SPINAL CORD AND PROPERTIES OF CEREBROSPINAL FLUID:

OPTIONS FOR DRUG DELIVERY





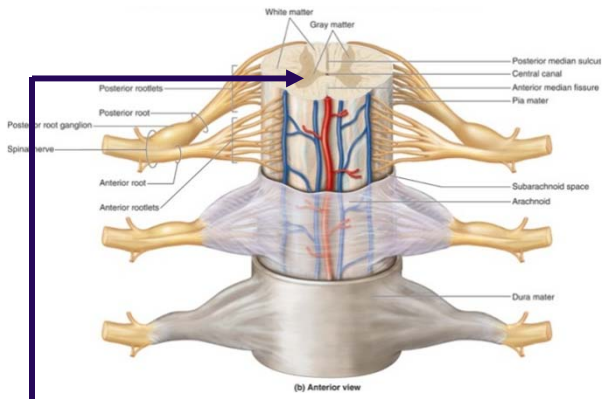
WHY DO WE NEED TO KNOW ABOUT THE SPINAL CORD ANATOMY AND PROPERTIES OF CEREBROSPINAL FLUID?

- SMA therapeutics need to reach cells in the spinal cord (primary target tissue)
- It is difficult to reach the spinal cord tissue because it is protected by the blood brain barrier
  - The blood brain barrier protects the spinal cord by only allowing certain molecules to reach the spinal cord tissue from the blood
- Some drugs are able to cross the blood brain barrier
- For molecules that are unable to penetrate the blood brain barrier, direct delivery to the spinal cord is a possible alternative

SUMMARY OF ROUTES OF DRUG ADMINISTRATION THAT BYPASS THE BLOOD BRAIN BARRIER

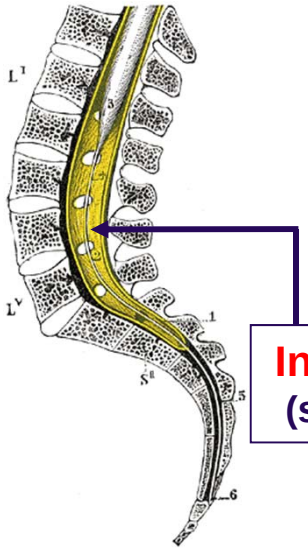
- Drugs can be delivered directly into the central nervous system (CNS)
  - Spinal cord tissue: intraparenchymal delivery
  - Subarachnoid space filled with cerebrospinal fluid
    - Intrathecal delivery into the lumbar area
    - Intracerebroventricular delivery into ventricles of the brain

Direct delivery into the spinal cord

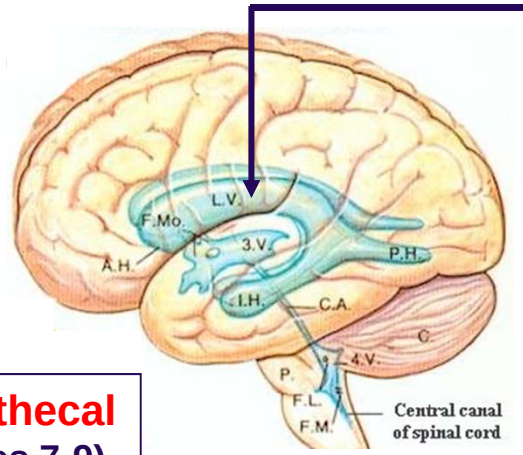


Intraparenchymal
(slide 6)

Delivery through cerebrospinal fluid



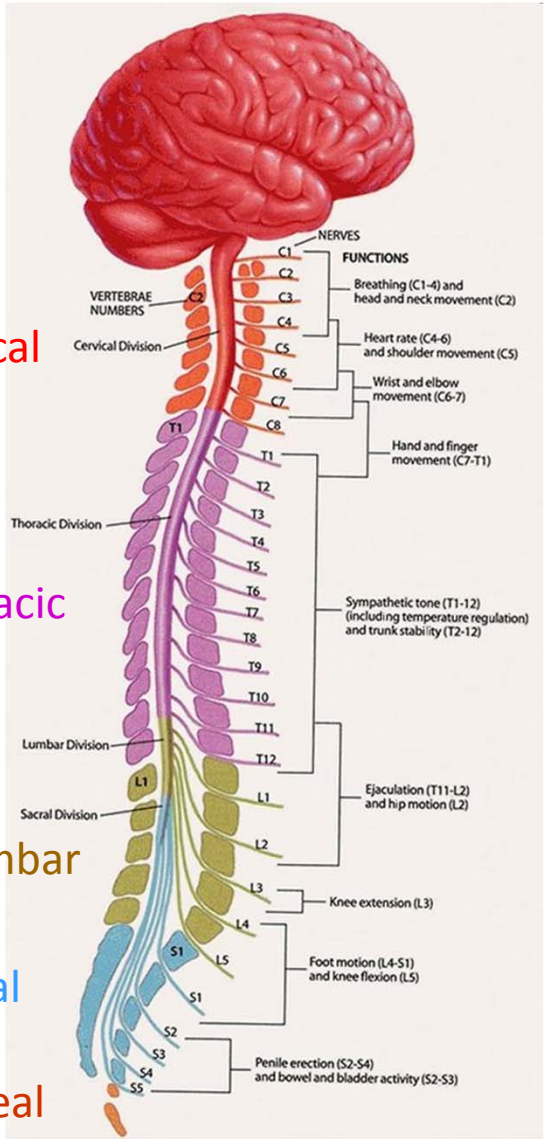
Intrathecal
(slides 7-9)



Intracerebroventricular
(slide 11)

CNS ANATOMY: THE SPINAL CORD IS AN EXTENSION OF THE BRAIN

- The spinal cord is an extension of the brain, and together with the brain, forms the central nervous system (CNS)
- Surrounded by specialized bones comprising the spinal column or vertebral column
- Spinal nerves are named according to where they exit the spinal column but not the spinal cord
- Spinal cord is regionally organized:
  - The cervical region innervates the upper limbs
  - The lumbar region innervates the lower limbs



cervical

thoracic

lumbar

sacral

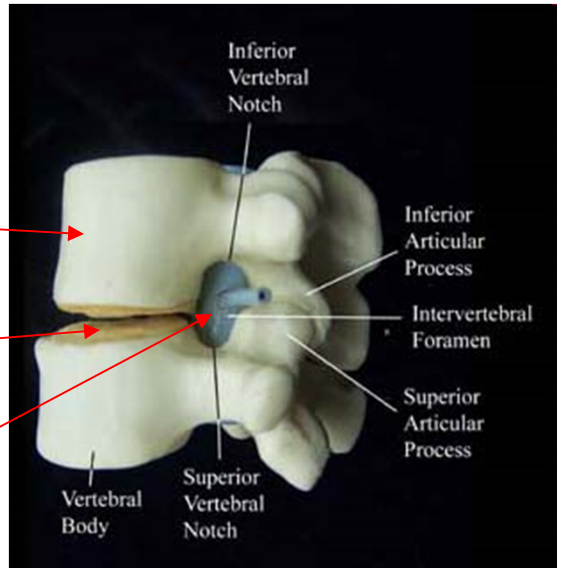
coccygeal

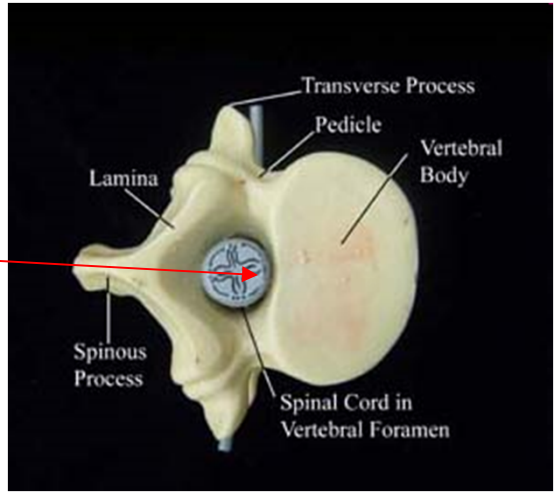
http://www.daviddarling.info/encyclopedia

THE SPINAL CORD IS ENTIRELY PROTECTED BY BONE

- Well-protected by the vertebral (spinal) column
- The vertebral column is made up of individual vertebrae
- The vertebrae are separated by tough intervertebral discs
- Nerves enter and exit the spinal cord through intervertebral foramina
- Vertebral foramen: space where the spinal cord resides

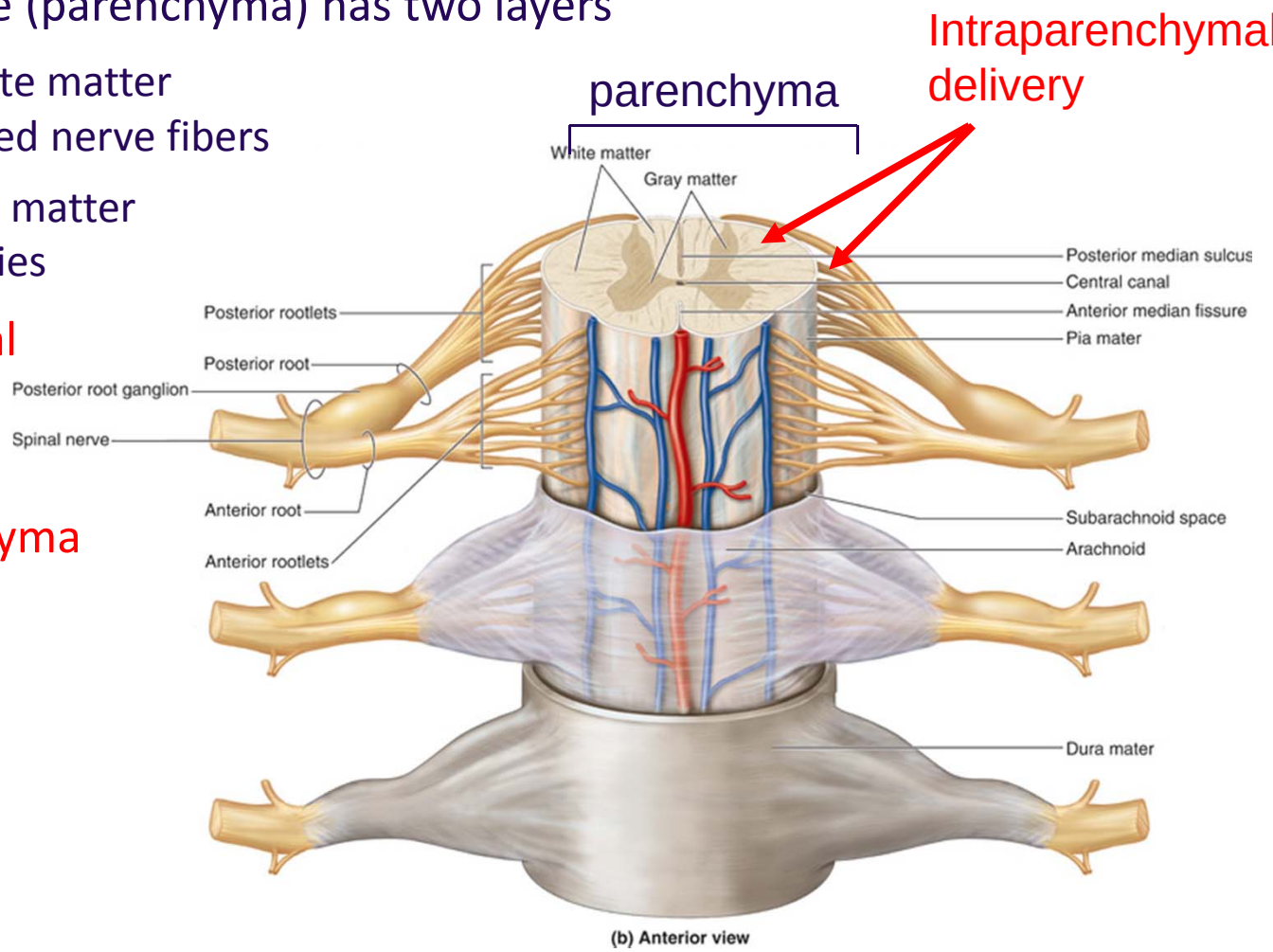
http://anatomy.med.umich.edu/modules/spinal_cord_module/spinalcord_01.html





INTRAPARENCHYMAL ROUTE OF ADMINISTRATION DELIVERS DRUGS INTO SPINAL CORD TISSUE

- Spinal cord tissue (parenchyma) has two layers
  - Outer layer: white matter
    – myelin sheathed nerve fibers
  - Inner layer: gray matter
    – nerve cell bodies
- Intraparenchymal delivery is administration into the parenchyma (either white or gray matter)

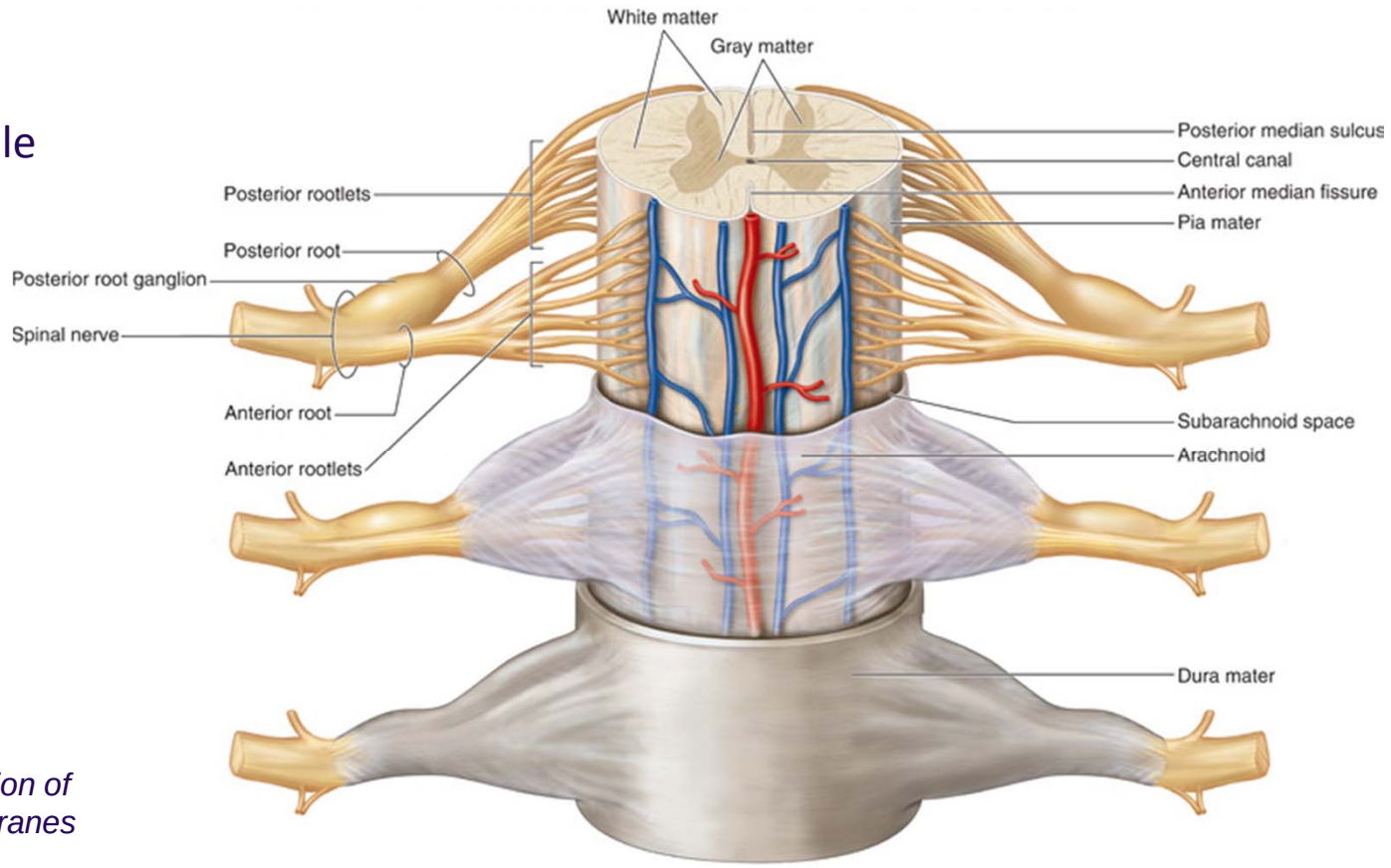


http://academic.kellogg.edu/herbrandsonc/bio201_McKinley/f16-2b_spinal_meninges__c.jpg

SPINAL CORD TISSUE IS PROTECTED BY THREE MEMBRANES (MENINGES)

- **Dura mater**, outside layer
- **Arachnoid**, middle layer; comprises subarachnoid space, a drug delivery site
- **Pia mater**, innermost layer

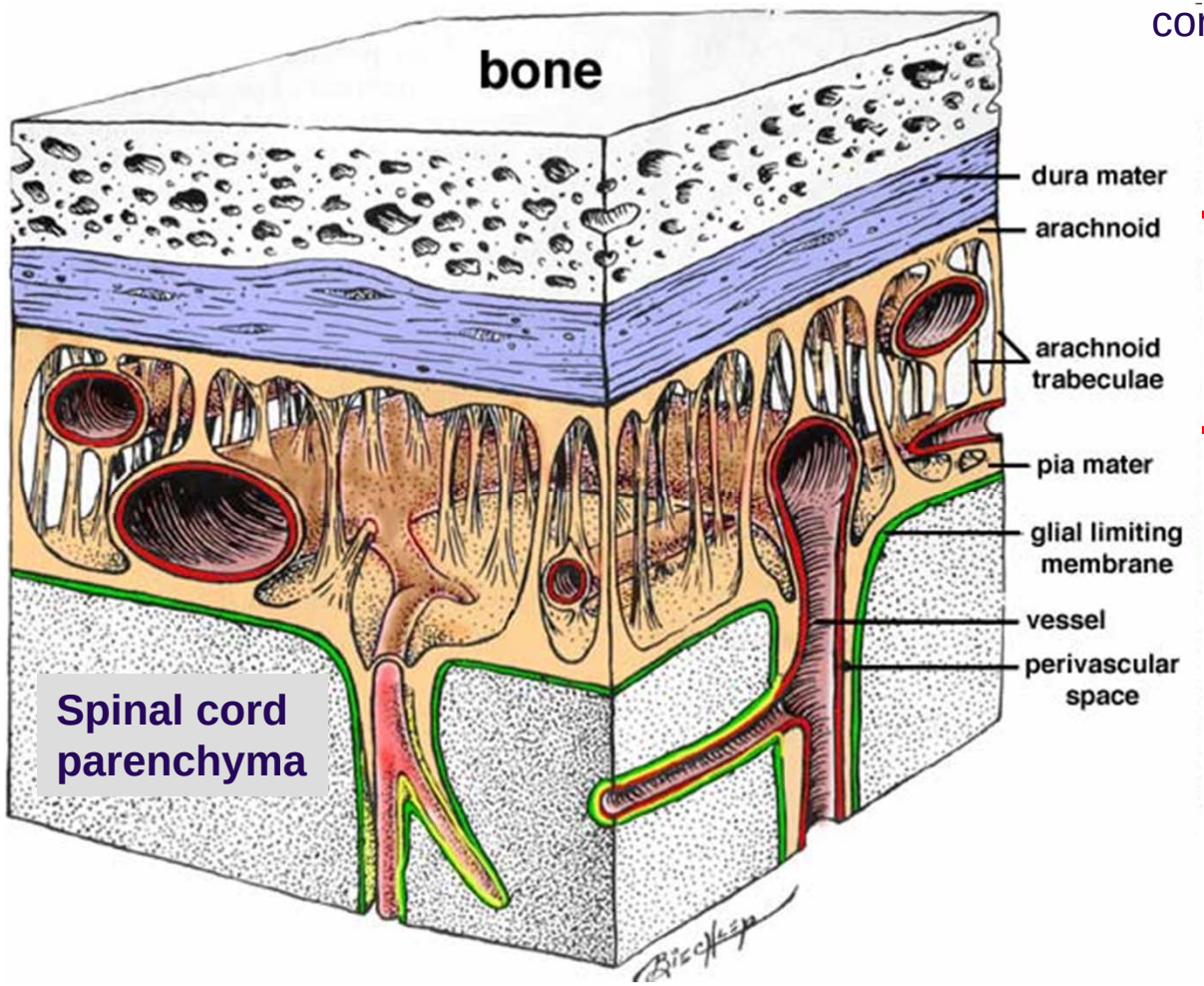
Cross-sectional representation of spinal cord protective membranes depicted on next slide



http://academic.kellogg.edu/herbrandsonc/bio201_McKinley/f16-2b_spinal_meninges__c.jpg

THE SUBARACHNOID SPACE IS FILLED WITH CEREBROSPINAL FLUID (CSF)

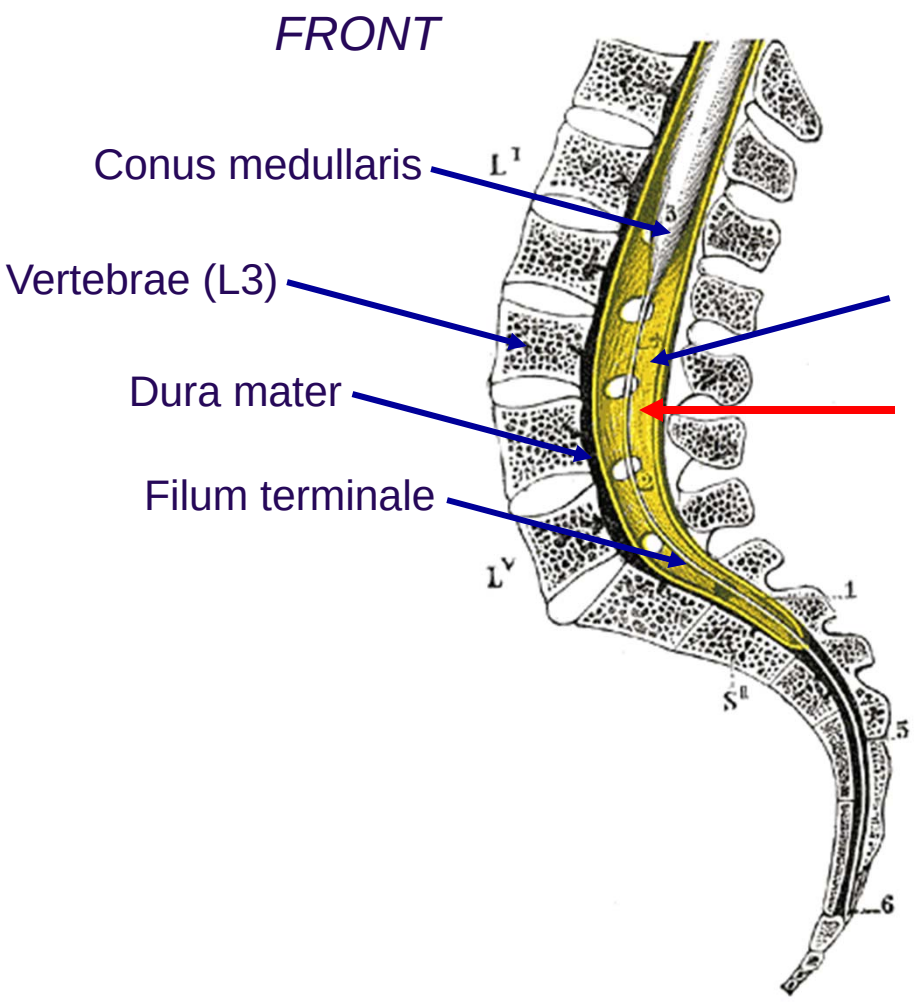
Cross-sectional representation of spinal cord protective membranes



Subarachnoid space; filled with CSF

http://vanat.cvm.umn.edu/neurHistAtls/pages/men1.html

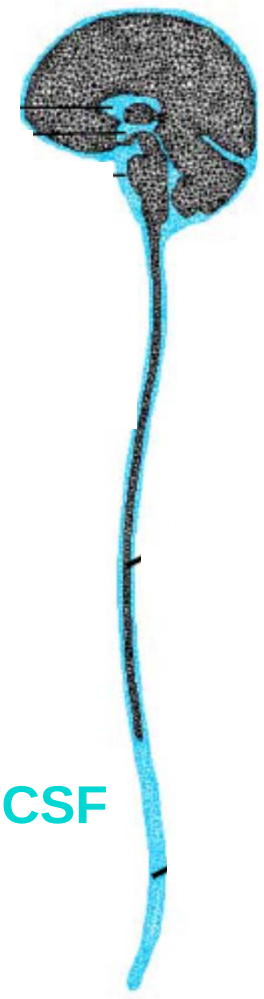
INTRATHECAL ROUTE OF ADMINISTRATION DELIVERS DRUGS INTO CSF OF THE SUBARACHNOID SPACE



- Spinal cord does not span the entire vertebral column and terminates at L1 vertebrae
- Intrathecal delivery at L3 avoids damaging the spinal cord
- Epidural injection is not the same as intrathecal delivery

DRUGS DELIVERED TO CSF CAN REACH THE BRAIN AND SPINAL CORD TISSUES

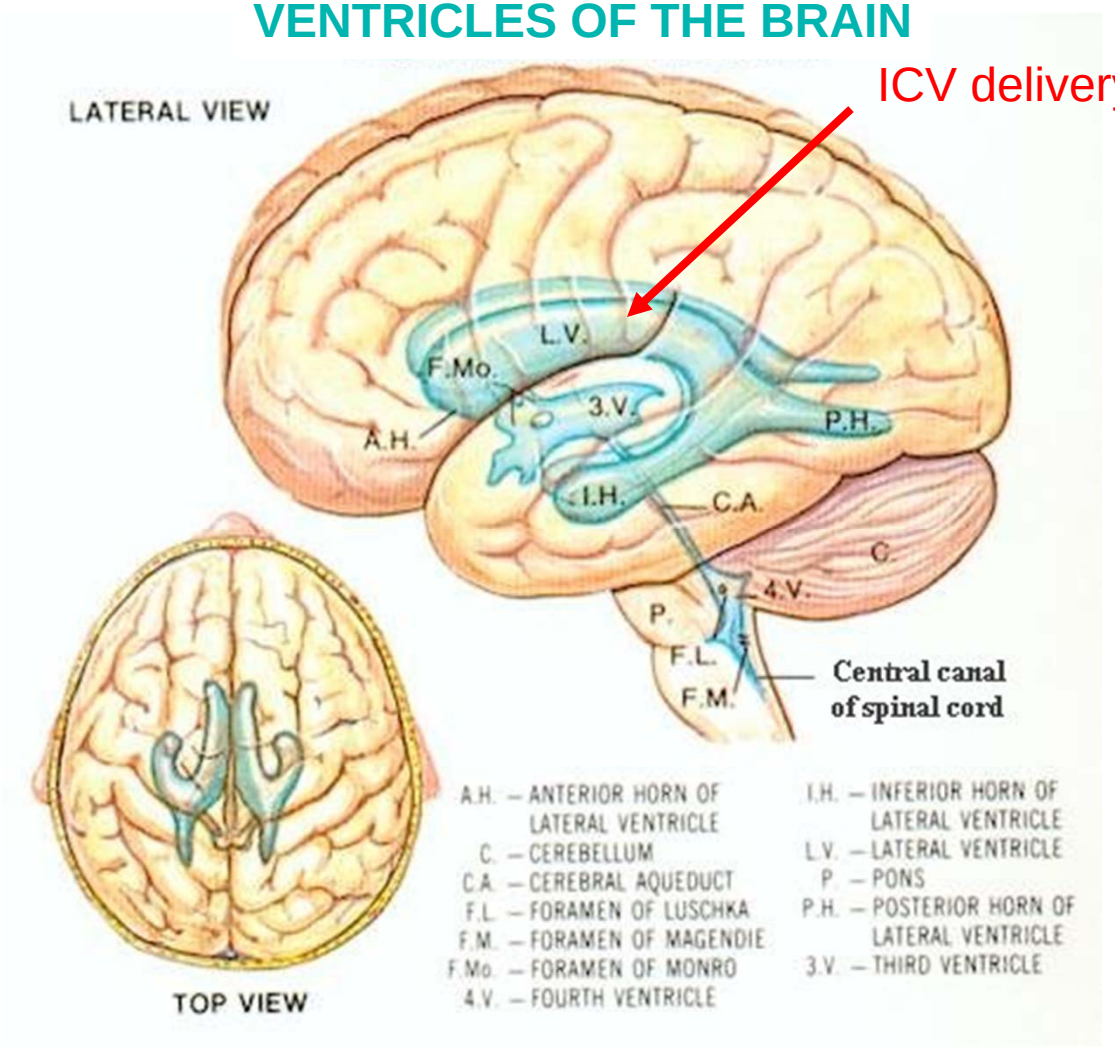
- Location of CSF
  - Subarachnoid space surrounding the brain and spinal cord
  - Central canal of the spinal cord
  - Brain ventricles
- Functions
  - Protection and buoyancy
  - Excretion of waste products
  - Transports hormones (endocrine medium of the brain)
- CSF is replaced several times a day and exchanges with the bloodstream
- CSF oscillates with the cardiac cycle, which provides constant mixing
- Volume (1/3 in the ventricles, 2/3 in subarachnoid space)
  - Newborns: 30-50 ml
  - Children: 65-100 ml
  - Adults: 90-150 ml



Lenninger et al, 2009

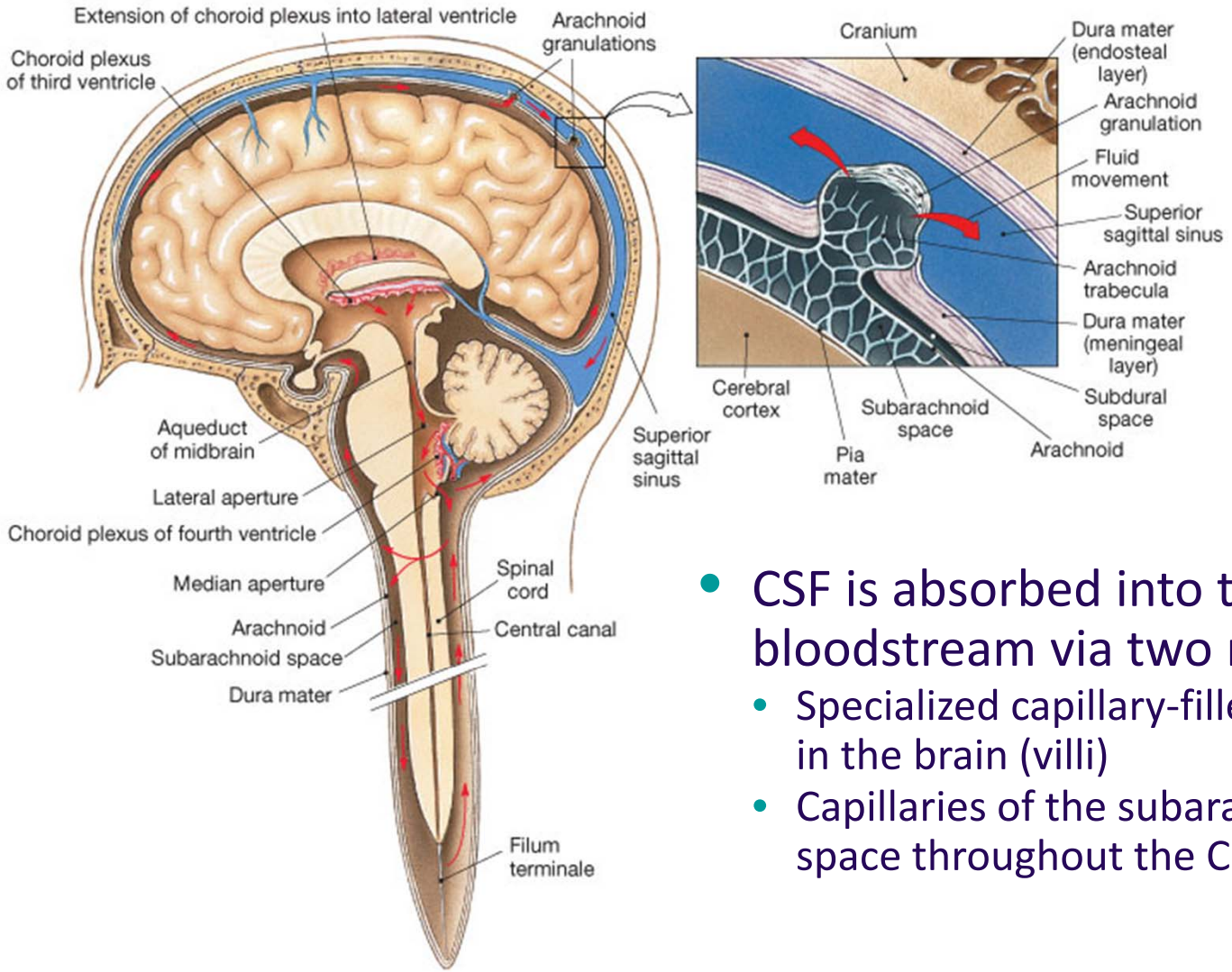
ICV ADMINISTRATION PROVIDES DELIVERY TO BOTH THE BRAIN AND THE SPINAL CORD

- Intracerebroventricular (ICV) delivery is administration into a brain ventricle
- Ventricles are 4 cavities within the brain where CSF is produced (400-500 ml per day)
- Ventricles are connected to the subarachnoid space of the brain and spinal cord



http://universe-review.ca/I10-80-ventricles.jpg

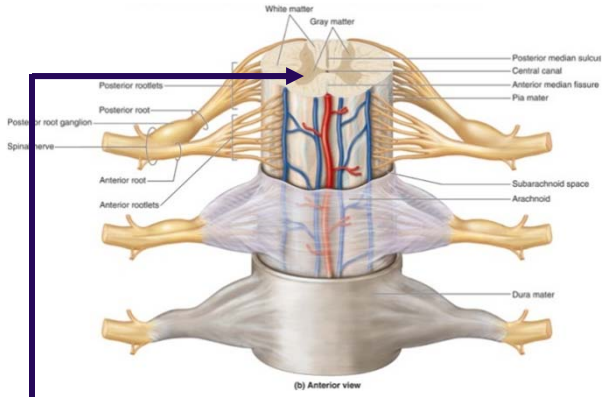
MOST DRUGS DELIVERED TO CSF REQUIRE REPEATED ADMINISTRATION



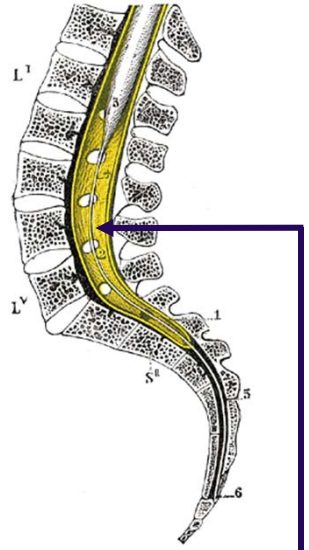
- CSF is absorbed into the bloodstream via two routes
  - Specialized capillary-filled structures in the brain (villi)
  - Capillaries of the subarachnoid space throughout the CNS

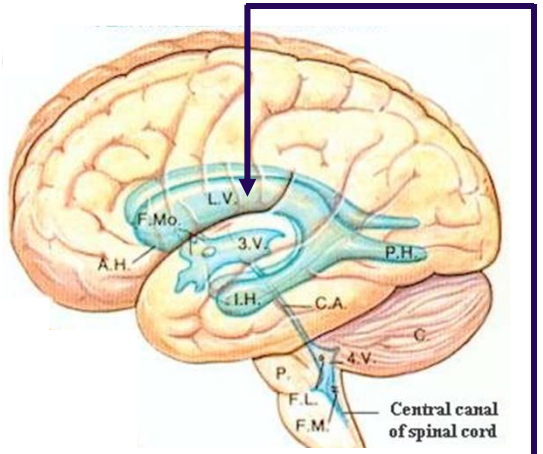
EACH DRUG MAY REQUIRE A SPECIFIC ROUTE TO ACHIEVE OPTIMAL RESULTS: OPTIONS FOR CNS DELIVERY

Direct delivery into the spinal cord



Delivery through cerebrospinal fluid





Intraparenchymal: direct delivery to spinal cord tissue (white or gray matter)

Intrathecal: delivery to spinal cord and brain; higher concentration in the spinal cord

Intracerebroventricular: delivery to brain and spinal cord; higher concentration in the brain

To learn more about intrathecal delivery, go to
http://www.learnaboutsma.org/antisense/5.html

WWW.SMAFOUNDATION.ORG