol, alcohol)
  - neurectomy of the trigeminal branch

www.regentstudies.com

- nerve branches
  - V_1 block at the supraorbital, supratrochlear nerves
  - V_2 block at the foramen rotundum or infraorbital nerves
  - V_3 block at the foramen ovale
- percutaneous trigeminal rhizotomy
  - glycerol injection
  - mechanotrauma via catheter balloon
- radiofrequency thermocoagulation
- Gamma Knife® radiosurgery
- microvascular decompression
  - posterior fossa craniotomy with microsurgical exploration of the root entry zone, displacement of the vessel impinging on the nerve with placement of non-absorbable Teflon® felt

References

Adzick N, Thom E, Spong C, et al. A randomized trial of prenatal versus postnatal repair of myelomeningocele. NEJM 2011;364:993-1004.
Ahn NU, Ahn UM, Nallamshetty L, et al. Cauda equina syndrome in ankylosing spondylitis (the CES-AS syndrome): meta-analysis of outcomes after medical and surgical treatments. J Spinal Disord 2001;14:427-433.
Al-Shahi Salman R, Hall JM, Horne MA, et al. Untreated clinical course of cerebral cavernous malformations: a prospective, population-based cohort study. Lancet Neurol 2012;11:217-224.
Asgeir SJ, Kristin SM, Roar K, et al. Comparison of a strategy favouring early surgical resection vs a strategy of watchful waiting in low-grade gliomas. JAMA 2012;308:1881-1888.
Barker FG 2nd, Ogilvy CS. Efficacy of prophylactic nimodipine for delayed ischemic deficit after subarachnoid hemorrhage: a metaanalysis. J Neurosurg 1996;84:405-414.
Barnett H, Taylor W, Eliasziw M, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. NEJM 1998;339:1415-1425.
Bor AS, Rinkel GJ, van Norden J, et al. Long-term, serial screening for intracranial aneurysms in individuals with a family history of aneurysmal subarachnoid haemorrhage: a cohort study. Lancet Neurol 2014;13:385-392.
Bracken MB, Shepard MJ, Holford TR, et al. Methylprednisolone or tirilazad mesylate administration after acute spinal cord injury: 1-year follow up. Results of the third National Acute Spinal Cord Injury randomized controlled trial. J Neurosurg 1998;89:699-706.
Cakir B, Schmidt R, Reichel H, et al. Lumbar disk herniation: what are reliable criterions indicative for surgery? Orthopedics 2009;32:589-597.
Chesnut RM, Temkin N, Carney N, et al. A trial of intracranial-pressure monitoring in traumatic brain injury. NEJM 2012;367:2471-2481.
Chinot OL, Wick W, Mason W, et al. Bevacizumab plus radiotherapy-temozolamide for newly diagnosed glioblastoma. NEJM 2014;370:709-722.
Crossman AR, Neary D. Neuroanatomy: an illustrated colour text. Toronto: Churchill Livingston, 1998.
Dorhout Mees SM, Rinkel GJ, Feigin VL, et al. Calcium antagonists for aneurysmal subarachnoid haemorrhage. Cochrane DB Syst Rev 2007;3:CD000277.
Edlow J, Caplan L. Avoiding pitfalls in the diagnosis of subarachnoid hemorrhage. NEJM 2000;342:29-36.
el Barzouhi A, Vleggeert-Lankamp CL, Lycklama à Nijeholt GJ, et al. Magnetic resonance imaging in follow-up assessment of sciatica. NEJM 2013;368:999-1007.
Executive Committee for the Asymptomatic Carotid Atherosclerosis Study (ACAS). Endarterectomy for asymptomatic carotid artery stenosis. JAMA 1995;273:1421-1428.
Fehlings MG, Tator CH. An evidence-based review of surgical decompression for acute spinal cord injury: rationale, indications, and timing based on experimental and clinical studies. J Neurosurg 1999;91(1 Suppl):1-11.
Fehlings MG, Vaccaro A, Wilson JR, et al. Early versus delayed decompression for traumatic cervical spinal cord injury: results of the surgical timing in acute spinal cord injury dtudy (STASCIS). PLoS ONE 2012;7:e32037. doi:10.1371/journal.pone.0032037.
Fitzgerald MJT. Neuroanatomy: basic and clinical, 3rd ed. Philadelphia: WB Saunders, 1997.
Goetz CG, Pappert EJ. Textbook of clinical neurology, 1st ed. Toronto: WB Saunders, 1999.
Greenberg MS. Handbook of neurosurgery, 7th ed. New York: Thieme Medical Publishers, 2010. Greving JP, Wermer MJ, Brown RD Jr, et al. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. Lancet Neurol 2014;13:59-66.
Hurlbert RJ, Hadley MN, Walters BC, et al. Pharmacological therapy for acute spinal cord injury. Neurosurgery 2013;72(Suppl 2):93-105.
International Study of Unruptured Intracranial Aneurysms Investigators. Unruptured intracranial aneurysms – risk of rupture and risks of surgical intervention. NEJM 1998;339:1725-1733.
Juttler E, Unterberg A, Woitzik J, et al. Hemicraniectomy in older patients with extensive middle-cerebral-artery stroke. NEJM 2014;370:1091-1100.
Kitchen N, McKhann II GM, Manji H. Clinical neurology and neurosurgery. Thieme Medical Publishers, 2003.
Kun LE. Brain tumours: challenges and directions. Pediat Clin N Am 1997;44:907-917.
Lindsay KW, Bone I. Neurology and neurosurgery illustrated. New York: Churchill Livingstone, 2004.
Mark DG, Hung YY, Offerman SR, et al. Nontraumatic subarachnoid hemorrhage in the setting of negative cranial computed tomography results: external validation of a clinical and imaging prediction rule. Ann Emerg Med 2012;pii:S0196-0644:1508-1509.
Molyneux AJ, Kerr RS, Birks J, et al. Risk of recurrent subarachnoid haemorrhage, death, or dependence and standardised mortality ratios after clipping or coiling of an intracranial aneurysm in the International Subarachnoid Aneurysm Trial (ISAT): long-term follow-up. Lancet Neurol 2009;8:427-433.
MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomized controlled trial. Lancet 2004;363:1491-1502.
Nieuwenhuys R, Voogd J, van Huijzen C. The human central nervous system, 3rd ed. New York: Springer-Verlag, 1988.
Ogilvy CS, Stieg PE, Awad I, et al. Recommendations for the management of intracranial arteriovenous malformations. Circulation 2001;103:2644-2657.
Panczkowski DM, Tomycz ND, Okonkwo DO. Comparative effectiveness of using computed tomography alone to exclude cervical spine injuries in obtunded or intubated patients: meta-analysis of 14,327 patients with blunt trauma. J Neurosurg 2011;115:541-549.
Portenoy RK, Lipton RB, Foley KM. Back pain in the cancer patient: an algorithm for evaluation and management. Neurology 1987;37:134-138.
Porter PJ, Willinsky RA, Harper W, et al. Cerebral cavernous malformations: natural history and prognosis after clinical deterioration with or without hemorrhage. J Neurosurg 1997;87:190-197.
Ross J, Al-Shahi Salman R. Interventions for treating brain arteriovenous malformations in adults. Cochrane DB Syst Rev 2010;7:CD003436.
Saal JS, Saal JA, Yurth EF. Nonoperative management of herniated cervical intervertebral disc with radiculopathy. Spine 1996;21:1877-1883.
Santarius T, Kirkpatrick PJ, Ganesan D, et al. Use of drains versus no drains after burr-hole evacuation of chronic subdural haematoma: a randomised control trial. Lancet 2009;374:1067-1073.
Sayer FT, Kronvall E, Nilsson OG. Methylprednisolone treatment in acute spinal cord injury: the myth challenged through a structured analysis of published literature. Spine 2006;6:335-343.
Shapiro S. Medical realities of cauda equina syndrome secondary to lumbar disc herniation. Spine 2000;25:348-351.
Shemie S, Doig C, Dickens B, et al. Severe brain injury to neurological determination of death: Canadian forum recommendations. CMAJ 2006;174:S1-30.
Spencer S, Huh L. Outcomes of epilepsy surgery in adults and children. Lancet Neurol 2008;7:525-37.
Spetzler RF, Martin NA. A proposed grading system for arteriovenous malformations. J Neurosurg 1986;65:476-83.
Stiell IG, Wells GA, Vandemheen K, et al. The Canadian CT head rule for patients with minor head injury. Lancet 2001;357:1391-1396.
The North American Symptomatic Carotid Endarterectomy Trial (NASCET). Beneficial effects of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. NEJM 1991;325:445-453.
Tsao MN, Rades D, Wirth A, et al. Radiotherapeutic and surgical management for newly diagnosed brain metastasis(es): an American radiation oncology evidence-based guideline. Pract Radiat Oncol 2012;2:210-225.
Vaccaro AR, Lehman RA, Hurlbert RJ, et al. A new classification of thoracolumbar injuries: The importance of injury morphology, the integrity of the posterior ligamentous complex, and neurological status. Spine 2005; 30: 2325-2333.
Walton JGR, Hutchinson M, McArdle MJF, et al. Aids to the examination of the peripheral nervous system. London: Bailliere Tindall, 1986.
Wiebe S, Blume WT, Girvin JP, et al. Effectiveness and efficiency of surgery for temporal lobe epilepsy study group. A randomized, controlled trial of surgery for temporal-lobe epilepsy. NEJM 2001;345:311-318.

www.regentstudies.com

OP Ophthalmology

Thomas A. Berk and **Carl Shen,** chapter editors
Hasaan Chaudhry and **Nardin Samuel,** associate editors
Alex Cressman and **Shany Gertzbein,** EBM editors
Dr. Iqbal K. Ahmed, Dr. Wai-Ching Lam, and **Dr. Marisa Sit,** staff editors

www.regentstudies.com

Acronyms

AION	anterior ischemic optic neuropathy	GCA	giant cell arteritis	POAG	primary open-angle glaucoma
AMD	age-related macular degeneration	HRT	Heidelberg retinal tomography	PRK	photorefractive keratectomy
BCVA	best corrected visual acuity	INO	internuclear ophthalmoplegia	PVD	posterior vitreous detachment
BRAO	branch retinal artery occlusion	IOL	intraocular lens	RA	rheumatoid arthritis
BRVO	branch retinal vein occlusion	IOP	intraocular pressure	RAPD	relative afferent pupillary defect
C:D	cup to disc ratio	LASIK	laser-assisted in situ keratomileusis	RD	retinal detachment
CMV	cytomegalovirus	MS	multiple sclerosis	ROP	retinopathy of prematurity
CRAO	central retinal artery occlusion	OCT	optical coherence tomography	RPE	retinal pigment epithelium
D	diopter	OHT	ocular hypertension	SLE	systemic lupus erythematosus
DM	diabetes mellitus	PACG	primary angle-closure glaucoma	SPK	superficial punctate keratitis
DR	diabetic retinopathy	PDR	proliferative diabetic retinopathy	TIA	transient ischemic attack
EOM	extraocular movement	PDT	photodynamic therapy	VEGF	vascular endothelial growth factor
FML	fluorometholone	PERRLA	pupils equal, round, and reactive to light and accommodation	YAG	yttrium aluminium garnet
GAT	Goldmann applanation tonometry				

Basic Anatomy Review

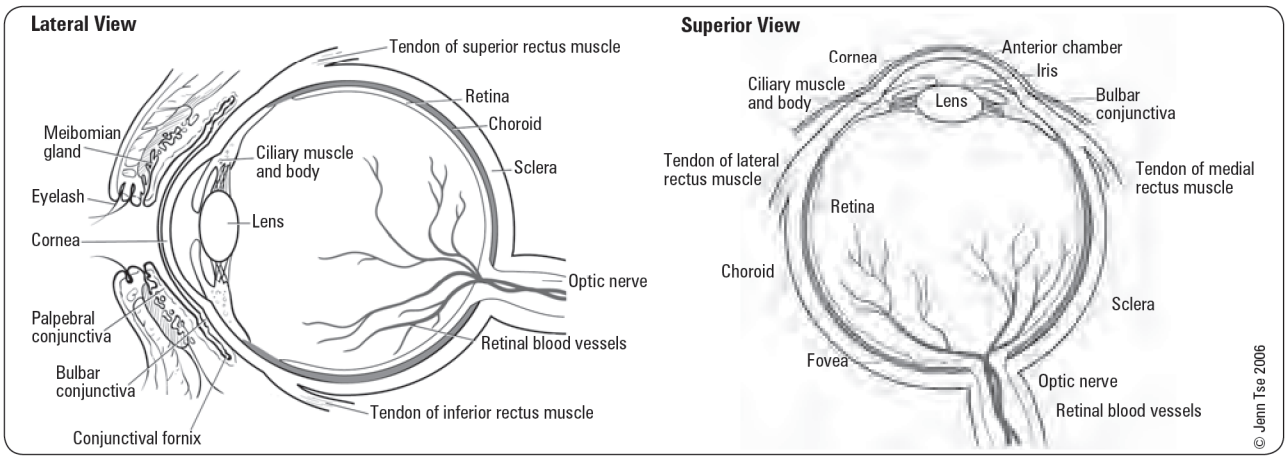


Figure 1. Anatomy of the eye

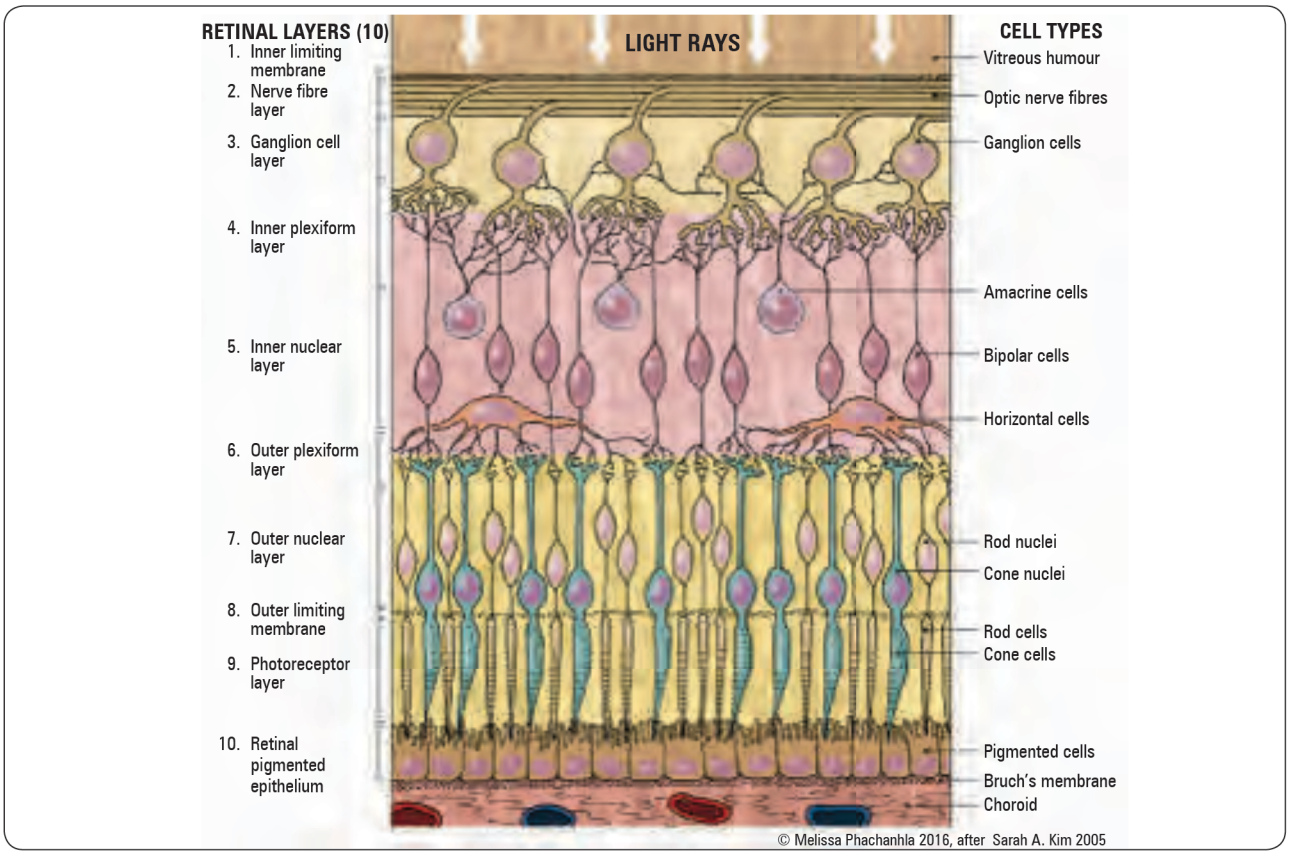


Figure 2. Layers of the retina

www.regentstudies.com

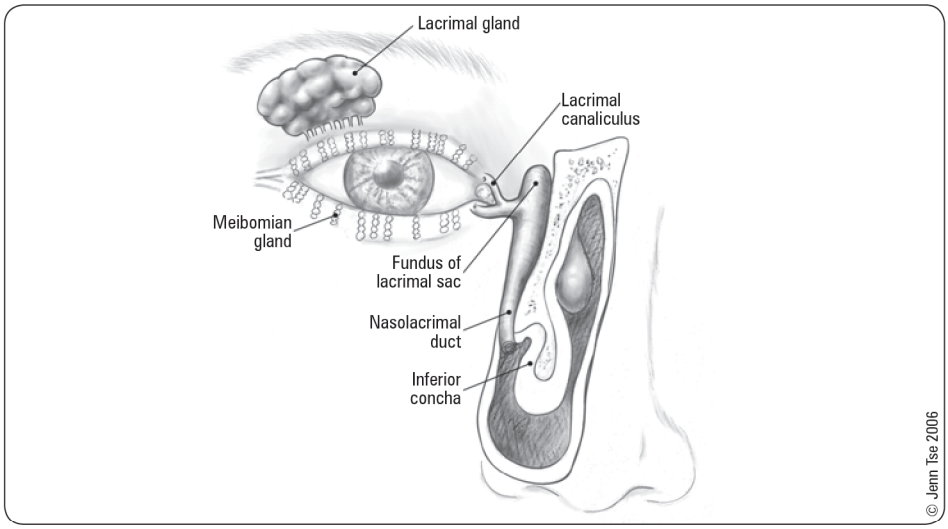


Figure 3. Tear drainage from the eye (lacrimal apparatus)

Differential Diagnoses of Common Presentations

Loss of Vision

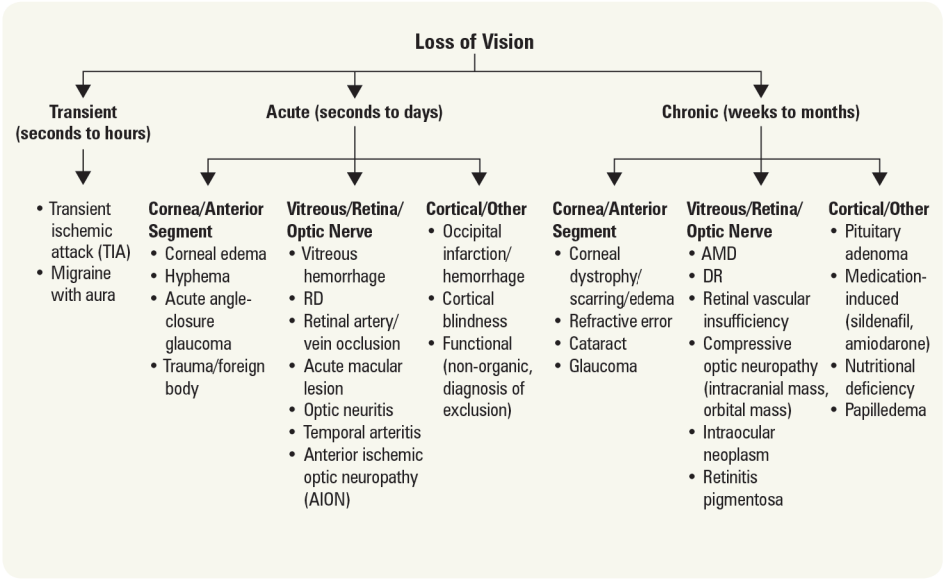


Figure 4. Loss of vision

Top 3 Differential Diagnosis of Acute Loss of Vision
- Vitreous hemorrhage
- Retinal artery/vein occlusion
- RD

Top 3 Differential Diagnosis of Chronic Loss of Vision

Reversible
- Cataract
- Refractive error
- Corneal dystrophy

Irreversible
- AMD
- Glaucoma
- DR

Note: Anti-VEGF treatment for exudative AMD and diabetic macular edema may reverse some vision loss

www.regentstudies.com

Red Eye

- lids/orbit/lacrimal system
  - hordeolum/chalazion
  - blepharitis
  - entropion/ectropion
  - foreign body/laceration
  - dacryocystitis/dacryoadenitis
- conjunctiva/sclera
  - subconjunctival hemorrhage
  - conjunctivitis
  - dry eyes
  - pterygium
  - episcleritis/scleritis
  - preseptal/orbital cellulitis
- cornea
  - foreign body (including contact lens)
  - keratitis
  - abrasion, laceration
  - ulcer
- anterior chamber
  - anterior uveitis (iritis, iridocyclitis)
  - acute glaucoma
  - hyphema (blood in anterior chamber)
  - hypopyon (pus in anterior chamber)

other
  - trauma
  - post-operative
  - endophthalmitis
  - pharmacologic (e.g. prostaglandin analogs)

Ocular Pain

- differentiate from eye fatigue (asthenopia)
- ocular surface disease
- herpes zoster prodrome
- trauma/foreign body
- blepharitis
- keratitis
- corneal abrasion, corneal ulcer
- acute glaucoma
- acute uveitis
- scleritis (rarely episcleritis)
- optic neuritis

Floaters

- PVD (often secondary to age-related vitreous syneresis)
- vitreous hemorrhage
- retinal tear/detachment
- intermediate uveitis (pars planitis)
- posterior uveitis (chorioretinitis)

Flashes of Light (Photopsia)

- PVD (often secondary to age-related vitreous syneresis)
- retinal tear/detachment
- migraine with aura

Photophobia (Severe Light Sensitivity)

- corneal abrasion, corneal ulcer
- keratitis
- acute angle-closure glaucoma
- iritis
- meningitis, encephalitis
- migraine
- subarachnoid hemorrhage (SAH)

Diplopia (Double Vision)

- binocular diplopia (occurs with both eyes open, eliminated with occlusion of either eye)
  - strabismus
  - CN palsy (III, IV, VI)
    - ischemia (DM)
    - tumour
    - trauma
  - myasthenia gravis
  - muscle restriction/entrapment
  - thyroid ophthalmopathy
  - INO
    - multiple sclerosis
    - brainstem infarct
- monocular diplopia (occurs with one eye open, remains with occlusion of unaffected eye)
  - refractive error
  - strands of mucus in tear film
  - keratoconus
  - cataracts
  - dislocated lens
  - peripheral laser iridotomy

Ocular Problems in the Contact Lens Wearer

- SPK from dry eyes
- solution hypersensitivity
- tight lens syndrome
- corneal abrasion
- giant papillary conjunctivitis/contact lens allergy
- limbal stem cell deficiency
- corneal neovascularization
- sterile corneal infiltrates (immunologic)
- infected ulcers (*Pseudomonas, Acanthamoeba*)

Acute Painless Vision Loss

- vitreous hemorrhage
- retinal artery/vein occlusion
- RD
- AION
- optic neuritis
- amaurosis fugax/TIA/stroke

www.regentstudies.com

Table 1. Common Differential Diagnoses of Red Eye

	Conjunctivitis	Acute Iritis	Acute Glaucoma	Keratitis (Corneal Abrasion/ Ulcer)
Discharge	Bacterial: purulent Viral: serous/mucoid Allergic: mucous	No	No	Profuse tearing
Pain	No	++ (tender globe)	+++ (nausea)	++ (on blinking)
Photophobia	No	+++	+	++
Blurred Vision	No	++	+++	Varies
Pupil	Normal	Smaller	Fixed in mid-dilation	Same or smaller
Injection	Conjunctiva with limbal pallor	Ciliary flush	Diffuse	Diffuse
Cornea	Normal	Keratic precipitates	Cloudy	Infiltrate, edema, epithelial defects
IOP	Normal	Varies	Increased markedly	Normal or increased
Anterior Chamber	Normal	+++ Cells and flare	Shallow	Cells and flare or normal
Other	Large, tender pre-auricular node(s) if viral	Posterior synechiae	Coloured halos Nausea and vomiting	

Not every red eye has conjunctivitis

Ocular Emergencies

These require urgent consultation to an ophthalmologist for management

Sight Threatening

- lid/globe lacerations
- chemical burn
- corneal ulcer
- gonococcal conjunctivitis
- acute iritis
- acute glaucoma
- CRAO
- intraocular foreign body
- RD (especially when macula threatened)
- endophthalmitis
- GCA

Life Threatening

- proptosis (rule out cavernous sinus fistula or thrombosis)
- CN III palsy with dilated pupil (intracranial aneurysm or externally compressive neoplastic lesion)
- papilledema (elevated increased intracranial pressure work up)
- orbital cellulitis
- leukocoria: white reflex (absent red reflex, must rule out retinoblastoma)

The Ocular Examination

Visual Acuity – Distance

- Snellen Acuity (Figure 5) = $\frac{\text{testing distance (usually 20 ft or 6 m)}}{\text{smallest line patient can read on the chart}}$
  - e.g. 20/40 = what the patient can see at 20 feet (numerator), what a "normal" person can see at 40 feet (denominator)
- distance visual acuity should be tested with distance glasses on in order to obtain best corrected visual acuity
- testing hierarchy for low vision: Snellen acuity (20/x) → counting fingers at a given distance (CF) → hand motion (HM) → light perception with projection (LP with projection) → light perception (LP) → no light perception (NLP)
- legal blindness is BCVA that is ≤20/200 in best eye
- minimum visual requirements to operate a non-commercial automobile in Ontario are: 20/50 BCVA with both eyes open and examined together, 120° continuous horizontal visual field, and 15° continuous visual field above and below fixation

Example 1

$\overline{SC}$ V 20/40 −1
20/80 +2 → 20/25 PH

Example 2

$\overline{CC}$ V CF 3'
HM

Note: RIGHT EYE visual acuity always listed on top.

V	Vision
SC	Without correction
CC	With correction
20/40 -1	All except one letter of 20/40
20/80+2	All of 20/80 plus two letters of 20/70
PH	Visual acuity with pinhole correction
CF	Counting fingers
HM	Hand motion

Figure 5. Ophthalmology nomenclature for VA

OD = oculus dexter = right eye
OS = oculus sinister = left eye
OU = oculus uterque = both eyes

Snellen visual acuity of 20/20 equates to "normal" vision

Normal Infant and Child Visual Acuity
- 6-12 mo: 20/120
- 1-2 yr: 20/80
- 2-4 yr: 20/20

www.regentstudies.com

Visual Acuity – Near
- use pocket vision chart (Rosenbaum Pocket Vision Screener)
- record Jaeger (J) or Point number and testing distance (usually 30 cm) e.g. J2 @ 30 cm
- conversion to distance VA possible (e.g. immobile patient, no distance chart available)

Visual Acuity for Infants, Children, Non-English Speakers, and Dysphasics
- newborns
  - VA cannot be tested
- 3 mo-3 yr (can only assess visual function, not acuity)
  - test each eye for fixation symmetry using an interesting object
  - normal function noted as "CSM" = central, steady, and maintained
- 3 yr until alphabet known
  - pictures or letter cards/charts such as HOTV or Sheridan-Gardner test (children point to optotypes on a provided matching card)
  - tumbling "E" chart

Colour Vision
- test with Ishihara pseudoisochromatic plates
- record number of correctly identified plates presented to each eye, specify incorrect plates
- important for testing optic nerve function (e.g. optic neuritis, chloroquine use, thyroid ophthalmopathy)
- note: red-green colour blindness is sex-linked and occurs in 7-10% of males

VISUAL FIELDS
- test "visual fields by confrontation" (4 quadrants, each eye tested separately) for estimation of visual field loss
- accurate, quantifiable assessment with automated visual field testing (Humphrey or Goldmann) or Tangent Screen
- use Amsler grid (each eye tested separately) to check for central or paracentral scotomas (island-like gaps in the vision) in patients with AMD

PUPILS
- use reduced room illumination with patient focusing on distant fixed object to prevent "near reflex"
- examine pupils for shape, size, symmetry, and reactivity to light (both direct and consensual response)
- test for RAPD with swinging flashlight test, check by reverse RAPD if one pupil non-reactive
- test pupillary constriction portion of near reflex by bringing object close to patient's nose
- "normal" pupil testing often noted as PERRLA (pupils equal, round, and reactive to light and accommodation)

ANTERIOR CHAMBER DEPTH
- shine light tangentially from temporal side
- if >2/3 of nasal side of iris in shadow → shallow anterior chamber

The van Herick Method
- shine thin-angled slit beam onto the peripheral cornea of each eye, view at a 60° angle from the beam
- estimate depth between the posterior surface of the cornea and the iris as a proportion of corneal thickness
- ratios ≤1/4 implies risk of occludable angle; however, if >1/4 this does not rule out. Gonioscopy is gold-standard

Gonioscopy
- allows direct visualization of the angle structures using mirrored contact lens
- angle considered open if trabecular meshwork, scleral spur, and iris processes are visualized
- angle considered narrow (occludable) if only Schwalbe's line (the termination of Descemet's membrane) or a small portion of the trabecular meshwork is seen
- angle considered open if scleral spur seen (insertion point of ciliary body muscles)

For patients with dark irides, test pupils using an ophthalmoscope focused on the red reflex; this will provide a better view than using a penlight

Ocular Changes for Near Fixation
- Eye convergence
- Pupil constriction
- Lens accommodation

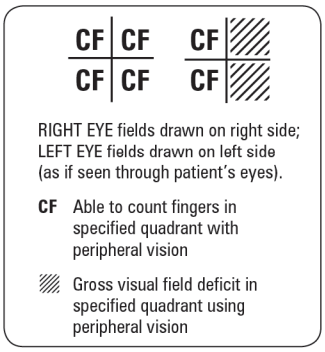


Figure 6. Ophthalmology nomenclature for visual fields by confrontation

4 Ps of Inspection

Pupil: shape, size, symmetry
Position: esotropia, exotropia, central
Ptosis
Primary nystagmus

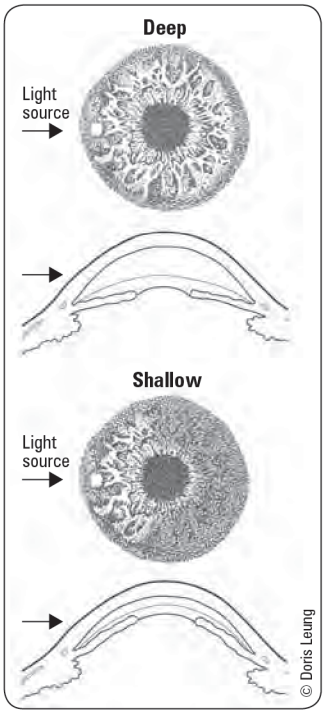


Figure 7. Estimation of anterior chamber depth

www.regentstudies.com

EXTRAOCULAR MUSCLES

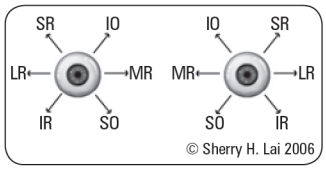


Figure 8. Diagnostic positions of gaze for isolated primary actions of extraocular muscles

Alignment

- Hirschberg corneal reflex test
  - examine in primary position of gaze (i.e. straight ahead) with patient focusing on distant object
  - shine light into patient's eyes from ~30 cm away
  - corneal light reflex should be symmetric and at the same position on each cornea
- strabismus testing as indicated (cover test, cover-uncover test, prism testing) (see *Strabismus*, OP38)

Movement

- examine movement of eyeball through six cardinal positions of gaze
- ask patient if diplopia or pain is present in any position of gaze
- observe for horizontal, vertical, or rotatory nystagmus (rhythmic, oscillating movements of the eye)
- resolving horizontal nystagmus at end-gaze is usually normal
- see sidebar for cranial nerve innervation of extraocular muscles

Extraocular Muscle Innervations

LR6 SO4 AE3
Lateral **R**ectus via CN **VI**
Superior **O**blique via CN **IV**
All **E**lse via CN **III** (superior, medial, and inferior rectus, inferior oblique)

Diplopia

- major symptom associated with dysfunction of extraocular muscles or abnormalities of the motor nerves innervating these muscles
- must first determine whether diplopia is monocular or binocular
- determine whether diplopia was sudden onset (due to an acute event such as ischemia) or gradual (due to progressive process such as tumour or inflammation)
- with myasthenia gravis, diplopia and ptosis usually worsen on prolonged upgaze; can rule out with a Tensilon® test (see Neurology, N40)
- if suspect compressive lesion (most commonly seen with CN III palsy with a blown pupil), need MRI and angiography to rule out aneurysm or tumour
- new-onset diplopia that disappears with occlusion of either eye (binocular diplopia) needs urgent referral while chronic binocular diplopia and monocular diplopia should be referred non-urgently

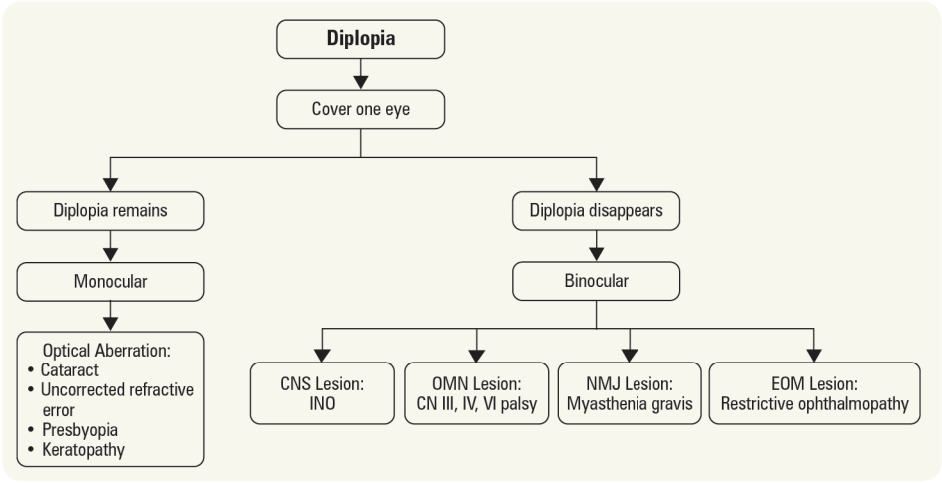


Figure 9. Diplopia

Aqueous Flare
- Resembles dust particles in a beam of light
- Results from protein leaking from blood vessels
- Distinguish from aqueous cells (individual cells in anterior chamber)

EXTERNAL EXAMINATION

- four Ls
  - lymph nodes (preauricular, submandibular)
  - lids
  - lashes
  - lacrimal system

www.regentstudies.com

SLIT-LAMP EXAMINATION
- systematically examine all structures of the anterior segment and anterior vitreous (for structures see Figure 1)
- when necessary, use:
  - fluorescein dye: stains Bowman's membrane in de-epithelialized cornea; dye appears fluorescent green with cobalt blue filtered light
  - Rose Bengal dye: stains devitalized corneal epithelium
- special lenses (78 or 90 D) used with the slit-lamp allow a binocular, stereoscopic, inverted and flipped view of the fundus and vitreous

TONOMETRY
- measurement of IOP
- normal range is 9-21 mmHg (average 15 mmHg)
- IOP has diurnal variation, so always record the time of day at which the measurement was taken
- commonly measured by:
  - Goldmann Applanation Tonometry (GAT): clinical gold standard, performed using the slit-lamp with special tip (prism)
  - Tono-Pen®: benefit is portability and use of disposable probe tips. Use when cornea is scarred/asymmetric (GAT inaccurate)
  - air puff (non-contact and least reliable)
- use topical anesthetic for GAT and Tono-Pen®; apply fluorescein dye when using GAT

OPHTHALMOSCOPY/FUNDOSCOPY
- performed with
  - direct ophthalmoscope (monocular with small field of view, only posterior pole visualized)
  - slit-lamp with 78 or 90 D lens (binocular view, visualization to mid-periphery of retina)
  - indirect ophthalmoscopy with headlamp and 20 or 28 D lens (binocular view, visualization of entire retina to ora serrata/edge of retina)
- best performed with pupils dilated (for list of mydriatics and cycloplegics see Table 11, OP45)
  1. assess red reflex
     - light reflected off the retina produces a "red reflex" when viewed from ~1 foot away
     - anything that interferes with the passage of light will diminish the red reflex (e.g. large vitreous hemorrhage, cataract, retinoblastoma)
  2. examine the posterior segment of the eye
     - vitreous
     - optic disc (colour, C:D ratio, sharpness of disc margin)
     - macula (~1.5-2 disc diameters temporal to disc), fovea (foveal light reflex)
     - retinal vessels
     - retinal background
- contraindications to pupillary dilatation
  - shallow anterior chamber – can precipitate acute angle-closure glaucoma
  - iris-supported anterior chamber lens implant
  - potential neurologic abnormality requiring pupil evaluation
  - use caution with cardiovascular disease – mydriatics may cause tachycardia

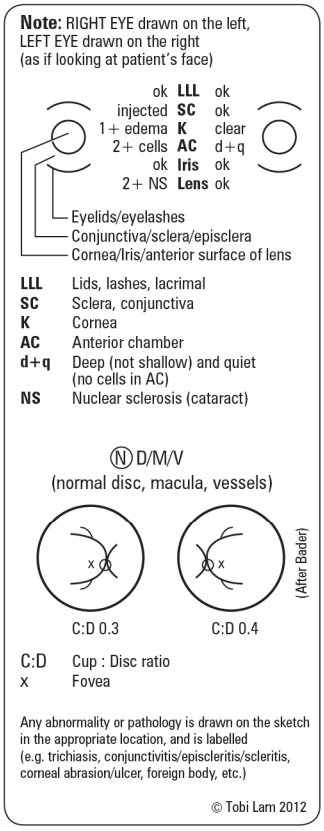


Figure 10. Slit-lamp examination note

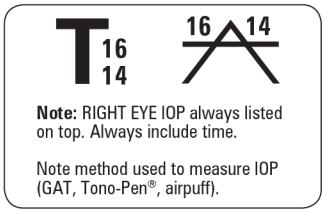


Figure 11. Tonometry

Optics

REFRACTION
- two techniques used
  - flash/streak retinoscopy: refractive error determined objectively by the examiner using lenses and retinoscope
  - manifest: subjective trial using loose lenses or a phoropter (device the patient looks through that is equipped with lenses)
- a typical lens prescription would contain
  - sphere power in D (measurement of refractive power of lens, equal to reciprocal of focal length in meters)
  - cylinder power in D to correct astigmatism (always positive value)
  - axis of cylinder in degrees
  - "add" (bifocal/progressive reading lens) for presbyopes
  - e.g. -1.50 + 1.00 x 120 degrees, add +2.00

REFRACTIVE EYE SURGERY
- permanently alters corneal refractive properties by ablating tissue to change curvature of the cornea
- used for correction of myopia, hyperopia, and astigmatism
- common types include PRK and LASIK (see *Surgical Ophthalmology*, OP44)
- potential risks/side-effects: infection, under/overcorrection, decreased night vision (nyctalopia), corneal haze, dry eyes, regression, complete sever of corneal flap (LASIK only)

Central Corneal Thickness (CCT)
Average CCT = 550 μm
By GAT, IOP is over-estimated with thick corneas and under-estimated with thin corneas

Desired Myers Pattern on GAT

Note: Thick Myers overestimate the IOP and are a result of excess fluorescein

Structures Responsible for Refractive Power
- Cornea (2/3)
- Lens (1/3)

www.regentstudies.com

Table 2. Optics

	Pathophysiology	Clinical Features	Treatment	Complications
Emmetropia	• Image of distant objects focus exactly on the retina	• No refractive error		
Myopia	• Globe too long relative to refractive mechanisms, or refractive mechanisms too strong • Light rays from distant object focus in front of retina → blurring of (distance) vision	• "Nearsightedness" • Usually presents in 1st or 2nd decade, stabilizes in 2nd and 3rd decade; rarely begins after age 25 except in patients with DM or cataracts • Blurring of distance vision; near vision usually unaffected • Prevalence: 30-40% in U.S. population	• Correct with negative diopter/ concave/ "negative" lenses to diverge light rays • Refractive eye surgery	• Retinal tear/ detachment, macular hole, open angle glaucoma • Other complications that are not prevented with refractive correction
Hyperopia	• Globe too short relative to refractive mechanisms, or refractive mechanisms too weak • Light rays from distant object focus behind retina → blurring of near ± distant vision • May be developmental or due to any etiology that shortens globe	• "Farsightedness" • Youth: usually do not require glasses (still have sufficient accommodative ability to focus image on retina), but may develop accommodative esotropia (see *Strabismus*, OP38) • 30s-40s: blurring of near vision due to decreased accommodation, may need reading glasses • >50s: blurring of distance vision due to severely decreased accommodation	• When symptomatic, correct with positive diopter/ convex/"plus" lenses to converge light rays • Refractive eye surgery	• Angle-closure glaucoma, particularly later in life as lens enlarges
Astigmatism	• Light rays not refracted uniformly in all meridians due to non-spherical surface of cornea or non-spherical lens (e.g. football-shaped) • Two types ▪ Regular – curvature uniformly different in meridians at right angles to each other ▪ Irregular – distorted cornea caused by injury, keratoconus (cone-shaped cornea), corneal scar, or severe dry eye	• Affects ~30% of population, with prevalence increasing with age • Mild astigmatism unnoticeable • Higher amounts of astigmatism may cause blurry vision, squinting, asthenopia, or headaches	• Correct with cylindrical lens (if regular), try contact lens (if irregular) • Refractive eye surgery	
Presbyopia	• Normal aging process (>40 yr) • Hardening/reduced deformability of lens results in decreased accommodative ability • Accommodative power is 14D at age 10, diminishes to 3.5D by age 40 yr • Near images cannot be focused onto the retina (focus is behind the retina as in hyperopia)	• If initially emmetropic, person begins to hold reading material farther away, but distance vision remains unaffected • If initially myopic, person removes distance glasses to read • If initially hyperopic, symptoms of presbyopia occur earlier	• Correct with positive diopter/ convex/"plus" lenses for reading	
Anisometropia	• Difference in refractive errors between eyes			• Second most common cause of amblyopia in children

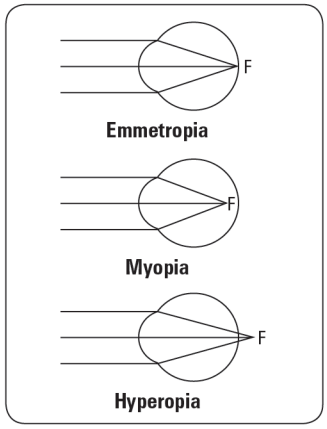


Figure 12. Emmetropia and refractive errors

Myopia

LMN
Long globe
Myopic
Negative correction/**N**earsighted

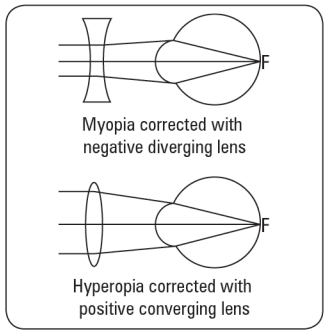


Figure 13. Correction of refractive errors

Imaging Modalities

- **adaptive optics scanning laser ophthalmology – optical coherence tomography (SLO-OCT)**
  - combines the surface detail of confocal ophthalmoscopy with the internal detail of OCT
  - allows 3D OCT images, volume and area maps, and retinal thickness maps, at the resolution of living rods and cones
  - can visualize photoreceptors, nerve fibers and blood cells in retinal capillaries
- **CT, MRI**
  - orbital imaging, particularly in orbital trauma and neuro-ophthalmology
- **fluorescein angiography**
  - non-invasive evaluation of vascular pattern of the fundus
  - wide-field fluorescent angiogram
  - commonly used in AMD, DR, retinal vascular diseases
- **indocyanine green angiography**
  - uses infra-red light and intravenous ICG dye for imaging of choroidal structure
  - particularly useful to detect polypoidal vasculopathy (variant of AMD) more commonly present among Asian patients

www.regentstudies.com

- **HRT**
  - confocal scanning laser tomography of retinal nerve head and surrounding nerve fiber layer
  - used to assess extent of structural glaucomatous changes
- **OCT**
  - non-invasive, cross-sectional, high-resolution imaging of vitreous, retinal layers, optic nerve
  - commonly used to assess macular pathology/edema/holes/cysts, AMD progression, epiretinal membrane, RD
- **anterior segment optical coherence tomography (AS-OCT)**
  - non-invasive, cross-sectional, high-resolution imaging of cornea, aqueous, iris, angle, and lens
- **perimetry**
  - quantitative evaluation of visual fields, used to screen for scotomas and monitor progression (e.g. in glaucoma)
- **ultrasonography**
  - evaluation of orbit in real-time. A-scans (one-dimensional), B-scans (two-dimensional), ultrasound biomicroscopy (UBM) (used for imaging the cornea, iris, angle) and Doppler are all used (e.g. large RDs, foreign bodies, monitoring intraocular tumours)

The Orbit

Globe Displacement

Table 3. Exophthalmos (Proptosis) and Enophthalmos

	Exophthalmos (Proptosis)	Enophthalmos
Definition	• Anterior displacement (protrusion) of the globe ▪ Exophthalmos generally refers to an endocrine etiology or protrusion of >18 mm (as measured by a Hertel exophthalmometer) ▪ Proptosis generally refers to other etiologies (e.g. cellulitis) or protrusion of <18 mm	• Posterior displacement (retraction) of the globe
Investigations	• CT/MRI head/orbits, ultrasound orbits, thyroid function tests	• CT/MRI orbits
Etiology	• Note: rule out pseudoexophthalmos (e.g. lid retraction) • Graves' disease (unilateral or bilateral, most common cause in adults) • Orbital cellulitis (unilateral, most common cause in children) • 1° or 2° orbital tumours • Orbital/retrobulbar hemorrhage • Cavernous sinus thrombosis or fistula	• "Blow-out" fracture (see *Ocular Trauma*, OP42) • Orbital fat atrophy • Congenital abnormality • Metastatic disease

Preseptal Cellulitis

- infection of soft tissue anterior to orbital septum

Etiology

- usually follows periorbital trauma or dermal infection

Clinical Features

Table 4. Clinical Features of Preseptal and Orbital Cellulitis

Finding	Preseptal Cellulitis	Orbital Cellulitis
Fever	May be present	Present
Lid edema	Moderate to severe	Severe
Conjunctival injection	Absent	Present
Chemosis	Absent or mild	Marked
Proptosis	Absent	Present
Pain on eye movement	Absent	Present
Ocular mobility	Normal	Decreased
Vision	Normal	Diminished ± diplopia
RAPD	Absent	May be seen
Leukocytosis	Moderate	Marked
ESR	Normal or elevated	Elevated
Additional findings	Skin infection	Sinusitis, dental abscess

www.regentstudies.com

Treatment
- systemic antibiotics (suspect *H. influenzae* in children; *S. aureus* or *Streptococcus* in adults)
  - e.g. amoxicillin-clavulanic acid
- if severe or child <1 yr, treat as orbital cellulitis

Orbital Cellulitis

- **OCULAR** and **MEDICAL EMERGENCY**
- inflammation of orbital contents posterior to orbital septum
- common in children, elderly, and immunocompromised

Etiology
- usually secondary to sinus/facial/tooth infections or trauma, can also arise from preseptal cellulitis

Clinical Features (see Table 4)

Treatment
- admit, blood cultures x2, orbital CT, IV antibiotics (ceftriaxone + vancomycin) for 1 wk
- surgical drainage of abscess with close follow-up, especially in children

Complications
- optic nerve inflammation, cavernous sinus thrombosis, meningitis, and brain abscess with possible loss of vision, death

Orbital cellulitis is life-threatening if untreated (mortality of 17-20% without antibiotic use); prompt diagnosis and treatment is essential

Role of Oral Corticosteroids in Orbital Cellulitis
Am J Ophthalmol 2013;156:178-183
Purpose: To evaluate the role of oral corticosteroids as an anti-inflammatory adjunct for the treatment of orbital cellulitis.
Study: RCT. Patients with acute onset (within 14 d) of orbital cellulitis with or without abscess. 21 patients total (7 patients in group 1: standard intravenous antibiotics; 14 patients in group 2: adjuvant steroids).
Results: Patients in group 2 showed earlier resolution of periorbital edema, conjunctival chemosis, pain, proptosis, and EOM deficits, including decreased duration of intravenous antibiotics and hospital stay ($p<0.05$ for all).
Conclusion: The use of oral steroids as an adjunct to intravenous antibiotics for orbital cellulitis may decrease inflammatory symptoms with a low risk of worsening infection.

Lacrimal Apparatus

- tear film made up of three layers
  - outer oily layer (reduces evaporation): secreted by the Meibomian glands
  - middle watery layer (forms the bulk of the tear film): constant secretion from conjunctival glands and reflex secretion by lacrimal gland with ocular irritation or emotion
  - inner mucinous layer (aids with tear adherence to cornea): secreted by conjunctival goblet cells
- tears drain from the eyes through the upper and lower lacrimal puncta → superior and inferior canaliculi → lacrimal sac → nasolacrimal duct → nasal cavity behind inferior concha (Figure 3)

Dry Eye Syndrome (Keratoconjunctivitis Sicca)

Etiology
- aqueous-deficient (lacrimal pathology)
  - Sjögren syndrome (autoimmune etiology e.g. RA, SLE)
  - non-Sjögren syndrome (idiopathic age-related disease; lacrimal gland scarring e.g. trachoma; decreased secretion e.g. contact lenses, CN VII palsy, anticholinergics, antihistamines, diuretics, β-blockers)
- evaporative (normal lacrimal function, excessive evaporation of aqueous layer)
  - Meibomian gland dysfunction (posterior blepharitis)
  - vitamin A deficiency (xerophthalmia with goblet cell dysgenesis)
  - eyelid abnormalities e.g. ectropion, CN VII palsy (decreased blinking)
  - preserved topical ocular medications
  - contact lenses, allergic conjunctivitis
- overlap of mixed etiologies is common

Clinical Features
- dry eyes, red eyes, foreign body sensation, blurred vision, tearing
- slit-lamp exam: decreased tear meniscus, decreased tear break-up time (normally should be 10 s), punctate staining of cornea with fluorescein

Investigations
- surface damage observed with fluorescein/Rose Bengal staining
- decreased distance in Schirmer's test

Complications
- erosions and scarring of cornea

Treatment
- medical: preservative-free artificial tears up to q1h and ointment at bedtime (preservative toxicity becomes significant if used >q1h PRN)
  - for severe cases, cyclosporine ophthalmic emulsion 0.05% (Restasis®) can be used
- procedural: punctal occlusion (punctal plug insertion), lid taping, tarsorrhaphy (sew lids together) if severe
- treat underlying cause

Long-term use of artificial tears with preservatives should be avoided when treating dry eyes

www.regentstudies.com

Epiphora (Excessive Tearing)

Etiology
- emotion, pain
- environmental stressor (cold, wind, pollen, sleep deprivation)
- lid/lash malposition: ectropion, entropion, trichiasis
- inflammatory: conjunctivitis, dacryoadenitis, uveitis, keratitis, corneal foreign body
- dry eyes (reflex tearing)
- lacrimal drainage obstruction (congenital failure of canalization, aging, rhinitis, dacryocystitis)
- paradoxical gustatory lacrimation reflex (crocodile tears)

Excessive tearing can be caused by dry eyes – if the tear quality is insufficient, "reflex tearing" may occur

Investigations
- using fluorescein dye, examine for punctal reflux by pressing on canaliculi
- Jones dye test: fluorescein placed in conjunctival cul-de-sac, and cotton applicator placed in nose to detect flow (i.e. rule out lacrimal drainage obstruction)

Treatment
- lid repair for ectropion or entropion
- eyelash removal for trichiasis
- punctal irrigation
- nasolacrimal duct probing (infants)
- tube placement: temporary (Crawford) or permanent (Jones)
- surgical: dacryocystorhinostomy (see *Surgical Ophthalmology*, OP44) – forming a new connection between the lacrimal sac and the nasal cavity

Dacryocystitis

- acute or chronic infection of the lacrimal sac
- most commonly due to obstruction of the nasolacrimal duct
- commonly associated with *S. aureus, S. pneumoniae, Pseudomonas* species

Clinical Features
- pain, swelling, redness over lacrimal sac at medial canthus
- epiphora, crusting, ± fever
- digital pressure on the lacrimal sac may extrude pus through the punctum
- in the chronic form, epiphora may be the only symptom

Treatment
- warm compresses, nasal decongestants, systemic and topical antibiotics
- if chronic, obtain cultures by aspiration
- once infection resolves, consider dacryocystorhinostomy (see *Surgical Ophthalmology*, OP44)

Dacryoadenitis

- inflammation of the lacrimal gland (outer third of upper eyelid)
- acute causes: *S. aureus*, mumps, EBV, herpes zoster, *N. gonorrhoeae*
- chronic causes (often bilateral): lymphoma, leukemia, sarcoidosis, tuberculosis, thyroid ophthalmopathy

Clinical Features
- pain, swelling, tearing, discharge, redness of the outer region of the upper eyelid
- chronic form is more common and may present as painless enlargement of the lacrimal gland

Treatment
- supportive: warm compresses, oral NSAIDs
- systemic antibiotics if bacterial cause
- if chronic, treat underlying disorder

Lids and Lashes

Lid Swelling

Etiology
- commonly due to allergy, with shriveling of skin between episodes
- dependent edema on awakening (e.g. CHF, renal or hepatic failure)
- orbital venous congestion due to mass or cavernous sinus fistula
- dermatochalasis (loose skin due to aging or heredity)
- lid cellulitis, thyroid disease (e.g. myxedema), trauma, chemosis

www.regentstudies.com

Ptosis

- drooping of upper eyelid

Etiology
- aponeurotic: disinsertion or dehiscence of levator aponeurosis (most common)
  - associated with advancing age, trauma, surgery, pregnancy, chronic lid swelling
- mechanical
  - incomplete opening of eyelid due to mass or scarring
- neuromuscular
  - myasthenia gravis (neuromuscular palsy), myotonic dystrophy
  - CN III palsy
  - Horner's syndrome (see *Constricted Pupil*, Horner's Syndrome, OP32)
- congenital
- pseudoptosis (e.g. dermatochalasis, enophthalmos, contralateral exophthalmos)
- drugs (e.g. high dose opioids, heroin abuse, pregabalin)

Treatment
- surgery (e.g. blepharoplasty, levator resection, Müller's muscle resection, frontalis sling)

Trichiasis

- eyelashes turned inwards
- may result from chronic inflammatory lid diseases (e.g. blepharitis), Stevens-Johnson syndrome, trauma, burns
- patient complains of red eye, foreign body sensation, significant discomfort, tearing
- may result in corneal ulceration and scarring

Treatment
- topical lubrication, eyelash plucking, electrolysis, cryotherapy

Entropion

- lid margin turns in towards globe causing tearing, foreign body sensation, and red eye
- most commonly affects lower lid
- may cause corneal abrasions with secondary corneal scarring

Etiology
- involutional (aging)
- cicatricial (herpes zoster, surgery, trauma, burns)
- orbicularis oculi muscle spasm
- congenital

Treatment
- lubricants, evert lid with tape, surgery

Testing for Entropion
Forced lid closure: Ask patient to tighten lid then open. In entropion, lid rolls inwards

Ectropion

- lid margin turns outward from globe causing tearing and possibly exposure keratitis

Etiology
- involutional (aging)
- paralytic (CN VII palsy)
- cicatricial (burns, trauma, surgery)
- mechanical (lid edema, tumour, herniated fat)
- congenital

Treatment
- topical lubrication, surgery

Testing for Ectropion
Snapback test: Pull eyelid inferiorly. In ectropion, lid remains away from globe

Hordeolum (Stye)

- acute inflammation of eyelid gland: either Meibomian glands (internal lid), glands of Zeis (modified sweat gland) or Moll (modified sebaceous gland in external lid)
- infectious agent is usually *S. aureus*
- painful, red swelling of lid

Treatment
- warm compresses, lid care, gentle massage
- topical antibiotics (e.g. erythromycin ointment bid)
- usually resolves in 2-5 d

www.regentstudies.com

Chalazion

- chronic granulomatous inflammation of Meibomian gland often preceded by an internal hordeolum
- acute inflammatory signs are usually absent
- differential diagnosis: basal cell carcinoma, sebaceous cell adenoma, Meibomian gland carcinoma

Hordeolum vs. Chalazion
Hordeolums are due to an infectious etiology, whereas chalazions are granulomatous inflammation

Treatment
- warm compresses
- if no improvement after 1 mo, consider incision and curettage
- chronic recurrent lesion must be biopsied to rule out malignancy

Blepharitis

- inflammation of lid margins

Etiology
- two main types
  - staphylococcal (*S. aureus*): ulcerative, dry scales
  - seborrheic: no ulcers, greasy scales

Clinical Features
- itching, tearing, foreign body sensation
- thickened, red lid margins, crusting, discharge with pressure on lids ("toothpaste sign")

Complications
- recurrent chalazia
- conjunctivitis
- keratitis (from poor tear film)
- corneal ulceration and neovascularization

Treatment
- warm compresses and lid scrubs with diluted "baby shampoo"
- topical or systemic antibiotics as needed
- if severe, ophthalmologist may prescribe a short course of topical corticosteroids, omega 3 fatty acids

Xanthelasma

- eyelid xanthoma (lipid deposits in dermis of lids)
- appear as pale, slightly elevated yellowish plaques or streaks
- most commonly on the medial upper lids, often bilateral
- associated with hyperlipidemia (~50% of patients)
- common in the elderly, more concerning in the young

Treatment
- excision for cosmesis only, commonly recurs

Conjunctiva

- thin, vascular mucous membrane/epithelium
- bulbar conjunctiva: lines sclera to limbus (junction between cornea and sclera)
- palpebral (tarsal) conjunctiva: lines inner surface of eyelid

Pinguecula

- yellow-white subepithelial deposit of hyaline and elastic tissue adjacent to the nasal or temporal limbus, sparing the cornea
- associated with sun and wind exposure, aging
- common, benign, sometimes enlarges slowly
- may be irritating due to abnormal tear film formation over the deposits
- surgery for cosmesis only
- irritative symptoms may be treated with lubricating drops

www.regentstudies.com

Pterygium

- fibrovascular, triangular, wing-like encroachment of epithelial tissue onto the cornea, usually nasally
- may induce astigmatism, decrease vision
- excision for chronic inflammation, threat to visual axis, cosmesis
- irritative symptoms may be treated with lubricating drops
- one-third recur after excision, lower recurrence with conjunctival autograft (5%)

Subconjunctival Hemorrhage

- blood beneath the conjunctiva, otherwise asymptomatic
- idiopathic or associated with trauma, Valsalva maneuver, bleeding disorders, HTN, anticoagulation
- give reassurance if no other ocular findings, resolves spontaneously in 2-3 wk
- if recurrent, consider medical/hematologic workup

Conjunctivitis

Etiology

- infectious
  - bacterial, viral, chlamydial, gonococcal, fungal, parasitic
- non-infectious
  - allergic: atopic, seasonal, giant papillary conjunctivitis (contact lens wearers)
  - toxic: irritants, dust, smoke, irradiation
  - secondary to another disorder: dacryocystitis, dacryoadenitis, cellulitis, systemic inflammatory disease

Types of Discharge
- Allergic: mucoid
- Viral: watery
- Bacterial: purulent
- Chlamydial: mucopurulent

Clinical Features

- red eye (conjunctival injection often with limbal pallor), chemosis, subepithelial infiltrates
- itching, foreign body sensation, tearing, discharge, crusting of lashes in the morning, lid edema
- preauricular and/or submandibular nodes
- follicles: pale lymphoid elevations of the conjunctiva, overlain by vessels
- papillae: fibrovascular elevations of the conjunctiva with central network of finely branching vessels (cobblestone appearance)

- Enlarged lymph nodes suggest infectious etiology, especially viral or chlamydial conjunctivitis
- Temporal conjunctival lymphatics drain to preauricular nodes, and nasal to submandibular nodes

ALLERGIC CONJUNCTIVITIS

Atopic

- associated with rhinitis, asthma, dermatitis, hay fever
- small papillae, chemosis, thickened and erythematous lids, corneal neovascularization
- seasonal (pollen, grasses, plant allergens)
- treatment: cool compresses, antihistamine, mast cell stabilizer (e.g. ketotifen, olopatadine), topical corticosteroids

- Follicles are usually seen in viral and chlamydial conjunctivitis
- Papillae are usually seen in allergic and bacterial conjunctivitis

Giant Papillary Conjunctivitis

- immune reaction to mucus debris on lenses in contact lens wearers
- large papillae form on superior palpebral conjunctiva
- treatment: clean, change or discontinue use of contact lens

Vernal Conjunctivitis

- large papillae (cobblestones) form on superior palpebral conjunctiva with corneal ulcers and keratitis
- seasonal (warm weather)
- occurs in children, lasts for 5-10 yr then resolves
- treatment: consider topical steroid, topical cyclosporine (by ophthalmologist)

Antibiotics vs. Placebo for Acute Bacterial Conjunctivitis
Cochrane DB Syst Rev 2012;9:CD001211
Purpose: To assess the benefits and harms of antibiotic therapy in the management of acute bacterial conjunctivitis.
Criteria: RCTs with any form of antibiotic treatment compared with placebo including topical, systemic or combined (e.g. antibiotics and steroids) antibiotic treatments.
Results: 11 RCTs, 3,673 participants. Topical antibiotics improve early (2-5 d) clinical and microbiological remission rates (RR 1.36, 95% CI 1.15-1.61; RR 1.55; 95% CI 1.37-1.76) and benefit clinical remission and microbiological cure rates at a late time point (6-10 d) (RR 1.21, 95% CI 1.10-1.33; RR 1.37, 95% CI 1.24-1.52). By 6-10 d 41% of cases had resolved in the placebo group. No serious outcomes were reported in any group.
Conclusion: The use of antibiotic eye drops is associated with modestly improved rates of clinical and microbiological remission in comparison to placebo. Antibiotic eye drops should therefore be considered in order to speed the resolution of symptoms and infection although acute bacterial conjunctivitis is frequently self-limiting.

VIRAL CONJUNCTIVITIS

- serous discharge, lid edema, follicles
- subepithelial corneal infiltrates
- may be associated with rhinorrhea
- preauricular node often palpable and tender
- initially unilateral, often progresses to the other eye
- mainly due to adenovirus – highly contagious for up to 12 d

Treatment

- cool compresses, topical lubrication
- usually self-limiting (7-12 d)
- proper hygiene is very important

www.regentstudies.com

BACTERIAL CONJUNCTIVITIS

- purulent discharge, lid swelling, papillae, conjunctival injection, chemosis
- common agents include *S. aureus, S. pneumoniae, H. influenzae* and *M. catarrhalis*
- in neonates or if sexually active must consider *N. gonorrhoeae* (invades cornea to cause keratitis)
- *C. trachomatis* is the most common cause in neonates

Treatment

- topical broad-spectrum antibiotic
- systemic antibiotics if indicated, especially in neonates and children
- usually a self-limited course of 10-14 d if no treatment, 1-3 d with treatment

GONOCOCCAL AND CHLAMYDIAL CONJUNCTIVITIS

- caused by *N. gonorrhea* and *C. trachomatis*, respectively
- affects sexually active individuals, neonates (ophthalmia neonatorum) in first 5 days of life when caused by gonorrhea (shorter incubation period) and days 3-14 of life when caused by chlamydia (longer incubation period)
- newborn prophylaxis with 0.5% erythromycin ointment no longer recommended
- causes trachoma and inclusion conjunctivitis (different serotypes)

Trachoma

- leading infectious cause of blindness in the world
- severe keratoconjunctivitis leads to corneal abrasion, ulceration, and scarring
- initially, follicles on superior palpebral conjunctiva
- treatment: topical and systemic tetracycline

Inclusion Conjunctivitis

- chronic conjunctivitis with follicles and subepithelial infiltrates
- most common cause of conjunctivitis in newborns
- newborn prophylaxis with 0.5% erythromycin ointment no longer recommended
- treatment: topical and systemic tetracycline, doxycycline, or erythromycin

Preventing Ophthalmia Neonatorum
Paediatr Child Health 2015;20(2):93-96
The use of silver nitrate as prophylaxis for neonatal ophthalmia was instituted in the late 1800s to prevent the devastating effects of neonatal ocular infection with Neisseria gonorrhoeae. At that time – during the preantibiotic era – many countries made such prophylaxis mandatory by law. Today, neonatal gonococcal ophthalmia is rare in Canada, but ocular prophylaxis for this condition remains mandatory in some provinces/territories. Silver nitrate drops are no longer available and erythromycin, the only ophthalmic antibiotic eye ointment currently available for use in newborns, is of questionable efficacy. Ocular prophylaxis is not effective in preventing chlamydial conjunctivitis. Applying medication to the eyes of newborns may result in mild eye irritation and has been perceived by some parents as interfering with mother-infant bonding. Physicians caring for newborns should advocate for rescinding mandatory ocular prophylaxis laws. More effective means of preventing ophthalmia neonatorum include screening all pregnant women for gonorrhea and chlamydia infection, and treatment and follow-up of those found to be infected. Mothers who were not screened should be tested at delivery. Infants of mothers with untreated gonococcal infection at delivery should receive ceftriaxone. Infants exposed to chlamydia at delivery should be followed closely for signs of infection.

Sclera

- white fibrous outer protective coat of the eye, composed of irregularly distributed collagen bundles
- continuous with the cornea anteriorly and the dura of the optic nerve posteriorly
- episclera is a thin layer of vascularized tissue between the sclera and conjunctiva

Episcleritis

- immunologically mediated inflammation of episclera
- 1/3 bilateral; simple (80%) or nodular (20%)
- more frequent in women than men (3:1)

Etiology

- mostly idiopathic
- in 1/3 of cases, associated with collagen vascular diseases, infections (herpes zoster, herpes simplex, syphilis), inflammatory bowel disease, rosacea, atopy

Clinical Features

- usually asymptomatic; may have discomfort, heat sensation, red eye (often interpalpebral), rarely pain
- sectoral or diffuse injection of radially-directed vessels, chemosis, small mobile nodules
- blanches with topical phenylephrine (constricts superficial conjunctival vessels)

To differentiate between episcleritis and scleritis, place a drop of phenylephrine 2.5% (Mydfrin®; AK-Dilate®) in the affected eye. Re-examine the vascular pattern 10-15 min later; episcleral vessels should blanch, scleral vessels should not

Treatment

- generally self-limited, recurrent in 2/3 of cases
- topical steroid for 3-5 d if painful (prescribed and monitored by ophthalmologist)
- oral NSAID

Scleritis

- usually bilateral: diffuse, nodular, or necrotizing
- anterior scleritis: pain radiating to face, may cause scleral thinning, in some cases necrotizing

www.regentstudies.com

- posterior scleritis: rapidly progressive blindness, may cause exudative RD
- more common in women and elderly

Etiology
- may be a manifestation of systemic disease
- collagen vascular disease, e.g. SLE, RA, ankylosing spondylitis
- granulomatous, e.g. tuberculosis, sarcoidosis, syphilis
- metabolic, e.g. gout, thyrotoxicosis
- infectious, e.g. *S. aureus, S. pneumoniae, P. aeruginosa*, herpes zoster
- chemical or physical agents, e.g. thermal, alkali, or acid burns
- idiopathic

Scleromalacia Perforans
- Asymptomatic anterior necrotizing scleritis without inflammation
- Strongly associated with RA
- May result in scleral thinning
- Traumatic perforation can easily occur – examine eye very gently

Clinical Features
- severe pain, photophobia, red eye, decreased vision
- pain is best indicator of disease progression
- inflammation of scleral, episcleral, and conjunctival vessels
- may have anterior chamber cells and flare, corneal infiltrate, scleral thinning, scleral edema
- sclera may have a blue hue (best seen in natural light), due to rearranged scleral fibres
- failure to blanch with topical phenylephrine

Treatment
- systemic NSAID or steroid (topical steroids are not effective)
- treat underlying etiology

Cornea

- function
  - transmission of light
  - refraction of light (2/3 of total refractive power of eye)
  - barrier against infection, foreign bodies
- transparency due to avascularity, uniform collagen structure and deturgescence (relative dehydration)
- 6 layers (anterior to posterior): epithelium, Bowman's membrane, stroma, Dua's layer, Descemet's membrane, endothelium (dehydrates the cornea; dysfunction leads to corneal edema)
- extensive sensory fibre network (V1 distribution); therefore abrasions and inflammation (keratitis) are very painful

Learn the Layers of the Cornea
A – Anterior epithelium
B – Bowman's Membrane
C – Corneal Stroma
D – Dua's Layer, Descemet's Membrane
E – Endothelium

A new corneal layer was discovered by H. Dua in 2013 and is characterized as a pre-Descemet's membrane

Foreign Body

- foreign material in or on cornea
- may have associated rust ring if metallic
- patients may note tearing, photophobia, foreign body sensation, red eye
- signs include foreign body, conjunctival injection, epithelial defect that stains with fluorescein, corneal edema, anterior chamber cells/flare

Foreign body behind lid may cause multiple vertical corneal epithelial abrasions due to blinking

Complications
- abrasion, infection, ulcer, scarring, rust ring, secondary iritis

Treatment
- remove under magnification using local anesthetic and sterile needle or refer to ophthalmology (depending on depth and location)
- treat as per corneal abrasion

Topical analgesics should only be used to facilitate examination. They should NEVER be used as treatment for any ocular problem

Corneal Abrasion

- epithelial defect usually due to trauma (e.g. fingernails, paper, twigs), contact lens (Figure 14)

Clinical Features (Table 5)
- pain, redness, tearing, photophobia, foreign body sensation
- de-epithelialized area stains with fluorescein dye
- pain relieved with topical anesthetic

NEVER patch abrasion if patient wears contact lenses (prone to *Pseudomonas* infection)

Complications
- infection, ulceration, recurrent erosion, secondary iritis

Treatment
- topical antibiotic (drops or ointment)
- consider topical NSAID (caution due to risk of corneal melt with prolonged use), cycloplegic (relieves pain and photophobia by paralyzing ciliary muscle), patch
- most abrasions clear spontaneously within 24-48 h

Corneal abrasions from organic matter (e.g. twig, finger nail, etc.) have higher recurrence, even years later

www.regentstudies.com

Recurrent Erosions

- recurrent episodes of pain, photophobia, foreign body sensation with a spontaneous corneal epithelial defect
- usually occurs upon awakening
- associated with improper adherence of epithelial cells to the underlying basement membrane

Etiology
- previous traumatic corneal abrasion
- corneal dystrophy
- idiopathic

Treatment
- as for corneal abrasion until re-epithelialization occurs
- topical hypertonic saline ointment at bedtime for 3 mo, topical lubrication
- bandage contact lens, anterior stromal puncture or phototherapeutic keratectomy for chronic recurrences

Corneal Abrasion: To Patch or Not to Patch
Patching for corneal abrasion. *Cochrane DB Syst Rev* 2006;2:CD004764
Patching is not indicated for simple corneal abrasions, measuring <10 mm
There is no improvement in healing rates on days 1-3, no changes in reported pain and no difference in the use of antibiotics between the patch and non-patch groups

Corneal Ulcer

Etiology
- local necrosis of corneal tissue due to infection
- infection is usually bacterial, rarely viral, fungal, or protozoan (*Acanthamoeba*)
- secondary to corneal exposure, abrasion, foreign body, contact lens use (50% of ulcers)
- also associated with conjunctivitis, blepharitis, keratitis, vitamin A deficiency

Clinical Features
- pain, photophobia, tearing, foreign body sensation, decreased VA (if central ulcer)
- corneal opacity that necroses and forms an excavated ulcer with infiltrative base
- overlying corneal epithelial defect that stains with fluorescein
- may develop corneal edema, conjunctival injection, anterior chamber cells/flare, hypopyon, corneal hypoesthesia (in viral keratitis)
- bacterial ulcers may have purulent discharge, viral ulcers may have watery discharge

Complications
- decreased vision, corneal perforation, iritis, endophthalmitis

Investigations
- Seidel test: fluorescein drop on the cornea under cobalt blue filter is used to detect leaking penetrating lesions; any aqueous leaking will dilute the green stain at site of wound

Treatment
- urgent referral to ophthalmology
- culture prior to treatment
- topical antibiotics every hour
- must treat vigorously to avoid complications

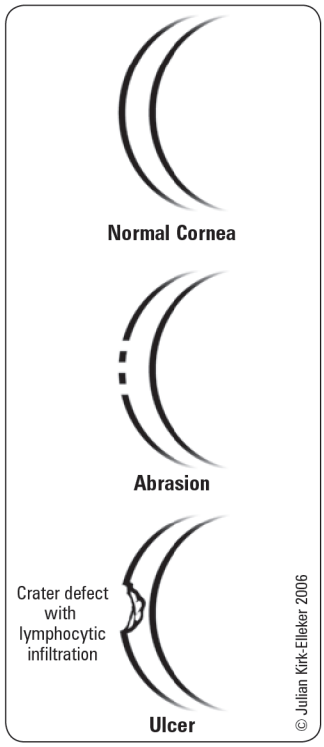


Figure 14. Corneal abrasion vs. ulcer

Table 5. Corneal Abrasion vs. Corneal Ulcer

	Abrasion	Ulcer
Time Course	Acute (instantaneous)	Subacute (days)
History of Trauma	Yes	Not usually
Cornea	Clear	White, necrotic area
Iris Detail	Clear	Obscured
Corneal Thickness	Normal	May have crater defect/thinning
Extent of Lesion	Limited to epithelium	Extension into stroma

Abrasion vs. Ulcer on Slit-Lamp
An abrasion appears clear while an ulcer is more opaque

Herpes Simplex Keratitis

- usually HSV type 1 (90% of population are carriers)
- may be triggered by stress, fever, sun exposure, immunosuppression

Clinical Features
- pain, tearing, foreign body sensation, red eye, may have decreased vision, eyelid edema
- corneal hypoesthesia
- dendritic (thin and branching) lesion in epithelium that stains with fluorescein

Antiviral Treatment and Other Therapeutic Interventions for Herpes Simplex Virus Epithelial Keratitis
Cochrane DB Syst Rev 2010;12:CD002898
Rates of corneal re-epithelialization after acute HSV corneal epithelial keratitis are similar after treatment with trifluridine or acyclovir, and significantly better than after treatment with idoxuridine or vidarabine. Brivudine and ganciclovir are not inferior to acyclovir. Combining an antiviral agent with Interferon or corneal epithelial debridement did not improve outcomes overall, but did hasten corneal healing. Debridement with concomitant antiviral treatment was more effective than debridement alone.

www.regentstudies.com

Complications
- corneal scarring (can lead to loss of vision)
- chronic interstitial keratitis due to penetration of virus into stroma
- secondary iritis, secondary glaucoma

Treatment
- topical antiviral such as trifluridine, consider systemic antiviral such as acyclovir
- dendritic debridement
- NO STEROIDS initially – may exacerbate condition
- ophthalmologist must exercise caution if adding topical steroids for chronic keratitis or iritis

Steroid treatment for ocular disorders should only be prescribed and supervised by an ophthalmologist, as they can impair corneal healing, exacerbate herpetic keratitis, and elevate IOP

Herpes Zoster

- dermatitis of the forehead (CN V1 territory) may involve globe
- Hutchinson's sign: if tip of nose is involved (nasociliary branch of V1) then eye will be involved in ~75% of cases
- if no nasal involvement, eye is involved in 1/3 of patients

Clinical Features
- pain, tearing, photophobia, red eye
- corneal edema, pseudodendrite, SPK
- corneal hypoesthesia

Complications
- corneal keratitis, ulceration, perforation and scarring
- secondary iritis, secondary glaucoma, cataract
- muscle palsies (rare) due to CNS involvement
- occasionally severe post-herpetic neuralgia

Treatment
- oral antiviral (acyclovir, valcyclovir, or famciclovir) immediately
- topical steroids, cycloplegia as indicated for keratitis, iritis
- erythromycin ointment if conjunctival involvement

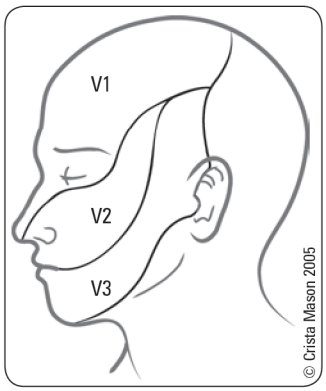


Figure 15. Trigeminal distribution

Keratoconus

- bilateral paracentral thinning and bulging (ectasia) of the cornea to form a conical shape
- usually sporadic, but associated with Down's syndrome, atopy, contact lens use (theorized to be related to chronic vigorous eye rubbing)
- associated with breaks in Descemet's and Bowman's membrane
- results in irregular astigmatism, scarring, stromal edema

Treatment
- attempt correction with spectacles or contact lens
- cross-linking treatment may halt or slow disease progression
- intrastromal corneal ring segments can help flatten the corneal cone
- penetrating keratoplasty (corneal transplant) 90% successful
- post-transplant complications: endophthalmitis, graft rejection, graft failure, graft dehiscence

To detect keratoconus, look for bulging of the lower eyelid when the patient looks downward (Munson's sign)

Arcus Senilis

- hazy white ring in peripheral cornea, <2 mm wide, clearly separated from limbus
- common, bilateral, benign corneal degeneration due to lipid deposition, part of the aging process
- may be associated with hypercholesterolemia if age <40 yr, check lipid profile
- no associated visual symptoms, no complications, no treatment necessary

Kayser-Fleischer Ring

- brown-yellow-green pigmented ring in peripheral cornea, starting inferiorly
- due to deposition of copper pigment in Descemet's membrane
- associated with Wilson's disease
- no associated symptoms or complications of ring
- treat underlying disease

www.regentstudies.com

The Uveal Tract

- uveal tract (from anterior to posterior) = iris, ciliary body, choroid
- vascularized, pigmented middle layer of the eye, between the sclera and the retina

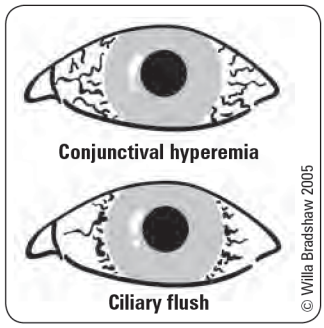


Figure 16. Conjunctival hyperemia vs. ciliary flush

Uveitis

- uveal inflammation which may involve one, two, or all three parts of the tract
- idiopathic or associated with autoimmune, infectious, granulomatous, malignant causes
- should be managed by an optometrist or ophthalmologist
- anatomically classified as anterior uveitis, intermediate uveitis, posterior uveitis, or panuveitis based on primary site of inflammation

Table 6. Anatomic Classification of Uveitis

	Anterior Uveitis (Iritis)	Intermediate Uveitis	Posterior Uveitis
Location	• Inflammation of iris, usually accompanied by cyclitis (inflammation of ciliary body), both = iridocyclitis • Usually unilateral	• The vitreous is the major site of the inflammation	• Inflammation of the choroid and/or retina
Etiology	• Usually idiopathic • Connective tissue diseases (see Rheumatology, RH8) ▪ HLA-B27: reactive arthritis, ankylosing spondylitis, psoriatic arthritis, inflammatory bowel disease ▪ Non-HLA-B27: juvenile idiopathic arthritis • Infectious: syphilis, Lyme disease, toxoplasmosis, TB, HSV, herpes zoster • Other: sarcoidosis, trauma, large abrasion, post ocular surgery	• Mostly idiopathic, secondary causes include sarcoidosis, Lyme disease, and multiple sclerosis	• Bacterial: syphilis, tuberculosis • Viral: herpes simplex virus, CMV in AIDS • Fungal: histoplasmosis, candidiasis • Parasitic: toxoplasmosis (most common cause), toxocara • Immunosuppression may predispose to any of the above infections • Autoimmune: Behçet's disease (triad of oral ulcers, genital ulcers, and posterior uveitis) • Malignancies (masquerade syndrome): metastatic lesions, malignant melanoma
Clinical Features	• Photophobia (due to reactive spasm of inflamed iris muscle), ocular pain, tenderness of the globe, brow ache (ciliary muscle spasm), decreased VA (in severe cases with hypopyon), lacrimation • Ciliary flush (perilimbal conjunctival injection), miosis (spasm of sphincter muscle) • Anterior chamber "cells" (WBC in anterior chamber due to anterior segment inflammation) and "flare" (protein precipitates in anterior chamber secondary to inflammation), hypopyon (collection of neutrophilic exudates inferiorly in the anterior chamber) • Occasionally keratic precipitates (clumps of cells on corneal endothelium) • Iritis typically reduces IOP because ciliary body inflammation causes decreased aqueous production; however, severe iritis, or iritis from herpes simplex and zoster may cause an inflammatory glaucoma (trabeculitis)	• Insidious onset of blurred vision, accompanied by vitreous floaters • Initial symptoms are usually unilateral but inflammatory changes are usually bilateral and asymmetric • Associated with anterior uveitis, most severe cases of secondary intermediate uveitis • Vitreous cells, condensations, and snowballs (vitreous aggregates of inflammatory cells) • Posterior segment 'snowbank' = grey-white fibrovascular plaque at the pars plana	• Painless as choroid has no sensory innervation • Often no conjunctival or scleral injection present • Decreased VA • Floaters (debris and inflammatory cells) • Vitreous cells and opacities • Hypopyon formation
Complications	• Inflammatory glaucoma • Posterior synechiae ▪ Adhesions of posterior iris to anterior lens capsule ▪ Indicated by an irregularly shaped pupil ▪ If occurs 360°, entraps aqueous in posterior chamber, iris bows forward "iris bombé" → angle closure glaucoma • Peripheral anterior synechiae (rare): adhesions of iris to cornea → secondary angle closure glaucoma • Cataracts • Band keratopathy (with chronic iritis) ▪ Superficial corneal calcification keratopathy • Macular edema with chronic iritis	• Cystoid macular edema (30% of cases), cataract, and glaucoma	• Macular edema • Vitritis • Neovascularization • Visual field loss/scotoma
Treatment	• Mydriatics: dilate pupil to prevent formation of posterior synechiae and to decrease pain from ciliary spasm • Steroids: topical, sub-tenon, or systemic • Systemic analgesia • If recurrent episodes, extensive medical workup may be indicated to rule out secondary causes	• Systemic or sub-tenon/intravitreal steroids and immunosuppressive agents • Vitrectomy, cryotherapy, or laser photocoagulation to the "snowbank"	• Steroids: sub-tenon, intravitreal, or systemic if indicated (e.g. threat of vision loss)

www.regentstudies.com

Lens

- consists of an outer capsule surrounding a soft cortex and a firm inner nucleus

Cataracts

- any opacity of the lens, regardless of etiology
- most common cause of reversible blindness worldwide
- types: nuclear sclerosis, cortical, posterior subcapsular

Etiology

- acquired
  - age-related (over 90% of all cataracts)
  - cataract associated with systemic disease (may have juvenile onset)
    - DM
    - metabolic disorders (e.g. Wilson's disease, galactosemia, homocystinuria)
    - hypocalcemia
  - traumatic (may be rosette shaped)
  - intraocular inflammation (e.g. uveitis)
  - toxic (steroids, phenothiazines)
  - radiation
- congenital
  - high myopia
  - present with altered red reflex or leukocoria
  - treat promptly to prevent amblyopia

Clinical Features

- gradual, painless, progressive decrease in VA
- glare, dimness, halos around lights at night, monocular diplopia
- "second sight" phenomenon: patient is more myopic than previously noted, due to increased refractive power of the lens (in nuclear sclerosis only)
  - patient may read without previously needed reading glasses
- diagnosis by slit-lamp exam, and by noting changes in red reflex using ophthalmoscope
- may impair view of retina during fundoscopy

Treatment

- medical: attempt correction of refractive error, no strong evidence suggesting benefit of vitamin supplementation
- surgical: definitive treatment
  - indications for surgery
    - to improve visual function in patients whose vision loss leads to functional impairment (no need to wait for "ripe" cataract, may postpone surgery as long as one eye has sufficient vision)
    - to aid management of other ocular disease (e.g. cataract that prevents adequate retinal exam or laser treatment of DR)
    - congenital or traumatic cataracts
  - phacoemulsification (phaco = lens)
    - most commonly used surgical technique (see *Surgical Ophthalmology*, OP44)
    - femtosecond laser for the anterior capsulotomy and fragmentation of the lens
  - post-operative complications
    - RD, endophthalmitis, dislocated IOL, macular edema, glaucoma
    - with new foldable IOLs that have truncated edges, <10% of patients get posterior capsular opacification, which should be treated with YAG laser

Prognosis

- excellent if not complicated by other ocular disease

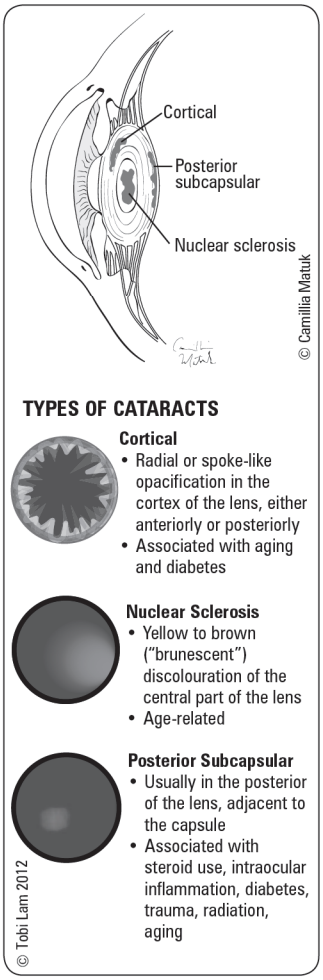


Figure 17. Types of cataracts

www.regentstudies.com

Dislocated Lens (Ectopia Lentis)

Etiology
- associated with Marfan's Syndrome, Ehlers-Danlos type VI, homocystinuria, syphilis, lens coloboma (congenital cleft due to failure of ocular adnexa to complete growth)
- traumatic

Clinical Features
- decreased VA
- may get monocular diplopia
- iridodenesis (quivering of iris with movement)
- direct ophthalmoscopy may elicit abnormal red reflex

Complications
- cataract, glaucoma, uveitis

Treatment
- surgical correction ± lens replacement

Vitreous

- clear gel (99% water plus collagen fibrils, glycosaminoglycans, and hyaluronic acid) that fills the posterior segment of eye
- normally adherent to optic disc, pars plana, and along major retinal blood vessels

Posterior Vitreous Detachment

Etiology
- central vitreous commonly shrinks and liquefies with age (syneresis)
- during syneresis, molecules that hold water condense causing vitreous floaters
- liquid vitreous moves between posterior vitreous gel and retina
- vitreous is peeled away and separates from the internal limiting membrane of the neurosensory retina posterior to the vitreous base

Clinical Features
- floaters, flashes of light

Complications
- traction at areas of abnormal vitreoretinal adhesions may cause retinal tears/detachment
- retinal tears/detachment may cause vitreous hemorrhage if bridging retinal blood vessel is torn
- complications more common in high myopes and following ocular trauma (blunt or perforating)

Treatment
- acute onset of PVD requires a dilated fundus exam to rule out retinal tears/detachment
- no specific treatment available for floaters/flashes of light

Weiss Ring: formed by glial tissue around the optic disc that remains attached to the detached posterior vitreous

Floaters: "bugs", "cobwebs", or "spots" of vitreous condensation that change with eye position

Although most floaters are benign, new or markedly increased floaters or flashes of light require a dilated fundus exam to rule out retinal tears/detachment

Vitreous Hemorrhage

- bleeding into the vitreous cavity

Etiology
- PDR
- retinal tear/detachment
- PVD
- retinal vein occlusion
- trauma

Clinical Features
- sudden loss of VA
- may be preceded by "shower" of many floaters and/or flashes of light
- ophthalmoscopy: no red reflex if large hemorrhage, retina not visible due to blood in vitreous

Treatment
- ultrasound (B-scan) to rule out RD
- expectant: in non-urgent cases (e.g. no RD), blood usually resorbs in 3-6 mo
- surgical: vitrectomy ± RD repair ± retinal endolaser to possible bleeding sites/vessels

Any time a vitreous or retinal hemorrhage is seen in a child, must rule out child abuse

www.regentstudies.com

Endophthalmitis and Vitritis

- intraocular infection: acute, subacute, or chronic

Etiology
- most commonly a post-operative complication; risk following cataract surgery is <0.1%
- also due to penetrating injury to eye (risk is 3-7%), endogenous spread, and intravitreal injections
- etiology usually bacterial, may be fungal

Remember to inquire about tetanus status in post-traumatic endophthalmitis

Clinical Features
- painful, red eye, photophobia, discharge
- severely reduced VA, lid edema, proptosis, corneal edema, anterior chamber cells/flare, hypopyon, reduced red reflex
- may have signs of a ruptured globe (severe subconjunctival hemorrhage, hyphema, decreased IOP, etc.)

Treatment (see *Ocular Trauma*, OP42)
- **OCULAR EMERGENCY:** presenting vision best indicates prognosis
- LP or worse: admission, immediate vitrectomy, and intravitreal antibiotics to prevent loss of vision
- HM or better: vitreous tap for culture and intravitreal antibiotics
- topical fortified antibiotics

Retina

- composed of two parts (Figure 2)
  - neurosensory retina: comprises 9 of the 10 retinal layers, including the photoreceptors and the ganglion cell layer
  - retinal pigmented epithelium (RPE) layer: external to neurosensory retina
- macula: rich in cones (for colour vision); most sensitive area of retina; looks darker due to increased luteal pigment, lack of retinal vessels, and thinning of retina in this region; 15° temporal and slightly below the optic disc
- fovea: centre of macula; responsible for detail, fine vision
- optic disc: slightly oval vertically, pinkish colour with centrally depressed yellow cup (normal C:D ratio is ≤0.4), retinal artery and vein pass through cup
- ora serrata: irregularly-shaped, anterior margin of the retina (can only be visualized with indirect ophthalmoscopy of the far peripheral retina, or through a Goldmann 3 mirror lens)

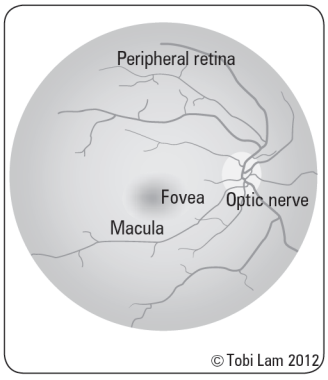


Figure 18. Retina

Central Retinal Artery Occlusion

Etiology
- emboli from carotid arteries or heart (e.g. arrhythmia, endocarditis, valvular disease)
- thrombus
- temporal arteritis

Clinical Features
- sudden, painless (except in GCA), severe monocular loss of vision
- RAPD
- patient may have experienced transient episodes in the past (amaurosis fugax)
- fundoscopy
  - "cherry-red spot"
  - retinal pallor
  - narrowed arterioles, boxcarring (segmentation of blood in arteries)
  - cotton wool spots (retinal infarcts)
  - cholesterol emboli (Hollenhorst plaques) – usually located at arteriole bifurcations
  - after ~6 wk cherry-red spot recedes and optic disc pallor becomes evident

Hallmark of CRAO
"Cherry-red spot" located at centre of macula (visualization of unaffected highly vascular choroid through the thin fovea)

Treatment
- **OCULAR EMERGENCY:** attempt to restore blood flow within 2 h
- the sooner the treatment = better prognosis (irreversible retinal damage if >90 min of complete CRAO)
  - massage the globe (compress eye with heel of hand for 10 s, release for 10 s, repeat for 5 min) to dislodge embolus
  - decrease IOP
    - topical β-blockers
    - inhaled oxygen-carbon dioxide mixture
    - IV acetazolamide
    - IV mannitol (draws fluid from eye)
    - drain aqueous fluid – anterior chamber paracentesis (carries risk of infection, lens puncture)
  - Nd:YAG laser embolectomy
  - intra-arterial or intra-venous thrombolysis

Treatment for a central retinal artery occlusion (CRAO) must be initiated within 2 h of symptom onset for any hope of restoring vision

www.regentstudies.com

Branch Retinal Artery Occlusion

- only part of the retina becomes ischemic resulting in a visual field loss
- more likely to be of embolic etiology than CRAO; need to search for source
- management: ocular massage to dislodge embolus if VA is affected

Central/Branch Retinal Vein Occlusion

- second most frequent "vascular" retinal disorder after DR
- usually a manifestation of a systemic disease (e.g. HTN, DM)
- thrombus occurs within the lumen of the blood vessel

Predisposing Factors

- arteriosclerotic vascular disease
- HTN
- DM
- glaucoma
- hyperviscosity (e.g. polycythemia rubra vera, sickle-cell disease, lymphoma, leukemia)
- drugs (e.g. oral contraceptive pill, diuretics)

Clinical Features

- painless, monocular, gradual or sudden vision loss
- ± RAPD
- fundoscopy
  - "blood and thunder" appearance
  - diffuse retinal hemorrhages, cotton wool spots, venous engorgement, swollen optic disc, macular edema
- two fairly distinct groups
  - venous stasis/non-ischemic retinopathy
    - no RAPD, VA ~20/80
    - mild hemorrhage, few cotton wool spots
    - resolves spontaneously over weeks to months
    - may regain normal vision if macula intact
  - hemorrhagic/ischemic retinopathy
    - usually older patient with deficient arterial supply
    - RAPD, VA ~20/200, reduced peripheral vision
    - more hemorrhages, cotton wool spots, congestion
    - poor visual prognosis

Complications

- degeneration of RPE
- neovascularization of retina and iris (secondary rubeosis), leading to secondary glaucoma
- vitreous hemorrhage
- macular edema

Treatment

- no treatment available to restore vision in CRVO/BRVO
- treat underlying cause/contributing factor
- fluorescein angiography to determine extent of retinal non-perfusion (risk of neovascularization)
- retinal laser photocoagulation, or intravitreal anti-VEGF injection to reduce retinal or iris neovascularization and prevent neovascular glaucoma
- macular grid laser photocoagulation for the treatment of macular edema in BRVO, not CRVO, intravitreal or slow-release biodegradable corticosteroid, or anti-VEGF injection is effective in the treatment of macular edema in both CRVO and BRVO

Efficacy and Safety of Widely Used Treatments for Macular Oedema Secondary to Retinal Vein Occlusion: A Systematic Review
BMC Ophthalmol 2014;14:7
Purpose: To assess the efficacy of widely used treatments for macular oedema (MO) secondary to retinal vein occlusion (RVO). MO secondary to RVO can cause vision loss due to blockage of the central retinal vein (CRVO) or a branch retinal vein (BRVO).
Outcomes: Mean change in best corrected visual acuity (BCVA) from baseline and/or number of patients gaining at least 10 letters from baseline to 6 mo or equivalent time point.
Results: 14 unique RCTs identified. Ranibizumab 0.5 mg produced greater improvements in BCVA at 6 mo compared to sham in BRVO (mean difference 11 letters; 95% CI 7.83-14.17) and CRVO (mean difference 14 letters; 95% CI 10.51-17.69). Improvements in BCVA were also observed with dexamethasone intravitreal implant (IVT) 0.7 mg compared with sham in patients with BRVO or CRVO (mean difference 2.5 letters; 95% CI 0.7-4.3). The difference was significant with BRVO alone, but not CRVO alone. At 36 mo in a large prospective RCT, a greater proportion of patients with BRVO gained >15 letters with laser therapy versus no treatment (OR 3.16; 95% CI 1.25-8.00), whereas no difference was observed in a 9 mo end point smaller study. Three studies showed no benefit for laser therapy in CRVO.
Conclusions: Both ranibizumab and dexamethasone IVT show significant improvements over previously accepted standard of care (laser therapy) for the treatment of BRVO and CRVO.

The "blood and thunder" appearance on fundoscopy is very characteristic of a CRVO

There is an 8-10% risk of developing CRVO or BRVO in other eye

GENEVA Phase 3 Trials in BRVO and CRVO
Ophthalmology 2010;117:1134-1146
Randomized sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion.
Dexamethasone intravitreal implant reduces the risk of vision loss and improves the speed and incidence of visual improvement in eyes with macular edema 2° to BRVO and CRVO.

Retinal Detachment

- cleavage in the plane between the neurosensory retina and the RPE
- three types
  - rhegmatogenous (most common)
    - caused by a tear or hole in the neurosensory retina, allowing fluid from the vitreous to pass into the subretinal space
    - tears may be caused by PVD, degenerative retinal changes, trauma, or iatrogenically
    - incidence increases with advancing age, in high myopes, and after ocular surgery/trauma
  - tractional
    - caused by traction (due to vitreal, epiretinal, or subretinal membrane) pulling the neurosensory retina away from the underlying RPE
    - found in conditions such as DR, CRVO, sickle cell disease, ROP, and ocular trauma
  - exudative
    - caused by damage to the RPE resulting in fluid accumulation in the subretinal space
    - main causes are intraocular tumours, posterior uveitis, central serous retinopathy

Superotemporal retina is the most common site for horseshoe tears

www.regentstudies.com

Clinical Features
- sudden onset
- flashes of light
  - due to mechanical stimulation of the retinal photoreceptors
- floaters
  - hazy spots in the line of vision which move with eye position, due to drops of blood from torn vessels bleeding into the vitreous
- curtain of blackness/peripheral field loss
  - darkness in one field of vision when the retina detaches in that area
- loss of central vision (if macula "off")
- decreased IOP (usually 4-5 mmHg lower than the other, normal eye)
- ophthalmoscopy: detached retina is grey-white with surface blood vessels, loss of red reflex
- ± RAPD

Treatment
- prophylactic: symptomatic tear (flashes or floaters) can be sealed off with laser/cryotherapy, with the goal of preventing progression to detachment
- therapeutic
  - rhegmatogenous
    - scleral buckle procedure (see *Surgical Ophthalmology,* OP44)
    - pneumatic retinopexy (see *Surgical Ophthalmology,* OP44)
    - both treatments above are used in combination with localization of retinal tears/holes and subsequent treatment with cryotherapy or laser to create adhesions between the RPE and the neurosensory retina
    - vitrectomy plus injection of gas or silicone oil in cases of recurrent detachment
  - tractional
    - vitrectomy ± membrane removal/scleral buckling/injection of intraocular gas or silicone oil as necessary
  - exudative
    - treat underlying cause

Complications
- loss of vision, vitreous hemorrhage, recurrent RD
- a RD is an emergency, especially if the macula is still attached (macula "on")
- prognosis for visual recovery varies inversely with the amount of time the retina is detached and whether the macula is attached or not

Retinitis Pigmentosa

- worldwide incidence between 1/3,500 and 1/7,000 people
- many forms of inheritance, most commonly autosomal recessive (60%)
- hereditary degenerative disease of the retina manifested by rod > cone photoreceptor degeneration and retinal atrophy

Clinical Features
- night blindness, decreased peripheral vision ("tunnel vision"), decreased central vision (macular changes), glare (from posterior subcapsular cataracts, common)

Investigations
- fundoscopy: areas of "bone-spicule" pigment clumping in mid-periphery of retina, narrowed retinal arterioles, pale optic disc
- electrophysiological tests: electroretinography (ERG) and electrooculography (EOG) assist in diagnosis

Treatment
- no treatments available to reverse the condition; cataract extraction improves visual function; vitamin A and vitamin E supplementation can reduce progression of disease in some patients

Leber's Congenital Amaurosis

- worldwide incidence 1/80,000
- inherited degeneration, autosomal recessive

Clinical Features
- symptoms: resting nystagmus, sluggish or no pupillary response, severe vision loss/blindness

Investigations
- diagnosis: 11 types, confirmed by genetic testing

Treatment
- no treatments available to reverse the conditions for most forms; one form (LCA2) shown to be successfully treatable by gene replacement using adeno-associated virus

Vitamin A and Fish Oils for Retinitis Pigmentosa
Cochrane DB Syst Rev 2013;12:CD008428
Purpose: To determine the efficacy and safety of vitamin A and fish oils (docosahexaenoic acid [DHA]) in preventing the progression of RP.
Selection Criteria: RCTs evaluating the effectiveness of vitamin, fish oils, or both as a treatment for RP.
Results: 3 RCTs with 866 participants. No toxicity or adverse events reported. No trial reported a statistically significant benefit of vitamin supplementation on the progression of visual field loss or visual acuity loss. 2 of 3 trials reported a statistically significant difference in ERG amplitudes among some subgroups, but these findings have not been replicated or substantiated in other trials.
Conclusions: There is no clear evidence for benefit of treatment with vitamin A and/or DHA for RP when measuring mean change in visual fields and ERG amplitudes at one yr and the mean change in visual acuity at 5 yr follow-up.

Triad of Retinitis Pigmentosa

APO
Arteriolar narrowing
Perivascular bony-spicule pigmentation
Optic disc pallor

Retinitis Pigmentosa Inherited Forms
- Autosomal recessive: most common
- Autosomal dominant: best prognosis
- X-linked: worst prognosis

Age-Dependent Effects of Gene Therapy for Leber's Congenital Amaurosis: A Phase 1 Dose-Escalation Trial
Lancet 2009;374:1597-1605
Objective: To evaluate the effect of gene therapy on retinal and visual function among patients with Leber's congenital amaurosis.
Methods: Phase 1 trial. Patients aged 8-44 (n = 12) with RPE65-associated Leber's congenital amaurosis received a single subretinal injection of adeno-associated virus (AAV) containing the gene encoding the protein needed for isomerohydrolase activity of the RPE (RPE65) (AAV2-hRPE65v2) in the worst eye at low, medium, or high dose. Patients were assessed before and after injections. Outcomes were subjective and objective measures of vision.
Results: AAV2-hRPE65v2 was tolerated. No serious adverse events were recorded. Visual improvement was noted for all patients. All patients reported improved vision in dimly lit environments. Visual fields improved in all patients. Pupillary light responses were increased by at least 2 log unit for all patients. Greatest visual improvement was noted in children.
Conclusion: AAV2-hRPEv2 is safe and improves vision among patients with Leber's congenital amaurosis.

www.regentstudies.com

Age-Related Macular Degeneration

- leading cause of irreversible blindness in the western world, associated with increasing age, usually bilateral
- 10% of people >65 yr old have some degree of AMD
- F>M
- degenerative changes are concentrated at the macula, thus only central vision is lost; peripheral vision (important for navigation) is maintained so patients can usually maintain an independent lifestyle

Classification

- **Non-Exudative/"Dry" (Non-Neovascular) AMD**
  - most common type of AMD (90% of cases)
  - slowly progressive loss of visual function
  - drusen: yellow-white deposits between the RPE and Bruch's membrane (area separating inner choroidal vessels from RPE)
  - RPE atrophy: coalescence of depigmented RPE, clumps of focal hyperpigmentation, or hypopigmentation
  - may progress to neovascular AMD

- **Exudative/"Wet" (Neovascular) AMD**
  - 10% of AMD, but 80% of AMD that results in severe vision loss
  - choroidal neovascularization: drusen predisposes to breaks in Bruch's membrane causing subsequent growth and proliferation of choroidal capillaries
  - may lead to serous detachment of overlying RPE and retina, hemorrhage and lipid precipitates into subretinal space
  - can also lead to an elevated subretinal mass due to fibrous metaplasia of hemorrhagic RD
  - leads to disciform scarring and severe central vision loss

Risk Factors

- female
- increasing age
- family history
- smoking
- Caucasian race
- blue irides

Clinical Features

- variable degree of progressive central vision loss
- metamorphopsia (distorted vision characterized by straight parallel lines appearing convergent or wavy) due to macular edema

Investigations

- Amsler grid: held at normal reading distance with glasses on, assesses macular function
- fluorescein angiography: assess type and location of choroidal neovascularization – pathologic new vessels leak dye
- OCT retinal imaging

Treatment

- non-neovascular "dry" AMD
  - monitor, Amsler grid allows patients to check for metamorphopsia
  - low vision aids (e.g. magnifiers, closed-circuit television)
  - anti-oxidants, green leafy vegetables
  - sunglasses/visors
  - see Age-related Eye Disease Study (AREDS) and Age-related Eye Disease Study 2 (AREDS2) in sidebar
- neovascular "wet" AMD
  - see *Common Medications*, OP44
  - intravitreal injection of anti-VEGF
    - pegaptanib (Macugen®), ranibizumab (Lucentis®), bevacizumab (Avastin®), aflibercept (Evlea®) (see *VEGF Inhibitors*, OP45)
  - laser photocoagulation for neovascularization
  - no definitive treatment for disciform scarring
  - PDT with verteporfin (Visudyne®)
    - IV injection of verteporfin followed by low intensity laser to area of choroidal neovascularization

Age-Related Eye Disease Study (AREDS)
The Age-Related Eye Disease Research Group: A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, β-carotene, and zinc for age-related macular degeneration and vision loss. AREDS Report No. 8. *Arch Ophthalmol* 2001;119:1417-1436
AREDS studied the effect of high-dose combination of vitamin C, vitamin E, β-carotene, and zinc in patients with and without AMD. Those who are already affected by AMD showed 19% decrease in risk of further visual loss, whereas high dose supplementation showed no benefit in patients with early or no AMD.

Wet AMD Lesions on Fluorescein Angiography
Classic: well-defined leakage
Occult: mottled or ill-defined leakage

Drusen vs. Exudate
Drusen: hyaline material secreted by RPE seen frequently in AMD typically in peri-macular region
Hard/Soft Exudates: lipid deposits in the retina associated with DR and HTN

Age-Related Eye Disease Study 2 (AREDS2)
Lutein + zeaxanthin and omega-3 fatty acids for AMD: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. *JAMA* 2013 May 15;309(19):2005-2015
Addition of lutein+zeaxanthin, DHA+EPA, or both to the AREDS formulation in primary analyses didn't reduce risk of progression to advance AMD. However, because of the potential increased incidence of lung cancer in former smokers, lutein+zeaxanthin could be an appropriate carotenoid substitute in the AREDS formulation.

Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration
CATT Research Group. *NEJM* 2011;364:1897-1908
Study: A multicentre, single-blind, randomized control trial comparing the effects of ranibizumab and bevacizumab on visual acuity in patients with age-related macular degeneration (AMD).
Patients: 1,208 patients aged 50 or more with previously untreated AMD and visual acuity between 20/25 and 20/320.
Intervention: Intravitreal injections of ranibizumab vs. intravitreal injections of bevacizumab.
Results: The monthly use of either bevacizumab or ranibizumab results in the same visual acuity outcome. This finding holds true for the mean visual acuity and the proportion of patients who gain 15 letters, lose 15 letters, or remain stable. Equivalent visual-acuity outcomes were observed with both the monthly and the as-needed regimens of ranibizumab.
Conclusion: This study supports the use of either bevacizumab or ranibizumab for the treatment of neovascular AMD. The continued global use of intravitreal bevacizumab is an equally effective, low-cost alternative to ranibizumab.

www.regentstudies.com

Glaucoma

Definition

- progressive optic neuropathy involving characteristic structural changes to optic nerve head with associated visual field changes
- commonly associated with high IOP, but not required for diagnosis

Background

- aqueous is produced by the ciliary body and flows from the posterior chamber to the anterior chamber through the pupil, and drains into the episcleral veins via the trabecular meshwork and the Canal of Schlemm
- an isolated increase in IOP is termed OHT (or glaucoma suspect) and these patients should be followed for increased risk of developing glaucoma (10% if IOP 20-30 mmHg; 40% if IOP 30-40 mmHg; and most if IOP >40 mmHg)
- pressures >21 mmHg are more likely to be associated with glaucoma; however, up to 50% of patients with glaucoma do not have IOP >21 mmHg
- loss of peripheral vision most commonly precedes central loss
- sequence of events: gradual pressure rise → increased C:D ratio → visual field loss

Investigations

- medical and family history
- VA testing
- slit-lamp exam to assess anterior chamber depth with goniscopic lens to assess angle patency
- ophthalmoscopy to assess the disc features
- tonometry by applanation or indentation to measure IOP
- visual field testing
- pachymetry to measure corneal thickness
- future follow-up includes optic disc examination, IOP measurement, and visual field testing to monitor course of disease

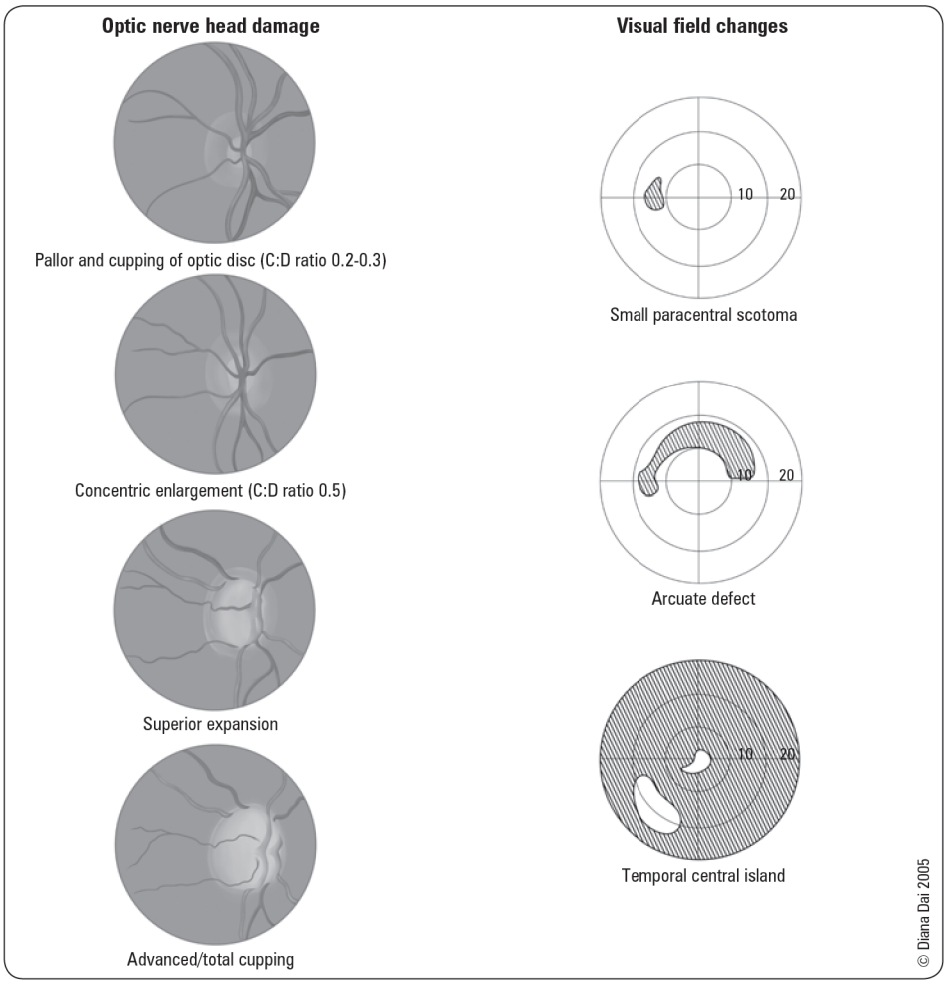


Figure 19. Glaucomatous damage

Ten Year Follow-Up of Age-Related Macular Degeneration in the Age-Related Eye Disease Study: AREDS Report No. 36
JAMA Ophthalmol 2014 Mar;132(3):272-7
Study: Randomized clinical trial.
Objective: To describe 10 yr progression rates to intermediate or advanced AMD.
Patients: Age-related eye disease study (AREDS) participants were observed for an additional 5 yr after RCT completion. Participants aged 55-80 yr with no AMD or AMD of varying severity (n = 4,757) were followed up in the AREDS trial for a median duration of 6.5 yr. When the trial ended, 3,549 of the 4,203 surviving participants were followed for 5 additional yr.
Intervention: Treatment with antioxidant vitamins and minerals.
Main Outcome: Development of varying stages of AMD and changes in visual acuity.
Results: The risk of progression to advanced AMD increased with increasing age (p=0.01) and severity of drusen. Women (p=0.005) and current smokers (p<0.001) were at increased risk of neovascular AMD. In the oldest participants with the most severe AMD status at baseline, the risks of developing neovascular AMD and central geographic atrophy by 10 yr were 48.1% and 26.0%, respectively. Similarly, rates of progression to large drusen increased with increasing severity of drusen at baseline, with 70.9% of participants with bilateral medium drusen progressing to large drusen and 13.8% to advanced AMD in 10 yr. Median visual acuity at 10 yr in eyes that had large drusen at baseline but never developed advanced AMD was 20/25; eyes that developed advanced AMD had a median visual acuity of 20/200.
Conclusion: The natural history of AMD demonstrates relentless loss of vision in persons who developed advanced AMD.

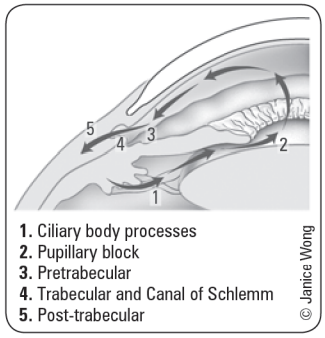


Figure 20. Aqueous flow and sites of potential resistance

Average IOP = 15 ± 3 mmHg
Normal C:D ≤0.4
Suspect glaucoma if C:D ratio >0.6, C:D ratio differs between eyes by >0.2, or cup approaches disc margin

www.regentstudies.com

Primary Open-Angle Glaucoma

- most common form, >95% of all glaucoma cases
- due to obstruction of aqueous drainage within the trabecular meshwork and its drainage into the Canal of Schlemm
- insidious and asymptomatic, screening is critical for early detection

Major Risk Factors
- elevated IOP (>21 mmHg)
- age: prevalence at 40 yr is 1-2% and at 80 yr is 10%
- ethnicity: African descent
- familial (2-3x increased risk); polygenic
- thin central cornea (OHTS trial)

Minor Risk Factors
- myopia
- HTN
- DM
- hyperthyroidism (Graves' disease)
- chronic topical ophthalmic steroid use in steroid responders – yearly eye exams recommended if >4 wk of steroid use
- previous ocular trauma
- anemia/hemodynamic crisis (ask about blood transfusions in past)

Clinical Features
- asymptomatic initially
- insidious, painless, gradual rise in IOP due to restriction of aqueous outflow
- bilateral, but usually asymmetric
- earliest signs are optic disc changes
  - increased C:D ratio (vertical C:D >0.6)
  - significant C:D asymmetry between eyes (>0.2 difference)
  - thinning, notching of the neuroretinal rim
  - flame shaped disc hemorrhage
  - 360° of peripapillary atrophy
  - nerve fibre layer defect
  - large vessels become nasally displaced
- visual field loss
  - slow, progressive, irreversible loss of peripheral vision
  - paracentral defects, arcuate scotoma, and nasal step are characteristics (Figure 19)
  - late loss of central vision if untreated

Treatment
- medical treatment: decrease IOP by increasing the drainage and/or decreasing the production of aqueous (see *Glaucoma Medications*, Table 12, OP45)
  - increase aqueous outflow
    - topical cholinergics
    - topical prostaglandin analogues
    - topical α-adrenergics
  - decrease aqueous production
    - topical β-blockers
    - topical and oral carbonic anhydrase inhibitor
    - topical α-adrenergics
- laser trabeculoplasty, cyclophotocoagulation in order to achieve selective destruction of ciliary body (for refractory cases)
- trabeculectomy or minimally invasive glaucoma surgery (MIGS) (see *Surgical Ophthalmology*, OP44)
- serial optic nerve head examinations, IOP measurements, and visual field testing to monitor disease course

Risk Factors for POAG

A FIAT
Age
Family history
IOP
African descent
Thin cornea

Open- and Closed-Angle Glaucoma

POAG	PACG
• Common (95%)	• Rare (5%)
• Chronic course	• Acute onset
• Painless eye without redness	• Painful red eye
• Moderately ↑ IOP	• Extremely ↑ IOP
• Normal cornea and pupil	• Hazy cornea
• No N/V	• Mid-dilated pupil unreactive to light
• No halos around light	• ± N/V, abdominal pain
	• Halos around light

The Ocular Hypertension Treatment Study
Arch Ophthalmol-Chic 2002;120:701-713
Study: Randomized clinical trial.
Patients: 1,636 patients with no evidence of glaucomatous damage, aged 40-80 yr, and with IOP between 24-32 mmHg in one eye and between 21-32 mmHg in the other eye.
Intervention: Randomized to observation or treatment with commercially available topical ocular hypotensive medication.
Main Outcome: Development of visual field abnormality or optic disc deterioration attributed to POAG.
Results: Mean reduction in IOP in the medication group was 22.5% ± 9.9% vs. 4.0% ± 11.6% in the observation group. At 5 yr the probability of developing POAG was 4.4% in the medication group and 9.5% in the observation group ($p<0.0001$).
Conclusions: Topical ocular hypotensive medication was effective in delaying or preventing the onset of POAG in individuals with elevated IOP.

Normal Tension Glaucoma

- POAG with IOP in normal range
- often found in women >60 but may occur earlier
- associated with migraines, peripheral vasospasm, systemic nocturnal hypotension, sleep apnea
- damage to optic nerve may be due to vascular insufficiency

Treatment
- treat reversible causes

www.regentstudies.com

Secondary Open Angle Glaucoma

- increased IOP secondary to ocular/systemic disorders that obstruct the trabecular meshwork
  - steroid-induced glaucoma
  - traumatic glaucoma
  - pigmentary dispersion syndrome
  - pseudoexfoliation syndrome

Rule of Fours
1/4 of general population using topical steroid for 4 wk, 4 x/d will develop an increase in IOP

Primary Angle-Closure Glaucoma

- 5% of all glaucoma cases
- peripheral iris bows forward in an already susceptible eye with a shallow anterior chamber obstructing aqueous access to the trabecular meshwork
- sudden forward shift of the lens-iris diaphragm causes pupillary block, and results in inability of the aqueous to flow from the posterior chamber to the anterior chamber resulting in a sudden rise in IOP

Risk Factors
- hyperopia: small eye, big lens – large lens crowds the angle
- age >70 yr
- female
- family history
- more common in people of Asian and Inuit descent
- mature cataracts
- shallow anterior chamber
- pupil dilation (topical and systemic anticholinergics, stress, darkness)

Clinical Features
- red, painful eye = **RED FLAG**
- unilateral, but other eye increased risk
- decreased visual acuity, vision acutely blurred from corneal edema
- halos around lights
- nausea and vomiting, abdominal pain
- fixed, mid-dilated pupil
- corneal edema with conjunctival injection
- marked increase in IOP; may be noticeable even to palpation (>40 mmHg)
- shallow anterior chamber ± cells in anterior chamber

Complications
- irreversible loss of vision within hours to days if untreated
- permanent peripheral anterior synechiae, resulting in permanent angle closure

Treatment
- **OCULAR EMERGENCY**: refer to ophthalmologist for acute angle closure glaucoma
  - aqueous suppressants and hyperosmotic agents
- medical treatment (see *Glaucoma Medications*, Table 12, OP45)
  - miotic drops (pilocarpine) to reverse pupillary block
  - decrease IOP
    - topical β-blockers
    - topical adrenergics
    - topical cholinergics
      - pilocarpine 1-4% q15min, up to q5min
    - systemic carbonic anhydrase inhibitors
      - IV acetazolamide 250-500 mg
    - systemic hyperosmotic agents
      - oral glycerine 1 g/kg
      - IV mannitol 1 g/kg
- laser iridotomy

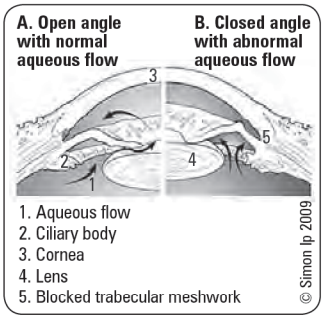


Figure 21. Normal open angle vs. angle-closure glaucoma

Angle Closure Glaucoma

BACH
Tx with miotics and **β**-blockers
Adrenergics
Cholinergics
Hyperosmotic agents

Collaborative Normal Tension Glaucoma Study
Curr Opin Ophthalmol 2003;14:86-90
Treatment aimed at lowering IOP by 30% in patients with normal tension glaucoma tends to reduce the rate of visual field loss. Due to variability in disease progression and a significant group that shows no visual field loss at 5 yr despite no treatment, further studies are needed to delineate which subgroups may benefit most from treatment.

Medical Interventions for Primary Open-Angle Glaucoma and Ocular Hypertension
Cochrane DB Syst Rev 2007;4:CD003167
Study: Cochrane systematic review of 26 trials and meta-analysis of 10 trials investigating the effectiveness of topical pharmacological therapies for POAG or OHT.
Patients: 4,979 participants randomized in 26 trials. Patients had OHT with IOP >21 mmHg or open angle glaucoma.
Intervention: Topical eye medications, including β-blockers, dorzolamide, brimonidine, pilocarpine, and epinephrine vs. each other and placebo.
Main Outcome: Reduction of progression or prevention of onset of visual field defects.
Results: Meta-analysis on all trials that tested drugs against placebo or untreated controls demonstrated that lowering IOP reduces incidence of glaucomatous visual field defects, with an odds ratio of 0.62 (95% CI 0.47-0.81). However, this result is of limited practical use since different therapies were pooled. No single drug demonstrated significant visual field protection. However, as a class, β-blockers showed borderline significance in reducing onset of glaucoma in patients with OHT when compared to placebo, with an OR of 0.67 (95% CI 0.45-1.00).
Conclusion: Lowering IOP can reduce progression of visual field defects in patients with OHT.

Secondary Angle-Closure Glaucoma

Uveitis
- inflamed iris adheres to lens (posterior synechiae)

Neovascular Glaucoma
- abnormal blood vessels develop on surface of iris (rubeosis iridis), in the angle, and within the trabecular meshwork
- due to retinal ischemia associated with PDR or CRVO
- treatment with laser therapy to retina reduces neovascular stimulus to iris vessels

www.regentstudies.com

Pupils

- pupil size is determined by the balance between the sphincter muscle and the dilator muscle
- sphincter muscle is innervated by the parasympathetic nervous system
  - carried by CN III: pre- and post-ganglionic fibres synapse in ciliary ganglion, and use acetylcholine as the neurotransmitter
- dilator muscle is innervated by the sympathetic nervous system (SNS)
  - first order neuron = hypothalamus → brainstem → spinal cord
  - second order/preganglionic neuron = spinal cord → sympathetic trunk via internal carotid artery → superior cervical ganglion in neck
  - third order/postganglionic fibres originate in the superior cervical ganglion, neurotransmitter is norepinephrine
    - as a diagnostic test, 4-10% cocaine prevents the re-uptake of norepinephrine, and will cause dilation of normal pupil, but not one with loss of sympathetic innervation (Horner's Syndrome)
  - see Neurology, Figure 8, N8

5 Targets of Retinal Signals
- Pre-tectal nucleus (pupillary reflex/eye movements)
- Lateral geniculate body of thalamus
- Superior colliculus (eye movements)
- Suprachiasmatic nucleus (optokinetic)
- Accessory optic system (circadian rhythm)

Pupillary Light Reflex

- light shone directly into eye travels along optic nerve (CN II, afferent limb) → optic tracts → bilateral midbrain
- impulses enter bilaterally in midbrain via pretectal area and Edinger-Westphal nuclei
- nerve impulses then travel down CN III (efferent limb) bilaterally to reach the ciliary ganglia, and finally to the iris sphincter muscle, which results in the direct and consensual light reflexes

α1 – Pupillary dilator muscle contraction (Mydriasis)
β2 – Ciliary muscle relaxation (Non-accommodation); increased aqueous humor production
M3 – Pupillary sphincter contraction (Miosis); increased ciliary muscle contraction (Accommodation)

Pupil Abnormalities

Denervation Hypersensitivity
- when post-ganglionic fibers are damaged, the understimulated end-organ attempts to compensate by developing an excess of neuroreceptors and becomes hypersensitive
- postganglionic parasympathetic lesions (i.e. Adie's pupil)
  - pupil will constrict with 0.125% pilocarpine (cholinergic agonist), normal pupil will not
- postganglionic sympathetic lesions (this test is used to differentiate between pre- and post-ganglionic lesions in Horner's syndrome)
  - pupil will dilate with 0.125% epinephrine, normal pupil will not

Local Disorders of Iris
- posterior synechiae (adhesions between iris and lens) due to iritis can present as an abnormally shaped pupil
- ischemic damage (e.g. post-acute angle-closure glaucoma) usually occurs at 3 and 9 o'clock positions resulting in a vertically oval pupil that reacts poorly to light
- trauma (e.g. post-intraocular surgery)

Anisocoria
- unequal pupil size
- idiopathic/physiologic anisocoria
  - 20% of population
  - round, regular, <1 mm difference
  - pupils reactive to light and accommodation
  - responds normally to mydiatrics/miotics
- post eye surgery
- see Table 7 for other causes of anisocoria

www.regentstudies.com

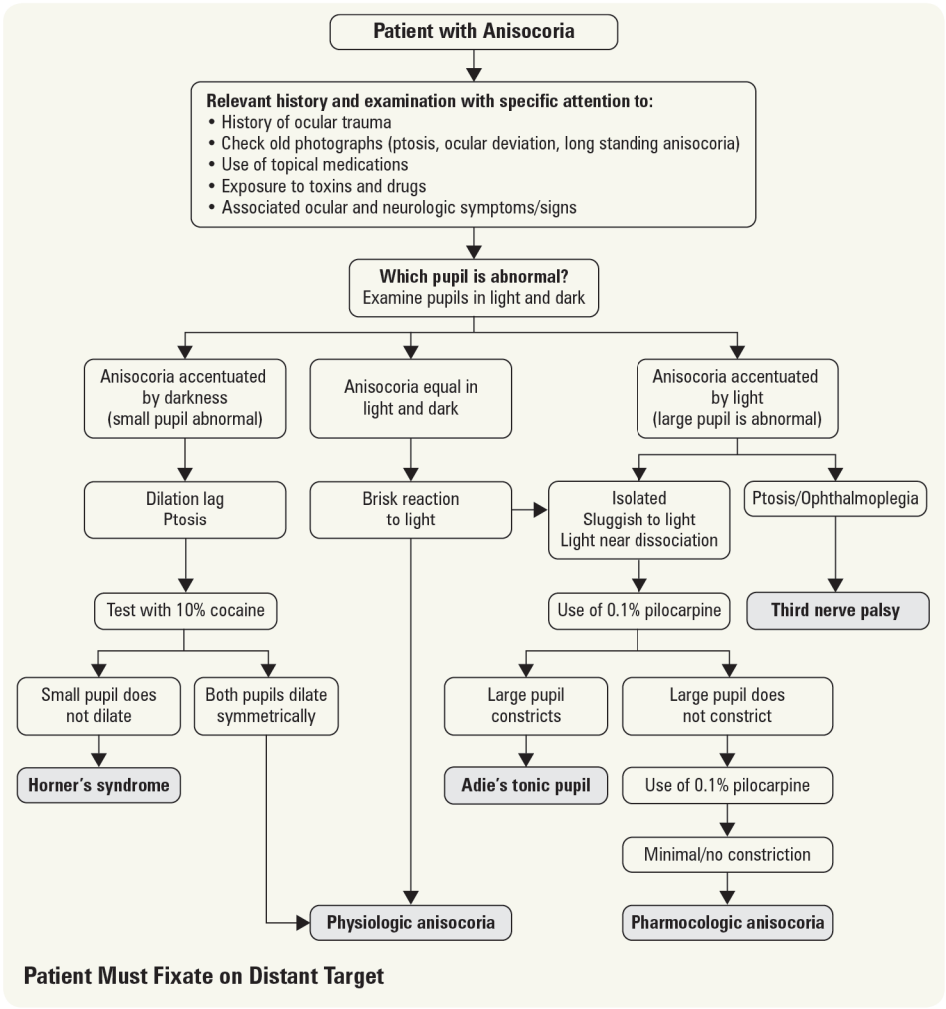


Figure 22. Approach to anisocoria

Reproduced with permission from: Kedar S, Biousse V, Newman NJ. *Approach to the patient with anisocoria.* In: UpToDate, Rose, BD (editor), UpToDate, Waltham, MA, 2011. Copyright 2011 UpToDate, Inc. For more information visit www.uptodate.com.

Table 7. Summary of Conditions Causing Anisocoria

	Features	Site of Lesion	Light and Accommodation	Anisocoria	Mydriatics/Miotics	Effect of Pilocarpine
ABNORMAL MIOTIC PUPIL (impaired pupillary dilation)						
Argyll-Robertson Pupil	Irregular, usually bilateral	Midbrain	Poor in light; better to accommodation		Dilates/Constricts	
Horner's Syndrome	Round, unilateral, ptosis, anhydrosis, pseudoenophthalmos	Sympathetic system	Both brisk	Greater in dark	Dilates/Constricts	
ABNORMAL MYDRIATIC PUPIL (impaired pupillary constriction)						
Adie's Tonic Pupil	Irregular, larger in bright light	Ciliary ganglion	Poor in light, better to accommodation	Greater in light	Dilates/Constricts	Constricts (hypersensitivity to dilute pilocarpine)
CN III Palsy	Round	Superficial CN III	± fixed (acutely) at 7-9 mm	Greater in light	Dilates/Constricts	Constricts
Mydriatic Pupil	Round, uni- or bilateral	Iris sphincter	Fixed at 7-8 mm	Greater in light	No effect	Will not constrict

www.regentstudies.com

Dilated Pupil (Mydriasis)

Sympathetic Stimulation
- fight or flight response
- mydriatic drugs: epinephrine, dipivefrin (Propine®), phenylephrine

Parasympathetic Understimulation
- cycloplegics/mydriatics: atropine, tropicamide, cyclopentolate (parasympatholytic)
- CN III palsy
  - eye deviated down and out with ptosis present
  - etiology includes stroke, neoplasm, aneurysm, acute rise in ICP, DM (may spare pupil), trauma
  - CN III palsy will respond to drugs (e.g. pilocarpine), unlike a pupil dilated from medication (mydriatics)

Acute Angle-Closure Glaucoma
- fixed, mid-dilated pupil

Adie's Tonic Pupil
- 80% unilateral, F>M
- pupil is tonic or reacts poorly to light (both direct and consensual) but constricts with accommodation
- if decreased deep tendon reflexes may be Adie's syndrome
- caused by benign lesion in ciliary ganglion; results in denervation hypersensitivity of parasympathetically innervated constrictor muscle
  - dilute (0.125%) solution of pilocarpine will constrict tonic pupil but have no effect on normal pupil
- long-standing Adie's pupils are smaller than unaffected eye

Trauma
- damage to iris sphincter from blunt or penetrating trauma
- iris transillumination defects may be apparent using ophthalmoscope or slit-lamp
- pupil may be dilated (traumatic mydriasis) or irregularly shaped from tiny sphincter ruptures

Constricted Pupil (Miosis)

Senile Miosis
- decreased sympathetic stimulation with age

Parasympathetic Stimulation
- local or systemic medications such as:
  - cholinergic agents: pilocarpine, carbachol
  - cholinesterase inhibitor: phospholine iodide
  - opiates, barbiturates

Horner's Syndrome
- lesion in sympathetic pathway
- difference in pupil size greater in dim light, due to decreased innervation of adrenergics to iris dilator muscle
- associated with ptosis, anhydrosis of ipsilateral face/neck
- application of cocaine 4-10% (blocks reuptake of norepinephrine) to eye does not result in pupil dilation (vs. physiologic anisocoria), therefore confirms diagnosis
- hydroxyamphetamine 1% (stimulates norepinephrine release) will dilate pupil if central or preganglionic lesion, not postganglionic lesion
- postganglionic lesions result in denervation hypersensitivity, which will cause pupil to dilate with 0.125% epinephrine, whereas normal pupil will not
- causes: carotid or subclavian aneurysm, brainstem infarct, demyelinating disease, cervical or mediastinal tumour, Pancoast tumour, goitre, cervical lymphadenopathy, surgical sympathectomy, Lyme disease, cervical ribs, tabes dorsalis, cervical vertebral fractures

Iritis
- miotic pupil initially
- later, may be irregularly shaped pupil due to posterior synechiae
- later stages non-reactive to light

CN III palsy with pupillary involvement may be associated with a posterior communicating artery aneurysm

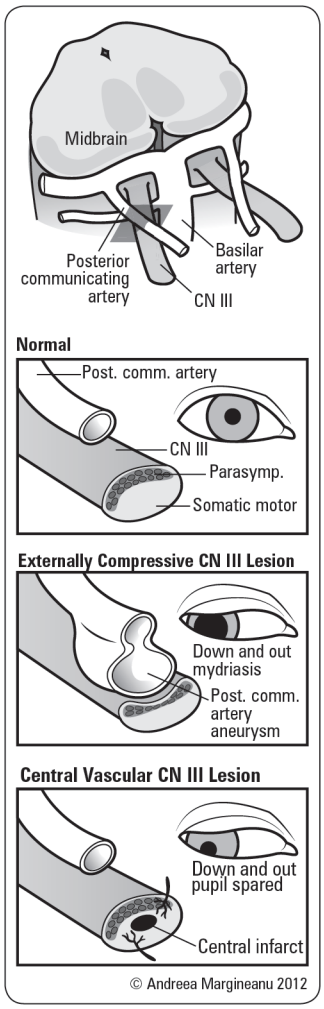


Figure 23. CN III lesions with and without mydriasis

Horner's MAP

Miosis
Anhydrosis
Ptosis

www.regentstudies.com

Argyll-Robertson Pupil

- both pupils irregular and <3 mm in diameter, ± ptosis
- does not respond to light stimulation
- responds to accommodation (light-near dissociation)
- suggestive of neurosyphilis or other conditions (DM, encephalitis, MS, chronic alcoholism, CNS degenerative diseases)

Argyll-Robertson Pupil

ARP-PRA
Accommodation **R**eflex **P**resent
Pupillary **R**eflex **A**bsent

Other Causes

- optic neuritis, retinal lesions

Relative Afferent Pupillary Defect

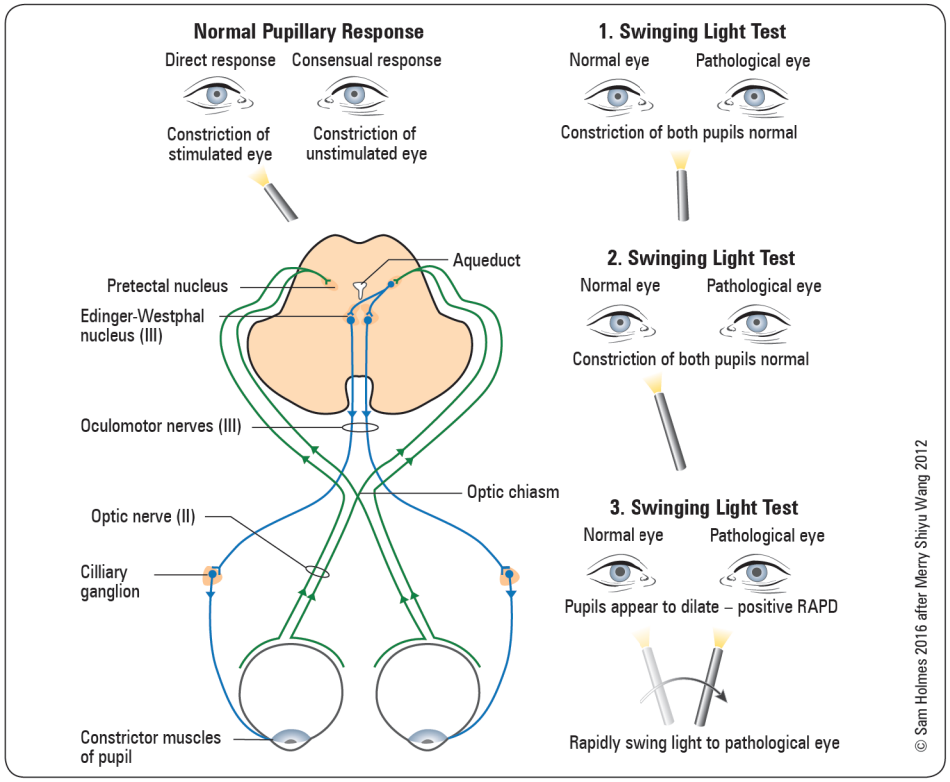


Figure 24. Relative afferent pupillary defect

- also known as Marcus Gunn pupil
- impairment of direct pupillary response to light, caused by a lesion in visual afferent (sensory) pathway anterior to optic chiasm
- differential diagnosis: large RD, BRAO, CRAO, CRVO, advanced glaucoma, optic nerve compression, optic neuritis (most common)
- does not occur with media opacity (e.g. corneal edema, cataracts)
- pupil reacts poorly to light and better to accommodation
- test: swinging flashlight
  - if light is shone in the affected eye, direct and consensual response to light is decreased
  - if light is shone in the unaffected eye, direct and consensual response to light is normal
  - if the light is moved quickly from the unaffected eye to the affected eye, "paradoxical" dilation of both pupils occurs
  - observe red reflex, especially in patients with dark irides
- if the defect is bilateral there is no RAPD, as dilation is measured relative to the other eye

Cataracts never produce an RAPD

It is possible to have RAPD and normal vision at the same time, e.g. in damaged superior colliculus caused by thalamic hemorrhage

Differentiate RAPD from physiologic pupillary athetosis ("hippus"), which is rapid, rhythmic fluctuations of the pupil, with equal amplitude in both eyes

www.regentstudies.com

Malignancies

- uncommon site for 1° malignancies
- eye usually affected secondarily by cancer or cancer treatments
- see *Retinoblastoma*, OP41

Lid Carcinoma

Etiology

- basal cell carcinoma (rodent ulcer) (90%)
  - spread via local invasion, rarely metastasizes
  - ulcerated centre, indurated base with pearly rolled edges, telangiectasia
- squamous cell carcinoma (<5%)
  - spread via local invasion, may also spread to nodes and metastasize
  - ulceration, keratosis of lesion
- sebaceous cell carcinoma (1-5%)
  - often masquerades as chronic blepharitis or recurrent chalazion
  - highly invasive, metastasize
- Kaposi's sarcoma, malignant melanoma, Merkel cell tumour, metastatic tumour

Treatment

- incisional or excisional biopsies
- may require cryotherapy, radiotherapy, chemotherapy, immunotherapy
- surgical reconstruction

Malignant Melanoma

- most common 1° intraocular malignancy in adults
- more prevalent in Caucasians
- arise from uveal tract, 90% choroidal melanoma
- hepatic metastases predominate

Treatment

- imaging to investigate spread
- depending on the size of the tumour, either radiotherapy, enucleation, limited surgery

Metastases

- most common intraocular malignancy in adults
- most commonly from breast and lung in adults, neuroblastoma in children
- usually infiltrate the choroid, but may also affect the optic nerve or extraocular muscles
- may present with decreased or distorted vision, irregularly shaped pupil, iritis, hyphema

Treatment

- local radiation, chemotherapy
- enucleation if blind, painful eye

Ocular Manifestations of Systemic Disease

HIV/AIDS

- up to 75% of patients with AIDS have ocular manifestations

External Ocular Signs

- Kaposi's sarcoma
  - secondary to human herpes virus 8 (HHV-8), affects conjunctiva of lid or globe
  - numerous vascular skin malignancies
  - differential diagnosis: subconjunctival hemorrhage (non-clearing), hemangioma
- multiple molluscum contagiosum
- herpes simplex keratitis
- herpes zoster keratitis

www.regentstudies.com

Retina

- HIV retinopathy (most common)
  - cotton wool spots in >50% of HIV patients
  - intraretinal hemorrhage
- CMV retinitis
  - ocular opportunistic infection that develops in late stages of HIV when severely immunocompromised (CD4 count ≤50)
  - a necrotizing retinitis, with retinal hemorrhage and vasculitis, "brushfire" or "pizza pie" appearance
  - presents with scotomas (macular involvement and RD), blurred vision, and floaters
  - untreated infection will progress to other eye in 4-6 wk
  - treatment: virostatic agents (e.g. gancyclovir or foscarnet) via IV or intravitreal injection
- necrotizing retinitis
  - from herpes simplex virus, herpes zoster, toxoplasmosis
- disseminated choroiditis
  - *Pneumocystis carinii, Mycobacterium avium intracellulare, Candida*

Other Systemic Infections

- herpes zoster
  - see *Herpes Zoster*, OP19
- candidal endophthalmitis
  - fluffy, white-yellow, superficial retinal infiltrate that may eventually result in vitritis
  - may present with inflammation of the anterior chamber
  - treatment: systemic amphotericin B, oral fluconazole
- toxoplasmosis
  - focal, grey-yellow-white, chorioretinal lesions with surrounding vasculitis and vitreous infiltration (vitreous cells)
  - can be congenital (transplacental) or acquired (caused by *Toxoplasma gondii* protozoa transmitted through raw meat and cat feces)
  - congenital form more often causes visual impairment (more likely to involve the macula)
  - treatment: pyrimethamine, sulfonamide, folinic acid, or clindamycin. Consider adding steroids if severe inflammation (vitritis, macular or optic nerve involvement)

Diabetes Mellitus

- see Endocrinology, E7
- most common cause of blindness in young people in North America
- consider DM if unexplained retinopathy, cataract, extraocular muscle palsy, optic neuropathy, sudden change in refractive error
- loss of vision due to
  - progressive microangiopathy leading to macular edema
  - progressive DR → neovascularization → traction → RD and vitreous hemorrhage
  - rubeosis iridis (neovascularization of the iris) leading to neovascular glaucoma (poor prognosis)
  - macular ischemia

Macular edema is the most common cause of visual loss in patients with background DR

DIABETIC RETINOPATHY

Background

- altered vascular permeability (loss of pericytes, breakdown of blood-retinal barrier, thickening of basement membrane)
- predisposition to retinal vessel obstruction (CRAO, CRVO, and BRVO)

Classification

- **non-proliferative:** increased vascular permeability and retinal ischemia
  - microaneurysms
  - dot and blot hemorrhages
  - hard exudates (lipid deposits), non-specific for DR
  - macular edema
- **advanced non-proliferative (or pre-proliferative)**
  - non-proliferative findings plus:
    - venous beading (in ≥2 of 4 retinal quadrants)
    - intraretinal microvascular anomalies (IRMA) in 1 of 4 retinal quadrants
      - IRMA: dilated, leaky vessels within the retina
    - cotton wool spots (nerve fibre layer infarcts)
- **proliferative**
  - 5% of patients with DM will reach this stage

Expanded 2 Year Follow-Up of Ranizumab Plus Prompt or Deferred Laser or Triamcinuclone Plus Prompt Laser for Diabetic Macular Edema
Ophthalmology 2011;118:609-614
Ranibizumab (Lucentis®) with prompt or deferred laser is more effective than intravitreal corticosteroid injections + laser or laser alone with sustained efficacy up to 24 mo.

www.regentstudies.com

- neovascularization of iris, disc, retina to vitreous
  - neovascularization of iris (rubeosis iridis) can lead to neovascular glaucoma
  - vitreous hemorrhage from bleeding, fragile new vessels, fibrous tissue can contract causing tractional RD
- high risk of severe vision loss secondary to vitreous hemorrhage, RD

Screening Guidelines for Diabetic Retinopathy

- type 1 DM
  - screen for retinopathy beginning annually 5 yr after disease onset
  - annual screening indicated for all patients over 12 yr and/or entering puberty
- type 2 DM
  - initial examination at time of diagnosis, then annually
- pregnancy
  - ocular exam in 1st trimester, close follow-up throughout as pregnancy can exacerbate DR
  - gestational diabetics are not at risk for DR

Treatment

- Diabetic Control and Complications Trial (DCCT)
  - tight control of blood sugar decreases frequency and severity of microvascular complications
- blood pressure control
- focal laser for clinically significant macular edema
- intravitreal injection of corticosteroid or anti-VEGF for foveal involved diabetic macular edema
- panretinal laser photocoagulation for PDR: reduces neovascularization, hence reducing the angiogenic stimulus from ischemic retina by decreasing retinal metabolic demand → reduces risk of blindness
- vitrectomy for non-clearing vitreous hemorrhage and tractional RD in PDR
- vitrectomy before vitreous hemorrhage does not improve the visual prognosis

Lens Changes

- earlier onset of senile nuclear sclerotic and cortical cataracts
- may get hyperglycemic cataract, due to sorbitol accumulation (rare)
- changes in blood glucose levels (poor control) can suddenly cause refractive changes by 3-4 diopters

Extraocular Muscle Palsy

- usually CN III infarct
- pupil usually spared in diabetic CN III palsy, but ptosis is observed
- may involve CN IV and VI
- usually recover within few months

Optic Neuropathy

- visual acuity loss due to infarction of optic disc/nerve

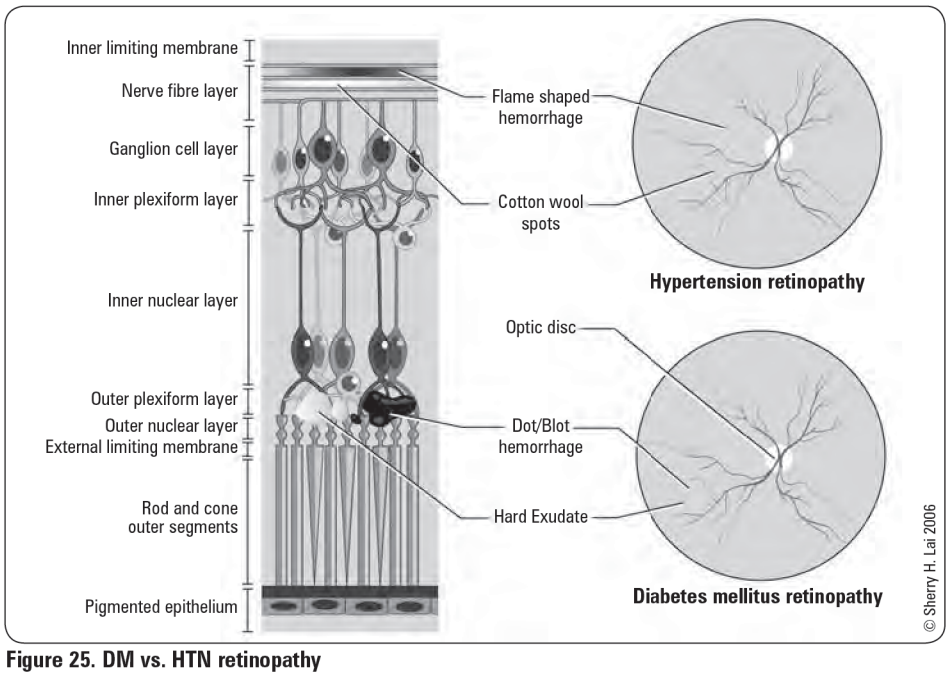


Figure 25. DM vs. HTN retinopathy

Clinically significant macular edema is defined as thickening of the retina at or within 500 μm of the centre of the macula

Presence of DR in Type 1 DM
- 25% after 5 yr
- 60% after 10 yr
- >80% after 15 yr

Type 2 DM
- 20% at time of diagnosis
- 60% after 20 yr

Effects of Medical Therapies on Retinopathy Progression in Type 2 DM
NEJM 2010;363:233-244

Purpose: To determine whether or not intensive glycemic control, combination therapy for dyslipidemia, and intensive blood-pressure control may limit the progression of DR in persons with type 2 DM.

Methods: RCT with 10,251 participants with type 2 DM at high risk of cardiovascular disease. Intensive or standard treatment for glycemia (glycated hemoglobin level <6.0% or 7.0-7.9%), dyslipidemia (160 mg daily fenofibrate plus simvastatin or placebo plus simvastatin), or systolic blood-pressure control (target <120 or <140 mm Hg).

Results: Rates of progression of DR at 4 yr were 7.3% with intensive glycemia treatment vs. 10.4% with standard therapy (OR 0.67; 95% CI 0.51-0.87); 6.5% with fenofibrate for intensive dyslipidemia therapy vs. 10.2% with placebo (OR 0.60; 95% CI 0.42-0.87) and 10.4% with intensive blood-pressure therapy vs. 8.8% with standard therapy (OR 1.23; 95% CI 0.84-1.79).

Conclusions: Intensive glycemic control and intensive combination treatment of dyslipidemia, but not intensive blood-pressure control, reduced the rate of DR.

www.regentstudies.com

Hypertension

- retinopathy is the most common ocular manifestation
- chronic HTN retinopathy: arteriovenous (AV) nicking, blot retinal hemorrhages, microaneurysms, cotton wool spots
- acute HTN retinopathy: retinal arteriolar spasm, superficial retinal hemorrhage, cotton wool spots, optic disc edema

Table 8. Keith-Wagener-Barker Classification

Group 1	Mild arterial narrowing
Group 2	Obvious arterial narrowing with focal irregularities
Group 3	Group 2 characteristics plus: Cotton wool spots Hemorrhage and/or exudate
Group 4	Group 3 plus papilledema

Multiple Sclerosis

- see Neurology, N54

Clinical Features

- blurred vision and decreased colour vision: secondary to optic neuritis
- central scotoma: due to damage to papillomacular bundle of retinal nerve fibres
- diplopia: secondary to INO
- RAPD, ptosis, nystagmus, uveitis, optic atrophy, optic neuritis
- white matter demyelinating lesions of optic nerve on MRI

Treatment

- IV steroids with taper to oral form for optic neuritis
  - DO NOT treat with oral steroids in isolation as this increases likelihood of eventual development of MS

Corticosteroids for Treating Optic Neuritis
Cochrane DB Syst Rev 2012;4:CD001430
Purpose: To assess the effects of corticosteroids on visual recovery in patients with acute optic neuritis.
Results/Conclusions: 6 RCTs, 750 participants. Follow-up at 6 mo or one yr. There is no conclusive evidence of benefit with respect to recovery to normal visual acuity, visual field or contrast sensitivity with either intravenous or oral corticosteroids at the doses evaluated in included trials.

TIA/Amaurosis Fugax

- sudden, transient blindness from intermittent vascular compromise
- ipsilateral carotid most frequent embolic source
- typically monocular, lasting <5-10 min
- Hollenhorst plaques (glistening microemboli seen at branch points of retinal arterioles)

Graves' Disease

- ophthalmopathy occurs despite control of thyroid gland status
- ocular manifestations occur secondary to sympathetic overdrive and/or specific inflammatory infiltrate of the orbital tissue

Clinical

- initial inflammatory phase is followed by a quiescent cicatricial phase

Treatment

- treat hyperthyroidism
- monitor for corneal exposure and maintain corneal hydration
- manage diplopia, proptosis and compressive optic neuropathy with one or a combination of:
  - steroids (during acute phase)
  - orbital bony decompression
  - external beam radiation of the orbit
- consider strabismus and/or eyelid surgical procedures once acute phase subsides

The most common cause of unilateral or bilateral proptosis in adults is Graves' disease

Progression of Signs and Symptoms of Graves' Ophthalmopathy

NO SPECS
No signs/symptoms
Only signs (lid retraction, lid lag)
Soft tissue swelling (periorbital edema)
Proptosis (exophthalmos)
Extraocular muscle weakness (causing diplopia)
Corneal exposure
Sight loss

Connective Tissue Disorders

- RA, juvenile idiopathic arthritis, SLE, Sjögren syndrome, ankylosing spondylitis, polyarteritis nodosa
- most common ocular manifestation: dry eyes (keratoconjunctivitis sicca)

www.regentstudies.com

Giant Cell Arteritis/Temporal Arteritis

- see Rheumatology, RH20

Clinical Features
- more common in women >60 yr
- abrupt monocular loss of vision, pain over the temporal artery, jaw claudication, scalp tenderness, constitutional symptoms, and past medical history of polymyalgia rheumatica
- ischemic optic atrophy
  - 50% lose vision in other eye if untreated

Diagnosis
- temporal artery biopsy + increased ESR (ESR can be normal, but likely 80-100 in first hour), increased CRP
- if biopsy of one side is negative, biopsy the other side

Treatment
- high dose corticosteroid to relieve pain and prevent further ischemic episodes
- if diagnosis of GCA is suspected clinically: start treatment + perform temporal artery biopsy to confirm diagnosis within 2 wk of initial presentation (**DO NOT WAIT TO TREAT**)

ESR in Temporal Arteritis
Males > age/2
Females > (age + 10)/2

Does this Patient have Temporal Arteritis?
JAMA 2002;287:92-101
Rule in: jaw claudication and diplopia on history, temporal artery beading, prominence of the artery and tenderness over the artery on exam.
Rule out: no temporal artery abnormalities on exam, normal ESR.

Sarcoidosis

- granulomatous uveitis with large "mutton fat" keratitic precipitates and posterior synechiae
- neurosarcoidosis: optic neuropathy, oculomotor abnormalities, visual field loss

Treatment
- steroids and mydriatics

Pediatric Ophthalmology

Strabismus

- ocular misalignment in one or both eyes, found in 3% of children
- object not visualized simultaneously by fovea of each eye
- terms used to describe strabismus depend upon
  - direction of deviation relative to the correctly fixating eye
  - conditions under which it presents: 'latent', 'manifest' misalignment
  - change with the position of gaze: 'comitant' (usually nonparalytic), 'incomitant' (usually occurs with paralytic or restrictive strabismus)
- often presents with parental concern about a wandering eye, crossing eye, or poor vision
- elicit a detailed family history of strabismus, amblyopia, type of eyeglasses and history of wear, extraocular muscle surgery or other eye surgery, and genetic diseases to identify children at higher risk
- distinguish from pseudostrabismus (prominent epicanthal folds, hypertelorism, markedly positive or negative angle κ)
- complications: amblyopia, cosmesis

Strabismus in children under 4 mo of age sometimes resolves, particularly if the deviation is intermittent, variable, or measures <40 prism diopters

All children with strabismus and/or possible reduced vision require prompt referral to an ophthalmologist

HETEROTROPIA
- manifest deviation
- deviation not corrected by the fusion mechanism (i.e. deviation is apparent when the patient is using both eyes)

Types
- exo- (lateral deviation), eso- (medial deviation)
- hyper- (upward deviation), hypo- (downward deviation)
- esotropia = "crossed-eyes"; exotropia = "wall-eyed"

Differentiate from Pseudostrabismus
- prominent epicanthal folds: give appearance of esotropia but Hirschberg test is normal, more common in Asians
- markedly elevated angle κ (the angle formed by the pupillary axis and the visual axis at the centre of the pupil)
  - caused by the failure of optical axis of the eye and the visual axis to coincide
  - a small positive (up to 5°) angle κ is physiologic
  - a large positive angle κ (nasally deviated fovea) simulates eso-appearance
  - a large negative angle κ (temporally deviated fovea) gives an exo-appearance

www.regentstudies.com

Tests
- Hirschberg test (corneal light reflex): positive if the light reflex on both corneas is asymmetrical
  - light reflex lateral to central cornea indicates esodeviation; light reflex medial to central cornea indicates exodeviation
  - false positives occur if visual axis and anatomic pupillary axis of the eye are not aligned (angle κ)
- cover test
- the deviation can be quantified using prisms

HETEROPHORIA
- latent deviation
- deviation corrected in the binocular state by the fusion mechanism (i.e. deviation not seen when patient is focusing with both eyes)
- Hirschberg test will be normal (light reflexes symmetrical)
- very common – majority are asymptomatic
- may be exacerbated or become manifest with asthenopia (eye strain, fatigue)

Tests
- cover-uncover test
- alternate cover test
  - alternating the cover between both eyes reveals the total deviation, both latent and manifest
  - maintain cover over one eye for 2-3 s before rapidly shifting to other eye

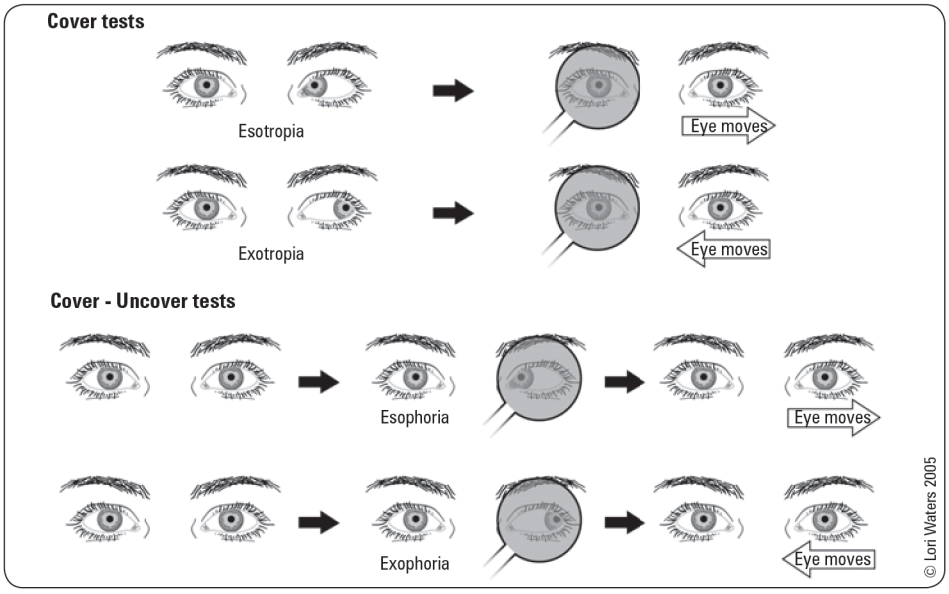


Figure 26. Cover and cover-uncover tests for detection of tropias and phorias

Table 9. Paralytic vs. Non-Paralytic Strabismus

Clinical Characteristics	Paralytic Strabismus	Nonparalytic Strabismus
Definition	Incomitant strabismus	Concomitant strabismus
Onset	Often sudden but may be gradual or congenital	Usually gradual or shortly after birth; rarely sudden
Age of Onset	Any age; most often acquired	Usually during infancy
Etiology	Reduction or restriction in range of eye movements due to: • Neural (CN III, IV, VI): ischemia (e.g. DM), MS, aneurysm, brain tumour, trauma • Muscular: myasthenia gravis (neuromuscular junction pathology), Graves' disease • Structural: restriction or entrapment of extraocular muscles due to orbital inflammation, tumour, fracture of the orbital wall	Develops early in childhood No restriction in range of eye movements Monocular, alternating, or intermittent
Diplopia	Common	Uncommon; image from the misaligned eye is suppressed (see *Amblyopia*, OP40)
Visual Acuity in Other Eye	Usually unaffected in the other eye, unless CN II is involved	Deviated eye may become amblyopic if not treated when the child is young Amblyopia treatment rarely successful after age 8-10 yr Amblyopia usually does not develop if child has alternating strabismus or intermittency, which allows neural pathways for both eyes to develop
Possibility of Amblyopia	Uncommon	Common
Neurologic Findings or Systemic Disease	May be present	Usually absent

www.regentstudies.com

Accommodative Esotropia
- normal response to approaching object is the triad of the near reflex: convergence, accommodation and miosis
- hyperopes must constantly accommodate – excessive accommodation can lead to esotropia in young children via over-activation of the near reflex
- average age of onset is 2.5 yr
- usually reversible with correction of refractive error

Non-accommodative Esotropia
- accounts for 50% of childhood strabismus
- most are idiopathic
- may be due to monocular visual impairment (e.g. cataract, corneal scarring, anisometropia, retinoblastoma) or divergence insufficiency (ocular misalignment that is greater at distance fixation than at near fixation)

Amblyopia

Definition
- a neurodevelopmental visual disorder with unilateral (or less commonly, bilateral) reduction of best corrected visual acuity that cannot be attributed only and directly to the effect of a structural abnormality of the eye. It is caused by abnormal visual experience early in life and cannot be remedied immediately by spectacle glasses alone
- in approximately half of the cases, amblyopia is secondary to strabismus (mainly esotropia). Other causes may include uncorrected refractive errors, anisometropia (asymmetric refractive errors), and concomitant structural ocular problems

Detection
- "Holler Test": young child upset if good eye is covered
- quantitative visual acuity by age 3-4 yr using picture charts and/or matching game (Sheridan-Gardiner), testing each eye separately
- amblyopia treatment less successful after age 8-10 yr, but a trial should be given no matter what age
- prognosis: 90% will have good vision restored and maintained if treated <4 yr old

Etiology and Management
- strabismus
  - correct with glasses for accommodative esotropia (50% of children experience relief of their esotropia with glasses and will not require surgery)
  - occlusion of unaffected eye forces brain to use previously strabismic eye; aims to bring vision in previously suppressed eye to normal before surgery
  - surgery: recession (weakening) – moving muscle insertion further back on the globe; or resection (strengthening) – shortening the muscle
  - botulinum toxin for single muscle weakening
  - after ocular alignment is restored (glasses, surgery, botulinum toxin), patching is frequently necessary to maintain vision until ~8 yr of age
- anisometropia
  - amblyopia usually in the more hyperopic eye
  - the more emmetropic (normal refraction) eye receives a clear image while the less emmetropic eye receives a blurred image; input from the blurred eye is cortically suppressed and visual pathway fails to develop normally
  - treat with glasses to correct refractive error
  - patching is required if visual acuity difference persists after 4-8 wk of using glasses
- deprivation amblyopia
  - occlusion due to ptosis, cataract, retinoblastoma, corneal opacity
  - occlusion amblyopia: prolonged patching of good eye may cause it to become amblyopic

Occlusion Therapy
- patching the good eye to force the brain to use the non-dominant eye and redevelop its vision
- atropine cycloplegic drops to impair accommodation and blur vision of the better seeing eye

Risks
- permanent loss of vision in the affected eye
- possibility of injury to 'remaining' good eye
  - safety glasses or polycarbonate lenses recommended if visual acuity in worse eye is <20/50
- loss of stereopsis

www.regentstudies.com

Leukocoria

- white reflex (red reflex is absent)

Differential Diagnosis
- cataract
- retinoblastoma
- retinal coloboma
- ROP
- persistent hyperplastic primary vitreous
- Coat's disease (exudative retinal telangiectasis)
- toxocariasis
- RD

Retinoblastoma

- most common primary intraocular malignancy in children
- incidence: 1/15,000; sporadic or genetic transmission; screening of siblings/offspring essential
- unilateral (2/3) or bilateral (1/3)
- malignant – direct or hematogenous spread
- diagnosis
  - often presents with leukocoria or strabismus
  - U/S or CT scan may demonstrate calcified mass (present in most cases)

Treatment
- radiotherapy, chemotherapy combined with laser, cryopexy, and/or enucleation

Retinopathy of Prematurity

- vasoproliferative retinopathy that is a major cause of blindness in the developed world

Risk Factors
- non-black race (black infants have lower risk of developing ROP)
- low gestational age, birth weight <1500 g
- high oxygen exposure after birth (iatrogenic)

Classification (ROP Staging)
- stage 1: faint demarcation line at the junction between the vascularized and avascular retina
- stage 2: elevated ridge
- stage 3: extra-retinal fibrovascular tissue extending into vitreous
- stage 4: partial RD (4A: macula "on", 4B: macula "off")
- stage 5: total RD
- plus (+) disease: dilatation and tortuosity of retinal vessels
- threshold disease: stage 3+ in zones 1 or 2 with 5 continuous or 8 cumulative clock hours of ROP involvement

Treatment
- threshold disease is treated with cryotherapy or laser (laser is now the standard treatment, with better refractive outcome), off label anti-VEGF intravitreal injections
- ROP beyond threshold level is either watched carefully (usually stage 4A) or treated with vitrectomy/scleral buckle

Prognosis
- higher incidence of myopia among ROP infants, even if treated successfully
- stage 4B and 5 have poor prognosis for visual outcome despite treatment

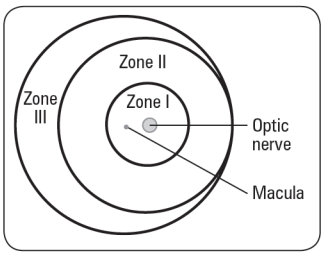


Figure 27. Zones of the retina in ROP

Retinal Zones
- Zone I: circle with radius twice the distance from the disc to the macula (most difficult to treat)
- Zone II: annulus from zone I to nasal extent of retina (nasal ora serrata)
- Zone III: remaining retina

Efficacy of Intravitreal Bevacizumab for Stage 3+ Retinopathy of Prematurity (ROP)
NEJM 2011;364:603-615
Study: Randomized controlled clinical trial.
Patients: 150 infants born at gestational age ≤30 wk and birth weight ≤1500 g.
Intervention: Randomized to conventional laser therapy or intravitreal bevacizumab monotherapy.
Main Outcome: Recurrence of ROP in one or both eyes requiring retreatment before 54 wk postmenstrual age.
Results: ROP recurrence was lower in the bevacizumab group (6 of 140 eyes [4%]) vs. the laser-therapy group (32 of 146 eyes [22%]) (p=0.002). A significant treatment effect was found for zone I ROP (p=0.003).
Conclusions: Intravitreal bevacizumab monotherapy is beneficial for infants with zone I state 3+ ROP and allows continued development of peripheral retinal vessels following treatment.

Nasolacrimal System Defects

- congenital obstruction of the nasolacrimal duct (failure of canalization), usually occurs at 1-2 mo of age
- epiphora, crusting, discharge, recurrent conjunctivitis
- can have reflux of mucopurulent material from lacrimal punctum when pressure is applied over lacrimal sac

Treatment
- massage over lacrimal sac at medial corner of eyelid
- vast majority spontaneously resolve in 9-12 mo, otherwise consider referral for duct probing

www.regentstudies.com

Ophthalmia Neonatorum

- newborn conjunctivitis in first mo of life
- causes
  - toxic: silver nitrate, erythromycin
  - infectious: bacterial (e.g. *N. gonorrhoeae* – most common, *C. trachomatis*), herpes simplex virus
- diagnose using stains and cultures

Gonococcal infection is the most serious threat to sight as it can rapidly penetrate corneal epithelium, causing corneal ulceration

Treatment
- systemic antibiotics with possible hospitalization if infectious etiology
- topical prophylaxis, most commonly with erythromycin (or silver nitrate), is required by law at birth

Congenital Glaucoma

- due to inadequate development of the filtering mechanism of the anterior chamber angle

Clinical Features
- cloudy cornea, increased IOP
- photophobia, epiphora
- buphthalmos (large cornea, "ox eye", secondary to increased IOP), blepharospasm

Epiphora in children – rule out congenital glaucoma

Treatment
- filtration surgery is required soon after birth to prevent blindness

Ocular Trauma

Blunt Trauma

- caused by blunt object such as fist, squash ball
- history: injury, ocular history, drug allergy, tetanus status
- exam: VA first, pupil size and reaction, EOM (diplopia), external and slit-lamp exam, ophthalmoscopy
- if VA normal or slightly reduced, globe less likely to be perforated
- if VA reduced may be perforated globe, corneal abrasion, lens dislocation, retinal tear
- bone fractures
  - blow out fracture: restricted EOM, diplopia, enophthalmos (sunken eye)
  - ethmoid fracture: subcutaneous emphysema of lid
- lids: swelling, laceration, emphysema
- conjunctiva: subconjunctival hemorrhage
- cornea: abrasion – detect with fluorescein staining and cobalt blue filter using slit-lamp or ophthalmoscope
- anterior chamber: assess depth, hyphema, hypopyon
- iris: prolapse, iritis
- lens: cataract, dislocation
- retinal tear/detachment

Always test VA first – medicolegal protection

Refer if You Observe Any of These Signs
- Decreased VA
- Shallow anterior chamber
- Hyphema
- Abnormal pupil
- Ocular misalignment
- Retinal damage

Penetrating Trauma

- include ruptured globe ± prolapsed iris, intraocular foreign body
- rule out intraocular foreign body, especially if history of "metal striking metal", orbit CT
- **OCULAR EMERGENCY**: initial management - REFER IMMEDIATELY
  - ABCs
  - don't press on eye globe!
  - don't check IOP if possibility of globe rupture
  - check vision, diplopia
  - apply rigid eye shield to minimize further trauma
  - keep head elevated 30-45° to keep IOP down
  - keep NPO
  - tetanus status
  - give IV antibiotics
    - selecting appropriate agents depends on the mechanism of injury; gram positive bacteria are more commonly involved than gram negatives; retained intraocular foreign objects increase the risk of infections with Bacillus species, whereas exposure to vegetable matter increased the risk of a fungal etiology

Management of Suspected Globe Rupture

CAN'T forget
CT orbits
Ancef (cefazolin) ± **A**minoglycoside IV
NPO
Tetanus status

Post-Traumatic Infectious Endophthalmitis
Surv Ophthalmol 2011;56:214-251
- Delayed primary repair (>24 h after open globe injury) increases risk for post-traumatic endophthalmitis in the absence of an intraocular foreign body (IOFB).
- If IOFB present, early vitrectomy and IOFB removal must be performed within 24 h of injury.
- Extreme pain with hypopyon and vitritis indicate endophthalmitis until proven otherwise, and samples must be obtained.
- Treat with empirical intravitreal and intravenous antibiotic guided by nature of trauma, and adjust based on culture.

www.regentstudies.com

Hyphema

- blood in anterior chamber often due to damage to root of the iris
- may occur with blunt trauma

Treatment
- refer to ophthalmology
  - shield and bedrest x 5 d or as determined by ophthalmologist
  - sleep with head upright
- may need surgical drainage if hyphema persists or if re-bleed

Complications
- risk of re-bleed highest on days 2-5, resulting in secondary glaucoma, corneal staining, and iris necrosis
- never prescribe Aspirin®, as it increases the risk of a re-bleed

Shaken Baby Syndrome
Syndrome of findings characterized by absence of external signs of abuse with respiratory arrest, seizures, or coma. Ocular exam findings are important diagnostically for Shaken Baby Syndrome. These findings include extensive retinal and vitreous hemorrhages that occur during the shaking process and are extremely rare in accidental trauma. A detailed fundoscopic exam or an ophthalmology referral should be conducted for all infants in whom abuse is suspected.

Blow-Out Fracture

- see Plastic Surgery, PL32
- blunt trauma causing fracture of orbital floor and herniation of orbital contents into maxillary sinus
- orbital rim remains intact
- inferior rectus and/or inferior oblique muscles may be incarcerated at fracture site
- infraorbital nerve courses along the floor of the orbit and may be damaged

Clinical Features
- pain and nausea at time of injury
- diplopia, restriction of EOM
- infraorbital and upper lip paresthesia (CN V2)
- enophthalmos (sunken eye), periorbital ecchymoses

Classic Signs of Blow-Out
- Enophthalmos
- Decreased upgaze (IR trapped)
- Cheek anesthetized (infraorbital nerve trapped)

Investigations
- plain films: Waters' view and lateral
- CT: anteroposterior and coronal view of orbits

Treatment
- refrain from coughing, blowing nose
- systemic antibiotics may be indicated
- surgery if fracture >50% orbital floor, diplopia not improving, or enophthalmos >2 mm
- may delay surgery if the diplopia improves

Chemical Burns

- alkali burns have a worse prognosis than acid burns because acids coagulate tissue and inhibit further corneal penetration
- poor prognosis if cornea opaque, likely irreversible stromal damage
- even with a clear cornea initially, alkali burns can progress for weeks (thus, very guarded prognosis)

Fluorescein lights up alkali so you can detect it and assess whether it has been removed

Treatment
- immediately irrigate at site of accident with water or buffered solution
  - IV drip for at least 20-30 min with eyelids retracted in emergency department
  - swab upper and lower fornices to remove possible particulate matter
- do not attempt to neutralize because the heat produced by the reaction will damage the cornea
- cycloplegic drops to decrease iris spasm (pain) and prevent secondary glaucoma (due to posterior synechiae formation)
- topical antibiotics and patching
- topical steroids (by ophthalmologist) to decrease inflammation, use for <2 wk (in the case of a persistent epithelial defect)

www.regentstudies.com

Surgical Ophthalmology

- **dacrocystorhinostomy (DCR):** excision of bone covering the nasolacrimal sac to restore tear drainage
- **blepharoplasty:** occuloplastic surgical correction of the eyelid by the excision and removal or repositioning of excess skin, fat, and/or the reinforcement of the corresponding muscle and tendon
- **LASIK (laser-assisted *in situ* keratomileusis):** a microkeratome is used to create a corneal flap followed by laser remodeling of the stroma to correct refractive error
- **trabeculectomy:** creation of a new outflow tract from anterior chamber to under conjunctiva; fibrosis prevented with mitomycin C or 5-FU injection during surgery
- **phacoemulsification (cataract extraction):** the use of ultrasonic waves to break up and aspirate a cataract followed by replacement with an artificial lens implant
- **femtosecond laser–assisted cataract surgery**: uses focused ultrashort pulses (10^{-15} of a second) to perform photodissection in achieving capsulorrhexis and lens fragmentation
- **vitrectomy**: the use of small gauge trochars to enter the posterior segment and remove vitreous; commonly used to treat vitreous hemorrhage and RD
- **pneumatic retinopexy**: intraocular injection of air or an expandable gas in order to tamponade a retinal break for repair of RD
- **scleral buckle**: a silicone band is secured on the outside of the globe that indents the eye wall, thereby relieving vitreous traction on the retina around any tears/holes and allowing the tears/holes to remain sealed for repair of RD
- **minimally invasive glaucoma surgery (MIGS):** implantation of IOP lowering drainage devices (e.g. iStent) through an ab interno microincisional approach during cataract surgery.

Ocular Drug Toxicity

Table 10. Drugs with Ocular Toxicity

Amiodarone	Corneal microdeposits and superficial keratopathy (vortex keratopathy) Rare: ischemic optic neuropathy
Atropine, benztropine	Pupillary dilation (risk of angle closure glaucoma)
Bisphosphonates (Fosamax®, Actonel®)	Inflammatory eye disease (iritis, scleritis, episcleritis)
Chloroquine, hydroxychloroquine	Bull's eye maculopathy Vortex keratopathy
Chlorpromazine	Anterior subcapsular cataract
Contraceptive pills	Decreased tolerance to contact lenses Migraine Optic neuritis Central vein occlusion, benign increase intracranial pressure
Digitalis	Yellow vision Blurred vision
Ethambutol	Optic neuropathy
Haloperidol (Haldol®)	Oculogyric crises Blurred vision
Indomethacin	Superficial keratopathy
Interferon	Retinal hemorrhages and cotton wool spots
Isoniazid	Optic neuropathy
Nalidixic acid	Papilledema
Steroids	Posterior subcapsular cataracts Glaucoma Papilledema (systemic steroids) Increased severity of HSV infections (geographic ulcers) Predisposition to fungal infections
Sulphonamides, NSAIDs	Stevens-Johnson syndrome
Tamsulosin (Flomax®)	Intraoperative Floppy Iris Syndrome, which can complicate cataract surgery
Tetracycline	Papilledema (associated with pseudotumour cerebri)
Thioridazine	Pigmentary degeneration of retina
Vigabatrin	Retinal deposition with macular sparing, peripheral visual field loss
Vitamin A toxicity	Papilledema
Vitamin D toxicity	Band keratopathy

www.regentstudies.com

Common Medications

TOPICAL OCULAR DIAGNOSTIC DRUGS

Fluorescein Dye
- water soluble orange-yellow dye
- green under cobalt blue light (ophthalmoscope or slit-lamp)
- absorbed in areas of epithelial loss (ulcer or abrasion)
- also stains mucus and contact lenses

Rose Bengal Stain
- stains devitalized epithelial cells and mucus

Anesthetics
- e.g. proparacaine HCl 0.5%, tetracaine 0.5%
- indications: removal of foreign body and sutures, tonometry, examination of painful cornea
- toxic to corneal epithelium (inhibit mitosis and migration) and can lead to corneal ulceration and scarring with prolonged use, therefore **NEVER** prescribe

Mydriatics
- dilate pupils
- two classes
  - cholinergic blocking (e.g. tropicamide – Mydriacyl®)
    - dilation plus cycloplegia (loss of accommodation) by paralysis of iris sphincter and the ciliary body
    - indications: refraction, ophthalmoscopy, therapy for iritis
  - adrenergic stimulating (e.g. phenylephrine HCl 2.5%)
    - stimulate pupillary dilator muscles, no effect on accommodation
    - usually used with tropicamide for additive effects
    - side effects: HTN, tachycardia, arrhythmias

Table 11. Mydriatic Cycloplegic Drugs and Duration of Action

Drugs	Duration of Action
Tropicamide (Mydriacyl®) 0.5%, 1%	4-5 h
Cyclopentolate HCL 0.5%, 1%	3-6 h
Homatropine HBr 1%, 2%	3-7 d
Atropine sulfate 0.5%, 1%	1-2 wk
Scopolamine HBr 0.25%, 5%	1-2 wk

GLAUCOMA MEDICATIONS

Table 12. Glaucoma Medications

Drug Category	Dose	Effect	Comment/Side Effects
α-Agonist **Non-selective** • epinephrine HCl 1% (Epifrin®) • dipivalyl epinephrine 0.1% (Propine®) **α_2-selective** • brimonidine 0.2% (Alphagan®) • apraclonidine 0.5% (Iopidine®)	1 gtt OS/OD bid/tid	1. Non-selective: ↓ aqueous production + ↑ TM outflow 2. Selective: ↓ aqueous production + ↑ uveoscleral outflow	1. Non-selective: mydriasis, macular edema, tachycardia 2. Selective: contact allergy, hypotension in children
β-Blocker **Non-selective** • timolol (Timoptic®) • levobunolol (Betagan®) **β_1-selective** • betaxolol (Betoptic®)	1 gtt OS/OD qd/bid	↓ aqueous production	**Bronchospasm (caution in asthma/COPD)** ↑ CHF Bradycardia Hypotension Depression Heart block Impotence
Carbonic Anhydrase Inhibitor • dorzolamide (Trusopt®) • brinzolamide (Azopt®) • oral: acetazolamide (Diamox®), methazolamide (Neptazane®)	1 gtt OS/OD tid Diamox®: 500 mg PO bid	↓ aqueous production	**Must ask about sulfa allergy** Generally local side effects with topical preparations Oral: diuresis, fatigue, paresthesias, GI upset, etc.
Parasympathomimetic (cholinergic stimulating) • pilocarpine (Pilopine®) • carbachol (Isopto Carbachol®)	1-2 gtts OS/OD tid/qid	↑ TM outflow	Miosis ↓ night vision ↑ GI motility Brow ache Headache ↓ heart rate
Prostaglandin Analogues • latanoprost (Xalatan®) • travaprost (Travatan®) • bimatoprost (Lumigan®)	1 gtt OS/OD qhs	↑ uveoscleral outflow (uveoscleral responsible for 20% of drainage)	Iris colour change Periorbital skin pigmentation Lash growth Conjunctival hyperemia

Cosopt® = timolol + dorzolamide; Xalacom® = timolol + latanoprost; Combigan® = timolol + brimonidine; DuoTrav® = tinolol + travaprost; gtt = drop, gtts = drops

Green	Cholinergics
Red	Anti-Cholinergics
White	Anaesthetics, Antibiotics, Artificial tears, Steroids
Yellow	Beta-Blockers
Blue	Beta-Blocker combinations
Purple	Alpha-Agonists
Teal	Prostaglandins
Orange	Carbonic Anhydrase Inhibitors
Tan	Fluoroquinolones
Grey	NSAIDs
Pink	Anti-inflammatories, Steroids

www.regentstudies.com

WET AGE-RELATED MACULAR DEGENERATION MEDICATIONS

VEGF Inhibitors
- block VEGF which prevents ocular angiogenesis and further development of choroidal neovascularization
- administered via intravitreal injections
- pegaptanib (Macugen®) is a selective anti-VEGF targeting VEGF isoform 165 (no longer widely used)
- ranibizumab (Lucentis®) is a non-selective anti-VEGF agent
- alflibercept (Eylea®) is an VEGF "trap" agent that binds VEGF-A and placental growth factor
- bevacizumab (Avastin®) is another non-selective anti-VEGF agent but is only FDA approved for metastatic breast cancer, colorectal cancer, and non-small cell lung cancer; therefore, its widespread ophthalmologic use is off-label

TOPICAL OCULAR THERAPEUTIC DRUGS

NSAIDs
- used for less serious chronic inflammatory conditions
- e.g. ketorolac (Acular®), diclofenac (Voltaren®), nepafenac (Nevanac®) drops

Anti-Histamines
- used to relieve red and itchy eye, often in combination with decongestants
- sodium cromoglycate – stabilizes membranes

Decongestants
- weak adrenergic stimulating drugs (vasoconstrictor)
- e.g. naphazoline, phenylephrine (Isopto Frin®)
- rebound vasodilation with overuse; rarely can precipitate angle closure glaucoma

Antibiotics
- indications: bacterial conjunctivitis, keratitis, or blepharitis
- commonly as topical drops or ointments, may give systemically
- e.g. sulfonamide (sodium sulfacetamide, sulfisoxazole), gentamicin (Garamycin®), erythromycin, tetracycline, bacitracin, polymyxin B, fluoroquinolones (ciprofloxacin [Ciloxan®], ofloxacin [Ocuflox®], moxifloxacin [Vigamox®], gatifloxacin [Zymar®])

Corticosteroids
- e.g. fluorometholone (FML®), betamethasone, dexamethasone (Maxidex®), prednisolone (Predsol® 0.5%, Pred Forte® 1%), rimexolone (Vexol®), loteprednol etabonate 0.5% (Lotamax®), difluprednate (Durezol®)
- primary care physicians should avoid prescribing topical corticosteroids due to risk of glaucoma, cataracts, and reactivation of HSV keratitis
- complications
  - potentiates HSV keratitis and fungal keratitis as well as masks symptoms
  - increased IOP, more rapidly in steroid responders (within weeks)
  - posterior subcapsular cataract (within months)

References

ACCORD Study Group; ACCORD Eye Study Group, Chew EY, Ambrosius WT, Davis MD, et al. Effects of medical therapies on retinopathy progression in type 2 diabetes NEJM 2010;363:233-244
Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. Arch Ophthalmol 2001;119:1417-1436.
Anderson DR, Normal Tension Glaucoma Study. Collaborative normal tension glaucoma study. Curr Opin Ophthalmol 2003;14:6-90.
Atlas of ophthalmology. Available from: www.atlasophthalmology.com/atlas/frontpage.jsf.
Bhagat N, Nagori S, Zarbin M. Post-traumatic Infectious Endophthalmitis. Surv Ophthalmol 2011;56:214-51.
Bradford C. Basic ophthalmology for medical students and primary care residents, 7th ed. San Francisco: American Academy of Ophthalmology, 1999.
CATT Research Group, Martin DF, Maguire MG, Ying GS, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. NEJM 2011;364:1897-1908.
Elman MJ, Bressler NM, Qin H, et al. Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthal 2011;118:609-614.
Friedman N, Pineda R, Kaiser P. The Massachusetts eye and ear infirmary illustrated manual of ophthalmology. Toronto: WB Saunders, 1998.
Gal RL, Vedula SS, Beck R. Corticosteroids for treating optic neuritis. Cochrane DB Syst Rev 2012;4:CD001430.
Glanville J, Patterson J, McCool R, et al. Efficacy and safety of widely used treatments for macular oedema secondary to retinal vein occlusion: a systematic review. BMC Ophthalmol 2014;14:7.
Haller JA, Bandello F, Belfort R Jr, et al. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macula edema due to retinal vein occlusion. Ophthal 2010;117:1134-1146.
Heijl A, Leske MC, Bengtsson B, et al. Reduction of intraocular pressure and glaucoma progression: results from the early manifest glaucoma trial. Arch Opthalmol 2002;120:1268-1279.
Kanski JJ. Clinical Ophthalmology: A systematic approach, 6th ed. Oxford: Butterworth-Heinemann, 2007.
Lichter PR, Musch DC, Gillespie BW, et al. Interim clinical outcomes in the collaborative initial glaucoma treatment study comparing initial treatment randomized to medications or surgery. Ophthal 2001;108:1943-1953.
Maguire AM, High KA, Auricchio A, et al. Age-dependent effects of RPE65 gene therapy for Leber's congenital amaurosis: a phase 1 dose-escalation trial. Lancet 2009;374:1597-1605.
Mintz-Hittner HA, Kennedy KA, Chuang AZ, BEAT-ROP Cooperative Group. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. NEJM 2011;364:603-615.
Pushker N, Tejwani LK, Bajaj MS, et al. Role of oral corticosteroids in orbital cellulitis. Am J Ophthalmol 2013;156:178-183.
Rayapudi S, Schwartz SG, Wang X, et al. Vitamin A and fish oils for retinitis pigmentosa Cochrane DB Syst Rev 2013;12:CD008428
Sheikh A, Hurwitz B, van Schayck CP, et al. Antibiotics versus placebo for acute bacterial conjunctivitis. Cochrane DB Syst Rev 2012;9:CD001211.Smetana GW, Shmerling RH. Does this patient have temporal arteritis? JAMA 2002;287:92-101.
Stein R, Stein H. Management of ocular emergencies, 4th ed. Montreal: Mediconcept, 2006.
Tasman W, Jaegar EA. Duane's ophthalmology, 2011 ed. Philadelphia: Lippincott Wiliams & Wilkins, 2010.
Turner A, Rabiu M. Patching for corneal abrasion. Cochrane DB Syst Rev 2006;2:CD004764.
University of Michigan Kellogg Eye Centre. Available from: www.kellogg.umich.edu/theeyeshaveit/index.html.
Vass C, Hirn C, Sycha T, et al. Medical interventions for primary open-angle glaucoma and ocular hypertension. Cochrane DB Syst Rev 2007;4:CD003167.
Vedula SS, Krzystolik MG. Antiangiogenic therapy with anti-vascular endothelial growth factor modalities for neovascular age-related macular degeneration. Cochrane DB Syst Rev 2008;2:CD005139.
Wilhelmus KR. Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis. Cochrane DB Syst Rev 2010;12:CD002898.
Wilson FM. Practical ophthalmology: a manual for beginning residents, 4th ed. American Academy of Ophthalmology, 2005.
Wong AM. New concepts concerning the neural mechanisms of amblyopia and their clinical implications. Can J Opthalmol 2012;47:399-409.

www.regentstudies.com