

# Neuroembryology of Neural Tube Defects

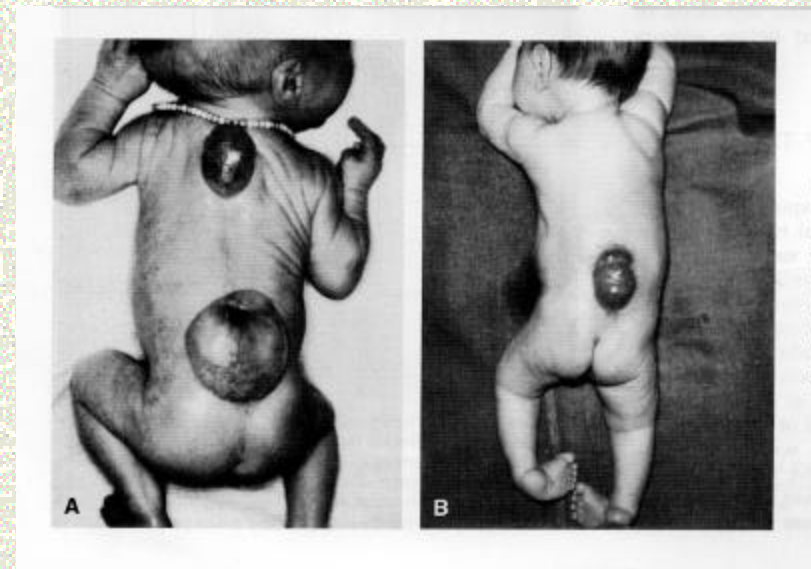
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Rebecca A. Code, PhD  
Dept. of Biomedical Sciences  
College of Osteopathic Medicine  
Ohio University

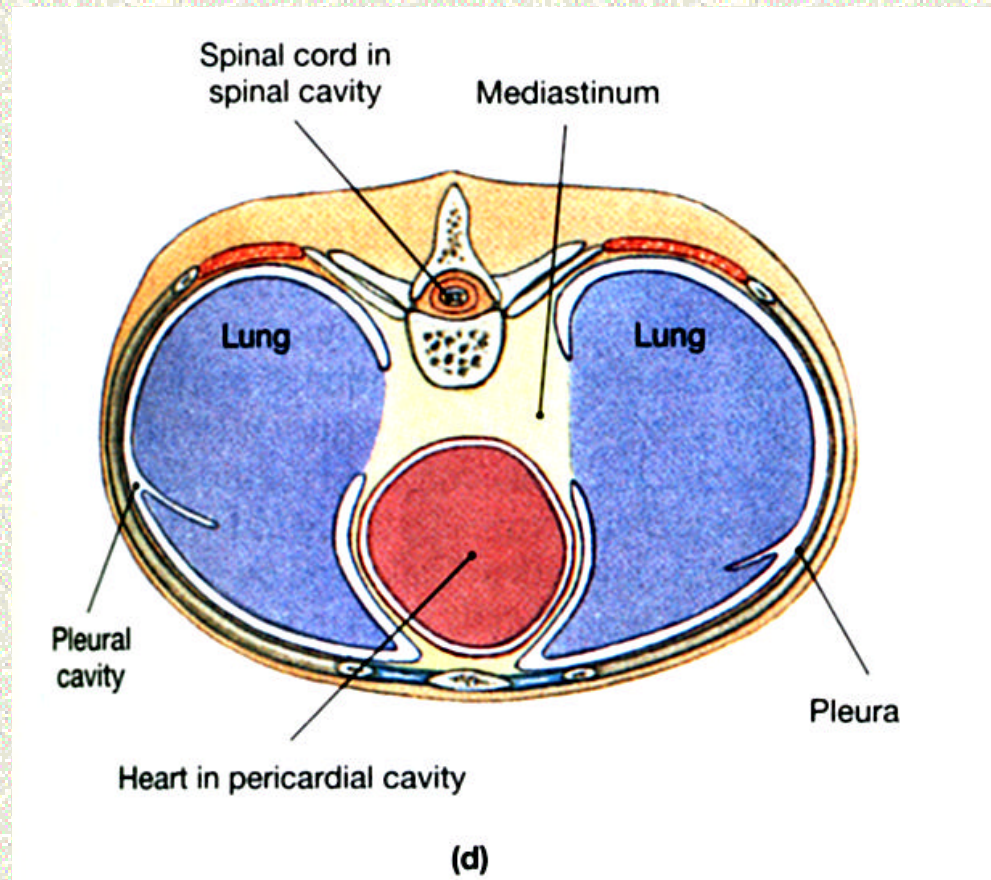
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# Congenital Anomalies of the Spinal Cord

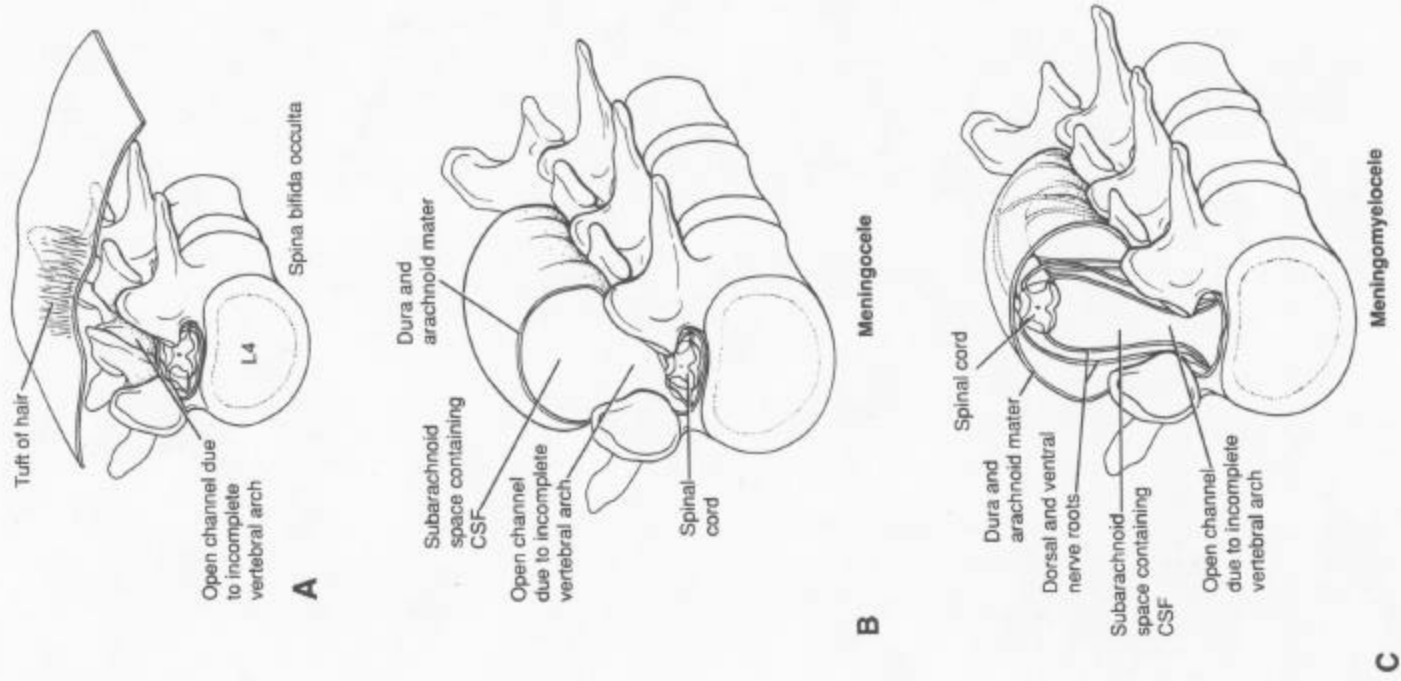
- ✦ Most are the result of defective closure of the neural tube during the 4th week of development.
- ✦ The resulting neural tube defects (NTDs) also involve tissue overlying the spinal cord: meninges, vertebral arch, muscles, skin.



# Normal vertebra enclosing the spinal cord



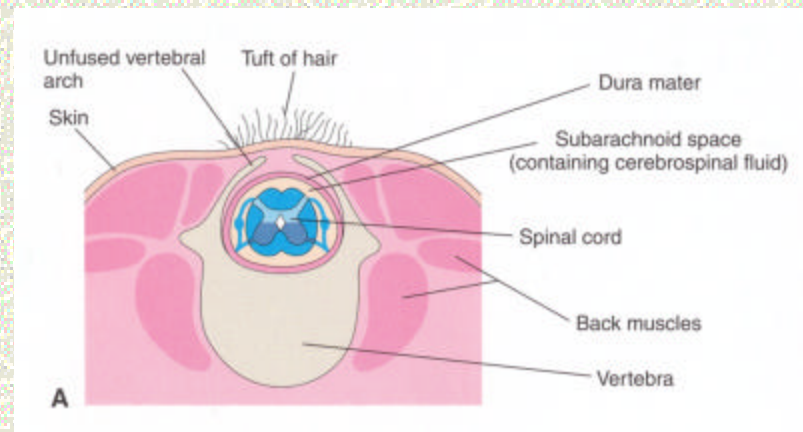
# Types of spina bifida



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# Spina Bifida Occulta

- # This defect in the vertebral arch is the result of the failure of the embryonic halves of the neural arch to grow together and fuse in the midline.
- # Occurs in about L5 or S1 vertebrae in about 10% of otherwise normal people.



# Minor form of spina occulta

- # Small dimple with tuft of hair arising from it.
- # Arrow indicates the opening of a spinal dermal sinus in a skin dimple in the sacral region.



# Photo of spina bifida occulta

- # Hairy patch in the lumbosacral region indicates the site of a spina bifida occulta.



# Spina Bifida Cystica

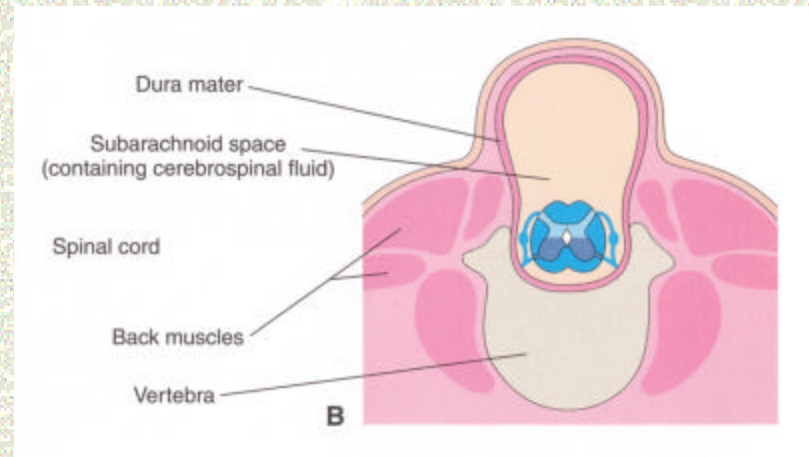
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- # Severe types of spina bifida, involving protrusion of the spinal cord and/or meninges through the defect in the vertebral arch.
  - # Referred to as s.b. cystica because of the cystlike sac that is associated with these anomalies.
  - # Occur in about 1/1,000 births. Types:
    - # Spina bifida with meningocele
    - # Spina bifida with meningomyelocele
    - # Spina bifida with myeloschisis (myelocele)
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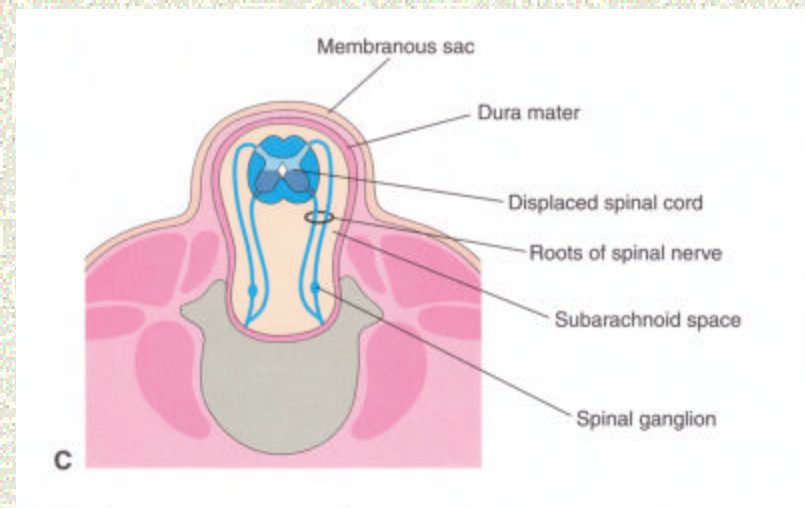
# Spina Bifida with Meningocele

- # Cyst contains meninges and cerebrospinal fluid
- # Spinal cord and spinal roots are in their normal position
- # May be spinal cord abnormalities



# Spina Bifida with Meningomyelocele

- # Cyst contains spinal cord and/or spinal nerve roots
- # May be covered by skin or a thin, easily ruptured membrane

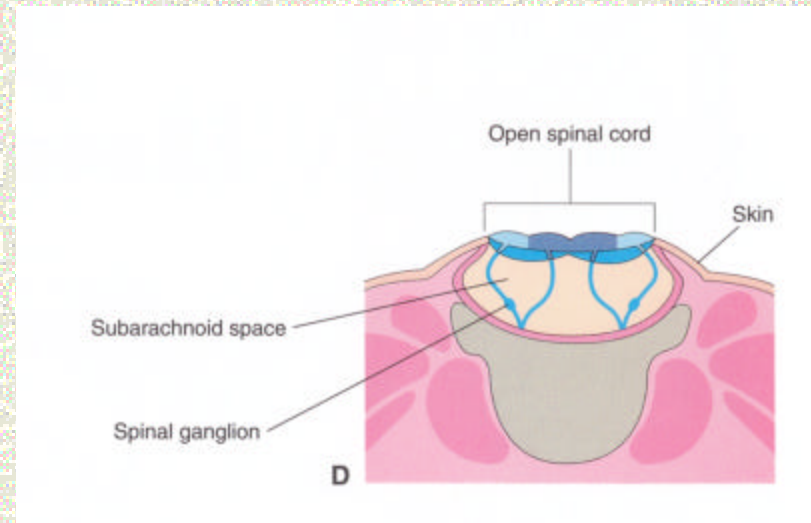


# Photo of meningocele



# Spina Bifida with Myeloschisis (Myelocele)

- # Most severe type of spina bifida
- # Spinal cord is open because the neural folds failed to fuse during the 4th week.
- # Spinal cord in the affected area is a flattened mass of nervous tissue.



# infant lumbar myeloschisis

- # The open spinal cord (arrow) is covered by a delicate, semitransparent membrane.



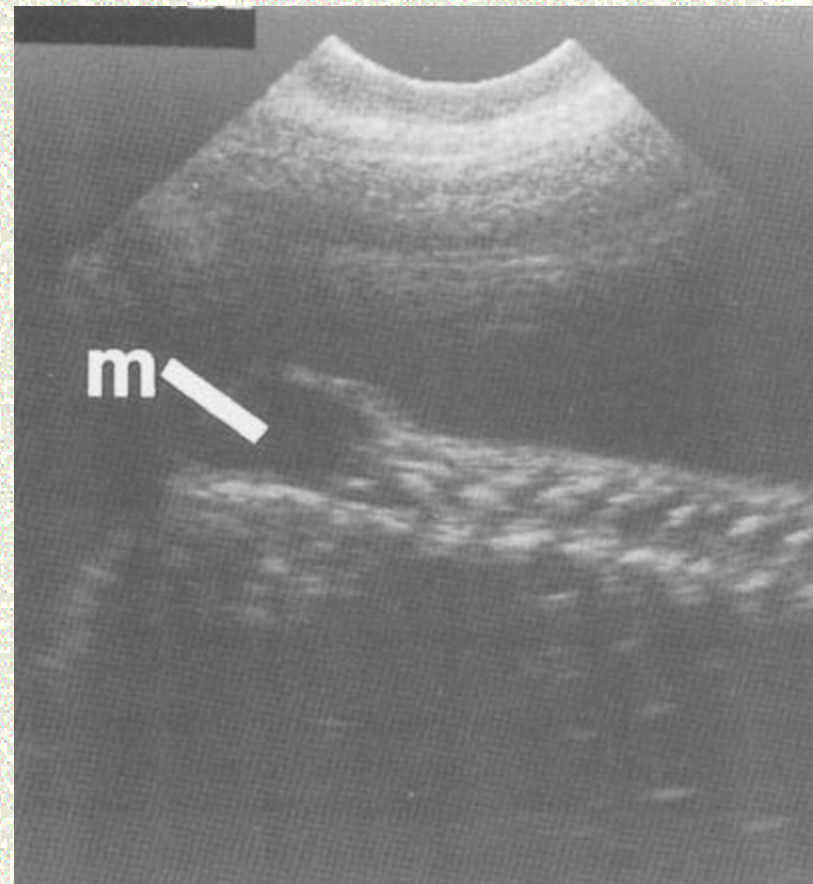
# Indications of Neural Tube Defects

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- # High level of alpha-fetoprotein (AFP) in the amniotic fluid.
  - # AFP escapes from the circulation into the amniotic fluid from fetuses with open (not covered with skin) NTDs.
  - # AFP may also be elevated in the maternal blood serum
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# Ultrasound of meningocele

- # 14-week-old fetus with a cystlike protrusion representing a meningocele (m) in the sacral region.
- # Vertebral arches on the right are visible.



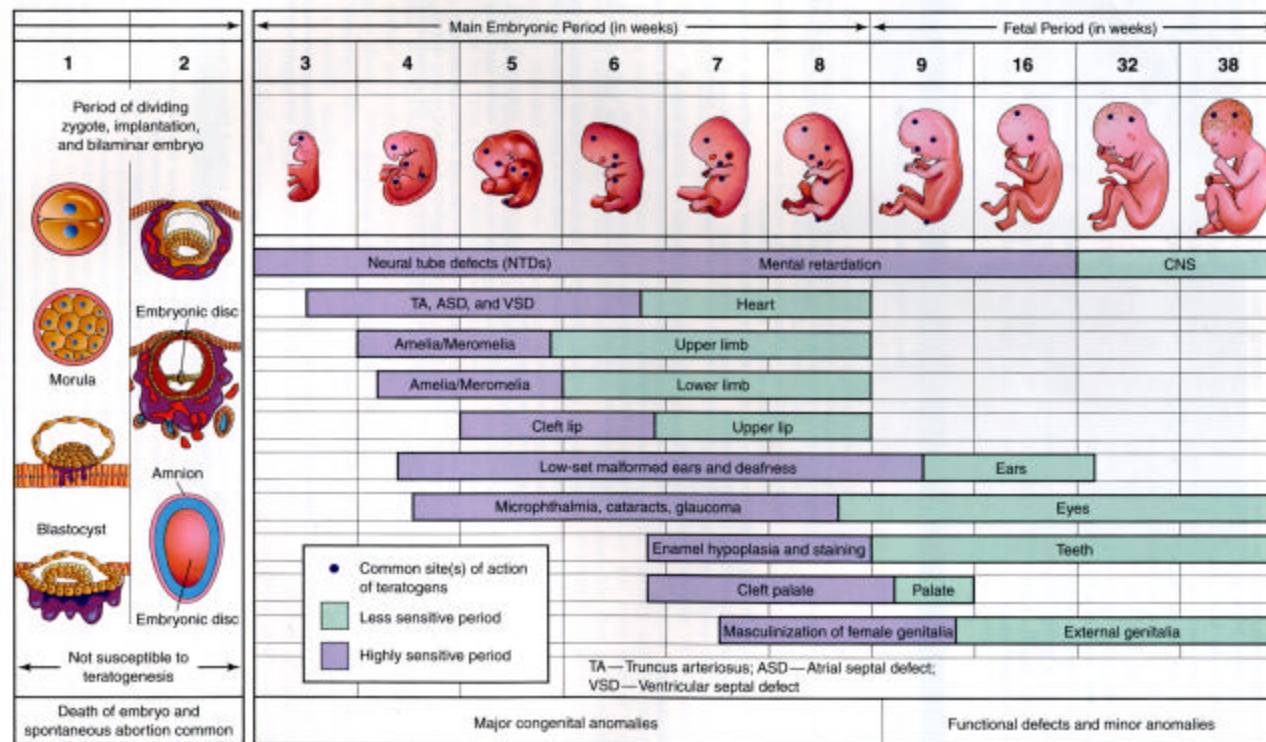
# Causes of Neural Tube Defects

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- # Actual mechanisms are unknown.
  - # Multiple factors (environmental, nutritional, and genetic) play a role.
  - # Certain drugs are known to increase the risk of meningocele (e.g, the anticonvulsant valproic acid) if given during the 4th week of pregnancy.
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# Sensitive periods



■ **Figure 8-15.** Schematic illustration of critical periods in human prenatal development. During the first 2 weeks of development, the embryo is usually not susceptible to teratogens; a teratogen either damages all or most of the cells, resulting in death of the embryo, or damages only a few cells, allowing the conceptus to recover and the embryo to develop without birth defects. Mauve denotes highly sensitive periods when major defects may be produced (e.g., amelia, absence of limbs). Green indicates stages that are less sensitive to teratogens when minor defects may be induced (e.g., hypoplastic thumbs).

# Role of Folic Acid

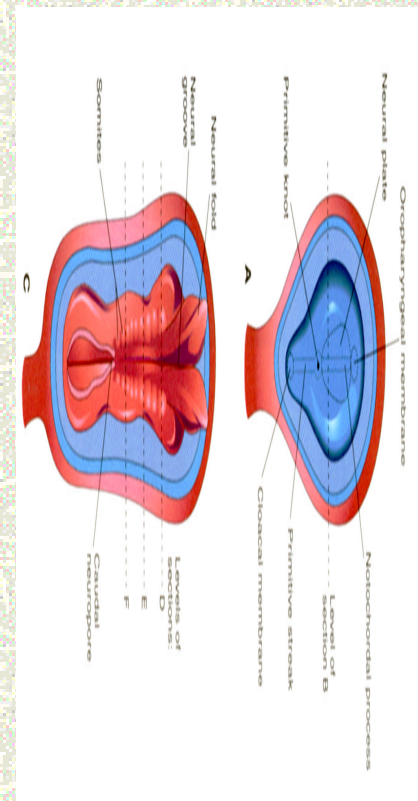
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- # Folic acid supplements taken during the periconceptional period reduce the incidence of NTDs by 50-70%.
  - # Involved in the synthesis of several amino acids and DNA.
  - # Important for rapidly dividing and proliferating cells.
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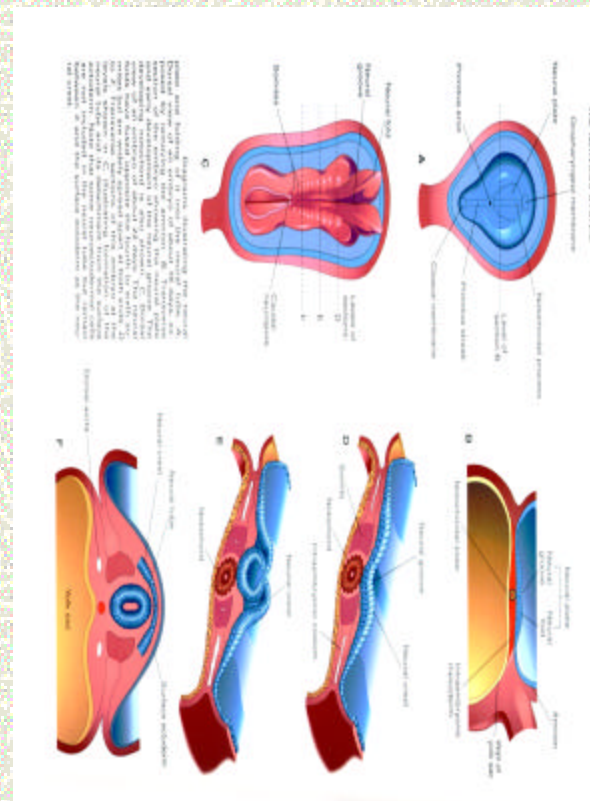
# Development of Nervous System - 3rd week

- # Neural plate appears.
- # Neural folds thicken on either side of the midline forming a neural groove.



# Development of Nervous System - 4th week

- ✦ Neurulation = formation of the neural tube begins (day 22-23).
- ✦ Neural folds begin fusing near the 4th-6th pairs of somites.
- ✦ Fusion proceeds in cranial and caudal directions.
- ✦ At neuropores, the lumen of the neural tube (neural canal) communicates freely with the amniotic cavity.



# Closure of Neuropores

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- Rostral neuropore closes on day 24. Caudal on day 26.
  - # Closure of the neuropores coincides with the establishment of a blood vascular circulation for the neural tube.
  - # Failure to close leads to escape of  $\alpha$ -fetoprotein from the circulation into amniotic fluid.
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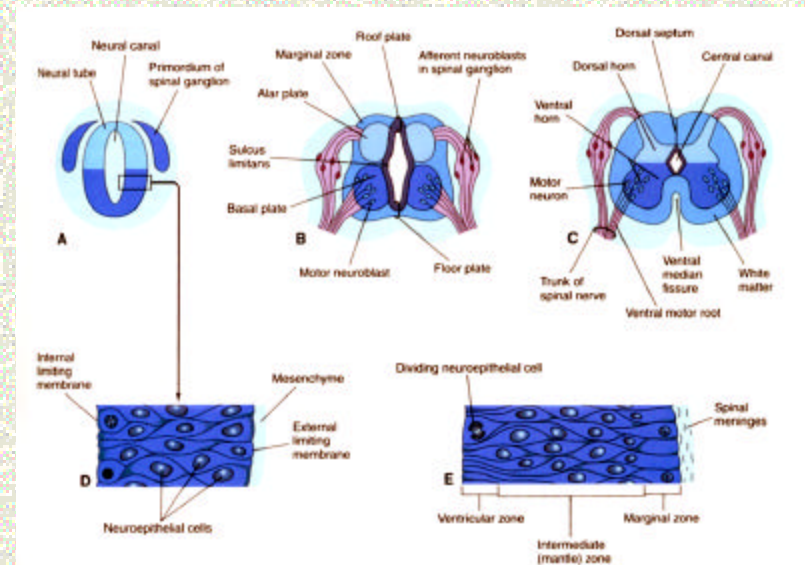
# Failure of closure of anterior neuropore

- # Although the neural folds may fail to neurulate in almost any region, the most frequent site is the cranial neuropore.



# Development of the Neural Tube

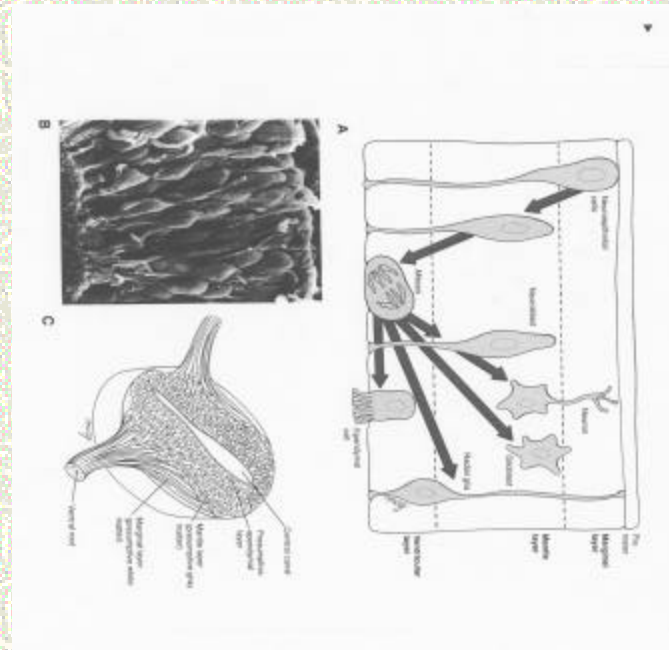
- ❏ Lateral walls of neural tube thicken, gradually reduce the size of the neural canal until only a small central canal remains.
- ❏ Differential thickening of the lateral walls produces a shallow longitudinal groove on each side = sulcus limitans.
- ❏ Dorsal part = alar plate (sensory)
- ❏ Ventral part = basal plate (motor)





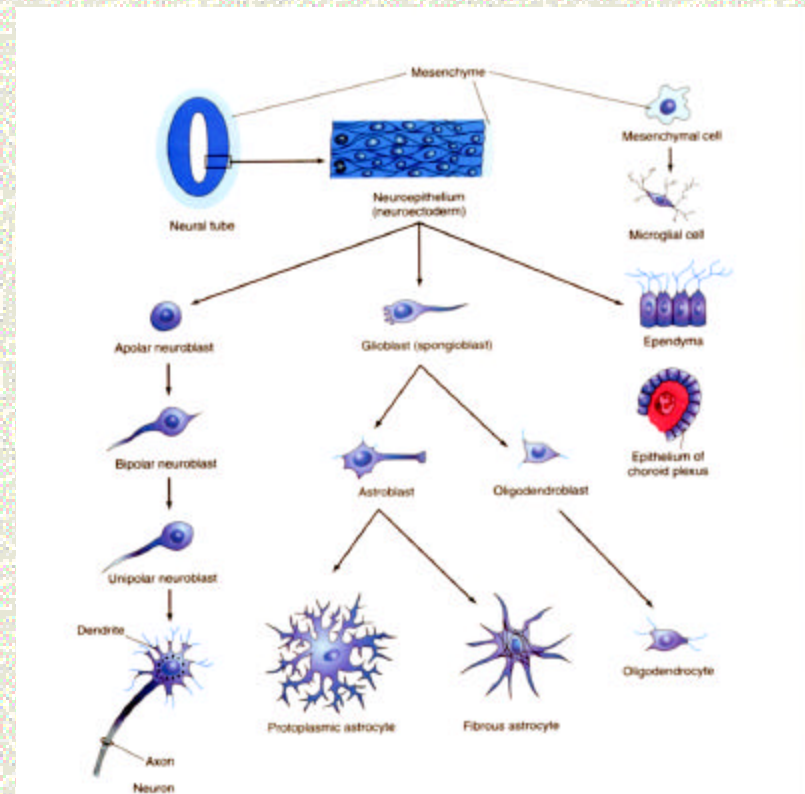
# Neural tube layers

- # Ventricular Zone -  
dividing  
neuroepithelial cells
- # Marginal Zone - the  
processes of the  
neuroepithelial cells
- # Intermediate Zone -  
mantle layer



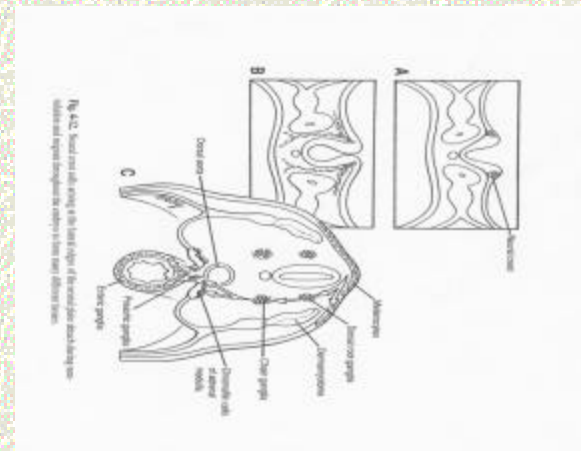
# Histogenesis of CNS Cells

- Initially, wall is made of pseudostratified columnar neuroepithelium and constitute the ventricular zone.
- # Ventricular zone gives rise to all neurons and macroglia.
- # Microglia (phagocytic) develop from monocyte-macrophage blood cells then invade the CNS.



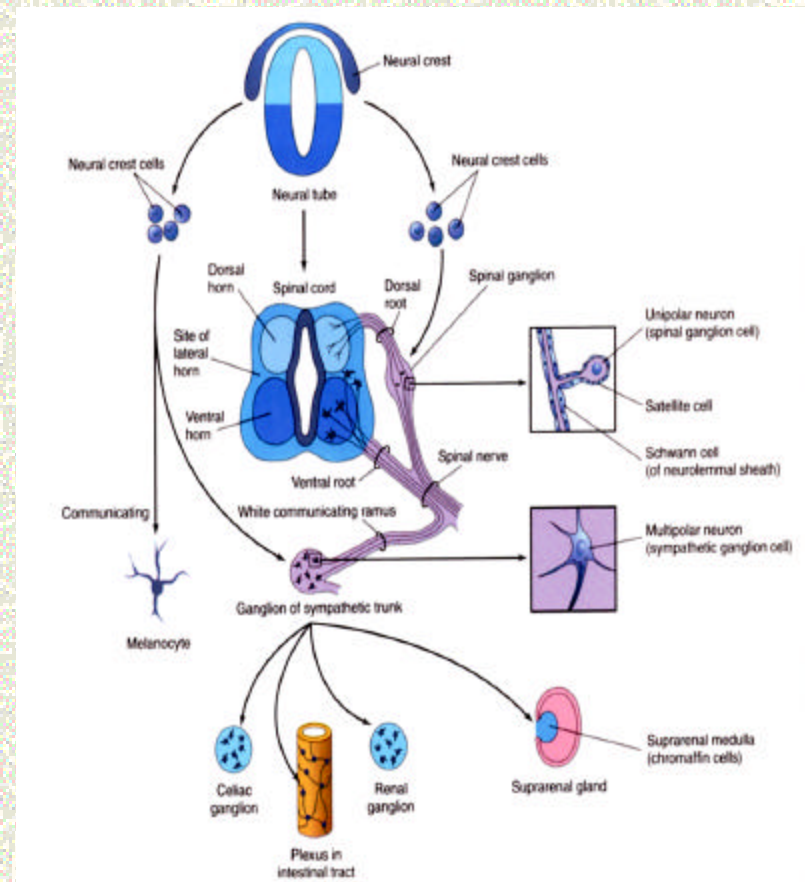
# Migration of Neural Crest

- Neural crest cells arise at the lateral edge of the neural plate, detach during neurulation and migrate throughout the embryo to form many different tissues.

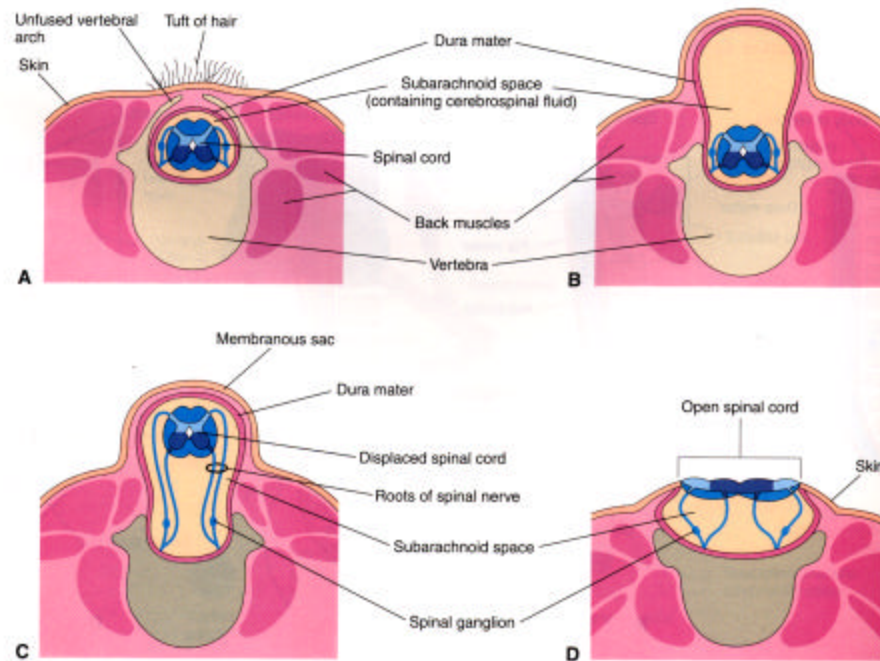


# Fate of Neural Crest

- Neural crest gives rise to most of the peripheral and autonomic nervous systems.



# Review of spina bifida



■ **Figure 18-12.** Diagrammatic sketches illustrating various types of spina bifida and the commonly associated anomalies of the vertebral arch, spinal cord, and meninges. *A*, Spina bifida occulta. Observe the unfused vertebral arch. *B*, Spina bifida with meningocele. *C*, Spina bifida with meningoencephalocele. *D*, Spina bifida with myeloschisis. The types illustrated in *B* to *D* are referred to collectively as spina bifida cystica because of the cystlike sac that is associated with them.

# Summary

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- # Neural tube defects arise from failure of closure of the cranial or caudal neuropore.
  - # NTDs are caused by environmental and genetic factors.
  - # Inadequate fetal folate acquisition by rapidly proliferating neural tube or neural crest cells during critical periods may explain many cases of folate-responsive NTDs and neurocristopathies.
  - # Review of neurulation.
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