CNS pathology
Third year medical students

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2018

Lecture 1: an introduction

CNS course

- This is a 7 hour course and the topics covered are important for your clinical years and your work as a doctor in any speciality you choose. Please give it the importance it deserves.
- We synchronised the lectures' topics between all disciplines (mainly anatomy, physiology and pathology) so you can understand subjects fully and easily and we minimised repetition of topics between disciplines.
- I sent the course syllabus, ILOS and lecture distribution. Please have a look at these to familiarise yourself with the course.
- Please note **the faculty is being very strict with attendance policy**, make sure you don't put yourself into trouble; we will not be able to help you with this.

Pathology lectures

- As usual we will have two sets of slides; one as a presentation, and a detailed slide for the content of the lectures.
- The detailed slides will contain all the information you need for the exam.
- At the beginning of each slide I will list the learning outcomes of the lecture, at the end I will put a summary of the main points you need to concentrate on as well as practice questions to check your understanding and to know what to expect in the exam.
- The slides will be available on your website and the the e learning before the lecture day.

Lecture 1: introduction
ILOS

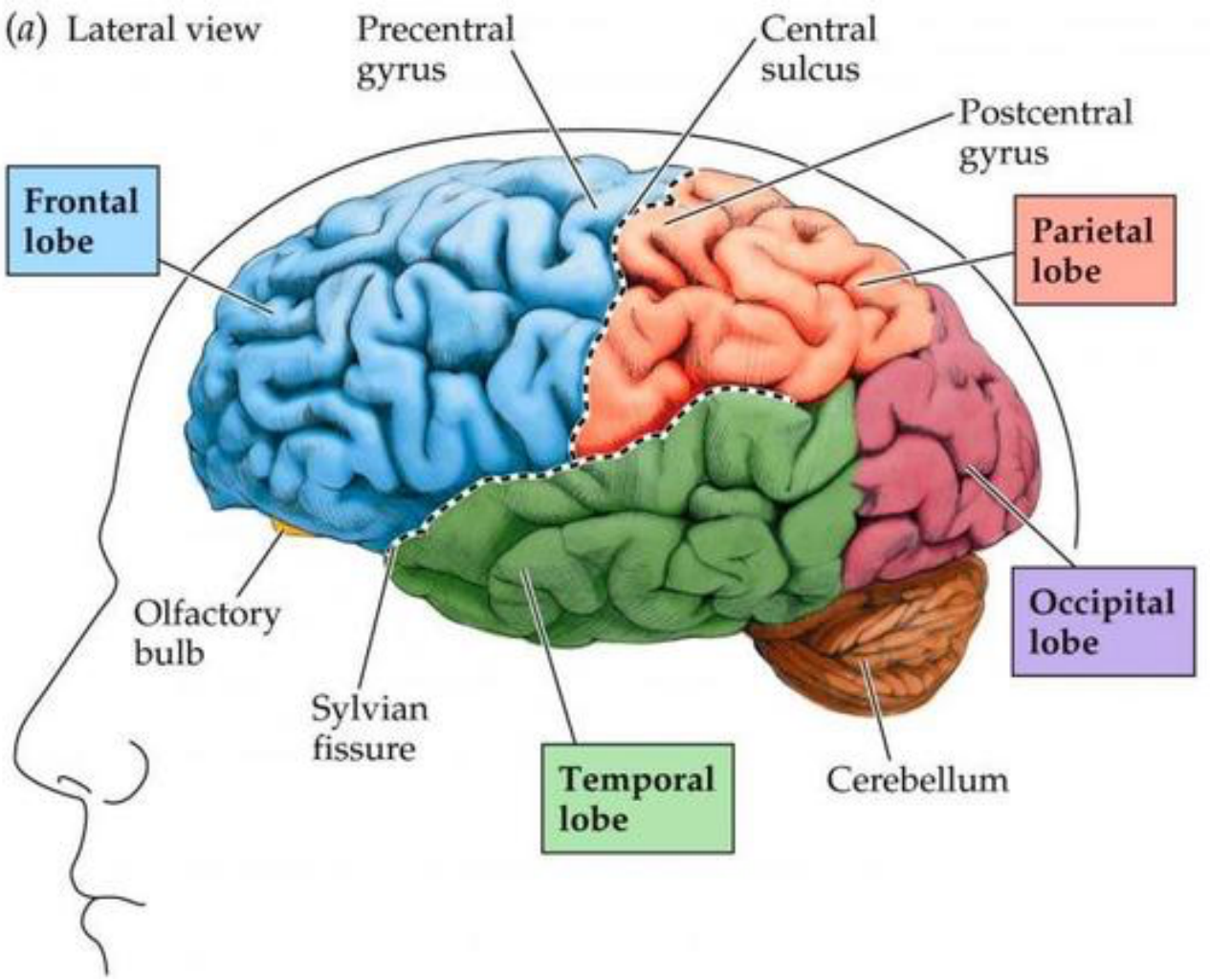
- A quick revision of the CNS structure including brain lobes and some of their functions
- To understand the asymmetry between the right and left hemispheres, with examples.
- To know the structure and function of neurons and glial cells
- To understand how neurons and glial cells respond to injury.
- To apply the above knowledge in understanding brain diseases

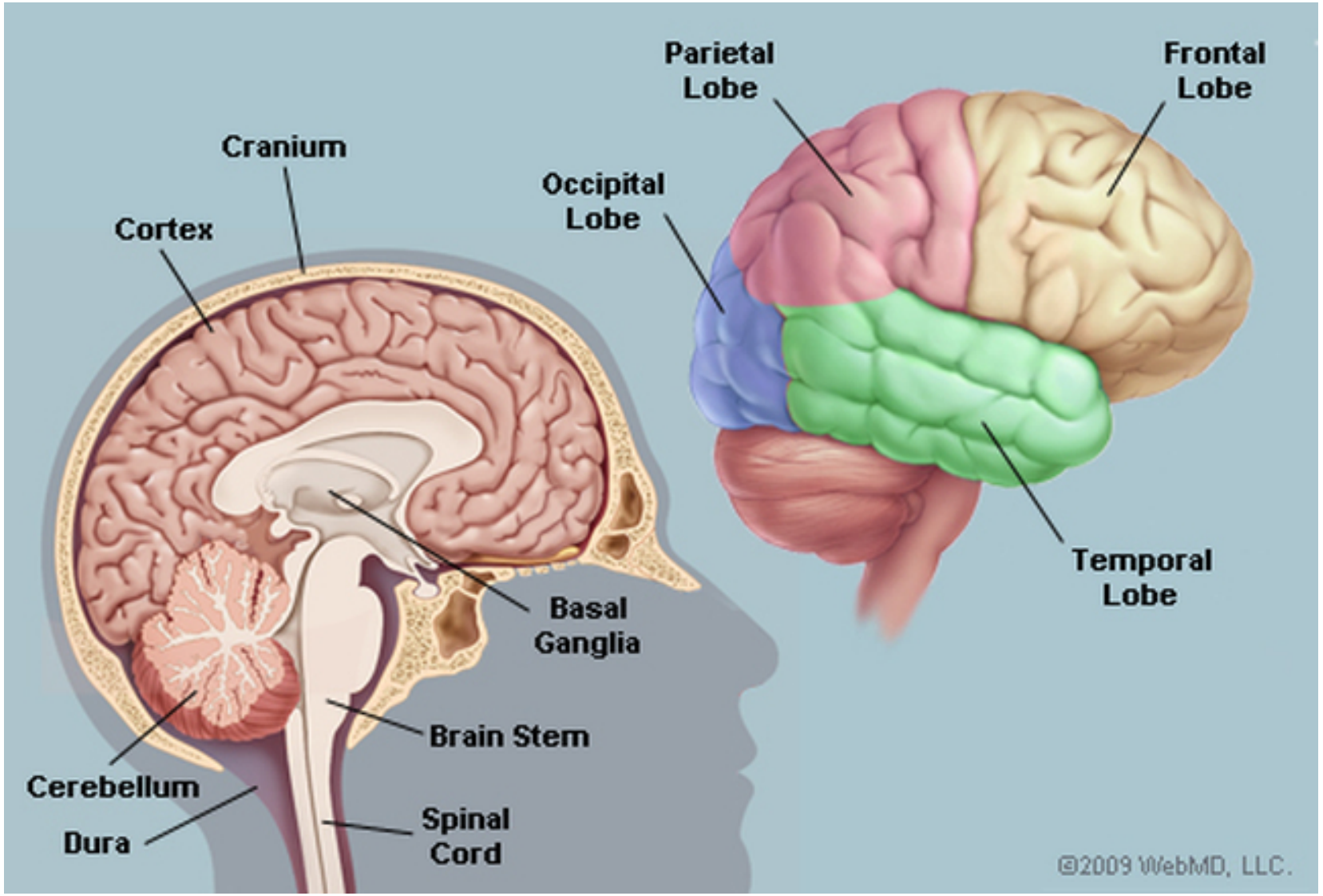
CNS

- The CNS is composed of the brain and the spinal cord.
- Its main function is to receive information, coordinate it and send appropriate commands to the rest of the body.
- CNS is composed of white and grey matter.
- The white matter is composed of myelinated axons (myelin composed of cell membranes of oligodendrocytes).
- The grey matter is composed of the neurones of the cortex and certain nuclei.

Brain lobes

the brain is composed of four anatomical lobes: frontal, occipital, temporal and parietal lobes.




Parietal Lobe
Frontal Lobe
Cranium
Occipital Lobe
Cortex
Temporal Lobe
Basal Ganglia
Brain Stem
Cerebellum
Spinal Cord
Dura
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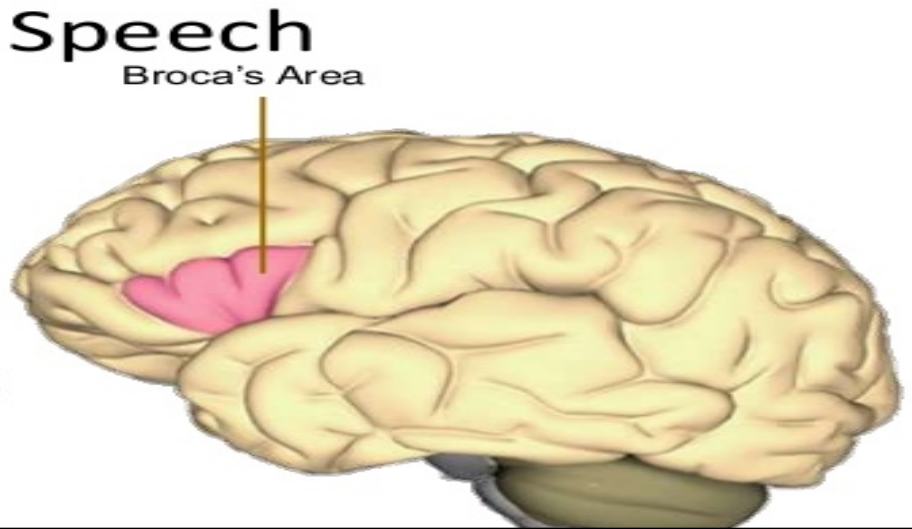
Cerebral cortex
1. frontal lobe

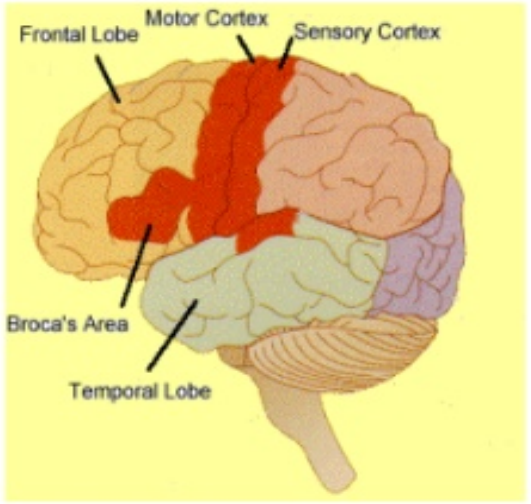
- Contains the primary motor cortex: performs final cortical motor processing
- Broca's area in the **left** frontal lobe controls motor pattern of speech, if damaged = expressive dysphasia = the person knows what he wants to say but cannot express them.

Broca's area is where we formulate speech and the area of the brain that sends motor instructions to the motor cortex.

Injury to Broca's area can cause difficulty in speaking. The individual may know what words he or she wishes to speak, but will be unable to do so.



FRONTAL LOBE



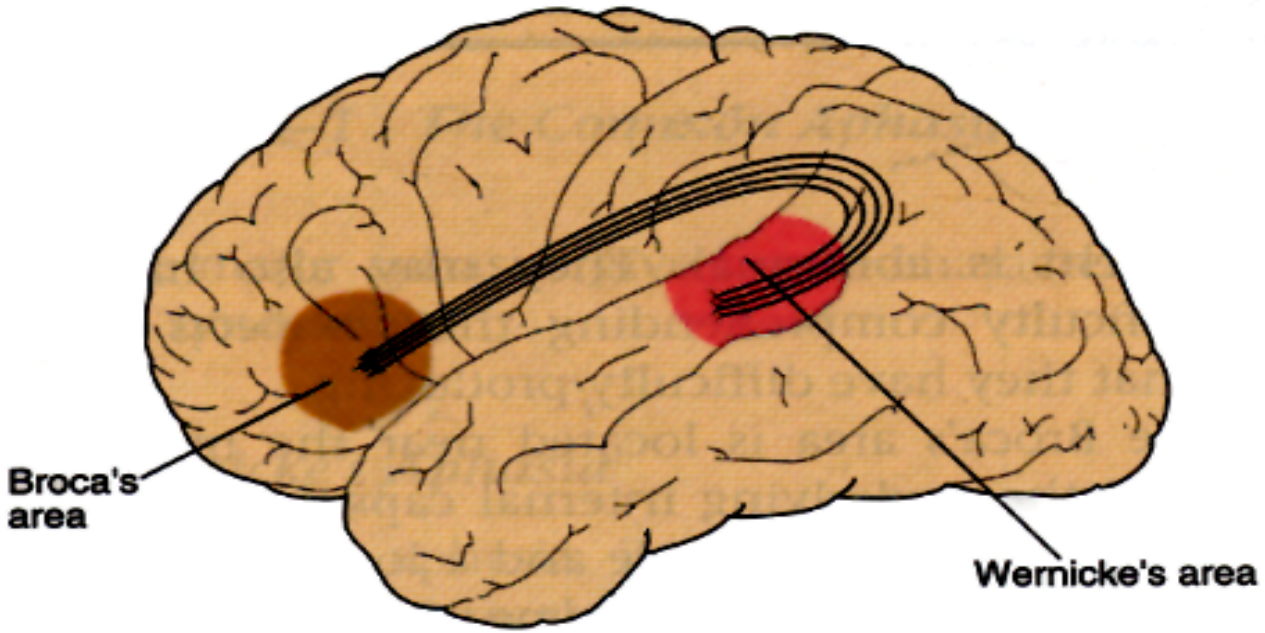
- Personality
- Behavior
- Voluntary motor function
- Motor speech (Broca's),
  Left side dominent
- Intellectual functions, problem solving
- Judgment; good/bad, right/wrong

Called the "MOM" portion of the Brain

2. Temporal lobe

- Important for complex processing of sensory input
- Contains **Wernicke's area** : auditory , visual and somatic associations coalesce in this area.
- If damaged: inability to understand spoken or written language. (receptive dysphasia)

There are associations between Broca's and Wernicke's areas



3. Parietal lobe

- Contains high order sensory areas
- Contains area for naming objects
- Contains area for processing of visual language= reading

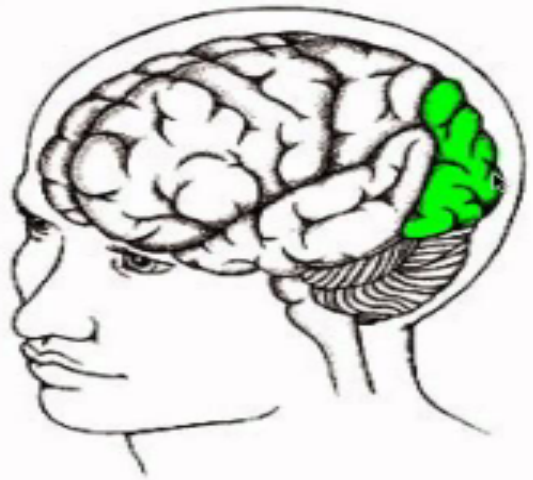
4. Occipital lobe: Contains the visual cortex

Occipital Lobe

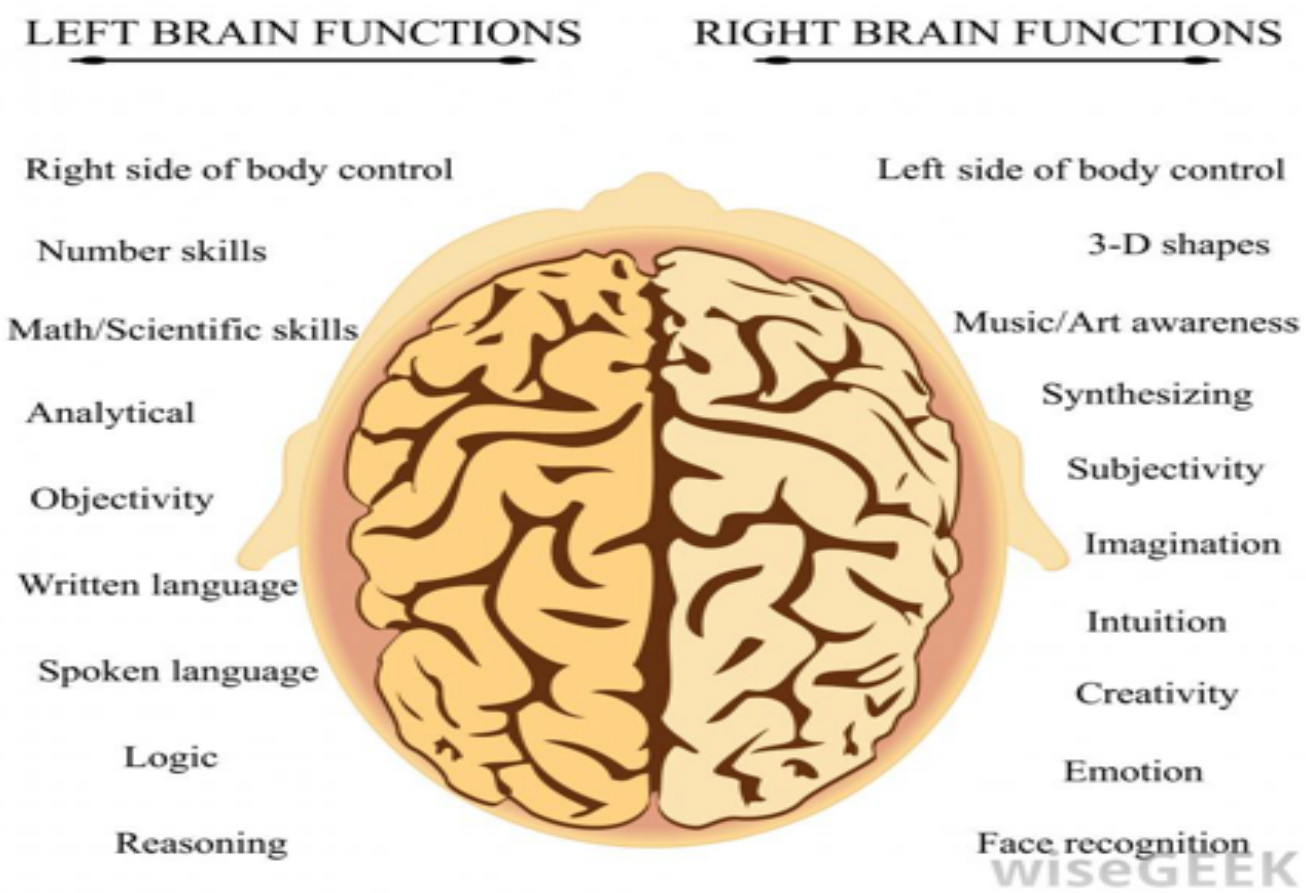
- Located at rear of brain
- **Involved** in vision
- Select, organise and integrate visual info
- Works with other lobes

Primary Visual Cortex

- Located at rear of lobe
- Processes information from sensory receptors on retinas
- Left half of each eye sends info to left hemisphere (R-L-L)
- Right half of each eye sends info to right hemisphere (L-R-R)
- Some neurons respond only to certain features



Brain asymmetry



Why understanding brain asymmetry is important ?

- Same disease processes can have different consequences according to the side affected
- Example: a stroke affecting the Broca’s area in the left frontal lobe can result in expressive dysphasia. Similar lesion in the mirror image area in the right side might result in no symptoms at all.

BRAIN CELLS

- The CNS contains 100 billion neurons.
- It also contains 10-50 times this number of glial cells.
- 40% of our genes participate in the formation of the CNS.

neuron

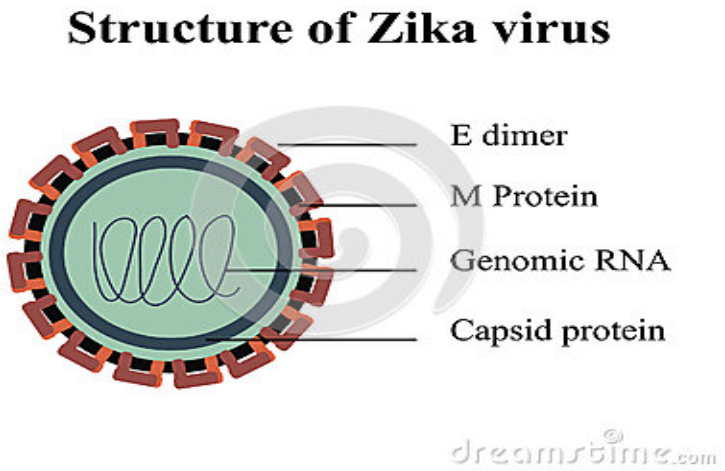
- Is the principal functional unit of the CNS.
- They receive and transmit information
- Mature neurons cannot divide: they are permanent cells
- However, **neural progenitors** are found in the brain and can divide….. ??? Expansion of these can help patients with CNS diseases (this is an area of active research)

Neural progenitors

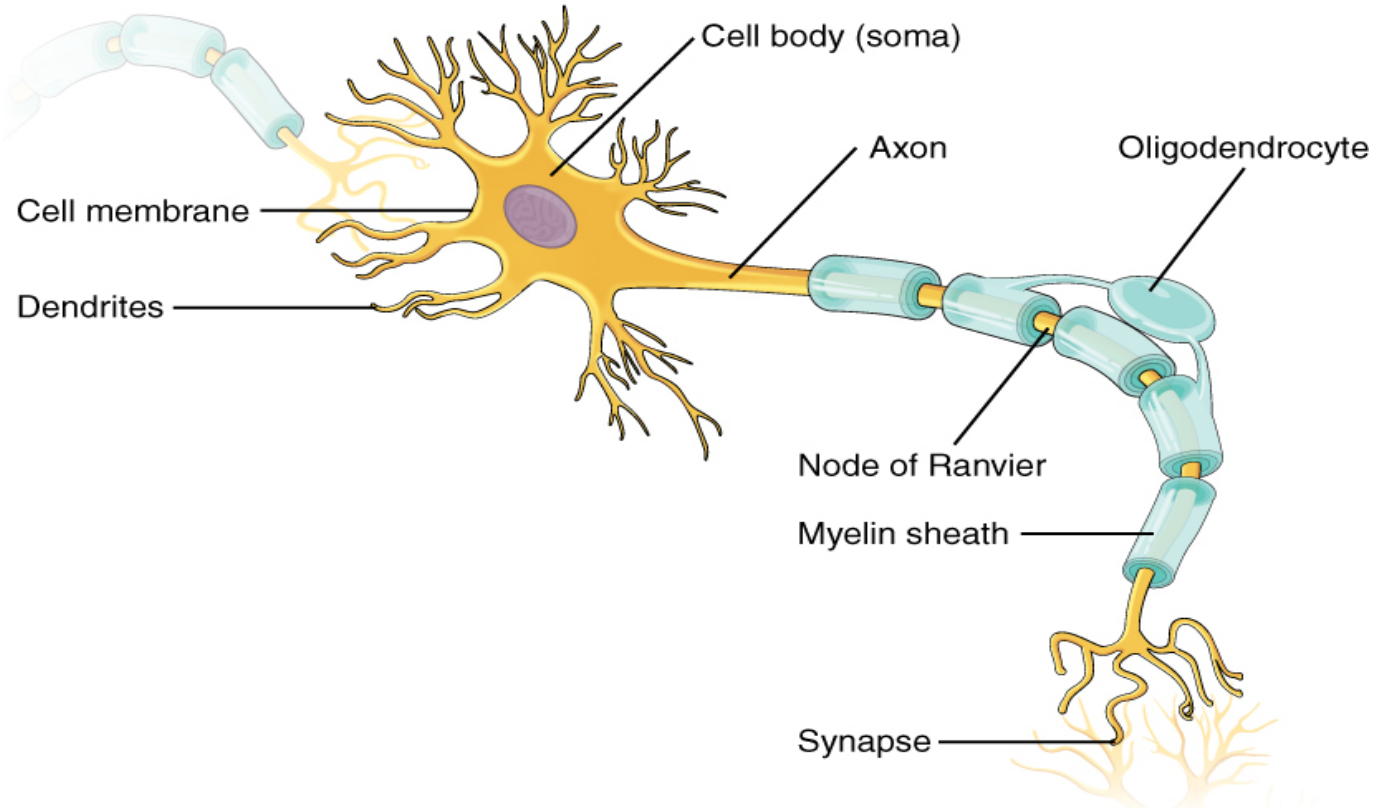
- Neural progenitors are cells that are capable of dividing a limited number of times and have the capacity to differentiate into a restricted number of neuronal and glial cell types.
- Zika virus infection is associated with microcephaly, probably through infecting neural progenitors causing their death and resulting in decreased brain growth in embryos.

ZIKA VIRUS

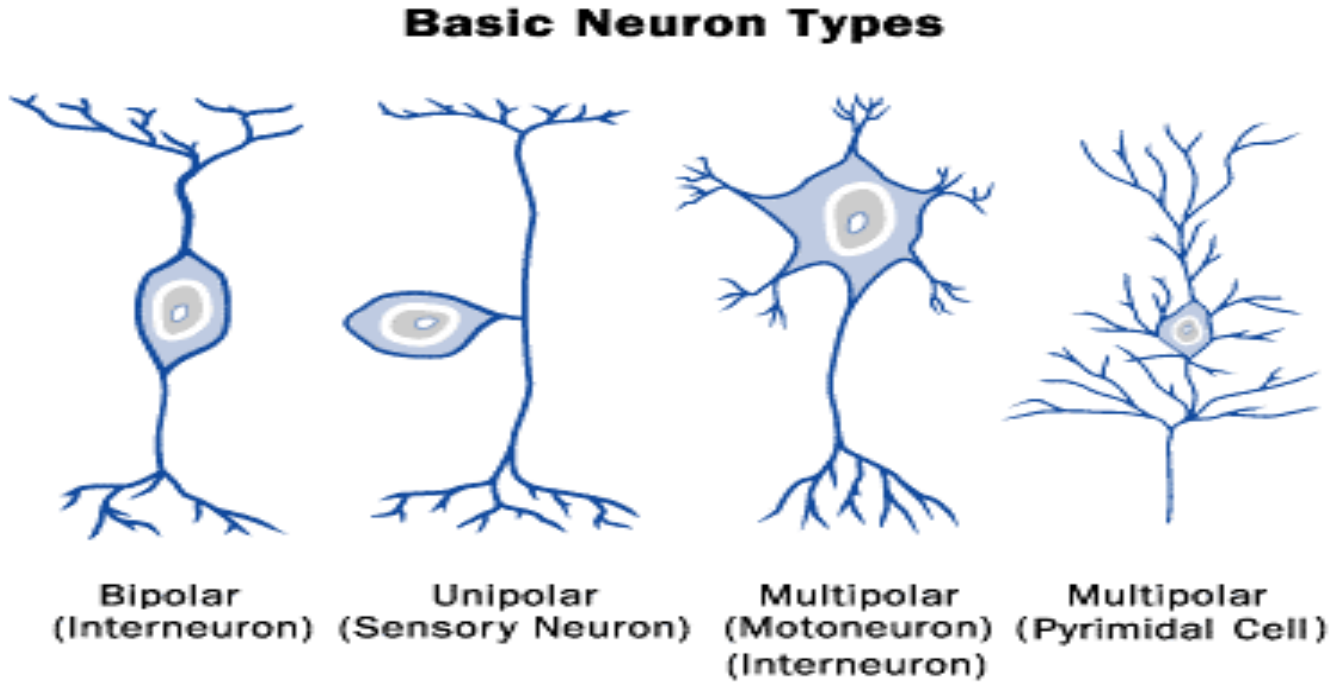
- Based on a systematic review of the literature up to 30 May 2016, WHO has concluded that Zika virus infection during pregnancy is a cause of congenital brain abnormalities, including microcephaly. it is thought that the virus does so by infecting progenitor cells.



Basic structure of neurons.



Neurons come in several shapes!



GLIAL cells = خَلاَيا دِبْقِيَّة

- Are supportive cells

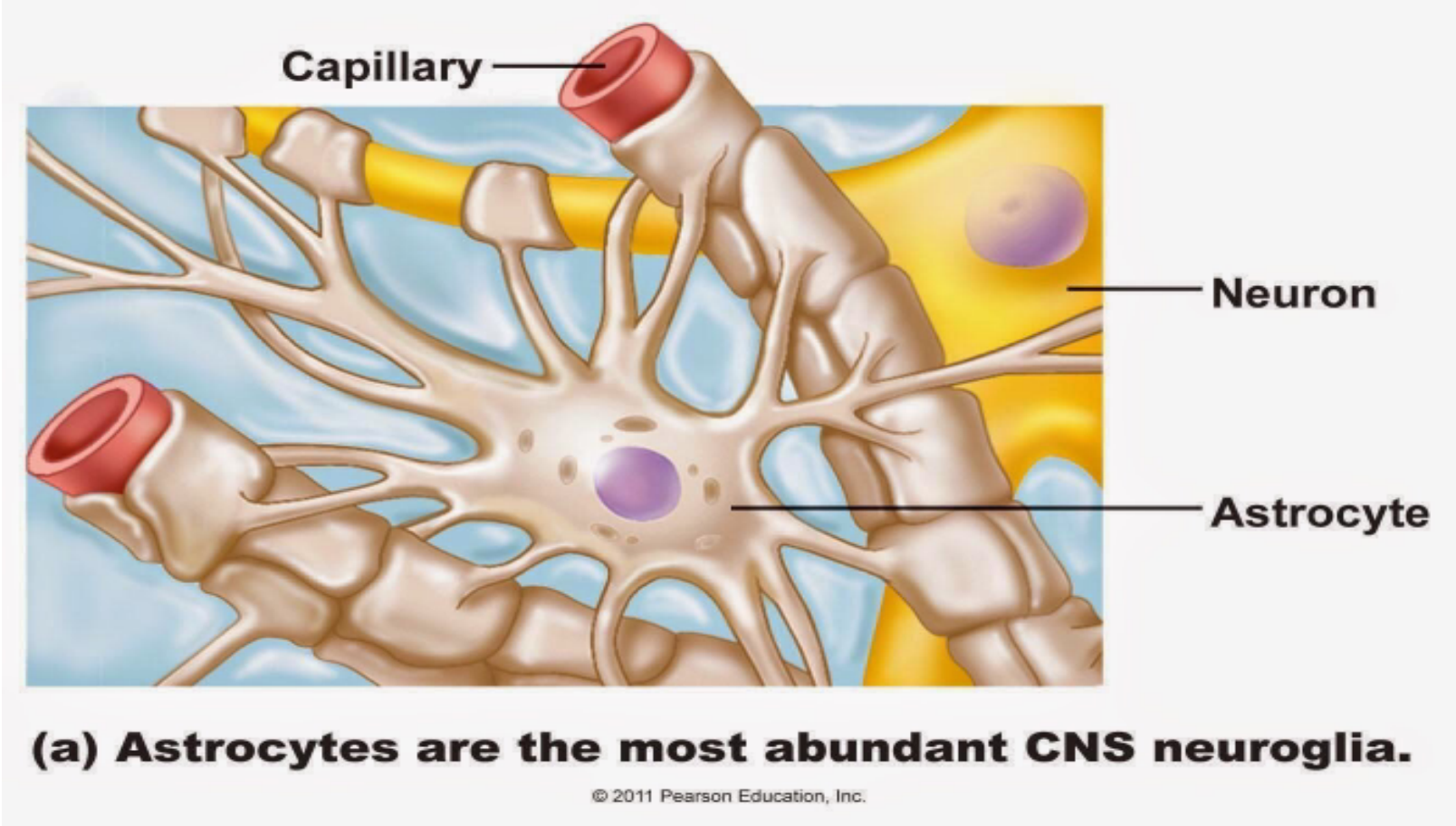
<u>4 types</u>:

1. Astrocytes
2. Oligodendrocytes
3. Microglial cells
4. Ependymal cells

Astrocytes = خَلايا نَجْمِيَّةٌ

- give structural support to neurons
- control neural biochemical environment.
- **Astrocyte processes are associated with the blood vessels to form the blood brain barrier**

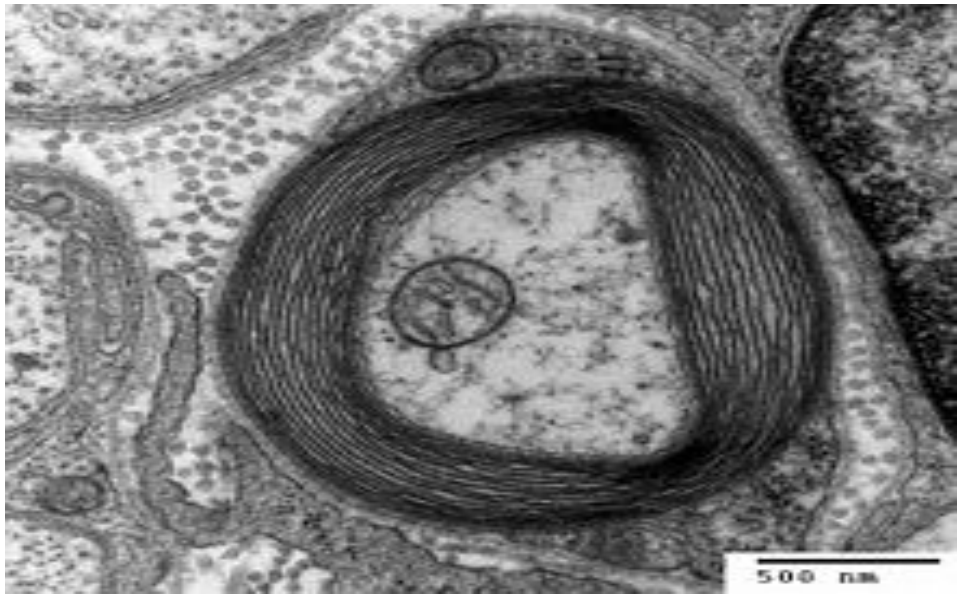
Astrocytes

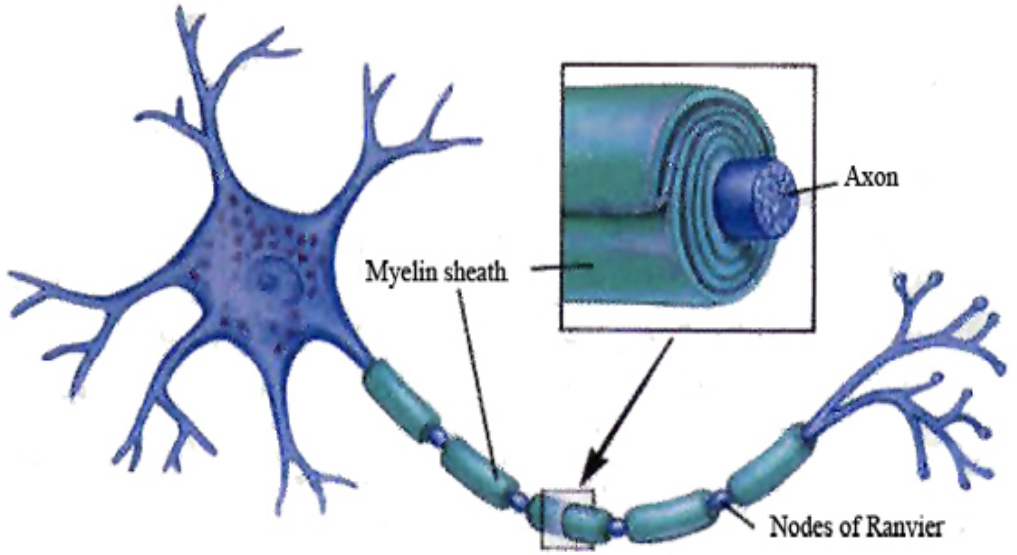


(a) Astrocytes are the most abundant CNS neuroglia.

Oligodendrocytes = دِبْقِيَّةٌ قَليلَةُ التَّغَصُّن

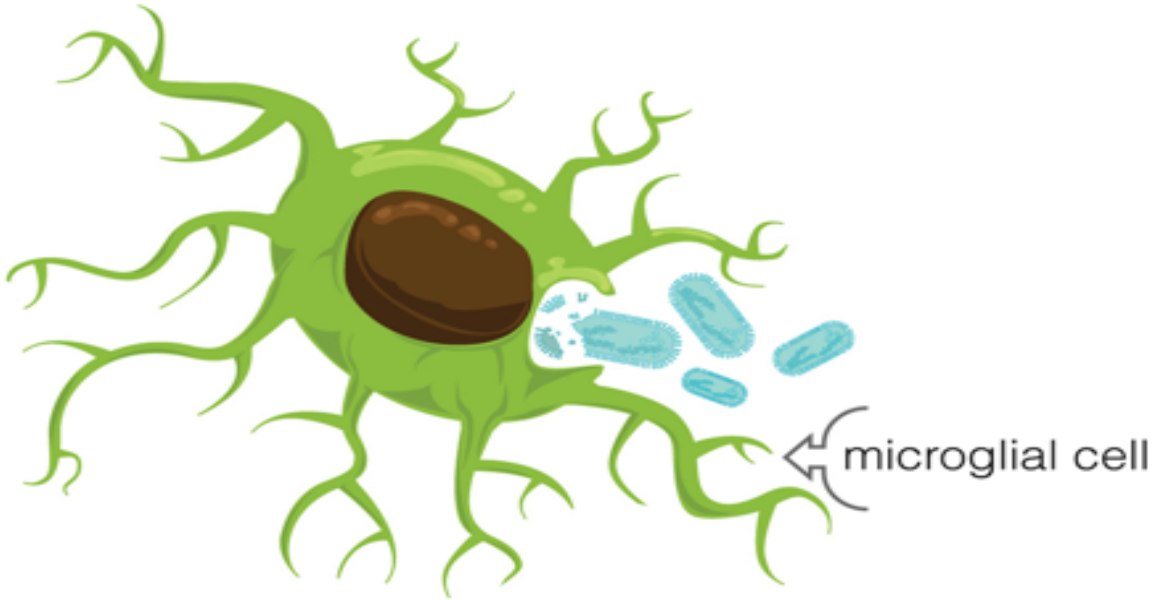
- Oligodendrocytes form the myelin sheath which surrounds axons and is important for fast transmission of action potential by salutatory conduction





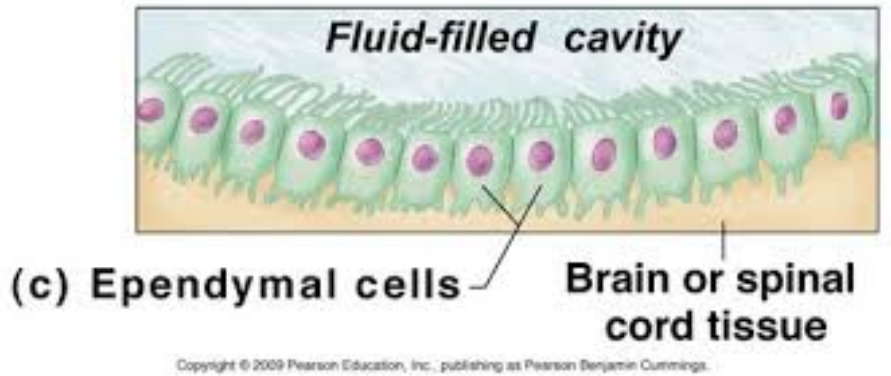
Microglial cells=الخلايا الدبقية الصغيرة

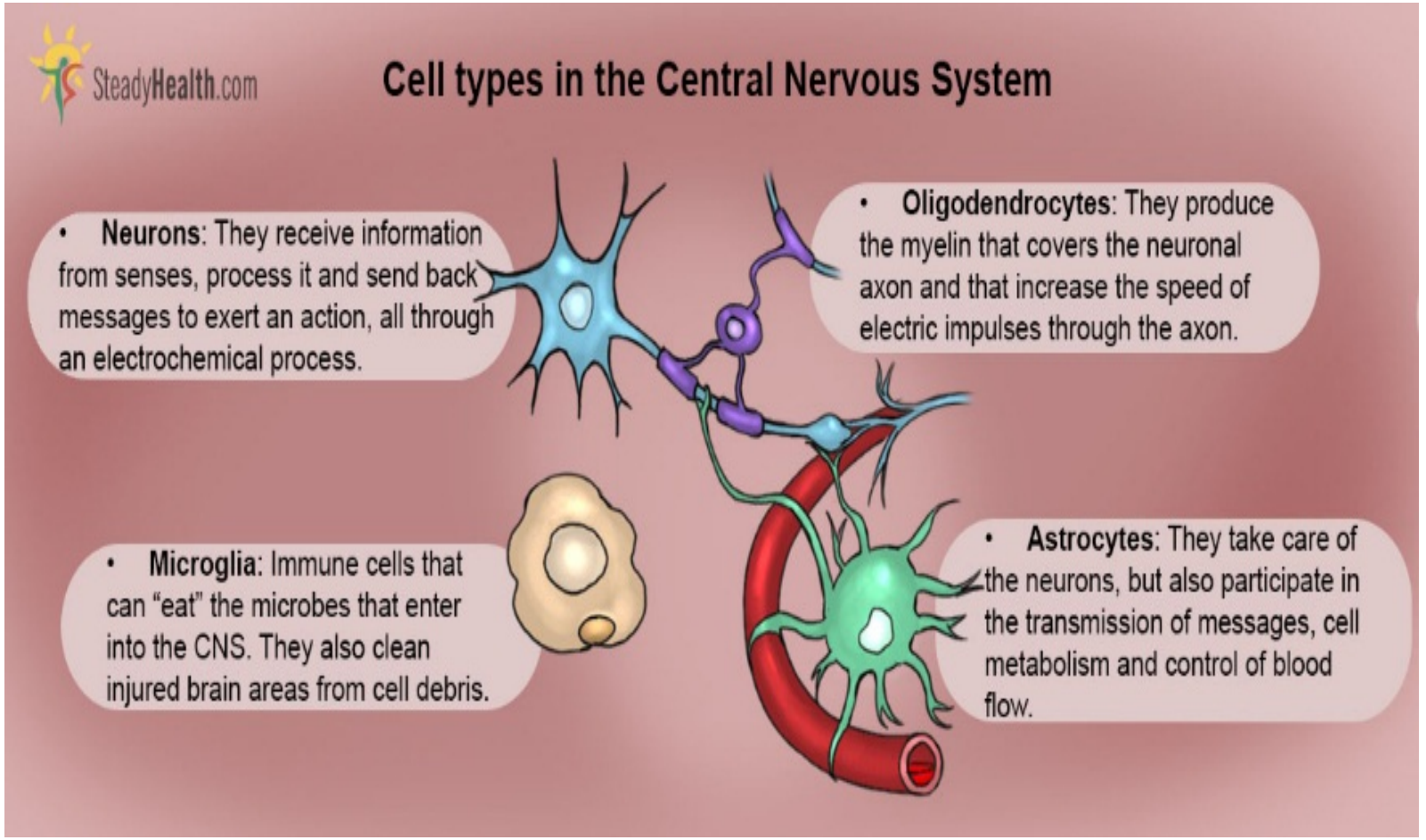
- Microglia: blood derived macrophages



Ependymal cells = خَلاَيا البِطانَةِ العَصَبِيَّة

- They line the ventricle and the spinal cord.



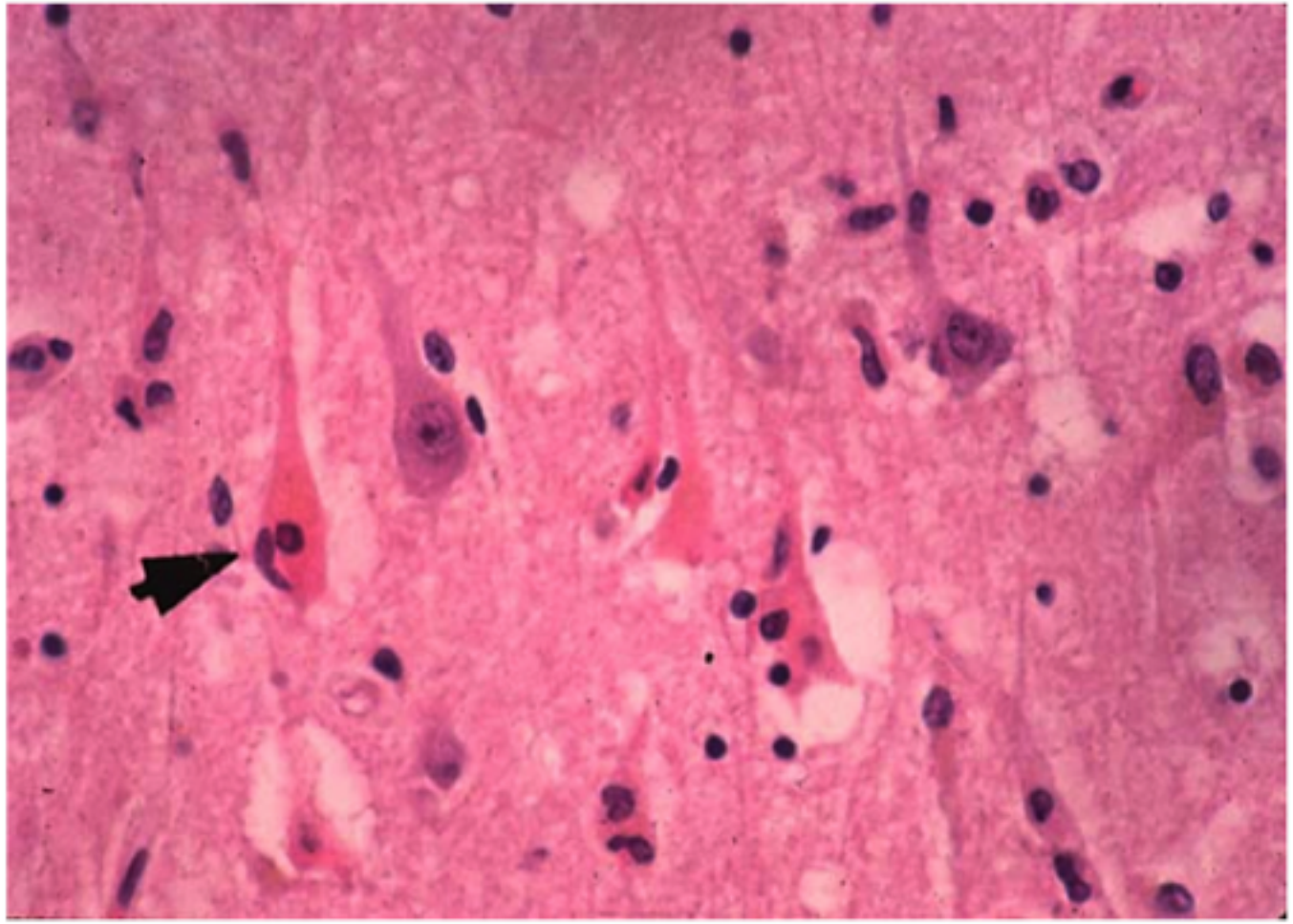

SteadyHealth.com
Cell types in the Central Nervous System
• Neurons: They receive information from senses, process it and send back messages to exert an action, all through an electrochemical process.
• Oligodendrocytes: They produce the myelin that covers the neuronal axon and that increase the speed of electric impulses through the axon.
• Microglia: Immune cells that can "eat" the microbes that enter into the CNS. They also clean injured brain areas from cell debris.
• Astrocytes: They take care of the neurons, but also participate in the transmission of messages, cell metabolism and control of blood flow.

Reaction of neurons to ACUTE injury

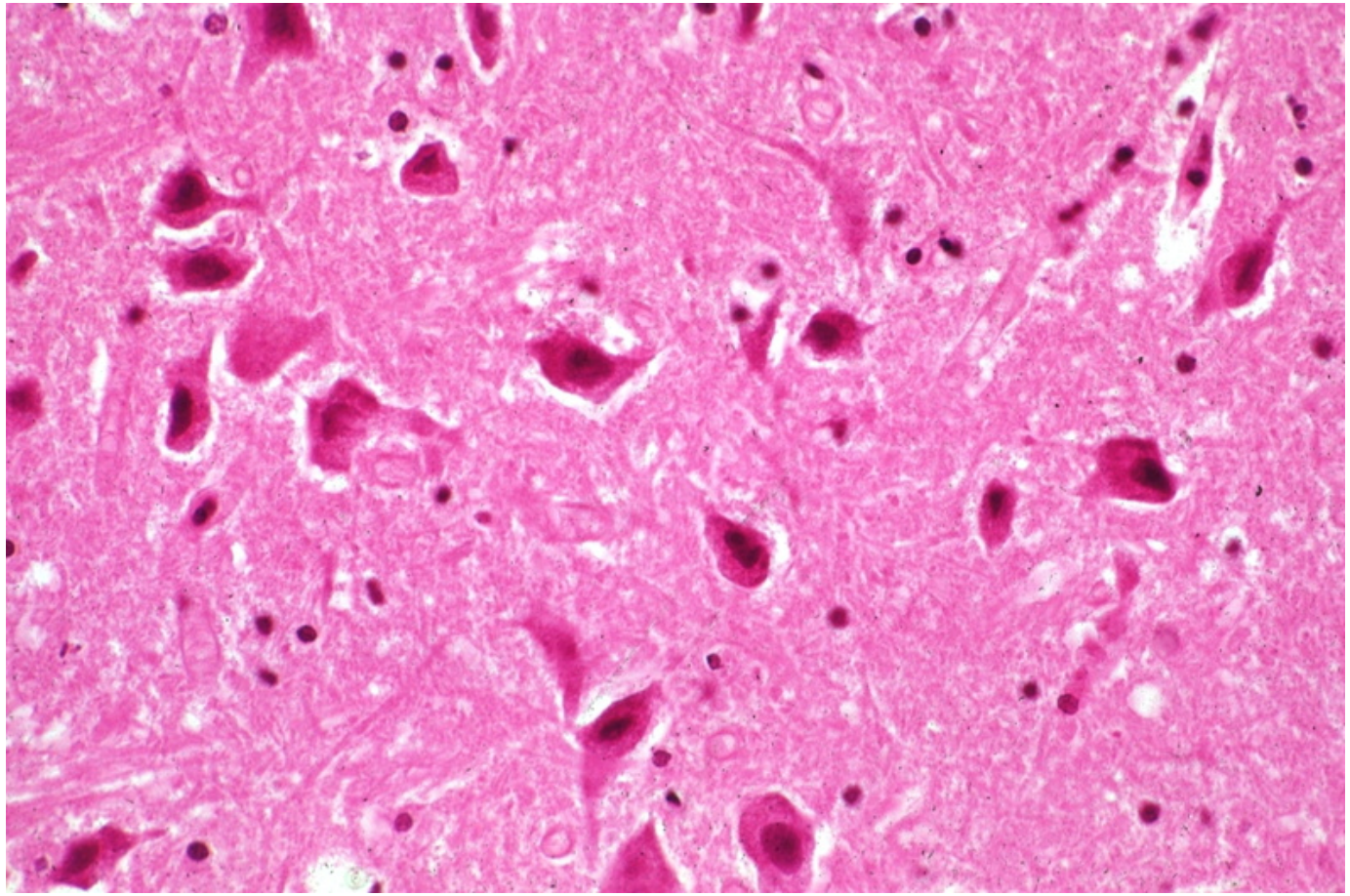
- Acute neuronal injury forms red neurons
- red neutrons result usually due to acute injury due to hypoxia or ischemia.
- red neuron is the earliest morphologic manifestation of neuronal cell death
- Appear after 12-24 hours of irreversible injury
- Characterised microscopically by shrinkage of cell body, pyknosis, disappearance of the nucleolus and Loss of Nissl substance (see next slide for definition)
- loss of Nissl substance results in intense cytoplasmic eosinophilia

- **Nissl substance**: large granular substance found in neurons. These **granules** are of rough endoplasmic reticulum (RER) with rosettes of free ribosomes, and are the site of protein synthesis.

Red neurons



Red neurons



Subacute and chronic neuronal injury

- =degeneration
- Neuronal death due to progressive disease
- Example: in Alzheimer
- Cell loss affecting functionally related neurons (not necessarily structurally related)

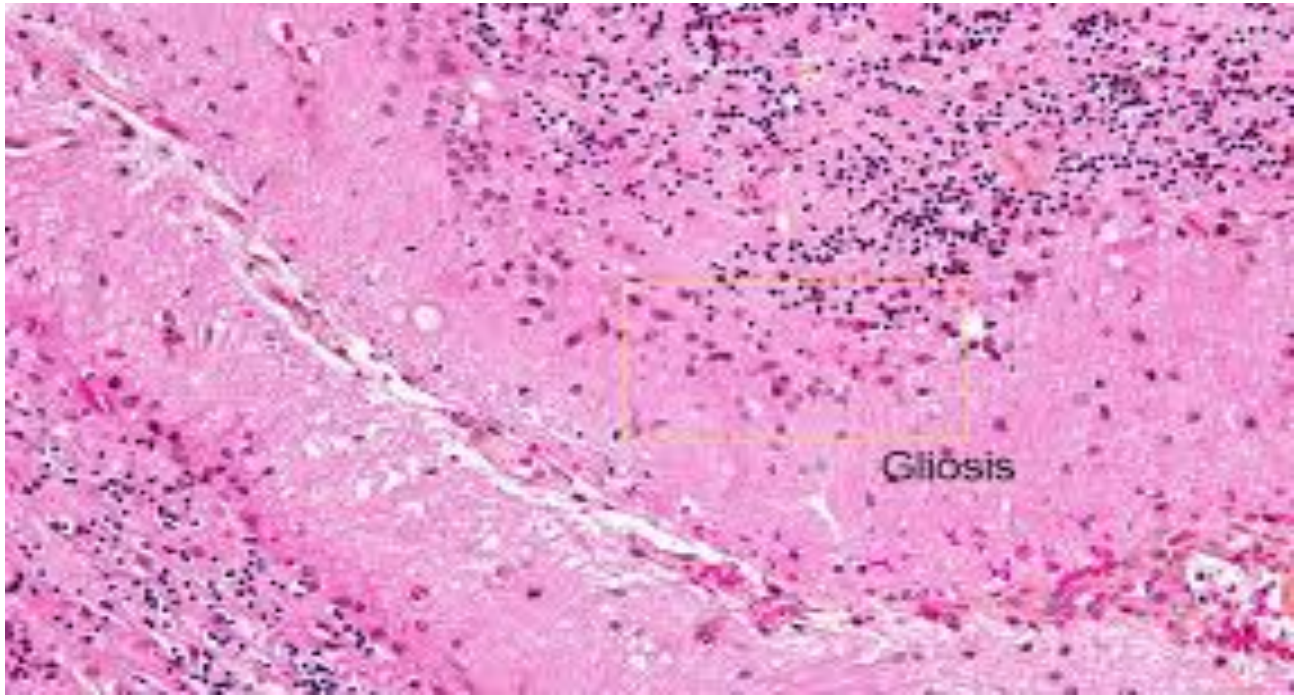
-Neuronal death usually is apoptotic death and is associated with reactive gliosis.

GLIOSIS

- **Gliosis** is a nonspecific reactive change of glial cells in response to damage to CNS. In most cases, **gliosis** involves the proliferation &/ or hypertrophy of several different types of glial cells, including astrocytes, microglia, and oligodendrocytes.

- SO: GLIAL CELLS **CAN PROLIFERATE AND DIVIDE** IN RESPONSE TO INJURY.

Gliosis simply means increased glial cells
think of it as counterpart of fibrosis in the rest of the body



Reaction of astrocytes to injury

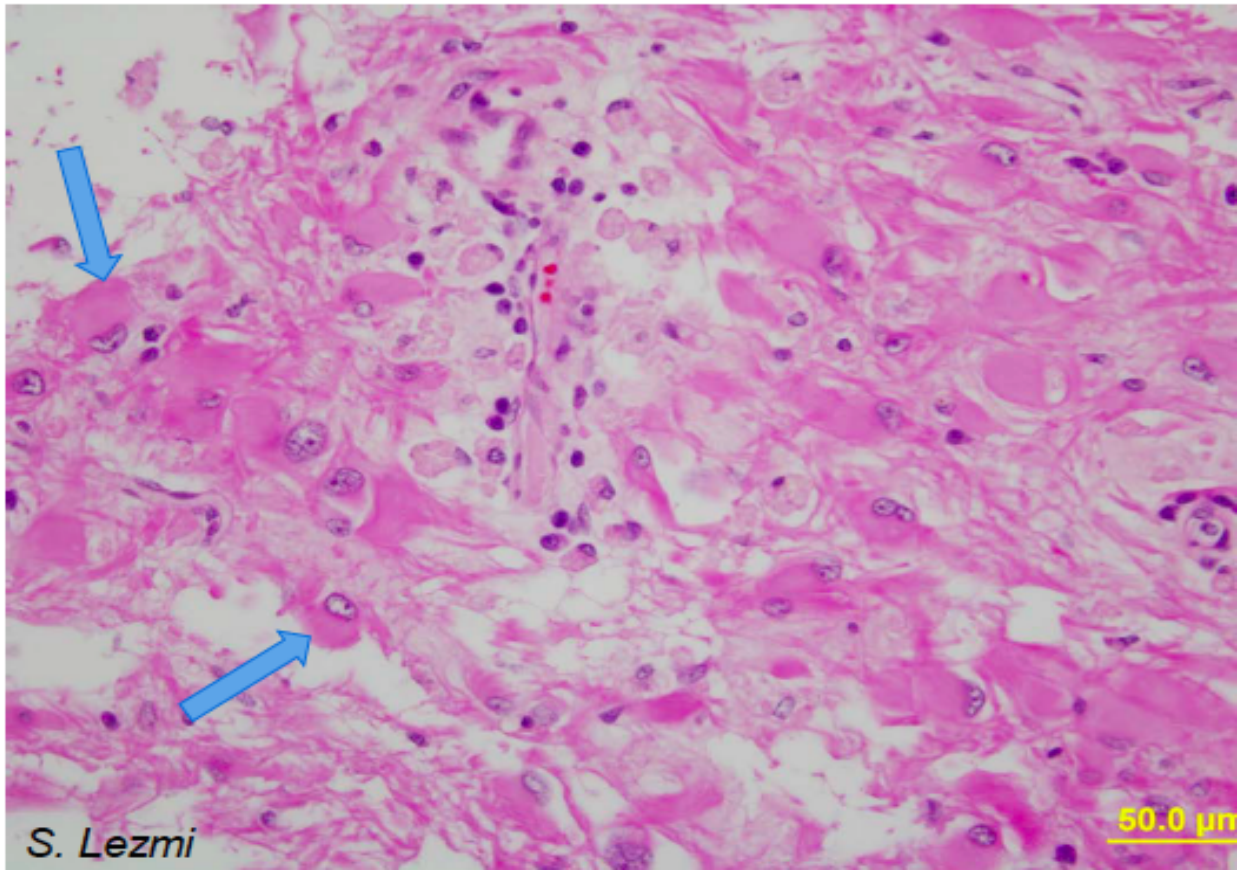
- Astrocytes are the principle cells responsible for repair and scar formation = gliosis
- Reactive astrocytes during repair undergo changes= gemistocytic astrocyte.

repair

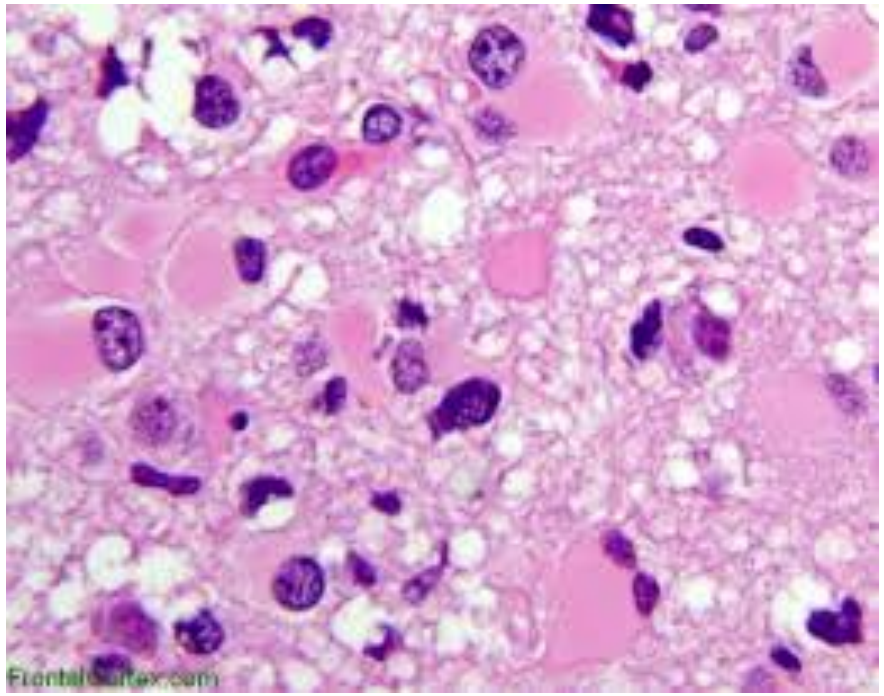
- Astrocytes are the main cells responsible for repair and scar formation (gliosis).
- **Injury causes the following changes in astrocytes**:
- 1. hypertrophy and hyperplasia in astrocytes.
- 2. enlarged nuclei
- 3. prominent nucleoli.
- 4. increased pink cytoplasm.
- 5. increased, ramifying processes

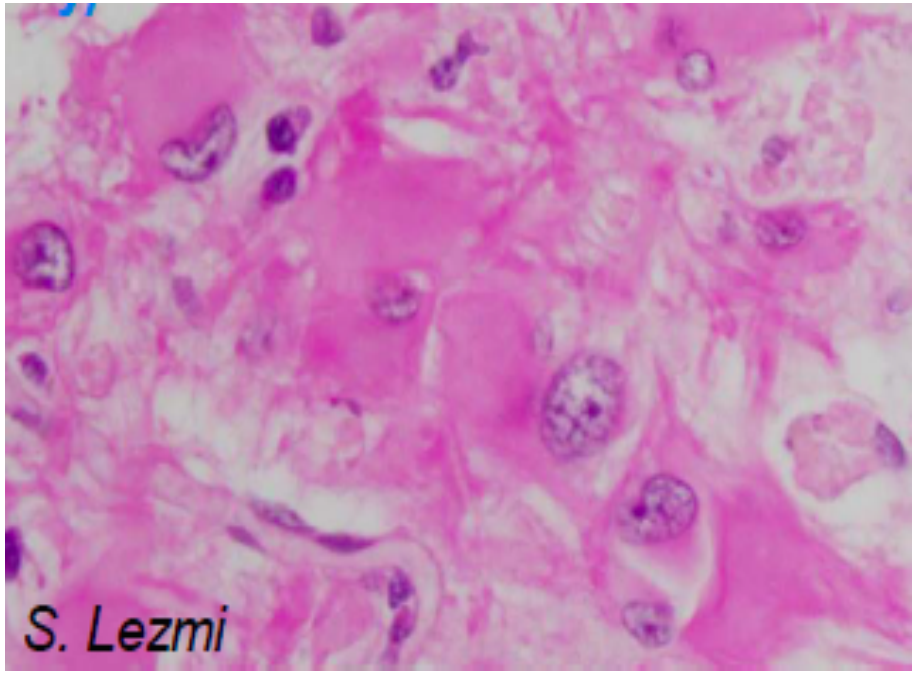
These changes in astrocytes: gemistocytic astrocyte.

gemistocytes



Gemistocytes

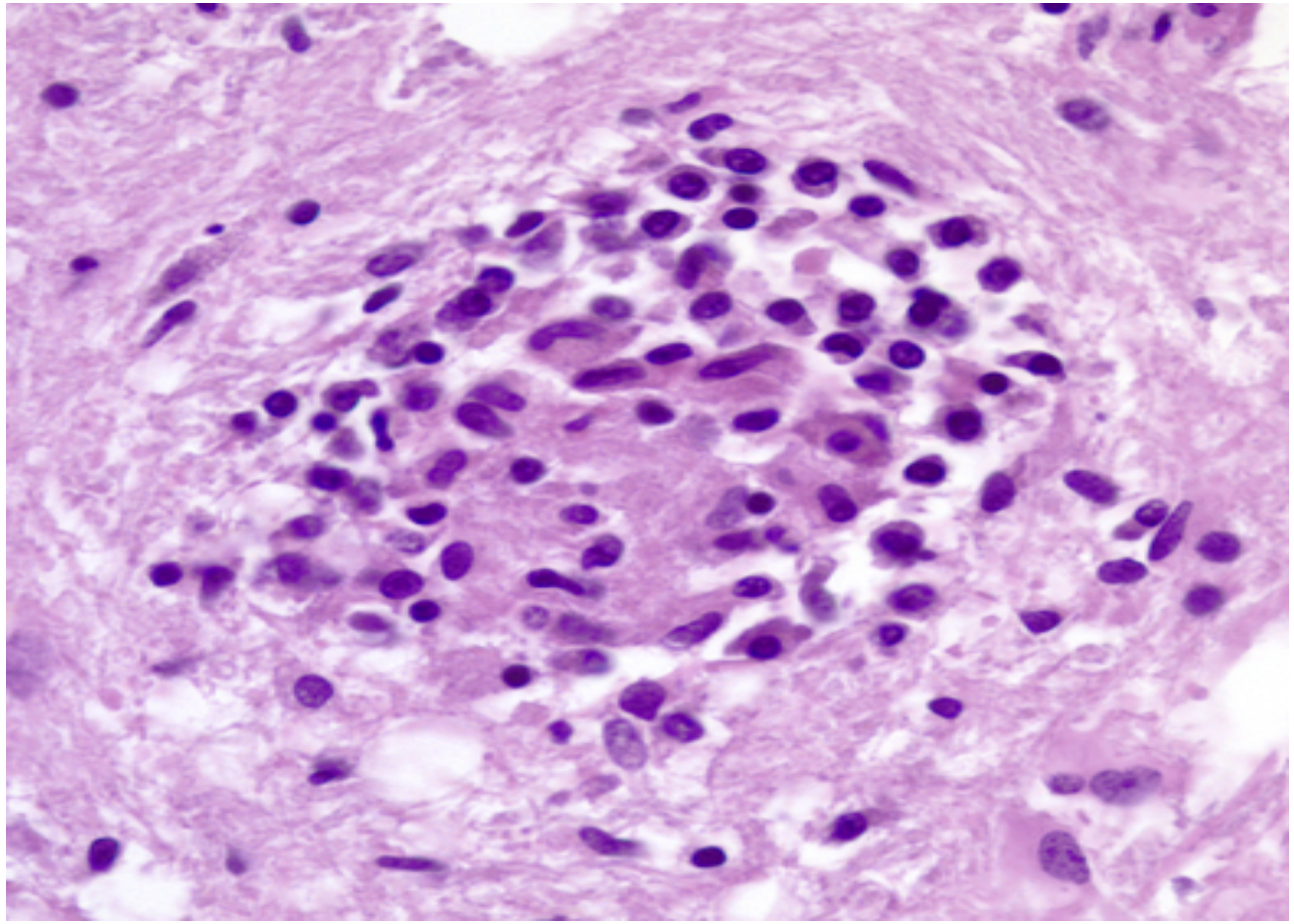




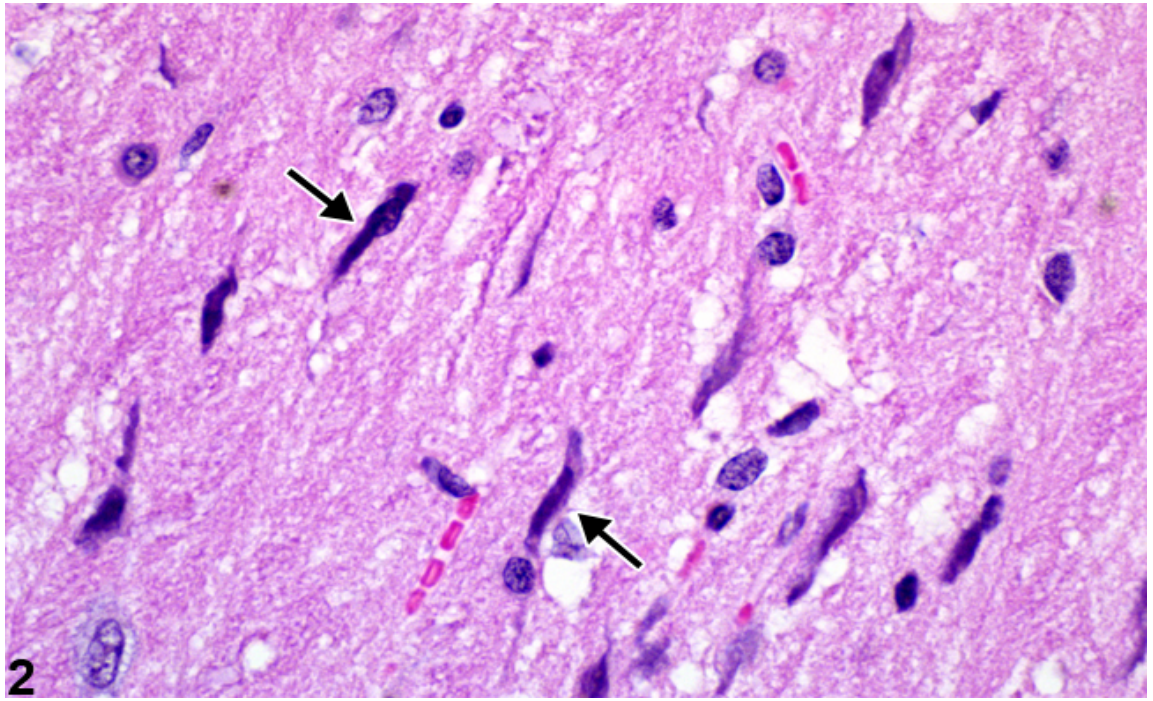
Reactions of Microglia to Injury

- Microglia are mesoderm-derived phagocytic cells that serve as the resident macrophages of the CNS.
- They respond to injury by (1) proliferating; (2) developing elongated nuclei *(rod cells)* (3) forming aggregates around small foci of tissue necrosis *(microglial nodules)*; or (4) congregating around cell bodies of dying neurons *(neuronophagia)*.
- In addition to resident microglia, blood-derived macrophages may also be present in inflammatory foci.

Microglial nodules.. you can think of these as granulomas= aggregates of microglia which are basically macrophages.



Rod cells



Exam question

All of the following statements are correct about the cells seen in this picture except:

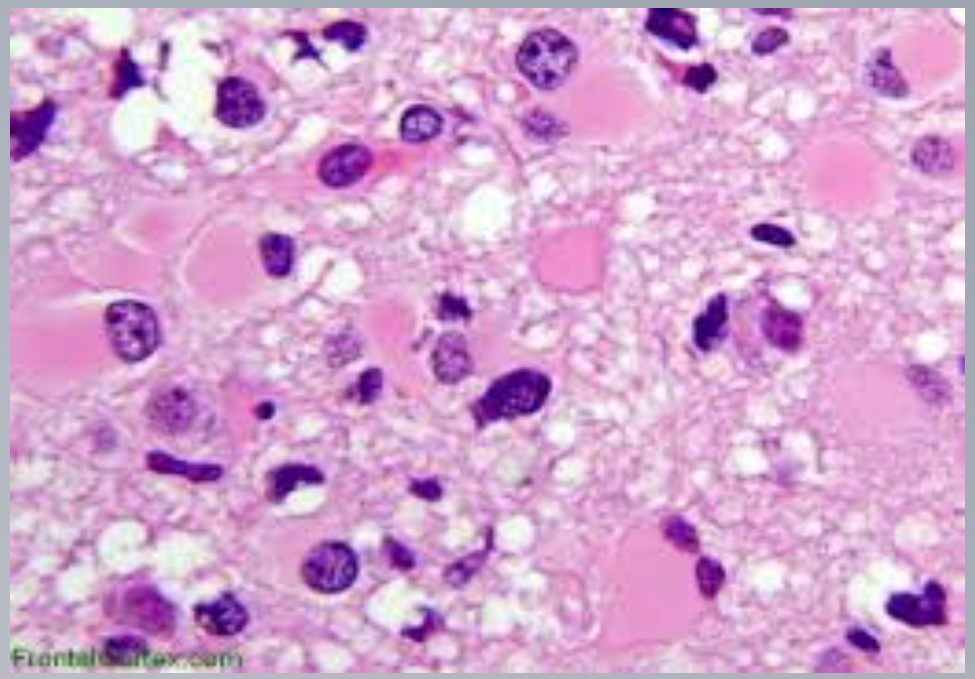
A. originate from astrocytes

B. indicate the start of a repair process after injury

C. can be seen around areas of demyelination.

D. cells of origin are permanent cells

E. can be seen in the vicinity of resolved infarction.



Answer to previous question

- D.. because gemistocytes originate from astrocytes which are glial cells and unlike neurones, glial cells do divide; they aren't permanent
- the rest of the choices are obviously correct. Note the gemistocytes can be a response to any form of injury so the choices about demyelination and old infarct are correct.

Exam style question

- A 27 year old female underwent a caesarian section during which she had massive bleeding. Her systolic blood pressure dropped to 45. The bleeding continued and she died 13 hours after the operation. If you were to do the autopsy exam you would expect to see which of the following changes in her neurons
- A. cytoplasmic basophilia
- B. Prominent nucleoli
- C. cell swelling
- D. pyknosis
- E. Gliosis

Explanation of the question

- The scenario here is about acute ischemic damage. the 13 hour period mean that the morphologic changes have developed. Remember that red neurones are the first morphologic manifestation of ischemic damage and they need 12 hours to develop.
- Obviously the only correct choice is D, the rest are wrong and gloss is wrong because it’s not a neuronal damage and is not an acute change.

A final note

- the exam questions will be similar to the questions in the examples above, and some will be clinically oriented.. so you know what to expect.

- For your information: the word neurone is written with an **e** at the end (British) or without an **e** (American style)

SUMMARY 1/3

- CNS cells are of two types: neurones that are the functional units and glial cells which are supportive. glial cells are much more abundant.
- Glial are four types:
- 1.**astrocytes** that are supportive, control the microenvironment, form part of the blood brain barrier and are responsible for gloss (fibrosis and scarring of CNS).
- 2. **Oligodendrocytes**: their cell membranes form myelin sheath important for insulating nerve impulses thus making transmission quicker
- 3. **Ependymal cells**, line the ventricles and spinal cord cavity. Specialised ependymal form choroid plexus that secretes CSF
- 4. **Microglia** are specialised resident macrophages important for inflammatory and immunologic reaction of CNS.

SUMMARY 2/3

- Neurones respond to **acute** injury by changing to **red** neutrons. they appear 12 hours after irreversible insult and characterised by cytoplasmic shrinkage and increased eosinophilia (due to loss of Nissl substance), pyknosis , loss of nucleolus and increased ramifying processes.
- subacute or chronic neuronal injury causes **degeneration and death of neurones, usually by apoptosis** (to decrease risk of damaging inflammation).
- chronic neuronal injury usually affects **functionally related** neurones

SUMMARY 3/3

- glial cells are less vulnerable to acute injury and respond during repair process and gliosis formation.
- Astrocytes are the main cells involved in repair and respond by forming gemistocytes: hypertophic cells with large eosinophilic cytoplasm, large nuclei and prominent nucleoli
- glial cells can proliferate while neurones cannot (although neuronal progenitors have a limited capacity to divide)
- Microglia respond to injury by: hyperplasia, rod cells, neurophagia and microglial nodule formations.


KEEP
CALM
WHATEVER HAPPENS
THINK
POSITIVE