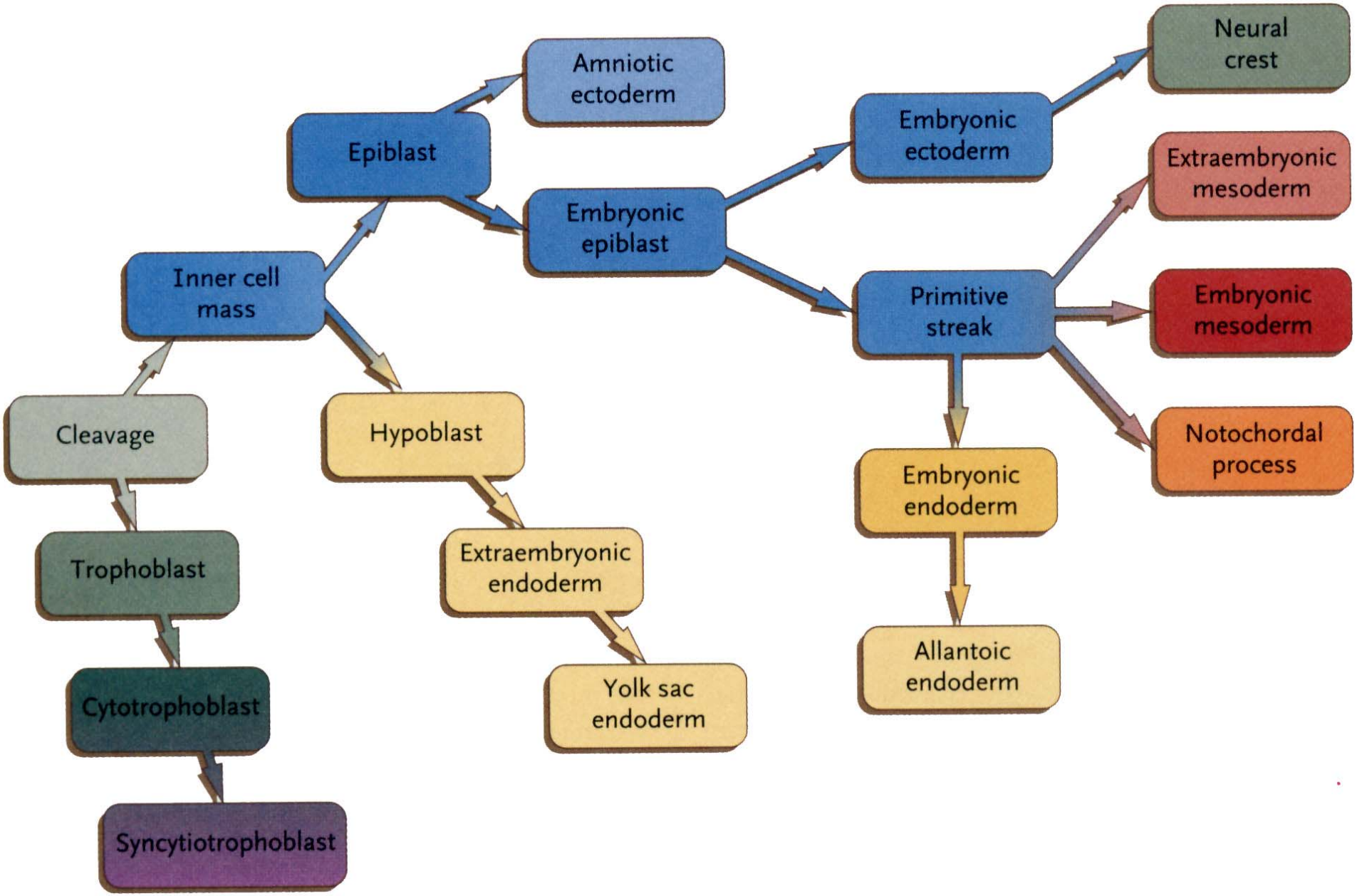
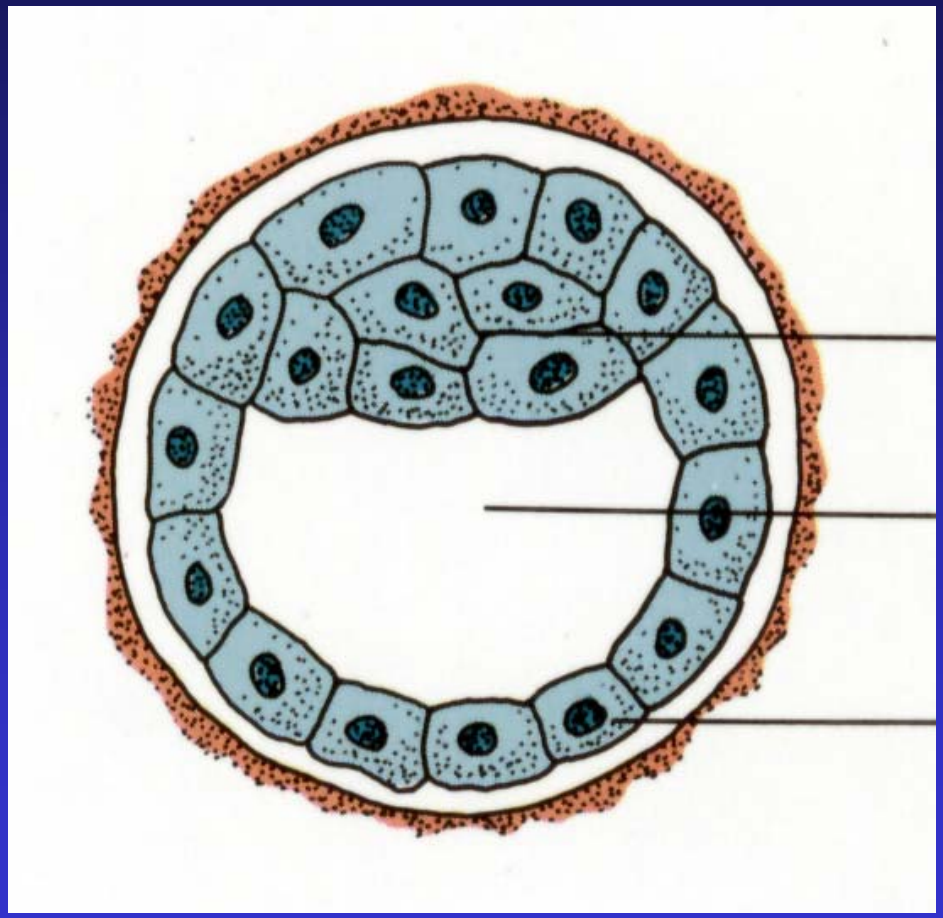
Gastrulation - Cell Lineages



Blastocyst

Embryo pole

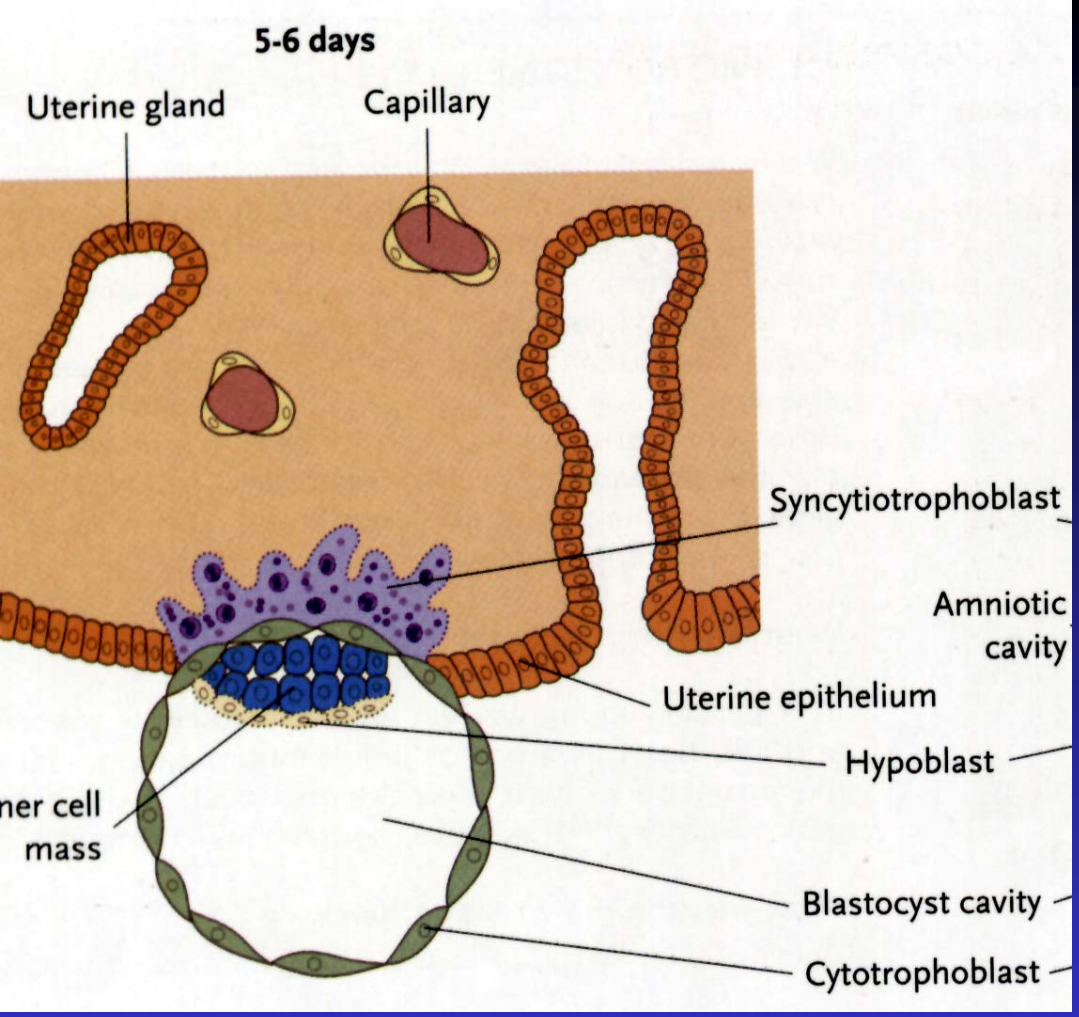


abembryonic pole

Inner cell mass
(**embryoblast)**

Blastocoel

Outer cell mass
(**trophoblast)**



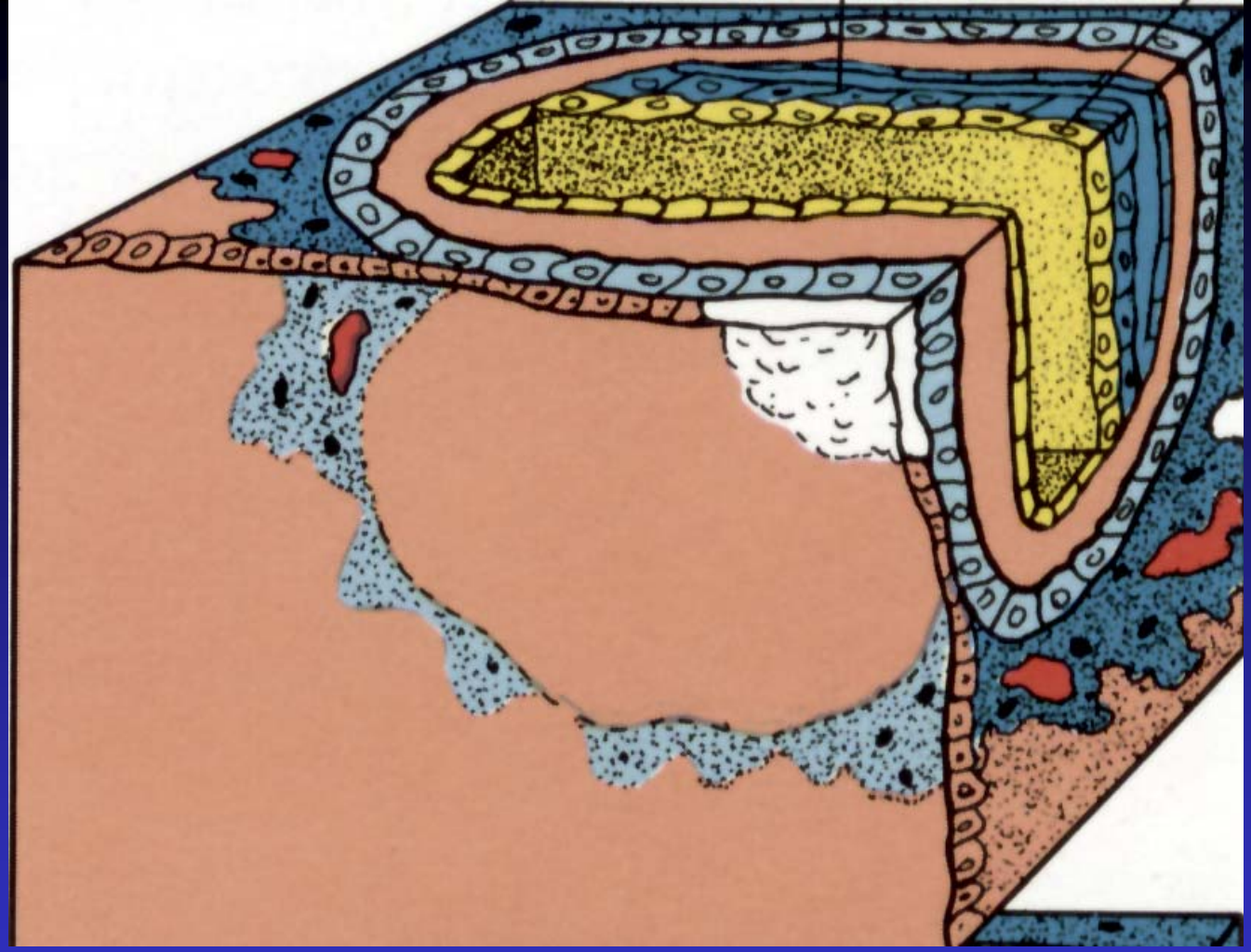
Day 6

Blastocyst adheres to endometrium at embryo pole

Trophoblast proliferation production of hCG (maintains corpus luteum)

Inner Cell Mass → Epiblast → Germ Layers

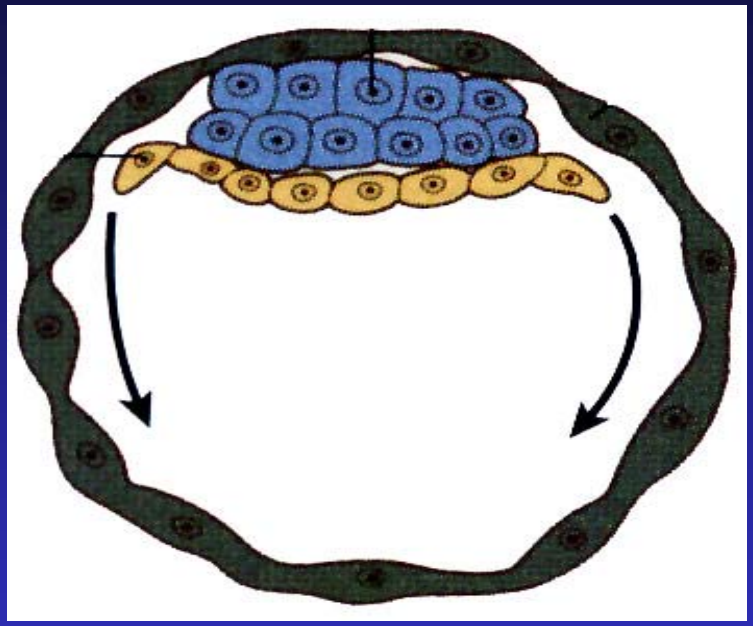
Inner Cell Mass → Hypoblast → Extraembryonic Endoderm/Mesoderm

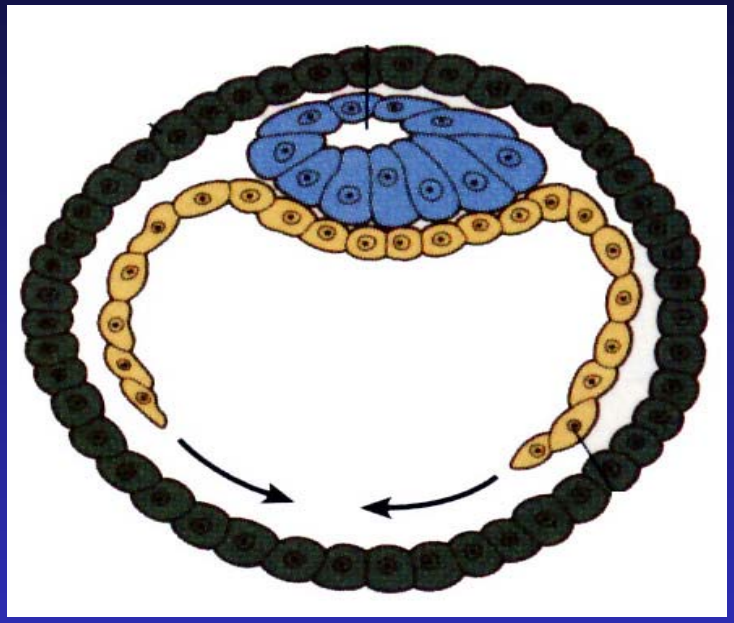


Bilaminar Disk – Epiblast and Hypoblast

Delamination – Separation of the Inner Cell Mass

Amnion





Amnion forms from epiblast

Cavitation – Formation of an internal space within a tissue

From BM Carlson, 1999

Gastrulation

Epiblast → Primary Germ Layers

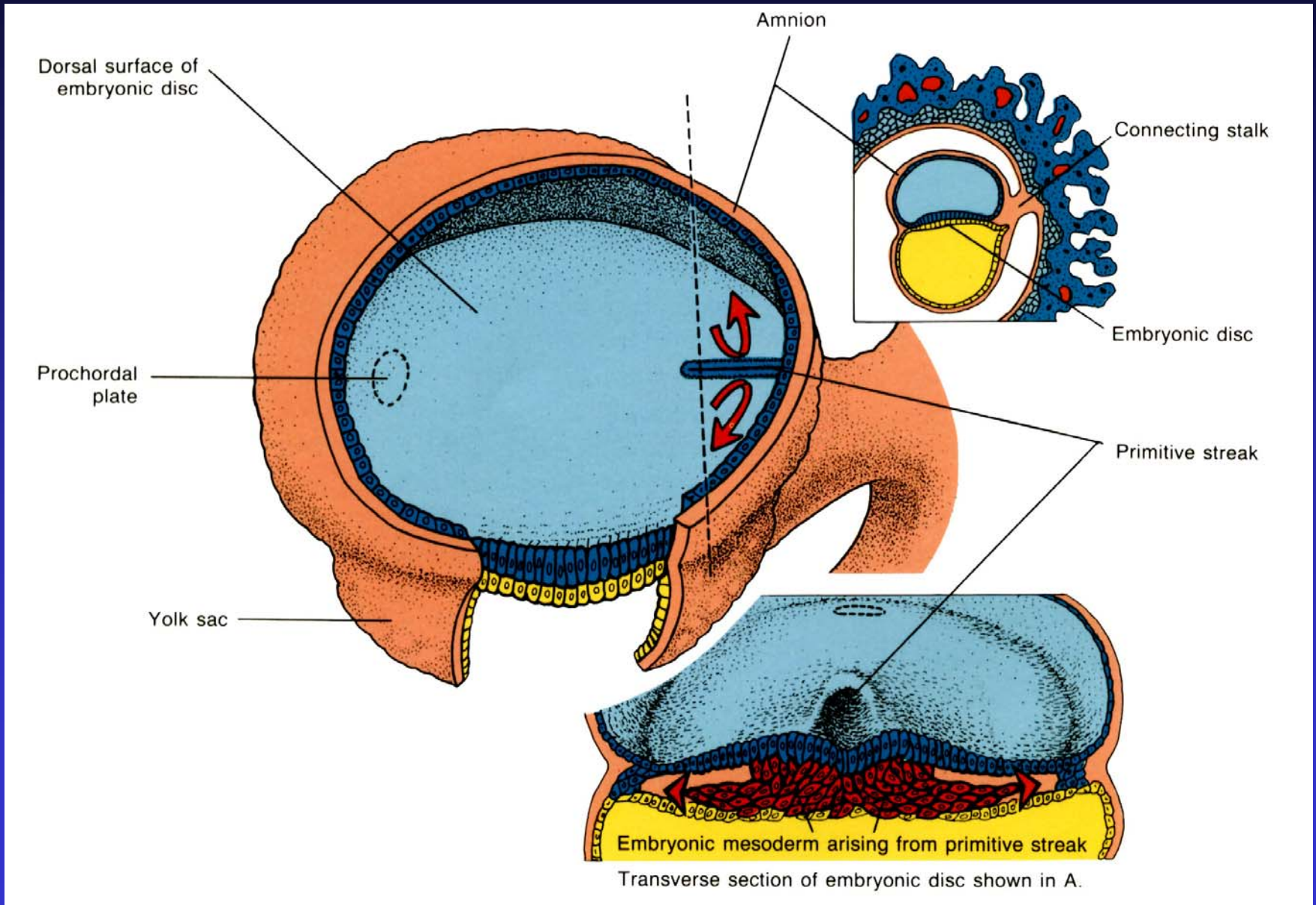
Ectoderm – outer layer – Skin, Nervous System, etc.

Mesoderm – middle layer – Muscle, Bones, etc.

Endoderm – Inner layer – Digestive Tract, Lungs, etc

Process – Morphogenetic Movements
Organized Cell Migration

Primitive Streak



Transverse section of embryonic disc shown in A.

Primitive Streak

Embryonic Day 15

Primitive groove – initiates gastrulation

Primitive Streak – includes groove, node and pit

The Primitive Streak defines

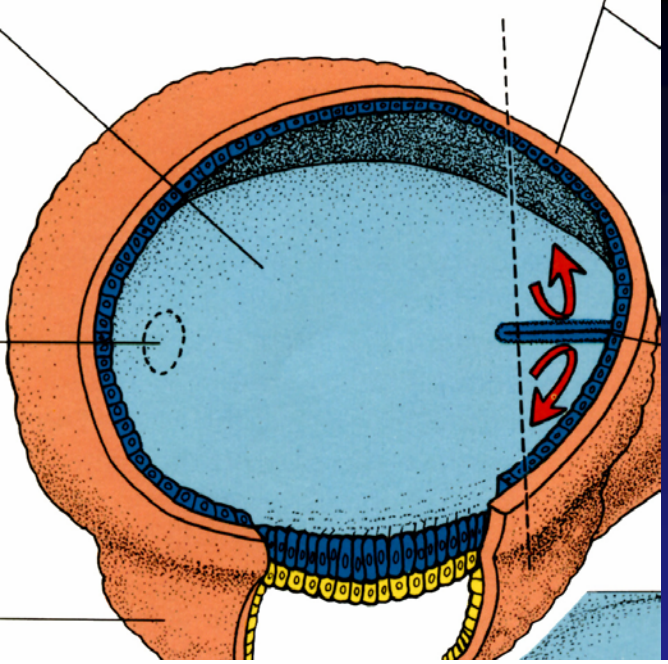
Anterior – cranial

Posterior – caudal

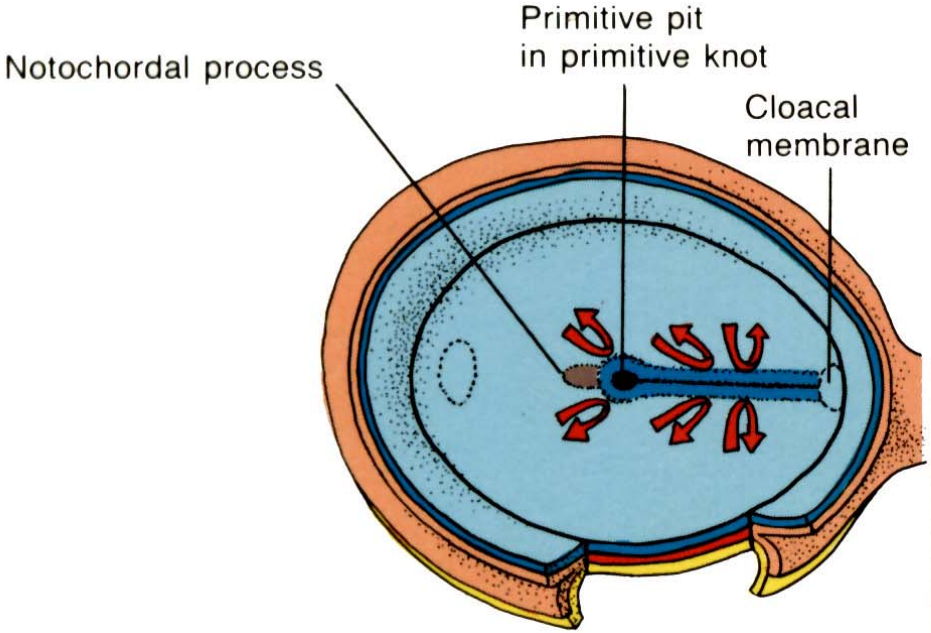
Right and Left – lateral

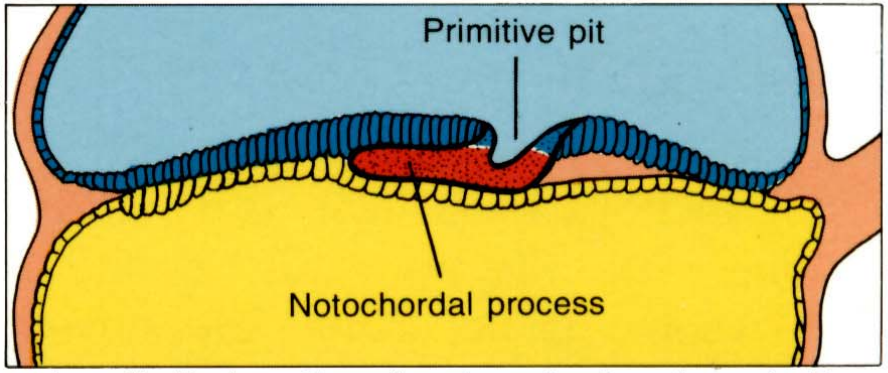
Streak extends cranially then regresses caudally – depositing the notochordal process during regression.

The tip of the regressing streak is the **Primitive Pit** and the **Primitive Node** (also called Hensen's Node)



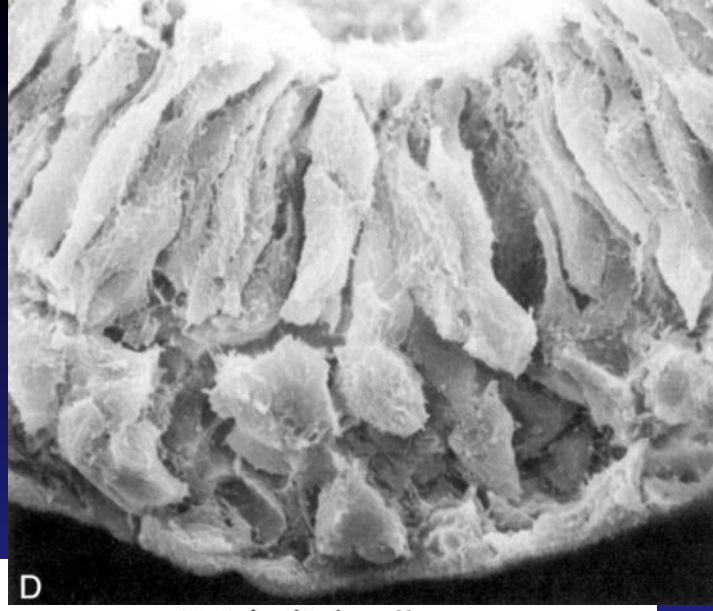
Primitive Node/Pit

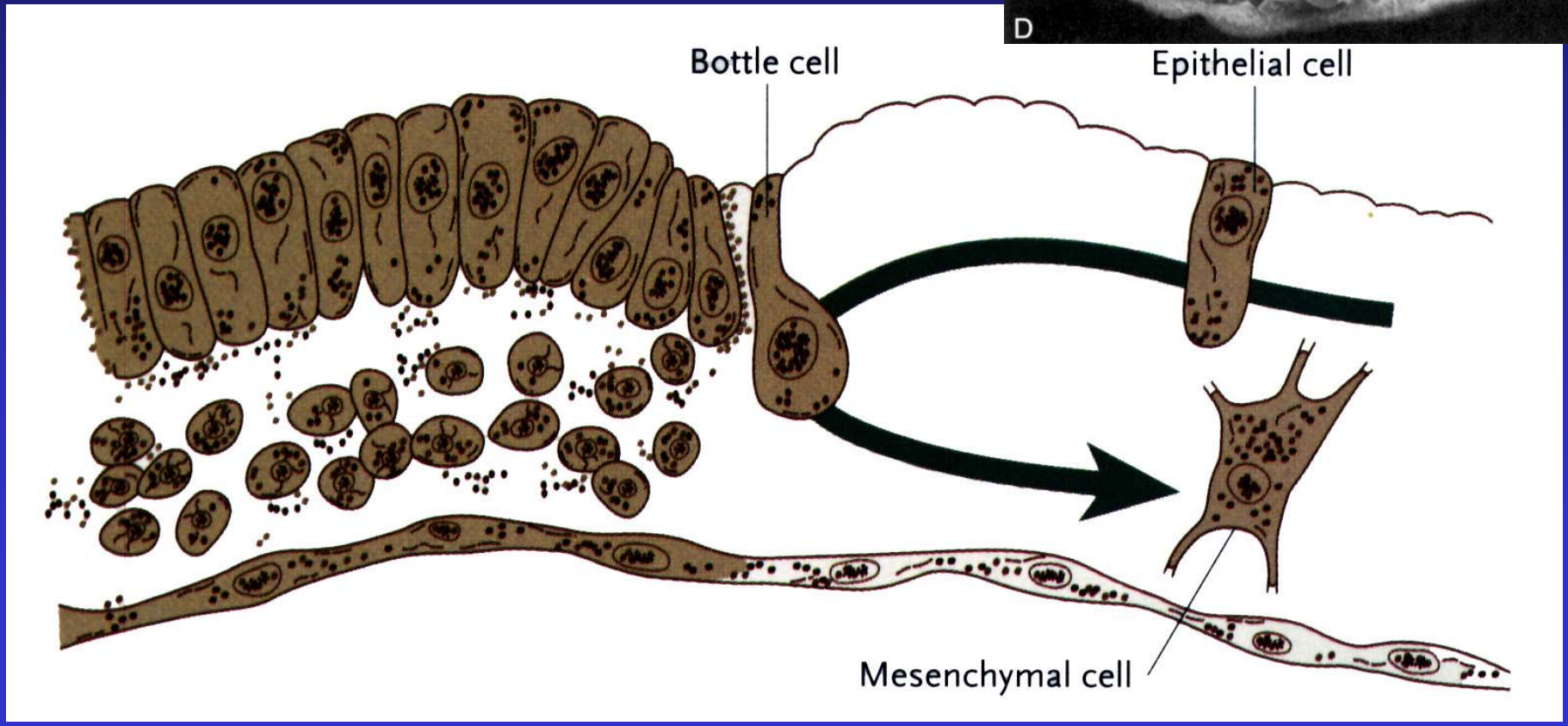




Longitudinal section of embryonic disc shown in B.

Bottle Cells





Endoderm

First cells to go through the Streak form the Endodermal

These cells integrate and displace hypoblast cells

Mesoderm

Complex pattern of movements

Streak formation – Lateral Migration – Cardiac mesoderm

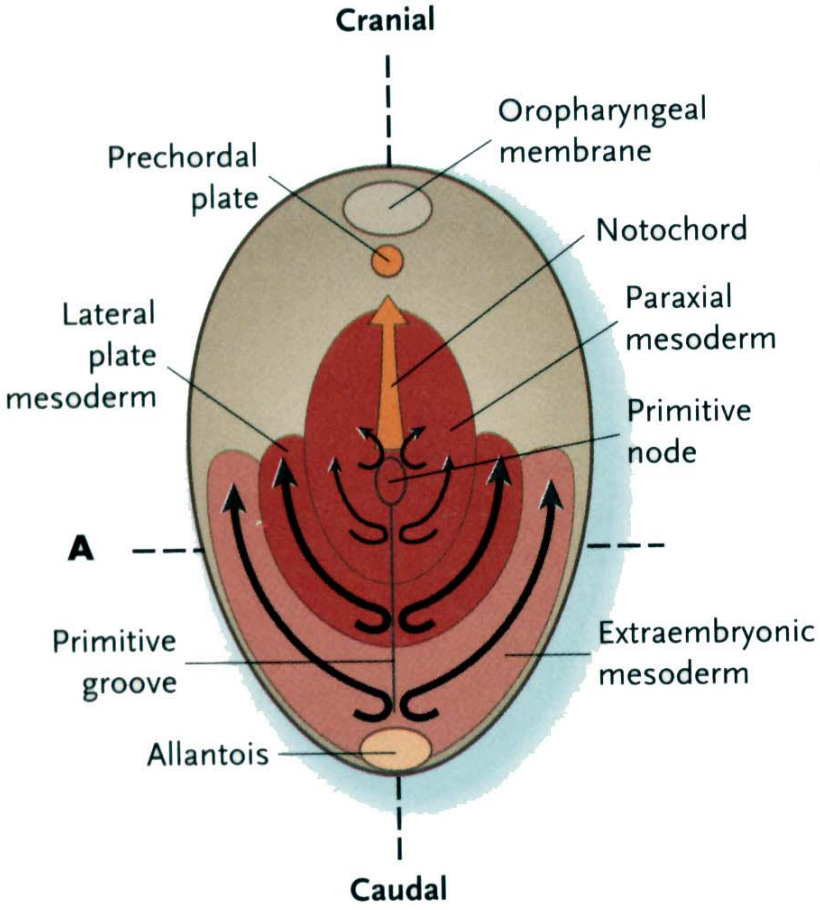
Streak regression - Lateral and Cranial Migration

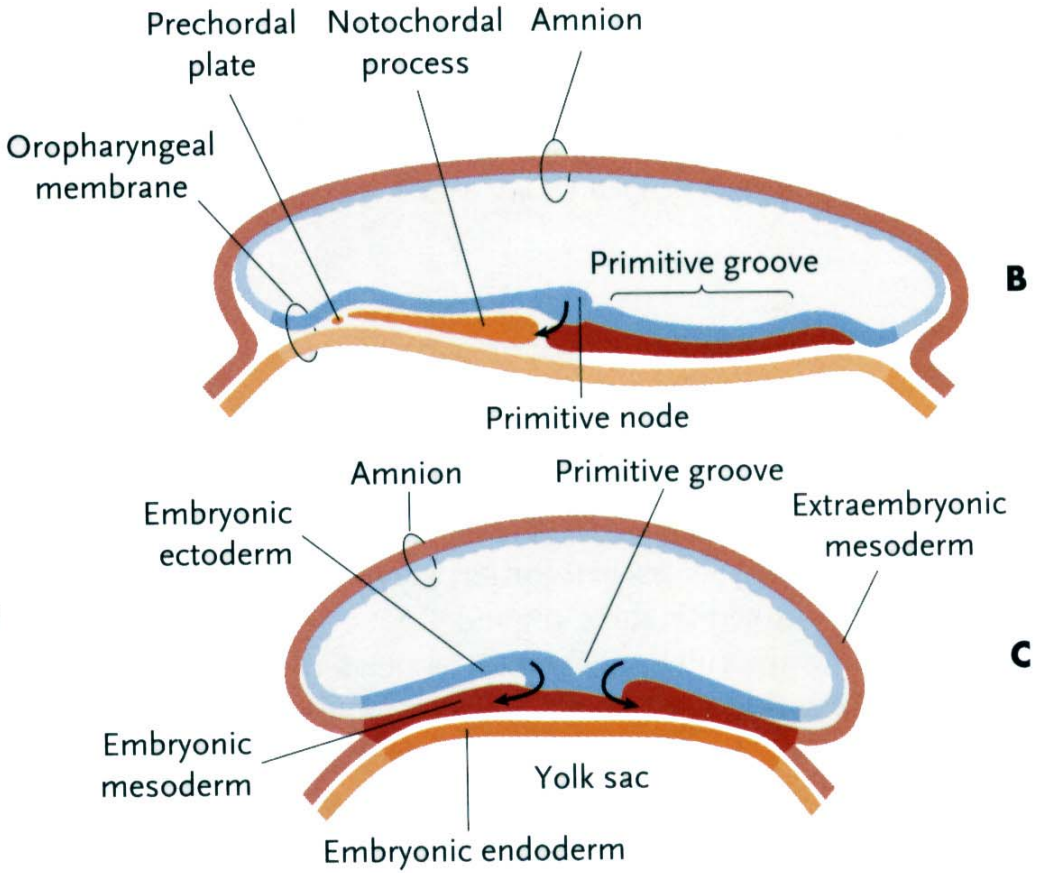
- Lateral Plate Mesoderm
- Somitic Mesoderm

Streak Regression – Central and Cranial Migration

- Notochord – cellular rod, central long axis of embryo

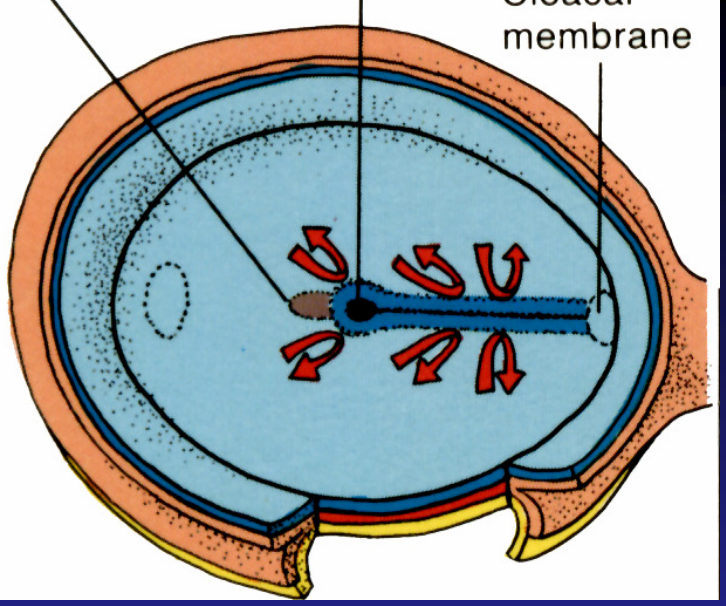
Mesoderm


Cranial
Oropharyngeal membrane
Prechordal plate
Notochord
Lateral plate mesoderm
Paraxial mesoderm
Primitive node
A
Primitive groove
Extraembryonic mesoderm
Allantois
Caudal

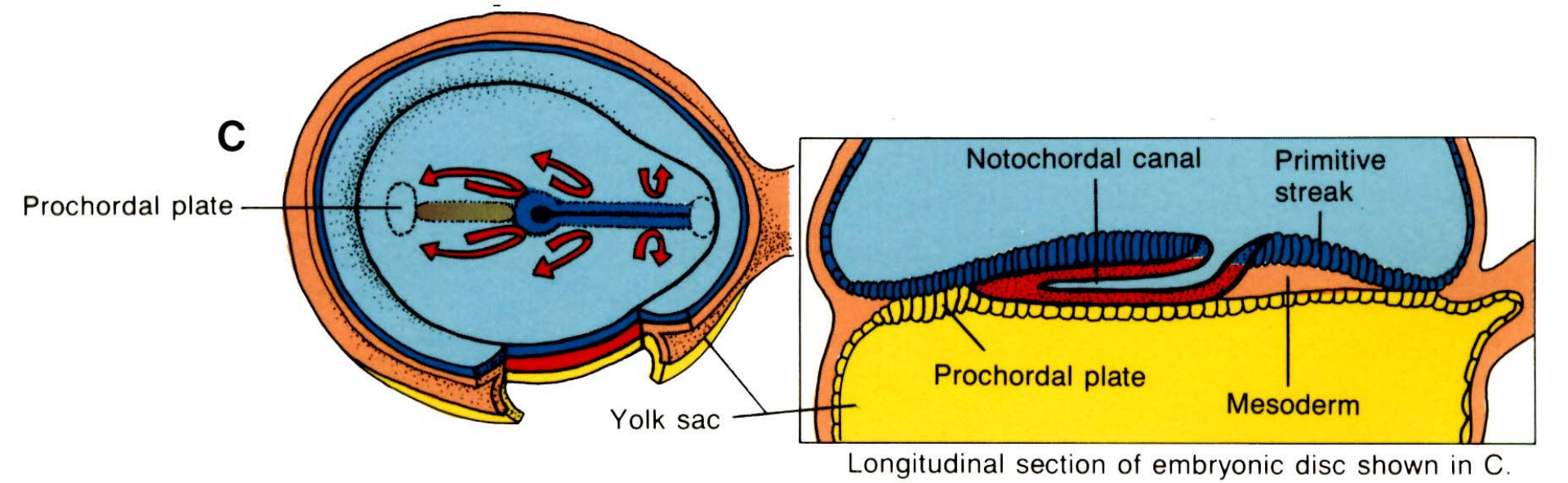

Prechordal plate
Notochordal process
Amnion
Oropharyngeal membrane
Primitive groove
B
Primitive node
Amnion
Primitive groove
Embryonic ectoderm
Extraembryonic mesoderm
C
Embryonic mesoderm
Yolk sac
Embryonic endoderm

Ectoderm

- Ectodermal cells don't enter the streak
- Cell layer expands as endodermal and mesodermal cells enter the streak
- Cranial to the notochord – ectoderm and endoderm are in direct contact Oropharyngeal membrane
- Between the Oropharyngeal membrane and the notochord is the pre-chordal plate – important for inducing the brain

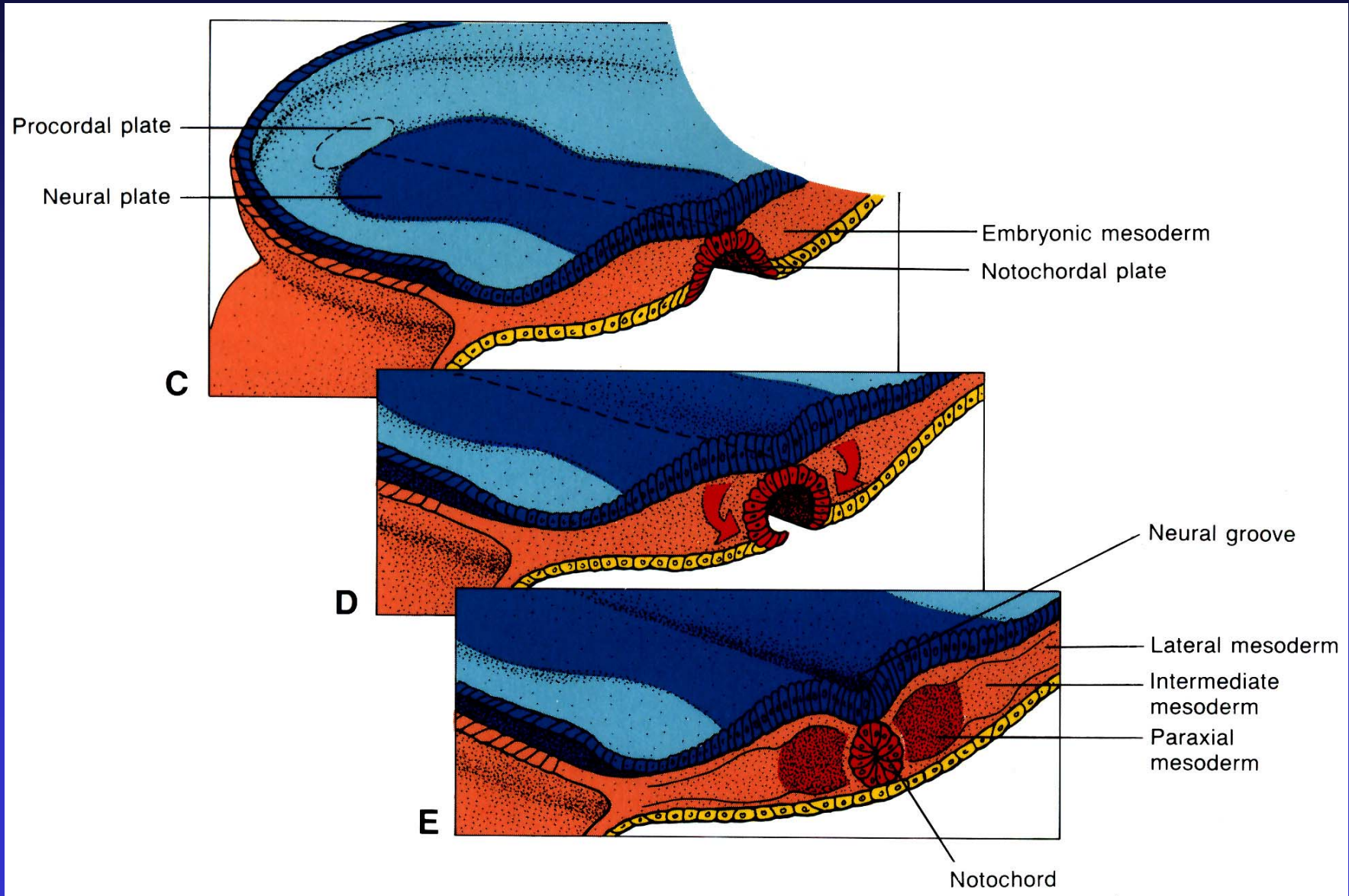


Notochordal Process



Longitudinal section of embryonic disc shown in C.

Notochord


Procordal plate
Neural plate
Embryonic mesoderm
Notochordal plate
C
D
Neural groove
Lateral mesoderm
Intermediate mesoderm
Paraxial mesoderm
E
Notochord

Embryonic Induction

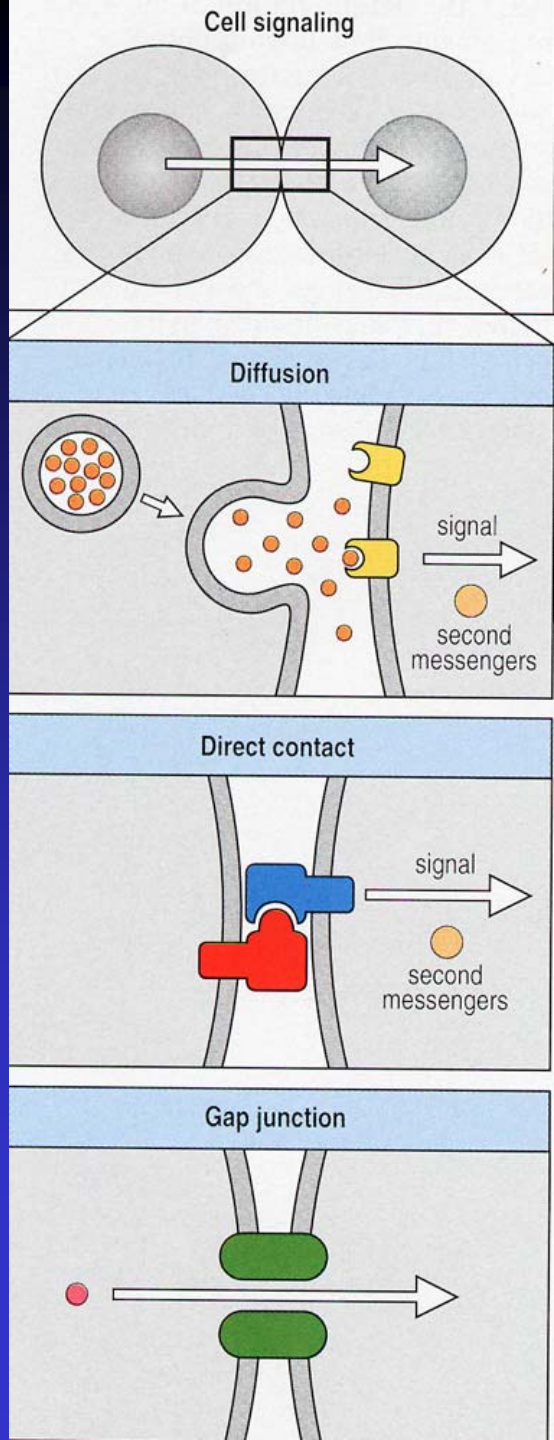
Definition: Signal from one group of cells influences the development of an adjacent group of cells

Inducing Tissue or Inducer

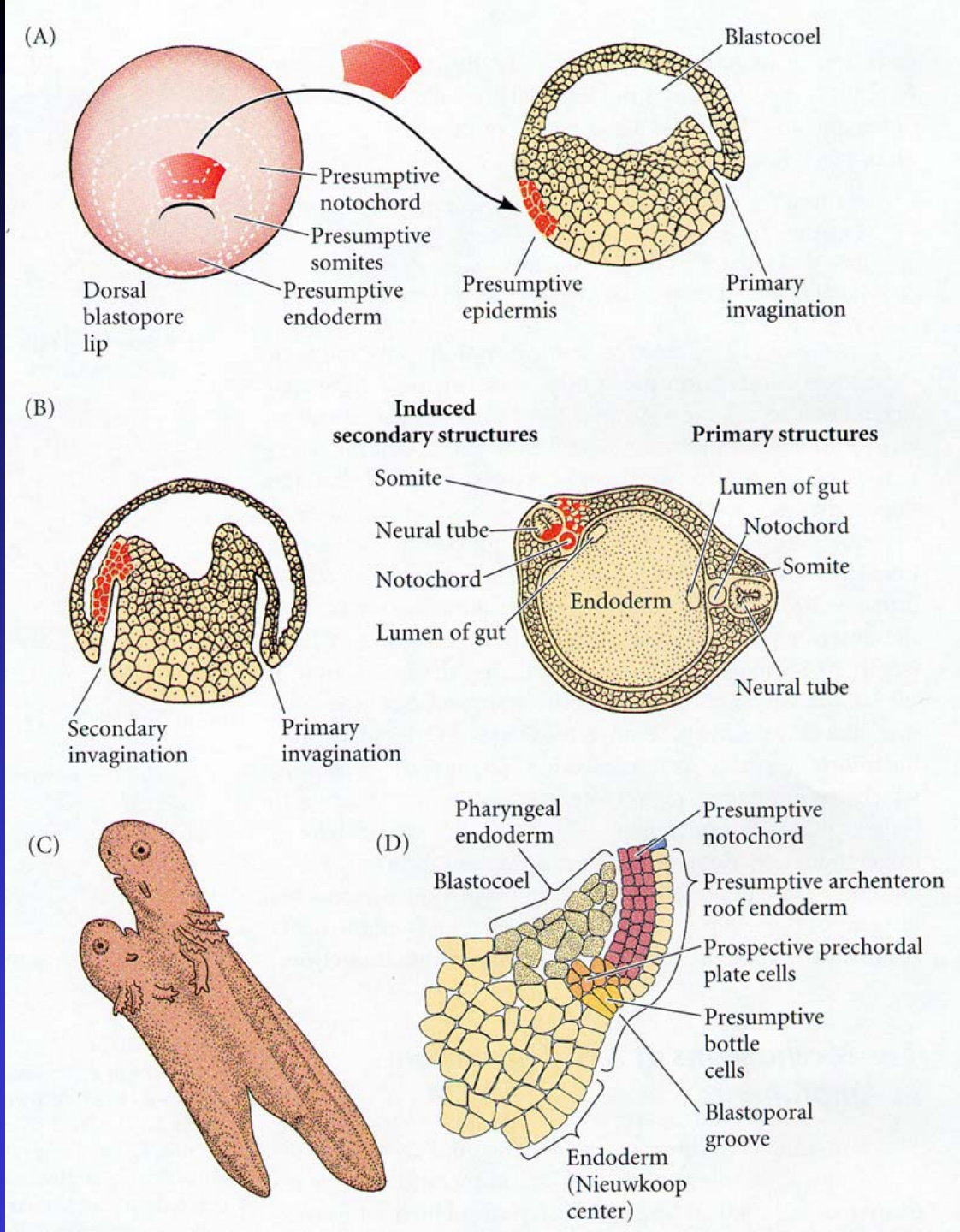
Inductive Signal - Morphogen

Responding Tissue
Competence

Expression of Target Gene



Primary Induction



Embryonic Induction

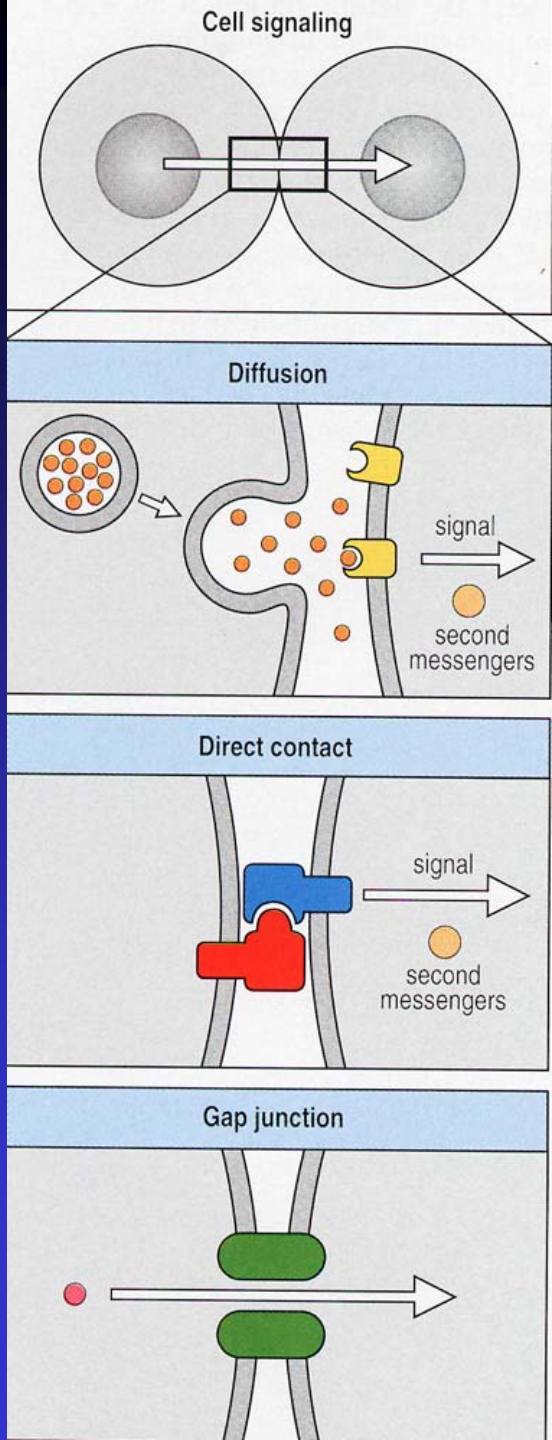
Definition: Signal from one group of cells influences the development of an adjacent group of cells

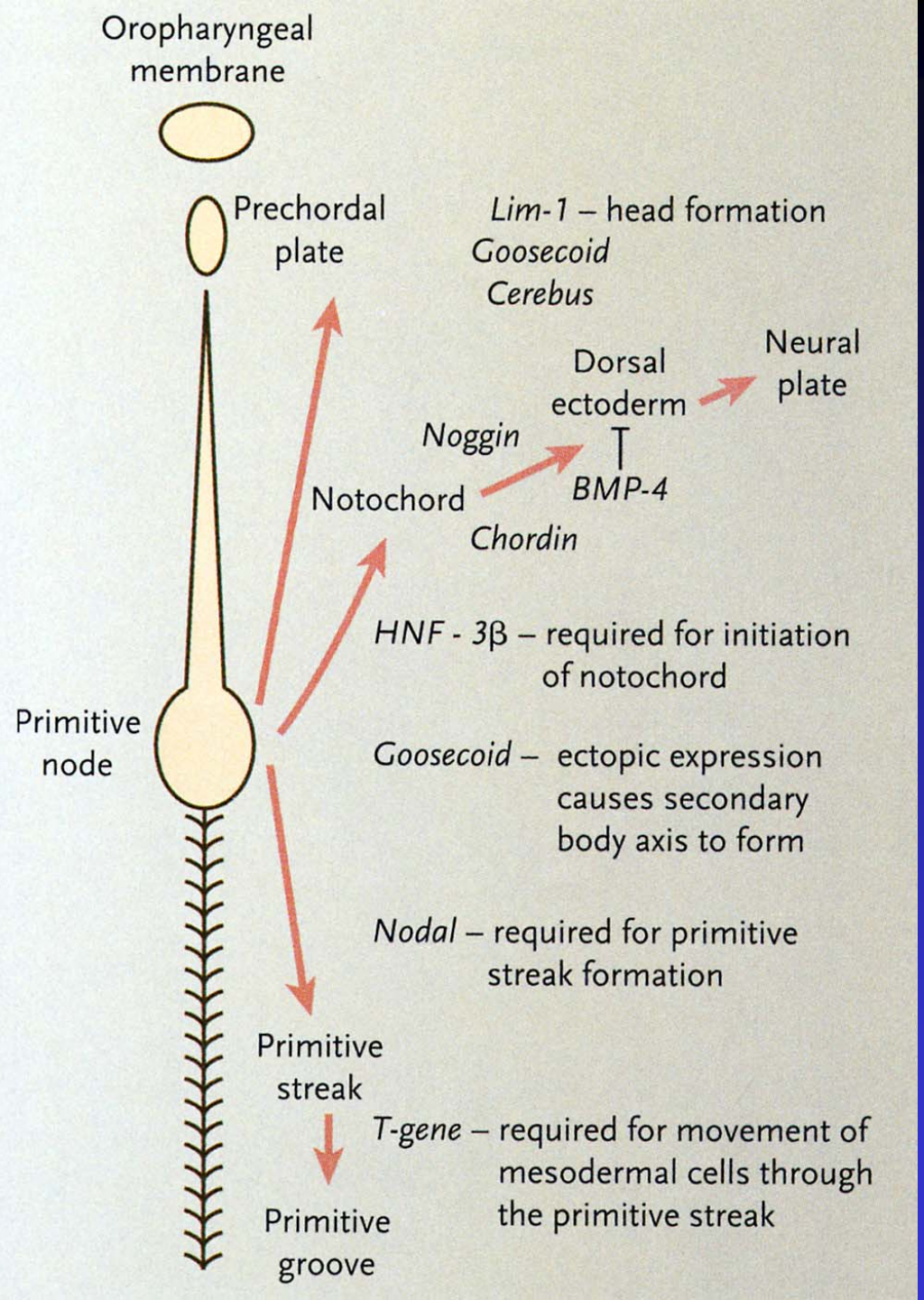
Inducing Tissue or Inducer

Inductive Signal – De-Repressor

Responding Tissue - Repressed Competence

Expression of Target Gene





Nodal – Required for primitive streak formation

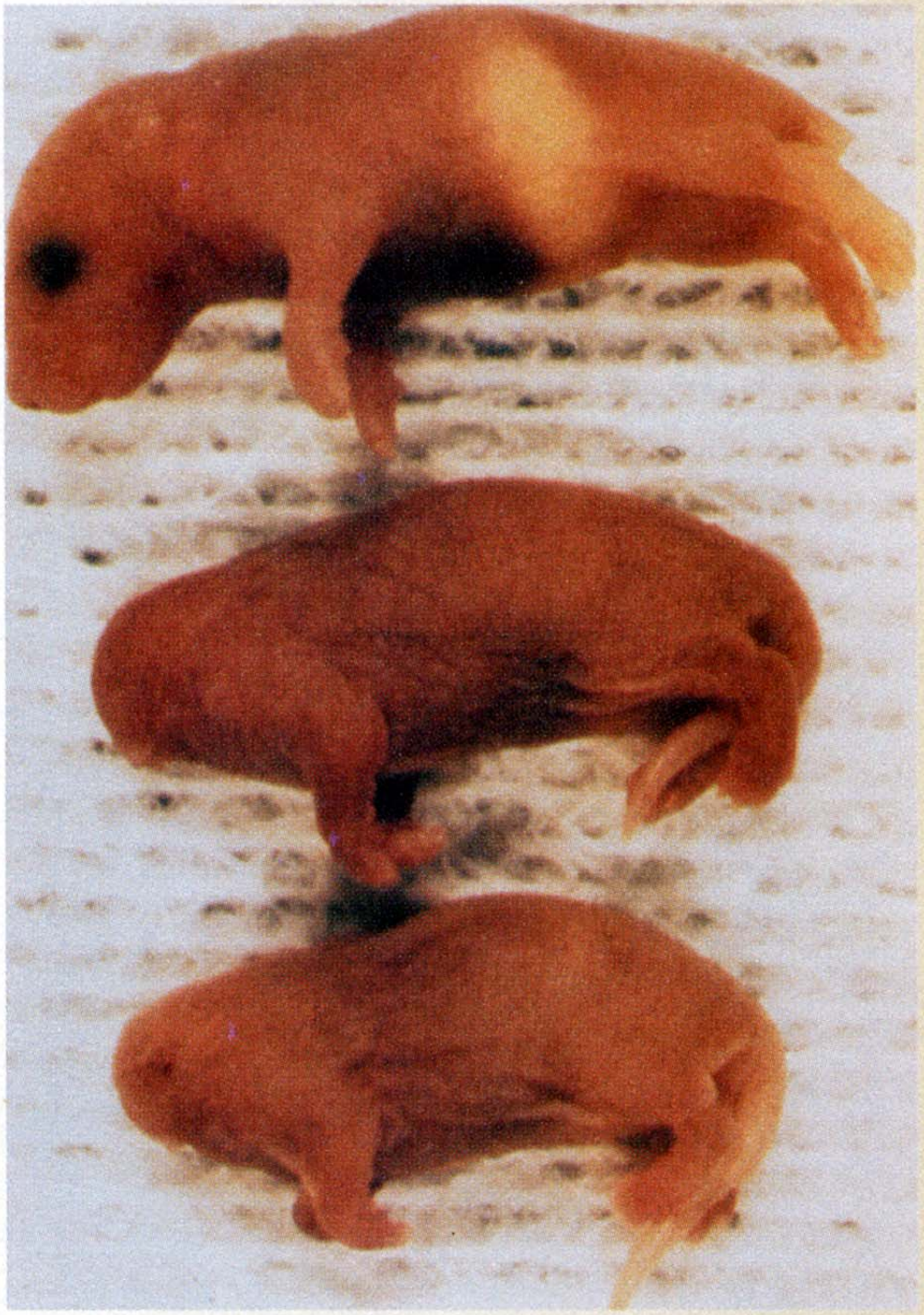
Lim1 – Homeobox containing; Node and pre-chordal plate Null - Headless

HNF3β – Hepatic nuclear factor; Notochord formation

BMP4 – Bone Morphogenetic Protein4; represses dorsal ectoderm

Noggin and Chordin – BMP4 inhibitors; de-represses ectoderm → neural tissue

Lim1 Mutant



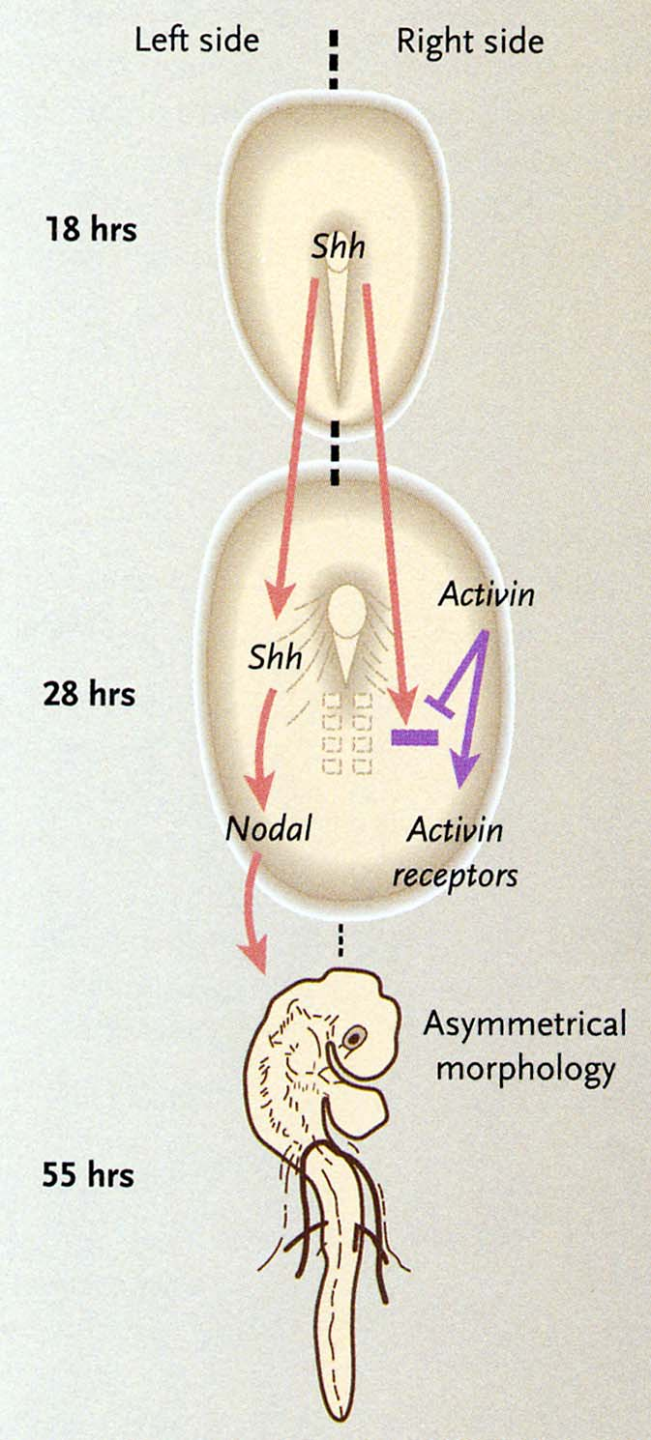
Left-Right Asymmetry

Node Signals:

SHH – Sonic Hedgehog – Left – induces Nodal

Activin – Right (inhibits SHH)

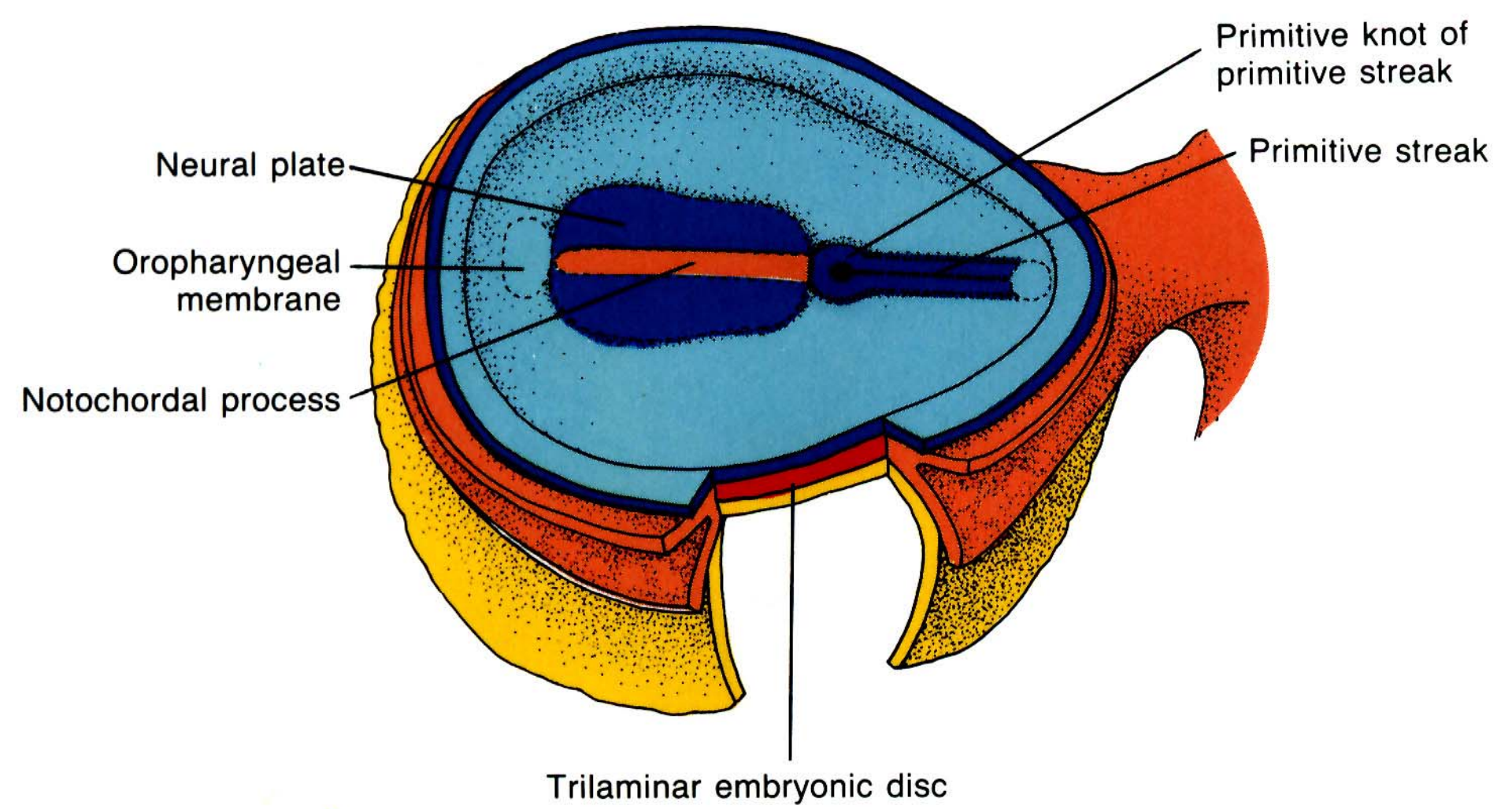
Reverse Asymmetry = situs inversus



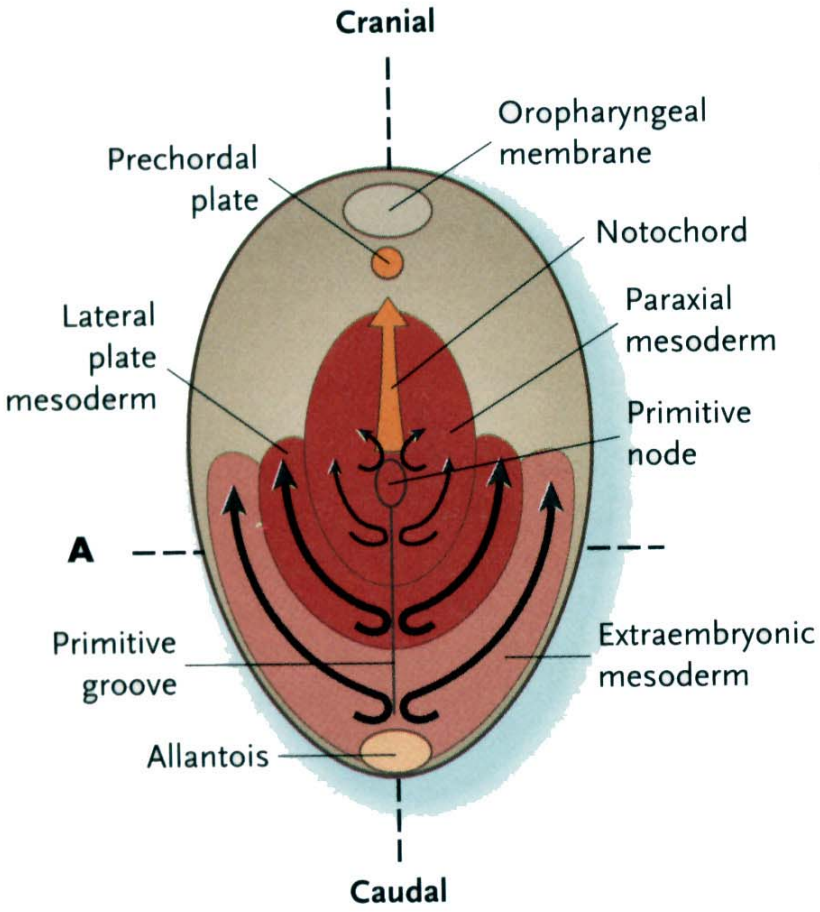
Notochord as Inducer

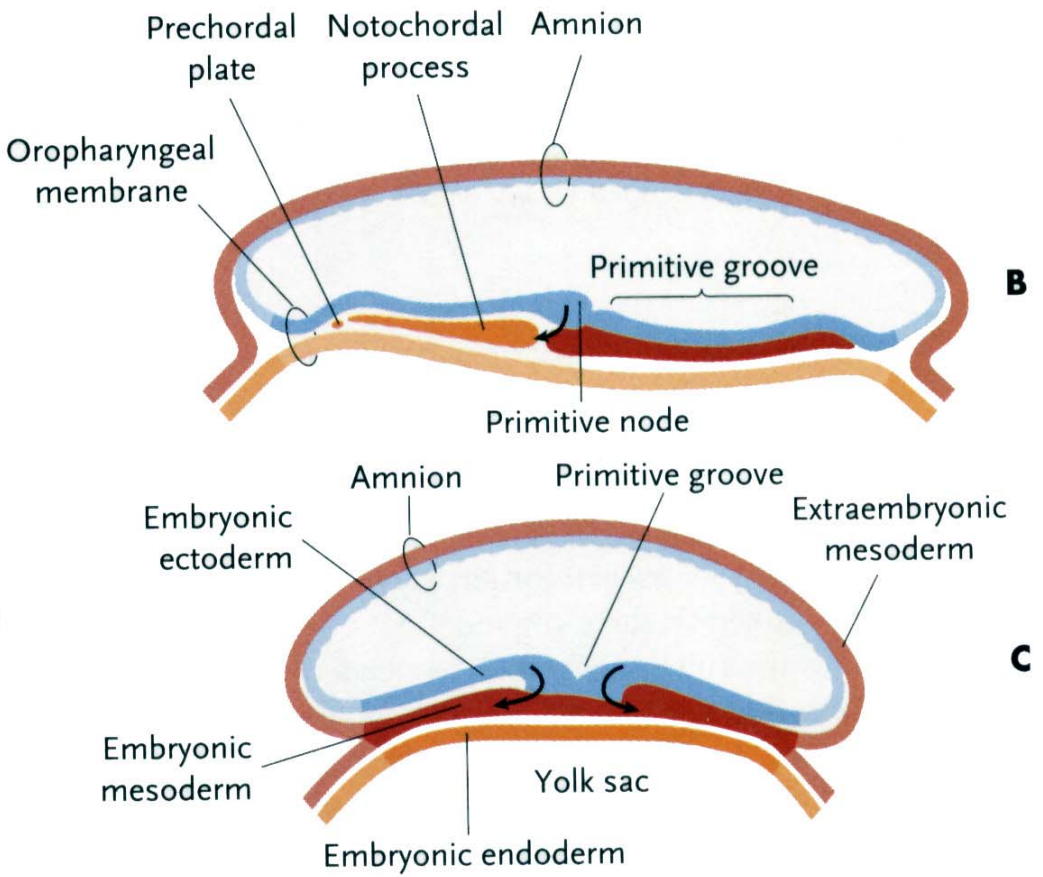
- Induces overlying ectoderm → Neural Tissue (Neural Induction)
- Specifies cell type in the Floor Plate of the Neural Tube
- Transforms para-axial mesoderm (somite) into vertebral bodies
- Stimulated early development of the dorsal pancreas

Neural Plate

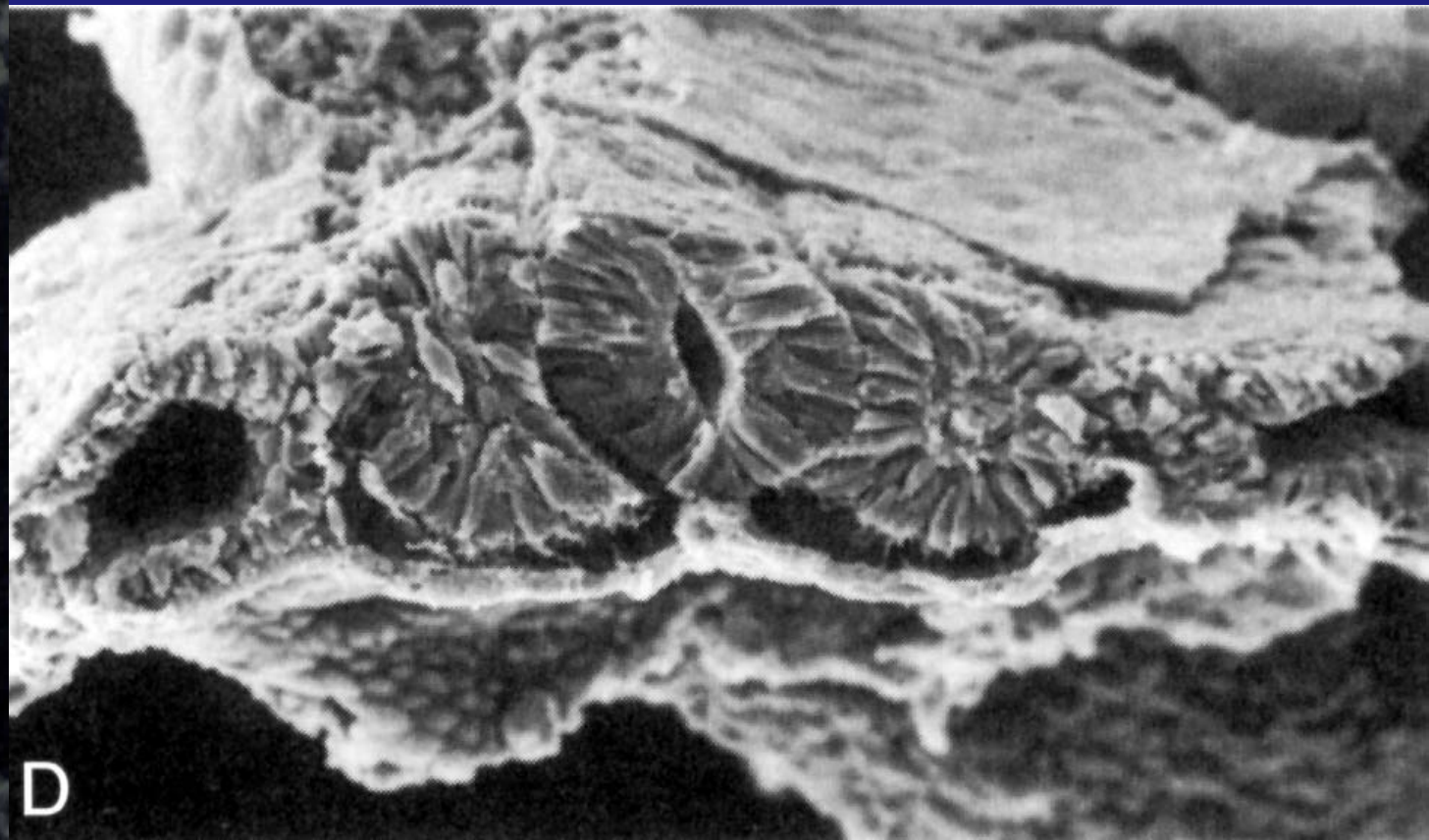


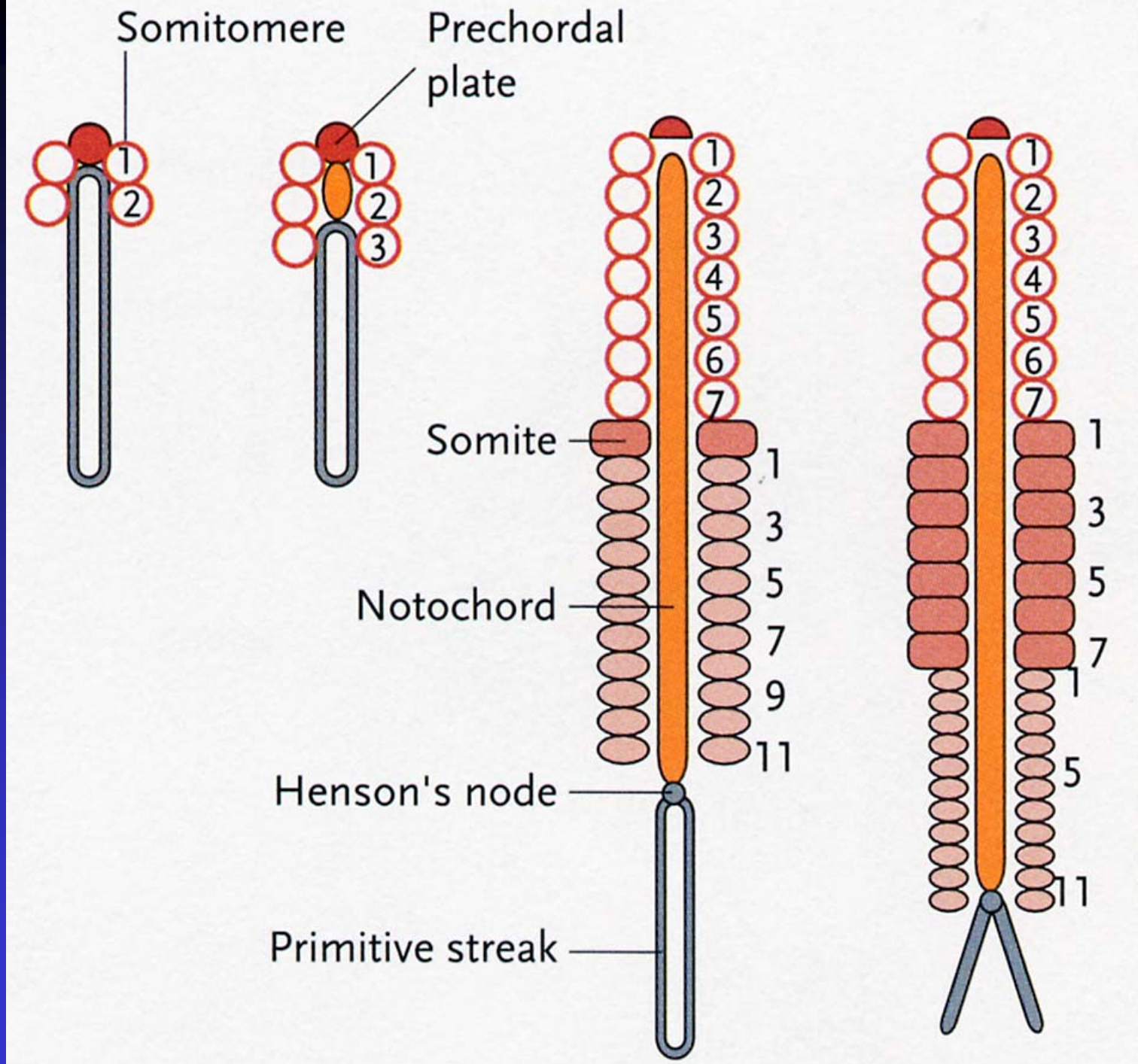
Mesoderm


Cranial
Oropharyngeal membrane
Prechordal plate
Notochord
Paraxial mesoderm
Lateral plate mesoderm
Primitive node
A
Primitive groove
Extraembryonic mesoderm
Allantois
Caudal


Prechordal plate
Notochordal process
Amnion
Oropharyngeal membrane
Primitive groove
B
Primitive node
Amnion
Primitive groove
Embryonic ectoderm
Extraembryonic mesoderm
C
Embryonic mesoderm
Yolk sac
Embryonic endoderm

Paraaxial Mesoderm - Somites




Somitomere
Prechordal plate
Somite
Notochord
Henson's node
Primitive streak
1
2
3
4
5
6
7
1
3
5
7
9
11
1
3
5
7
1
5
11

Somitogenesis

d18-d28 – Cranial to Caudal – 37 somites – form muscle, dermis, skeleton

Somitomeres 1-7 do not form somites – migrate to Pharyngeal Arches, muscles of face, jaw, throat

Somitomere 8 forms Somite; rate of 3-4 somites / day

Somite 1-4 – Occipital Region (skull, nose; ocular m., tongue

Somite 5-12 – Cervical Region (Cervical vertebrae, neck dermis)

Somite 13-24 – Thoracic Region (vertebrae, arms)

Somite 25-29 – Lumbar Region (abdomen, legs)

Somite 30-34 – Sacral Region (sacrum)

Somite 35-37 – Coccygeal Region (coccyx)

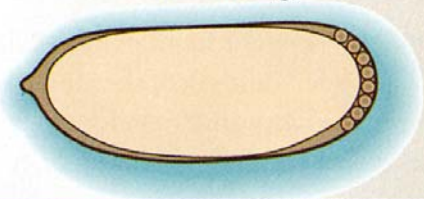
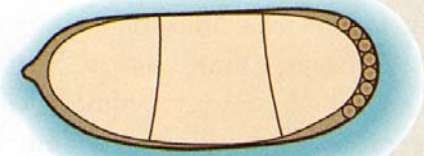
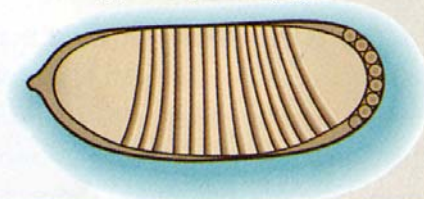
Segmentation of the Embryo

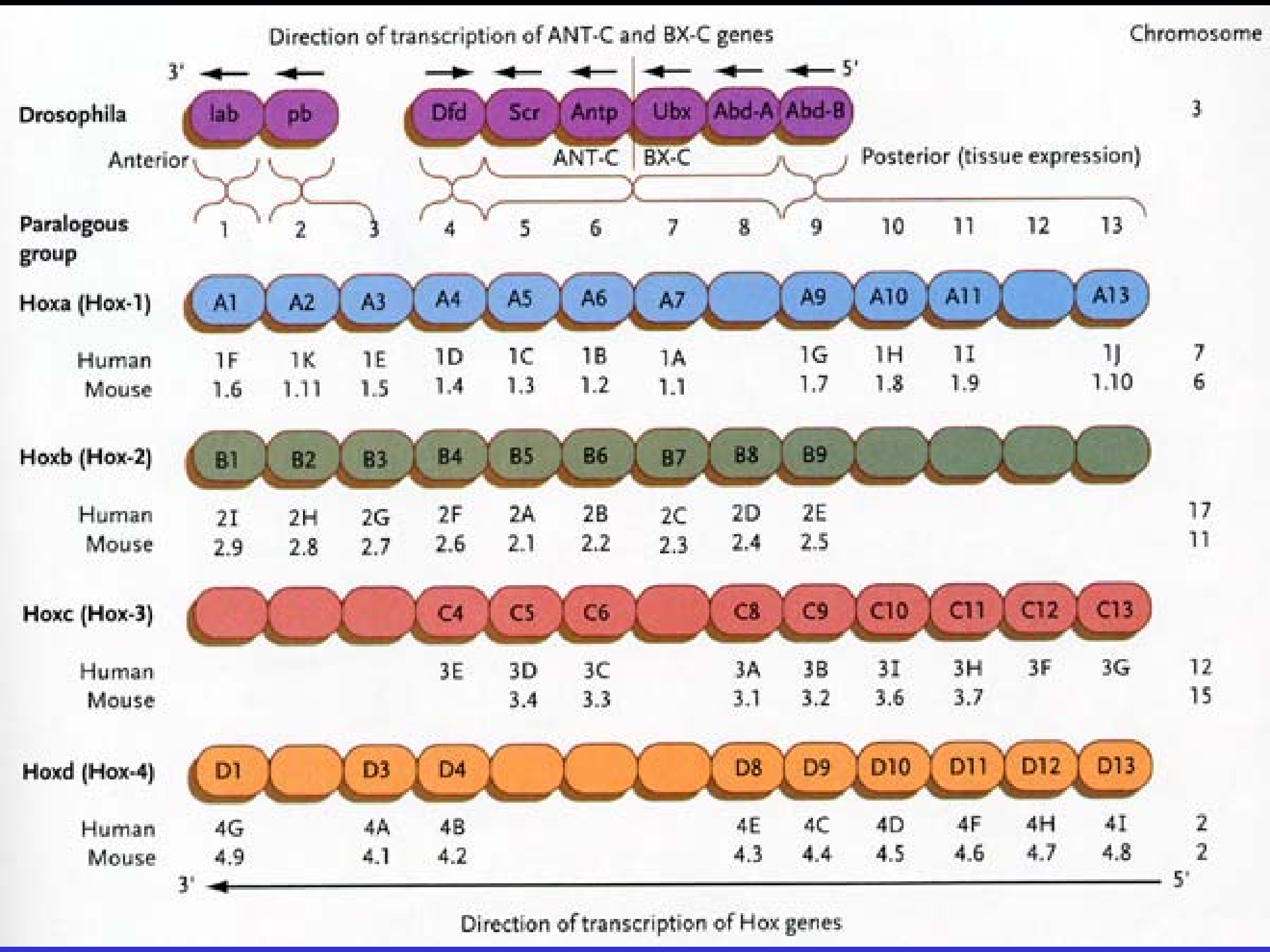
Segmentation occurs along the Anterior-Posterior Axis

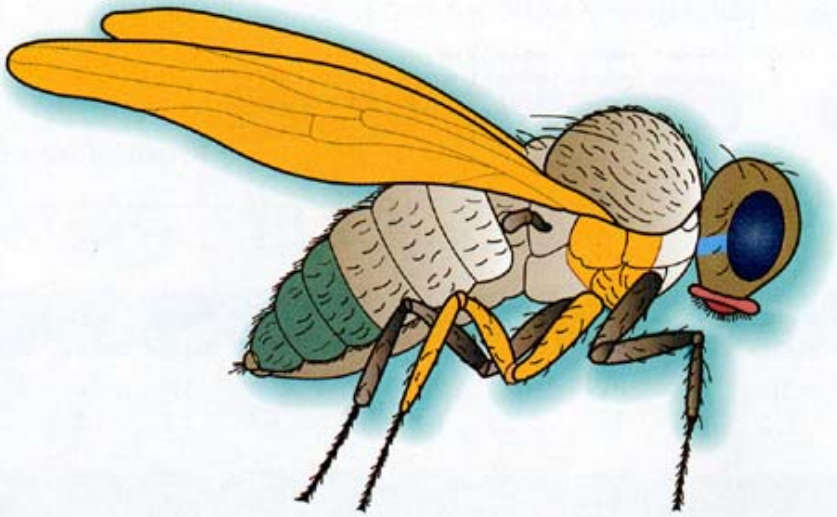
Each segment becomes an autonomous developing unit

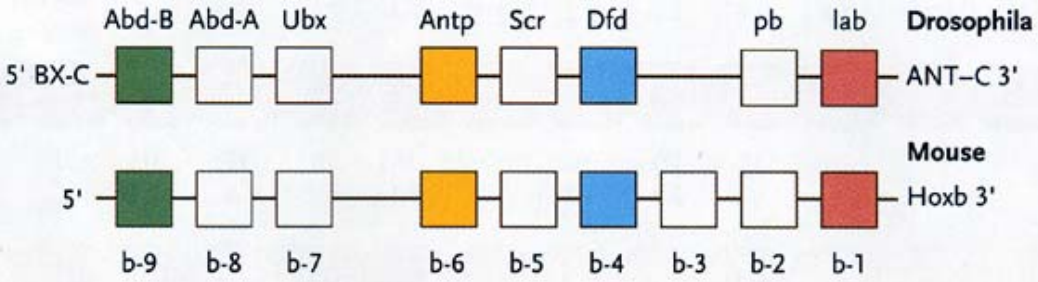
Each segment can grow and undergo further segmentation

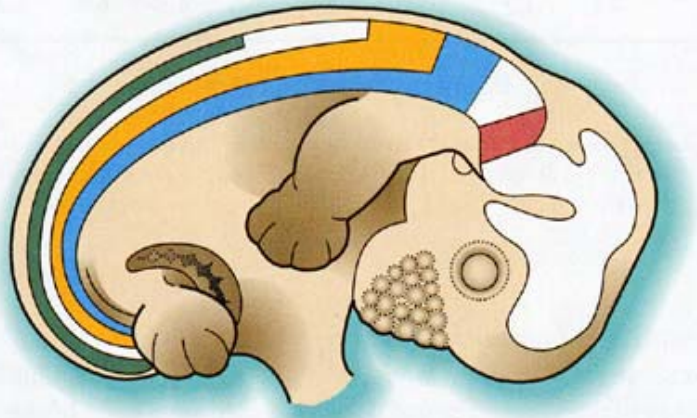
Molecular mechanisms are conserved

Genetic hierarchy	Functions	Representative genes	Effects of mutation
Maternal effect genes 	Establish gradients from anterior and posterior poles of the egg	Bicoid Swallow Oskar Caudal Torso Trunk	Major disturbances in anteroposterior organization
Segmentation genes  Gap genes	Define broad regions in the egg	Empty spiracles Hunchback Krüppel Knirps Tailless	Adjacent segments missing in a major region of the body
Pair-rule genes 	Define 7 segments	Hairy Even skipped Runt Fushi tarazu Odd paired Odd skipped Paired	Part of pattern deleted in every other segment
Segment polarity genes 	Define 14 segments	Engrailed Gooseberry Hedgehog Patched Wingless	Segments replaced by their mirror images
Homeotic genes 	Determine regional characteristics	Antennapedia complex Bithorax complex	Inappropriate structures form for a given segmental level

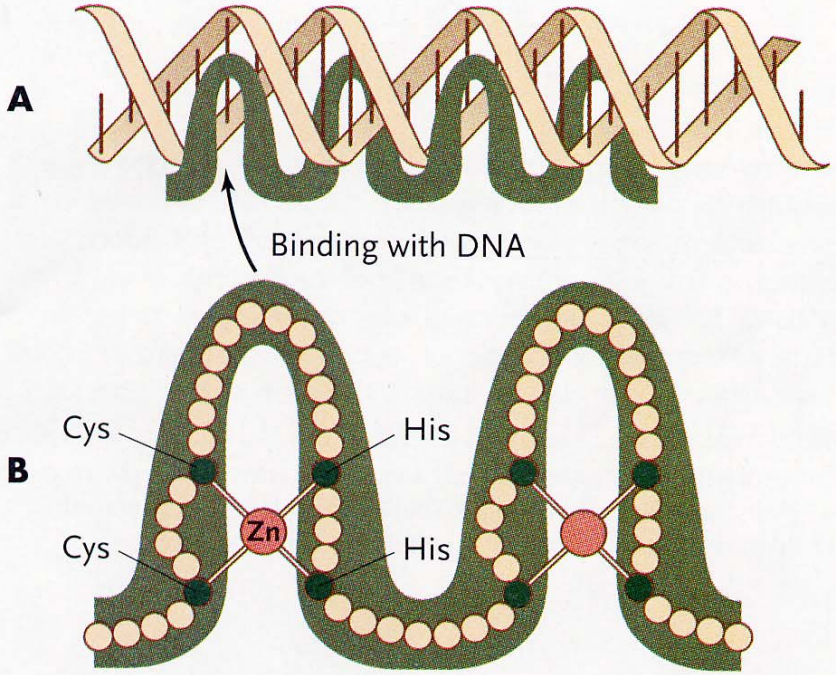

Direction of transcription of ANT-C and BX-C genes
Chromosome
3'
5'
Drosophila
lab
pb
Dfd
Scr
Antp
Ubx
Abd-A
Abd-B
3
Anterior
ANT-C
BX-C
Posterior (tissue expression)
Paralogous group
1
2
3
4
5
6
7
8
9
10
11
12
13
Hoxa (Hox-1)
A1
A2
A3
A4
A5
A6
A7
A9
A10
A11
A13
Human
1F
1K
1E
1D
1C
1B
1A
1G
1H
1I
1J
7
Mouse
1.6
1.11
1.5
1.4
1.3
1.2
1.1
1.7
1.8
1.9
1.10
6
Hoxb (Hox-2)
B1
B2
B3
B4
B5
B6
B7
B8
B9
Human
2I
2H
2G
2F
2A
2B
2C
2D
2E
17
Mouse
2.9
2.8
2.7
2.6
2.1
2.2
2.3
2.4
2.5
11
Hoxc (Hox-3)
C4
C5
C6
C8
C9
C10
C11
C12
C13
Human
3E
3D
3C
3A
3B
3I
3H
3F
3G
12
Mouse
3.4
3.3
3.1
3.2
3.6
3.7
15
Hoxd (Hox-4)
D1
D3
D4
D8
D9
D10
D11
D12
D13
Human
4G
4A
4B
4E
4C
4D
4F
4H
4I
2
Mouse
4.9
4.1
4.2
4.3
4.4
4.5
4.6
4.7
4.8
2
3'
5'
Direction of transcription of Hox genes

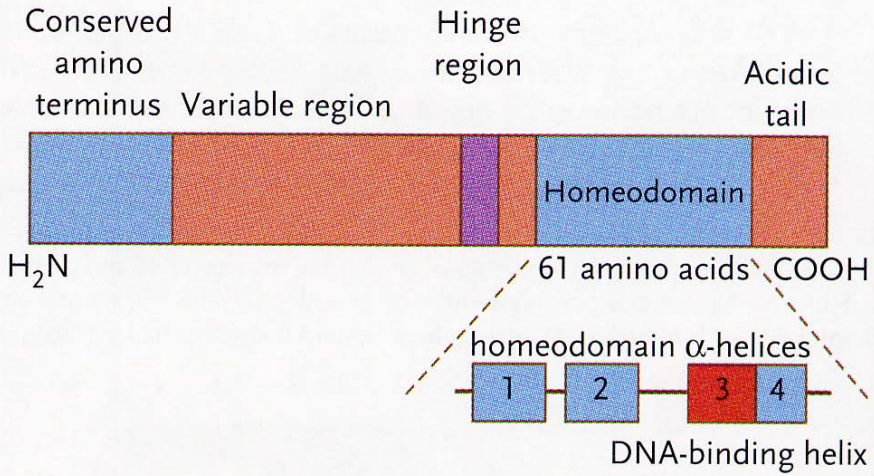



Abd-B
Abd-A
Ubx
Antp
Scr
Dfd
pb
lab
Drosophila
5' BX-C
ANT–C 3'
Mouse
5'
Hoxb 3'
b-9
b-8
b-7
b-6
b-5
b-4
b-3
b-2
b-1



Hox Genes Encode for Transcription Factors





Gastrulation Anomalies

Caudal Dysgenesis (Sirenomelia)
- Caudal defect
- Insufficient mesoderm formation
- Fused lower limbs, renal agenesis
- Genetic and Teratogenic
- Brachyury (T), Wnt

Holoprosencephaly
- Cranial defect
- Neuronal and craniofacial cell death
- Small forebrain, fused ventricles
- Teratogenic, e.g. alcohol

Neurulation

Readings:

- Chapter 5
- Chapter 10
  - P. 208-214
  - P. 218-219 (Peripheral Nerve)
  - p. 239-240 (Cranial Nerve)

Neurulation

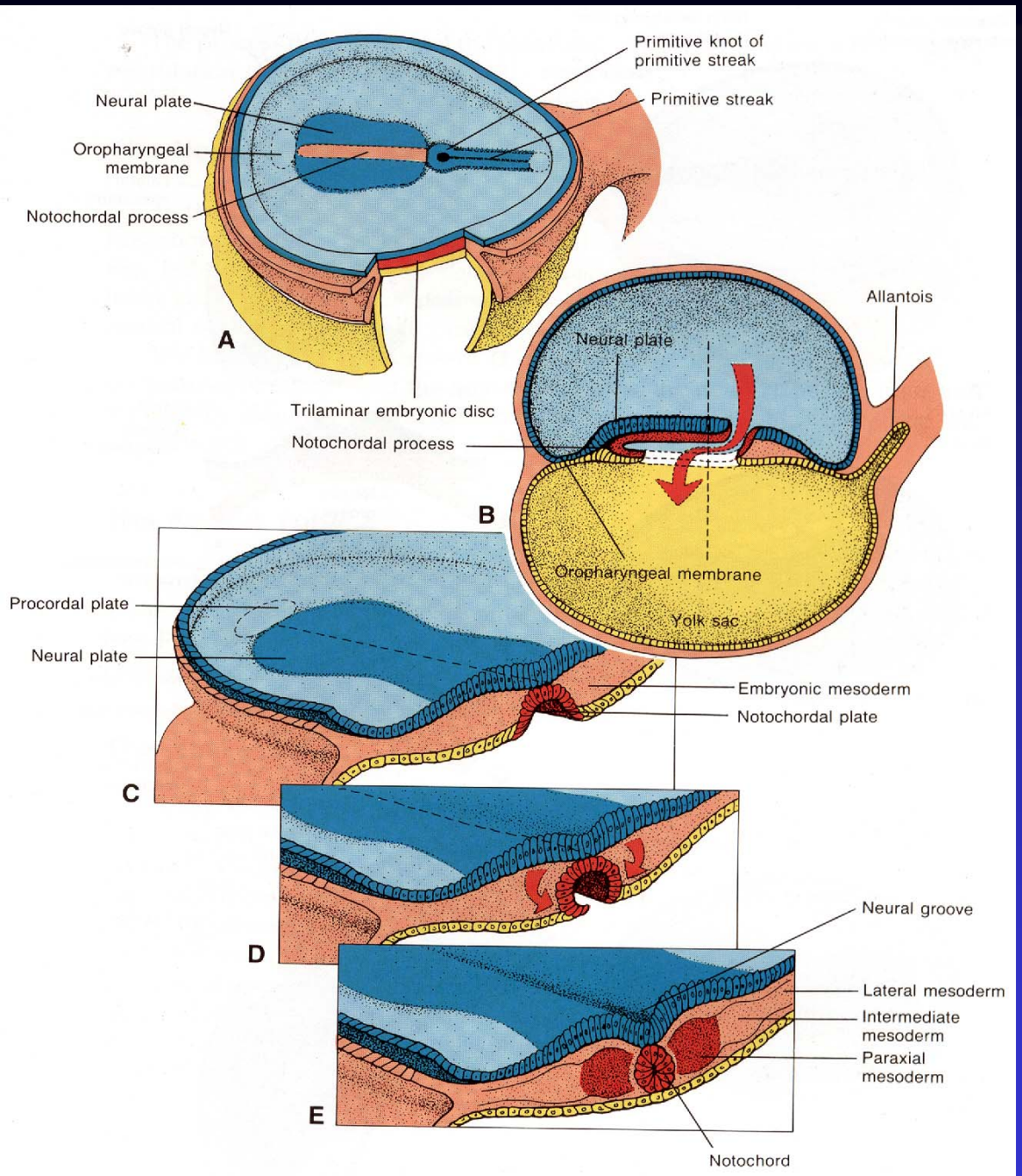
Induced by Notochord – Noggin/Chordin

Neural Plate → Neural Groove → Neural Tube

Regionalization – Subdivisions of the Central Nervous System (CNS)

Noggin, chordin → Anterior Neural Tissues Forebrain

FGF8 – Fibroblast Growth Factor 8 → Posterior neural tissues, i.e. spinal cord



Middle of third week:
Neural Plate

Notochord induces overlying ectoderm → neural plate –

Thickening of cell layer

Anterior Inducer:
Noggin/ Chordin

Posterior Inducer:
FGF-8,

Neural Plate → Neural Tube

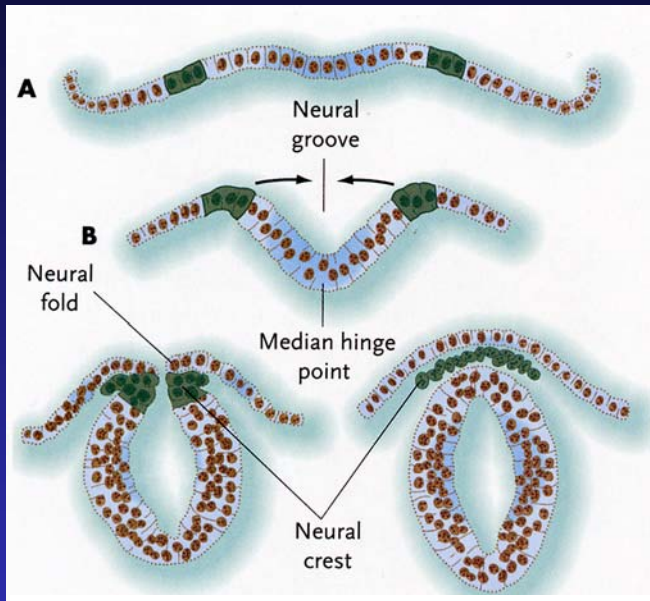
Four Stages of Neural Tube formation:

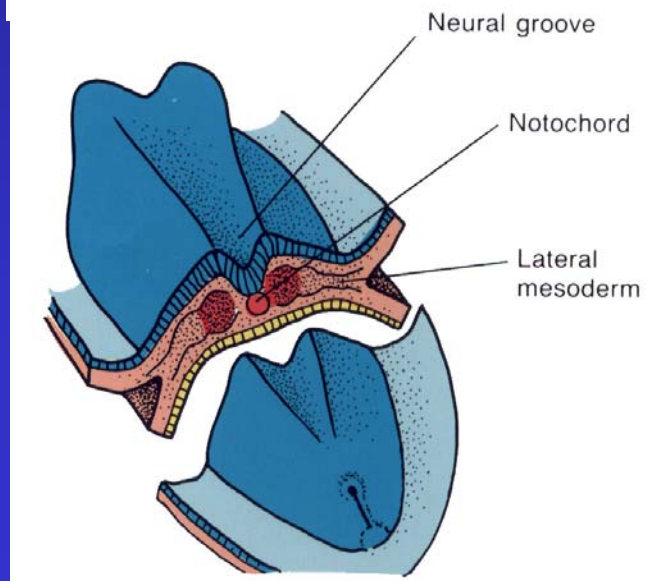
1) Thickening of the Neural Plate

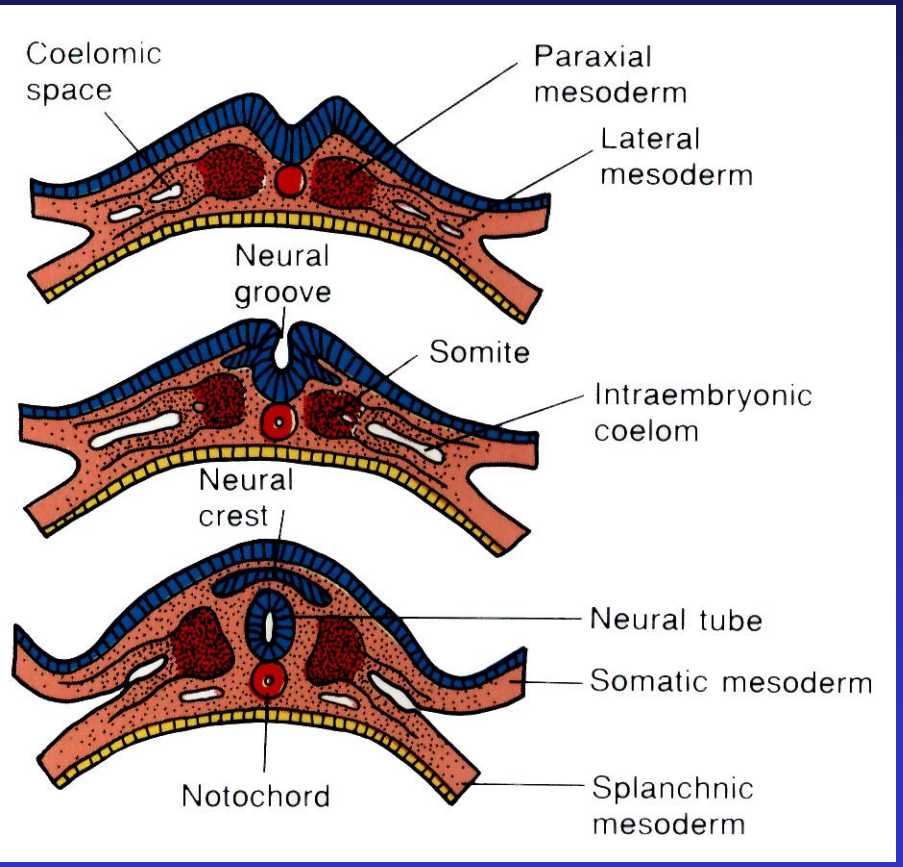
2) Establishing the contours of the Neural Plate: Cell shape changes and rearrangement of cells

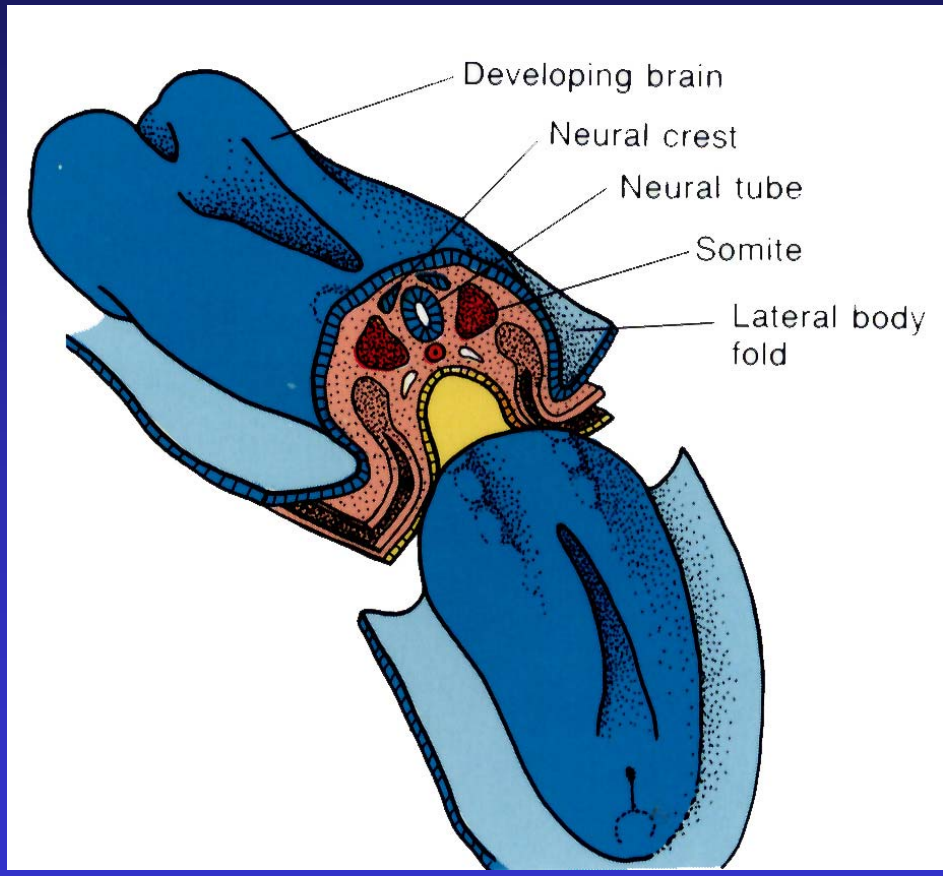
3) Lateral Neural Folds elevate to form the Neural Groove – medial hinge acts as an anchor, Cell shape changes apically, expanding lateral epidermis forces elevation

4) Apposition and fusion of the Neural Folds to form the Neural Tube

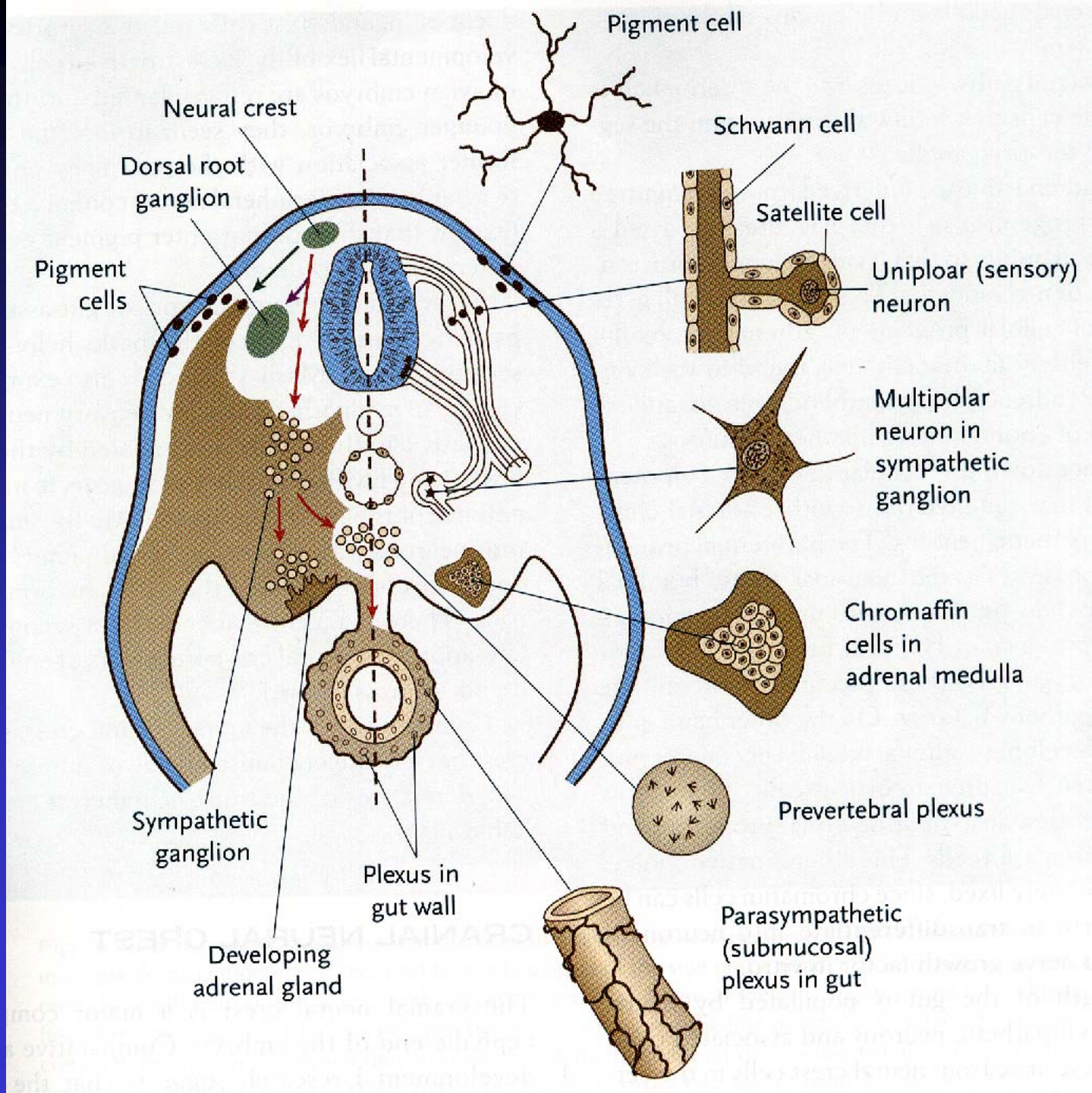




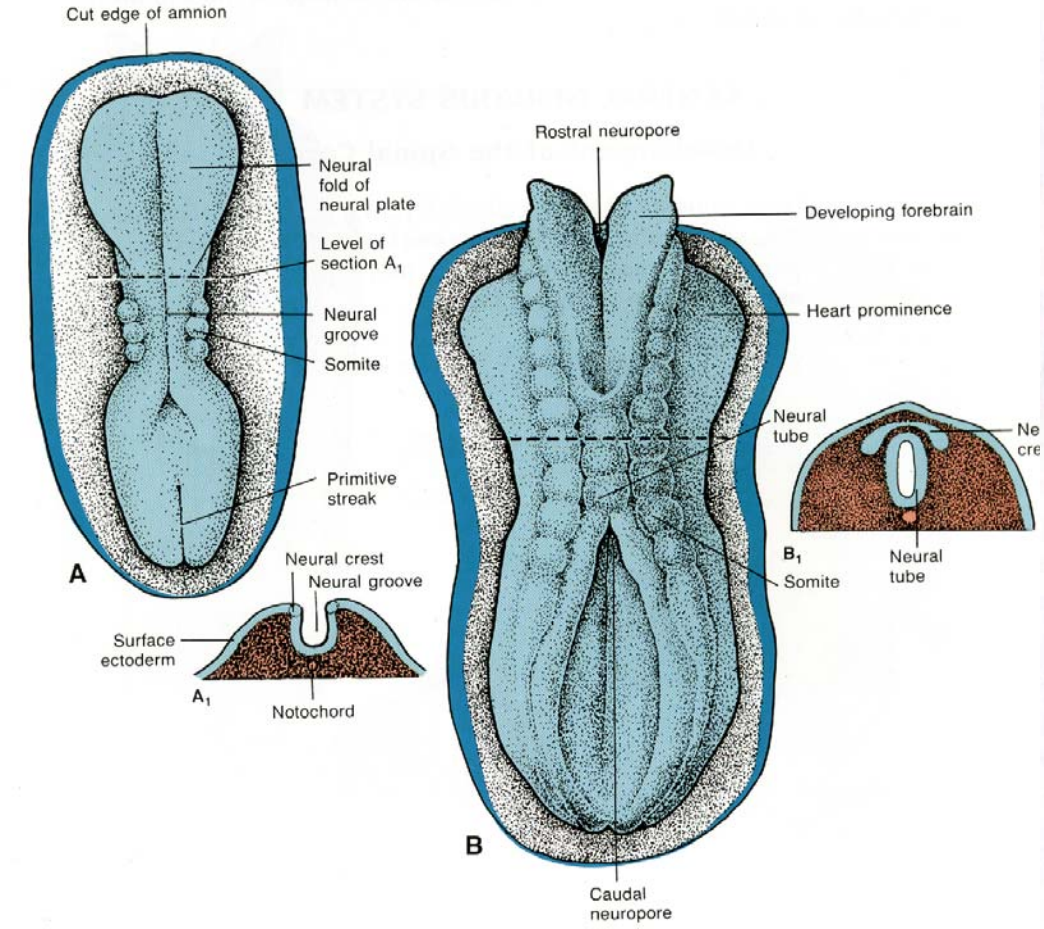

Coelomic space
Paraxial mesoderm
Lateral mesoderm
Neural groove
Somite
Intraembryonic coelom
Neural crest
Neural tube
Somatic mesoderm
Notochord
Splanchnic mesoderm

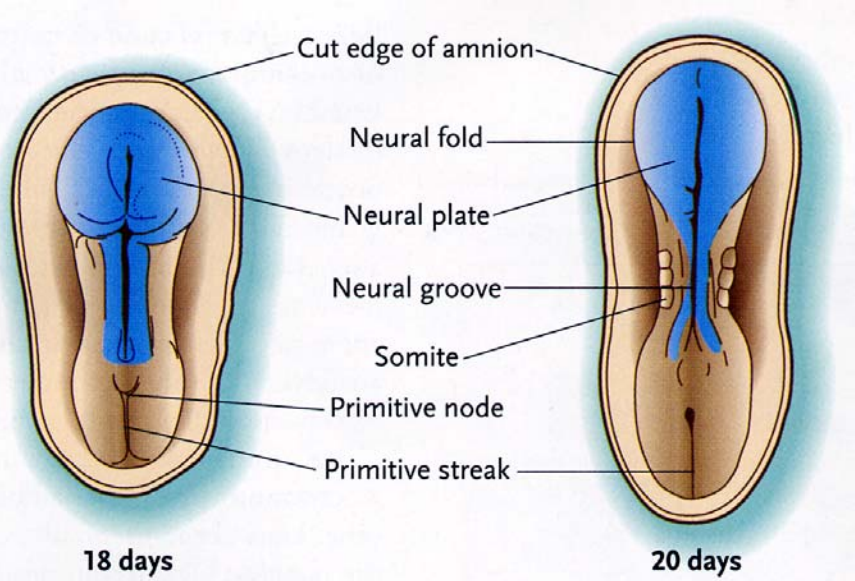

Developing brain
Neural crest
Neural tube
Somite
Lateral body fold

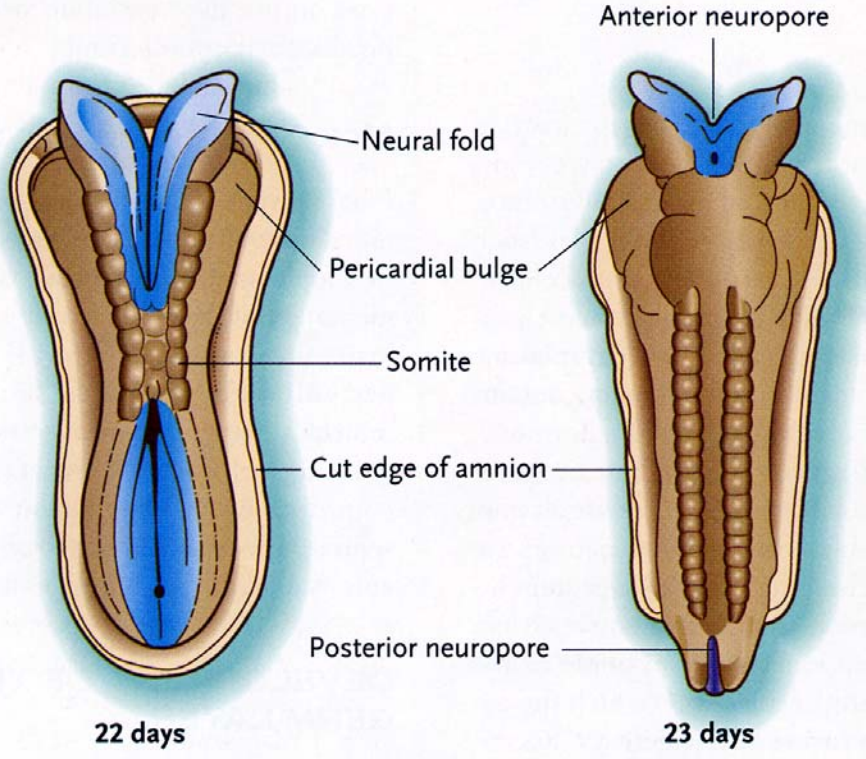
Neural Crest



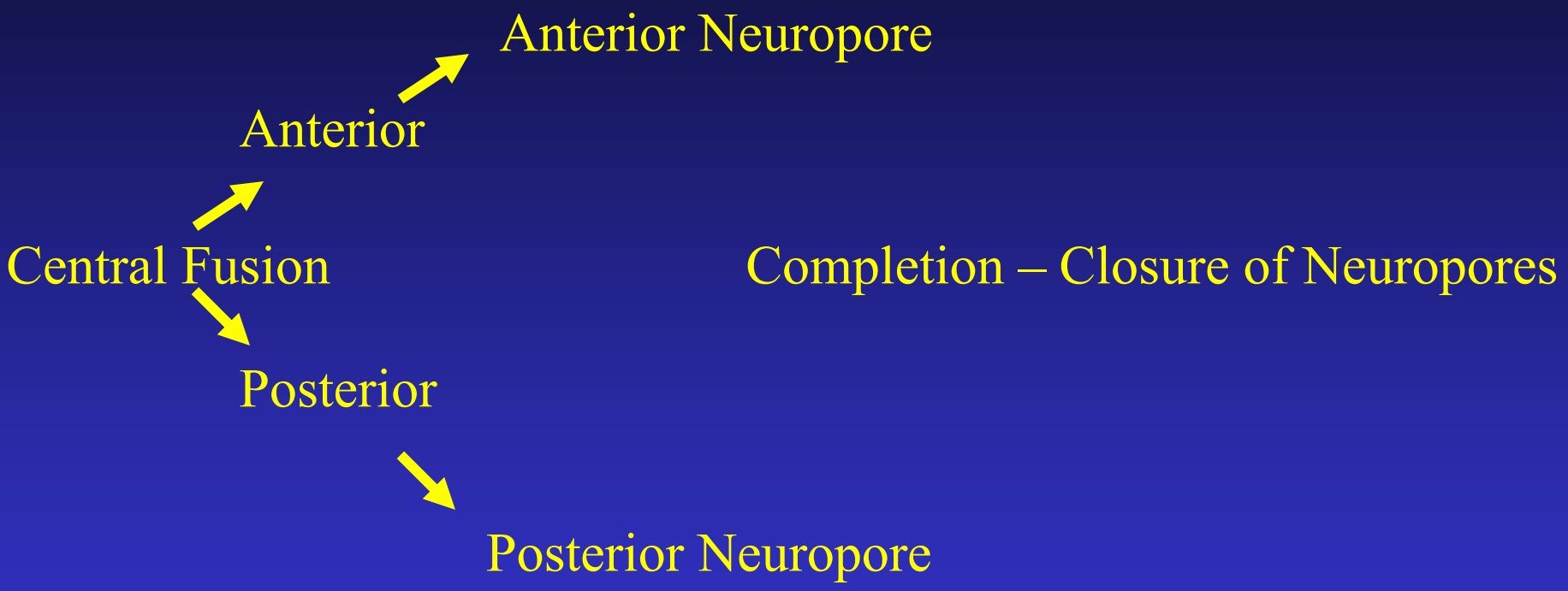
Early CNS Development





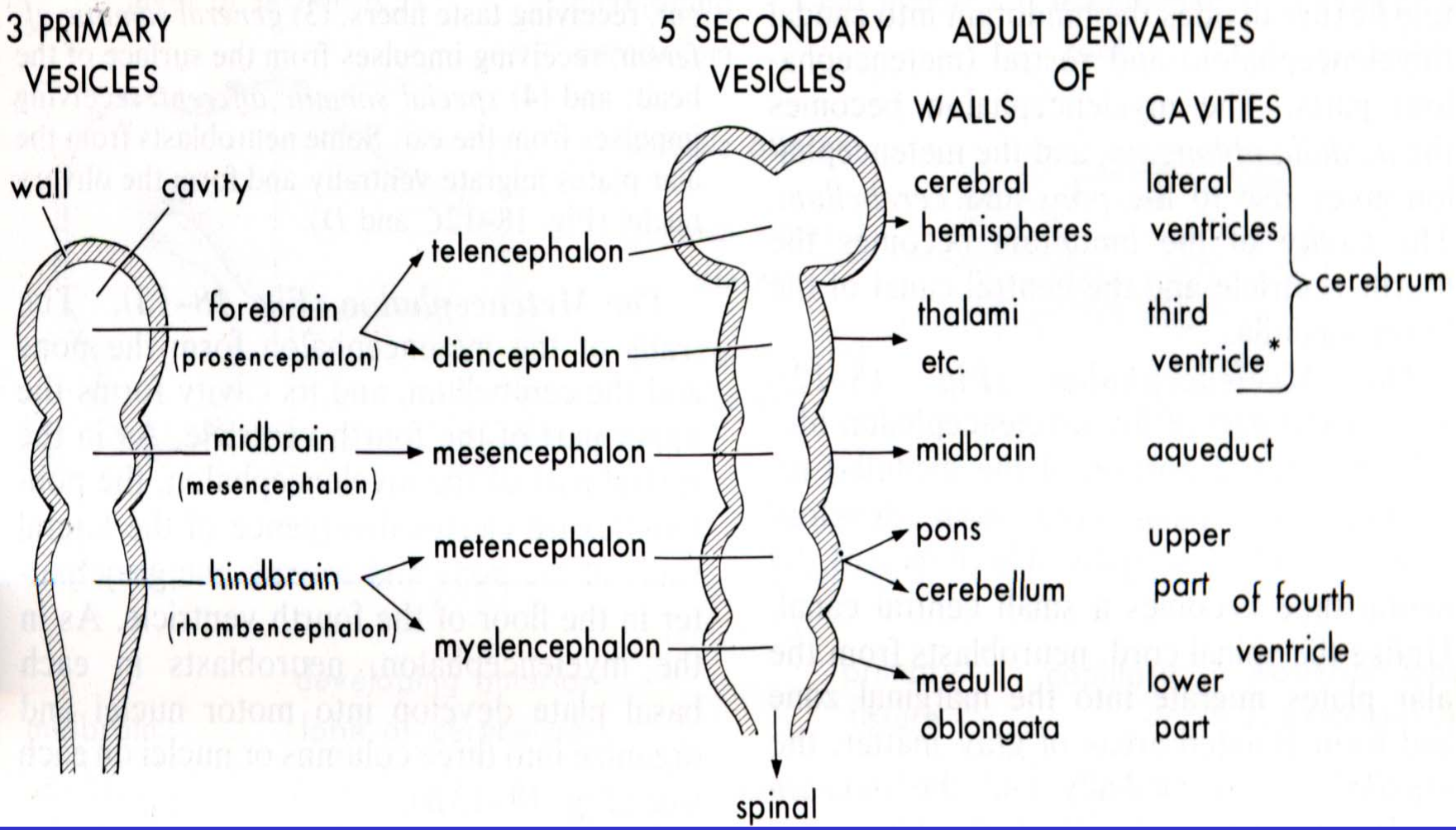


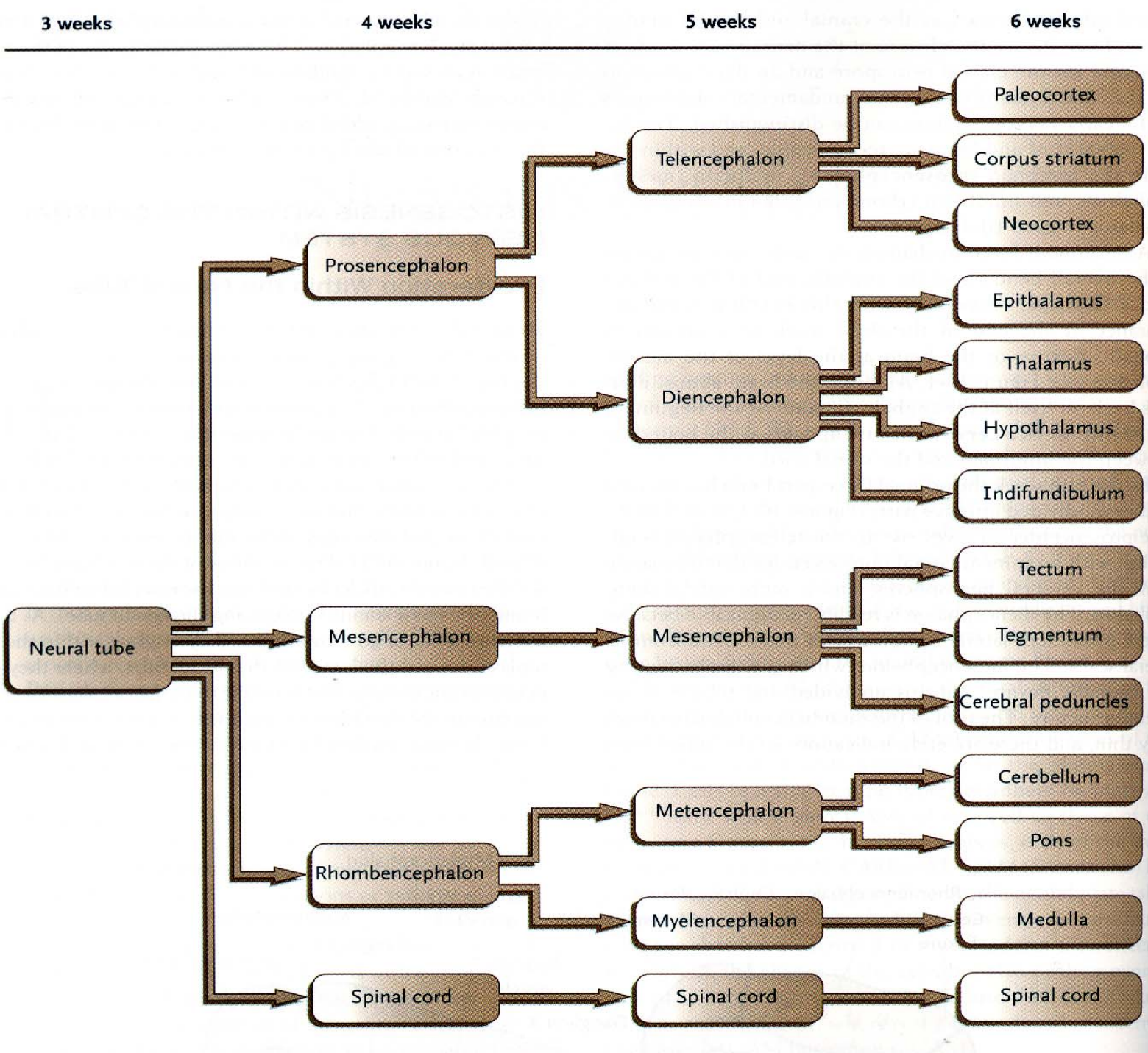
Neural Tube Formation



Secondary Neurulation – Posterior to the neuropore –
Mesenchymal condensation to form a rod that undergoes cavitation – secondary fusion with primary neural tube.

Segmentation of the Neural Tube




3 weeks
4 weeks
5 weeks
6 weeks
Neural tube
Prosencephalon
Mesencephalon
Rhombencephalon
Spinal cord
Telencephalon
Diencephalon
Mesencephalon
Metencephalon
Myelencephalon
Spinal cord
Paleocortex
Corpus striatum
Neocortex
Epithalamus
Thalamus
Hypothalamus
Indifundibulum
Tectum
Tegmentum
Cerebral peduncles
Cerebellum
Pons
Medulla
Spinal cord

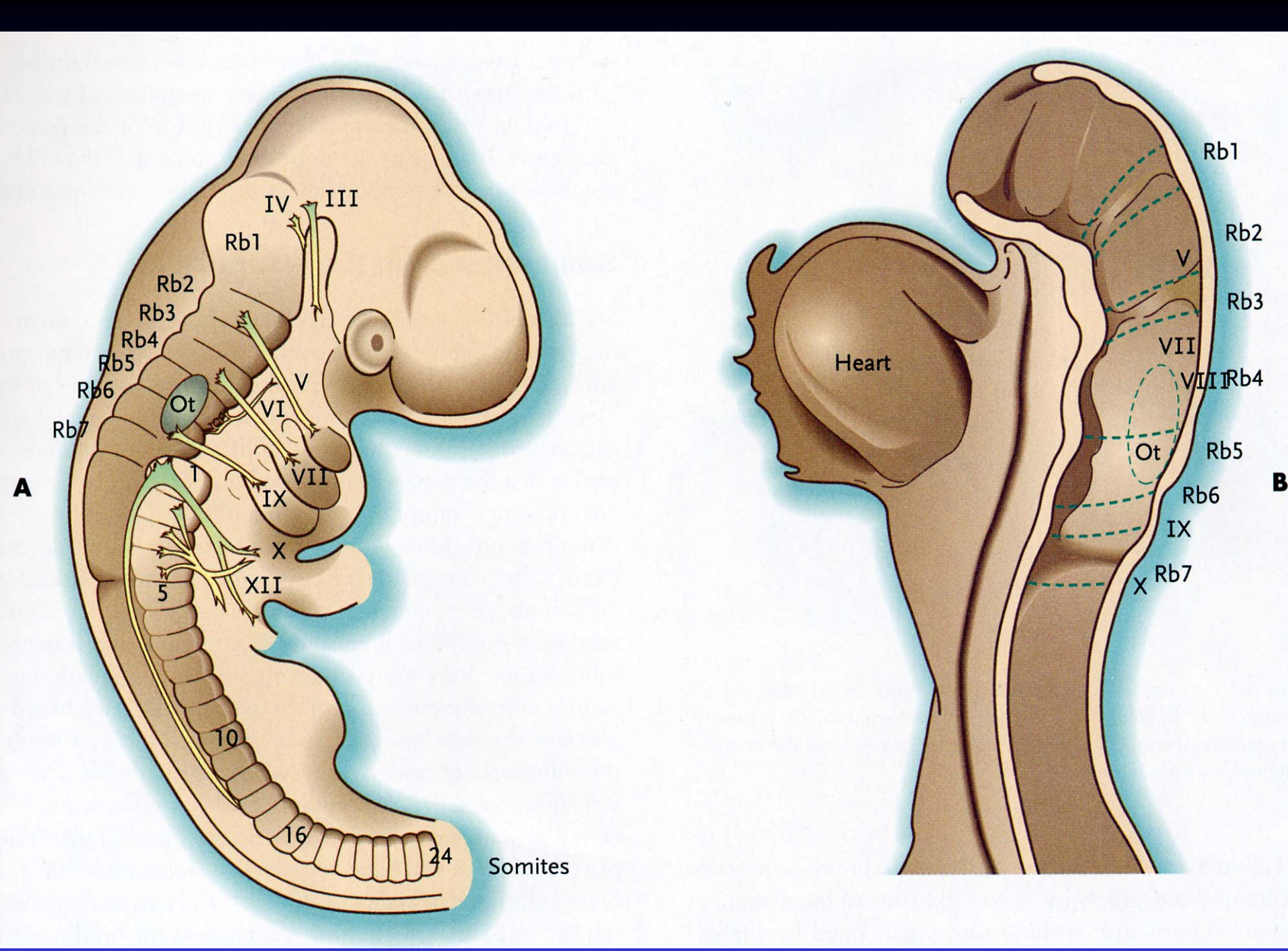
Segmentation of the Rhombencephalon

Neuromeres – Transient regularly spaced segments, also called Rhombomeres

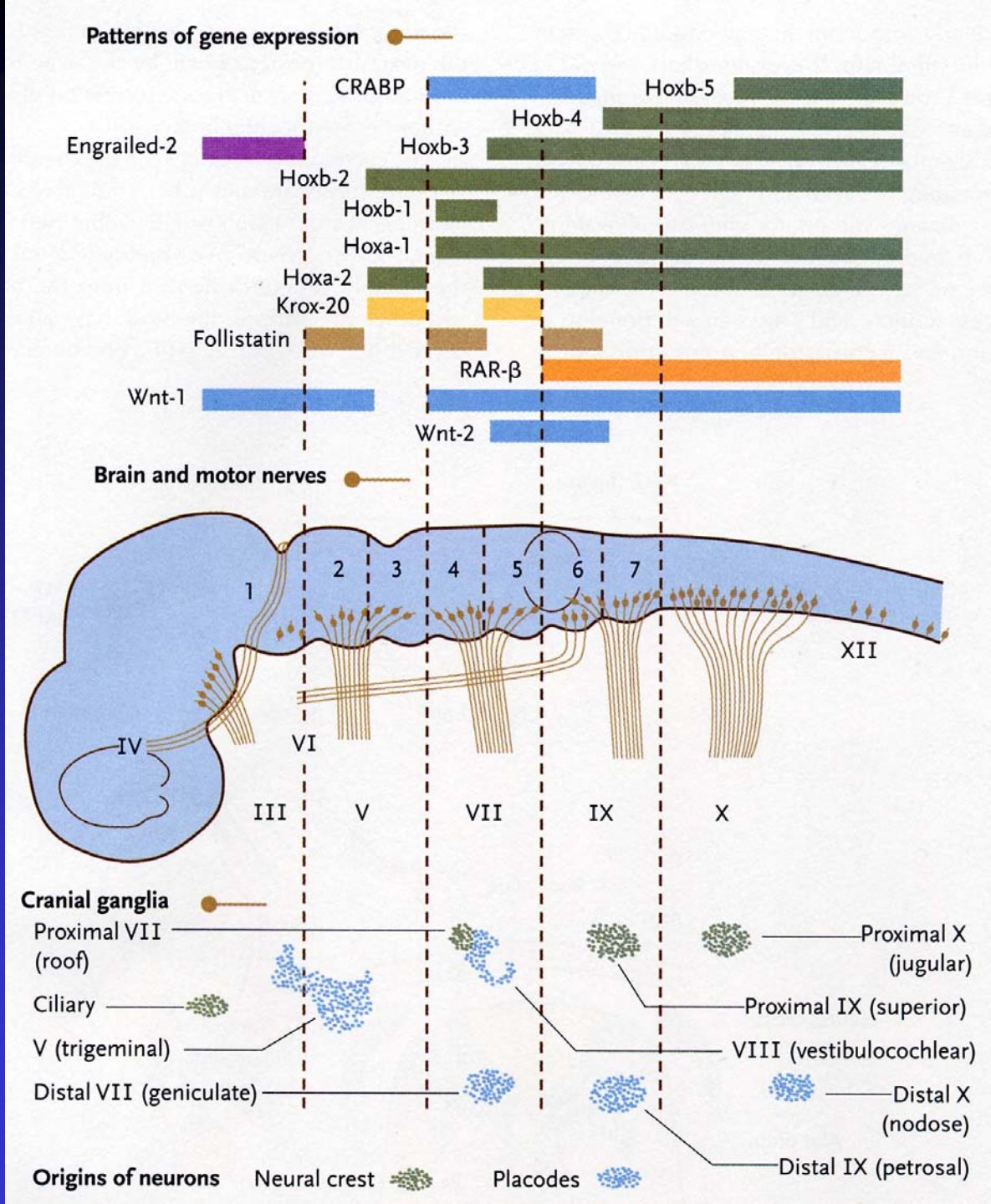
7 pairs – each an isolated compartment

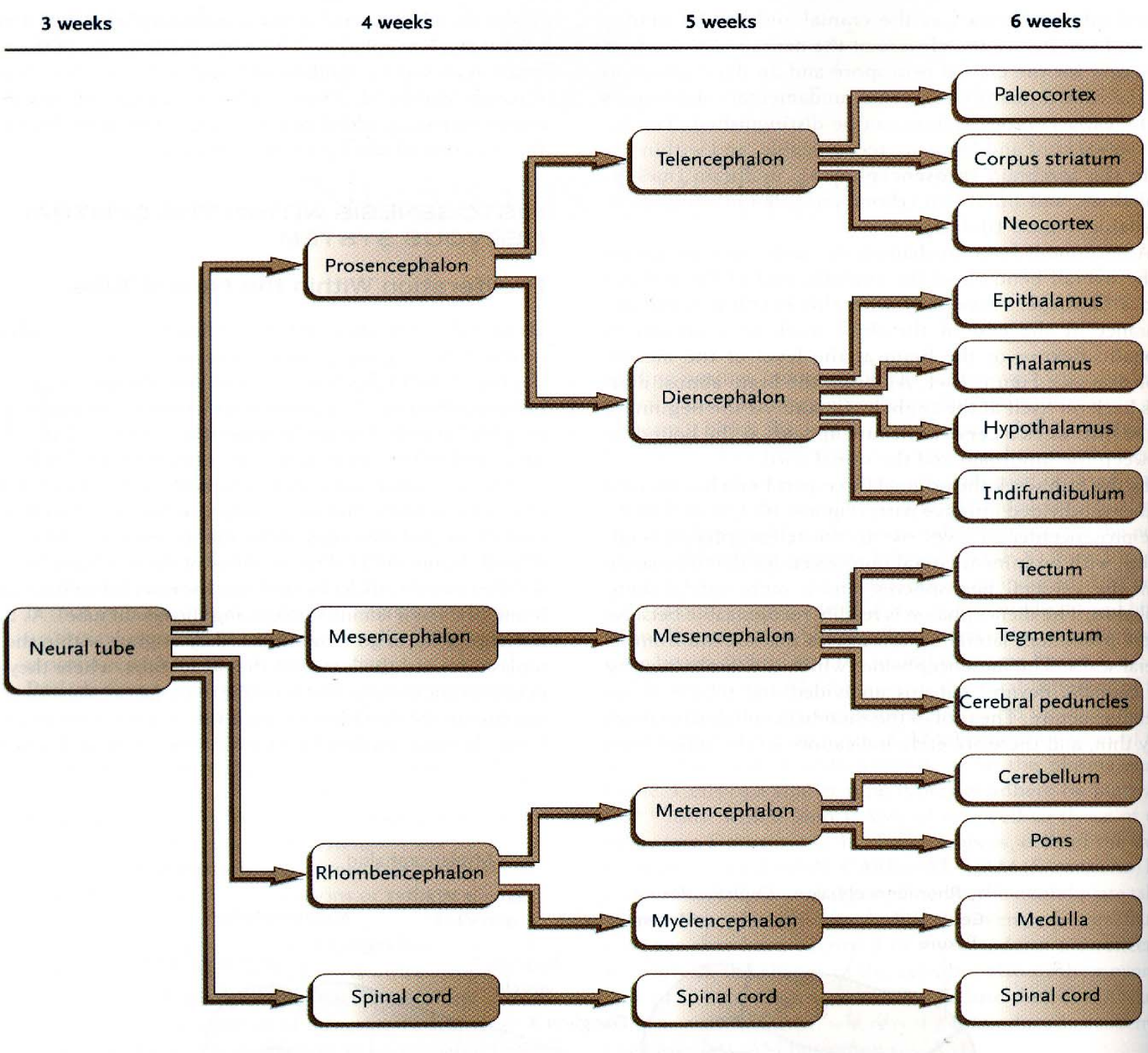
Alternating cell adhesive characteristics; alternating rhombomeres intermingle freely

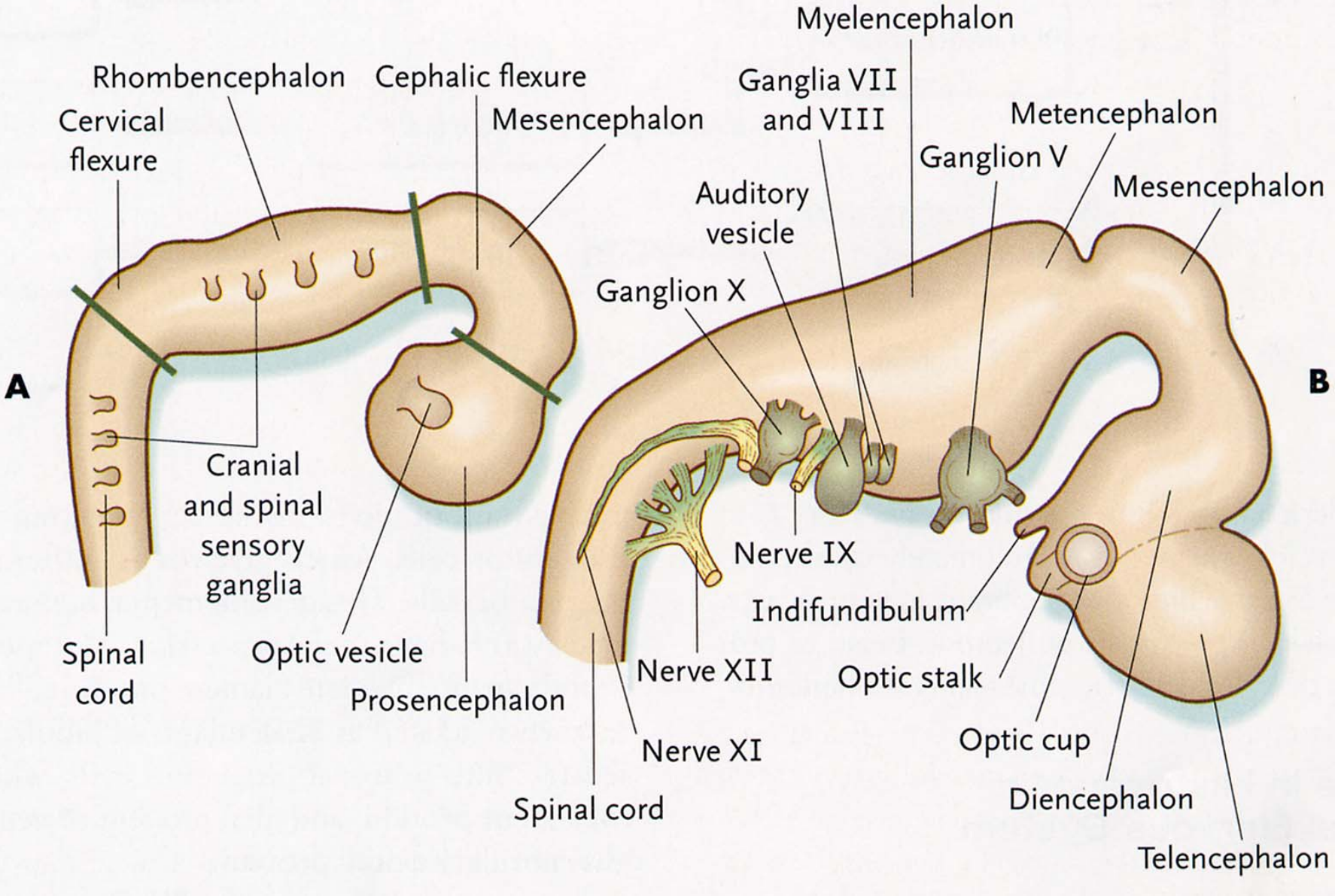
Segmental organization gives rise to specific cranial nerves


A
IV
III
Rb1
Rb2
Rb3
Rb4
Rb5
Rb6
Rb7
Ot
V
VI
VII
IX
X
XII
1
5
10
16
24
Somites
B
Heart
Rb1
Rb2
V
Rb3
VII
VIII
Rb4
Ot
Rb5
Rb6
IX
X
Rb7

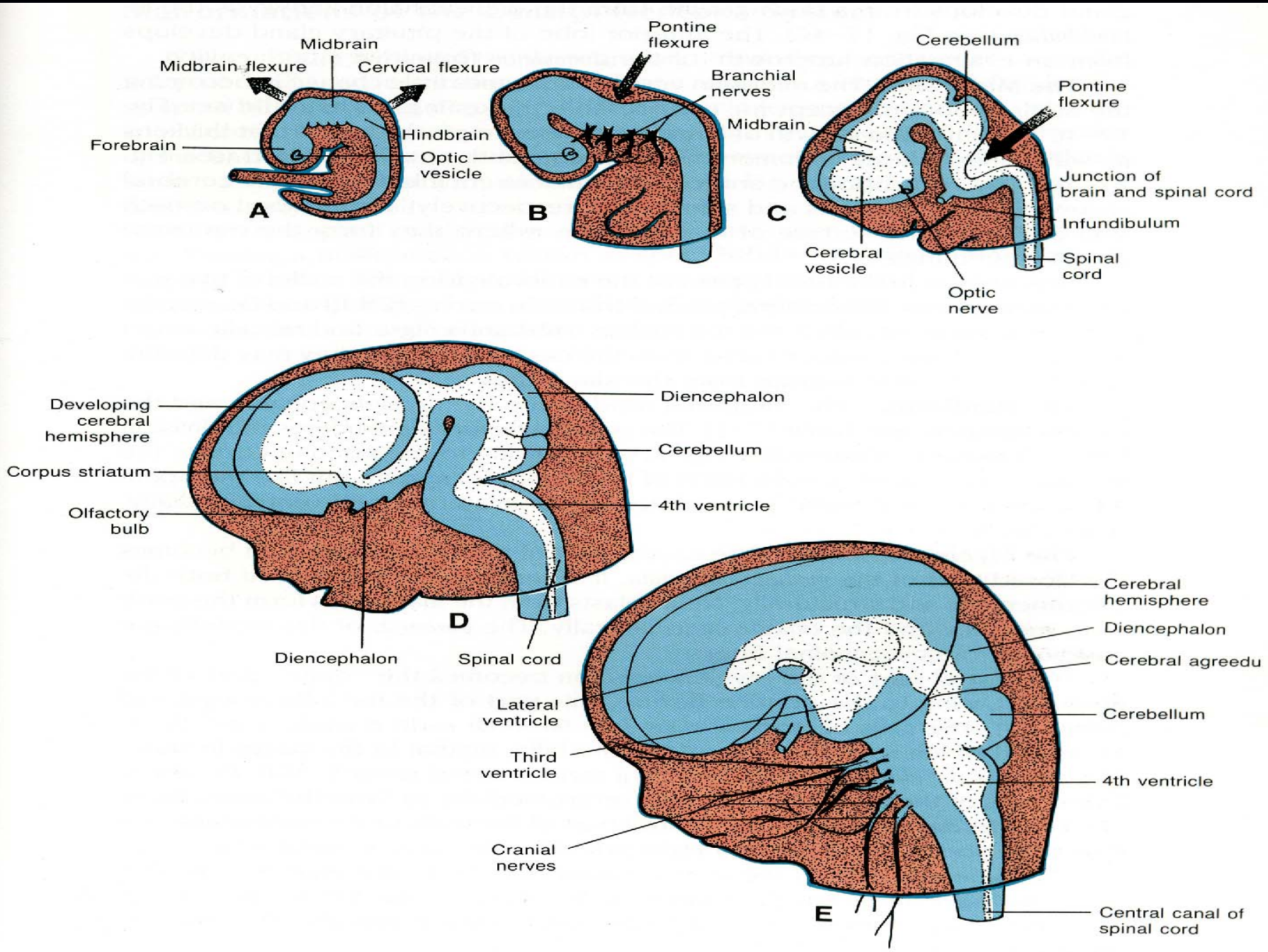
Specification and Position-Specific Gene Expression

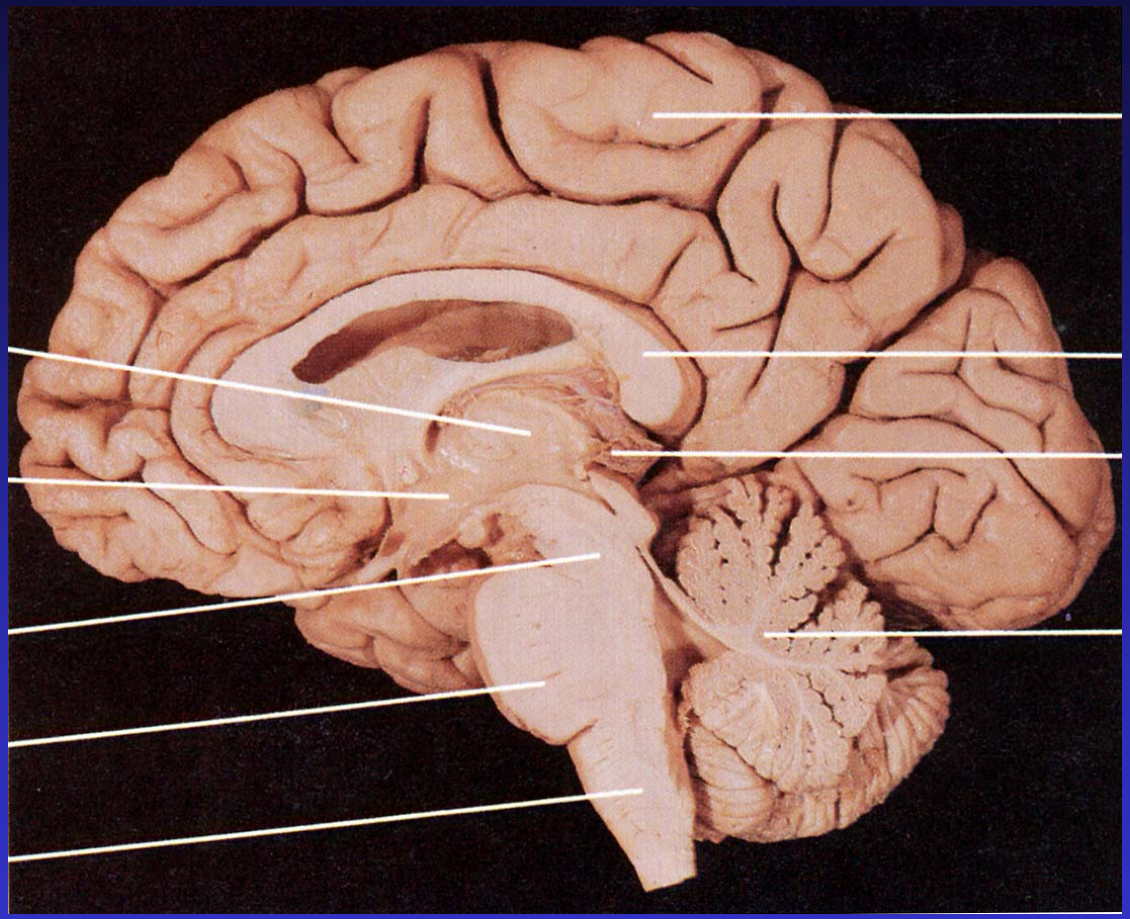



3 weeks
4 weeks
5 weeks
6 weeks
Neural tube
Prosencephalon
Mesencephalon
Rhombencephalon
Spinal cord
Telencephalon
Diencephalon
Mesencephalon
Metencephalon
Myelencephalon
Spinal cord
Paleocortex
Corpus striatum
Neocortex
Epithalamus
Thalamus
Hypothalamus
Indifundibulum
Tectum
Tegmentum
Cerebral peduncles
Cerebellum
Pons
Medulla
Spinal cord

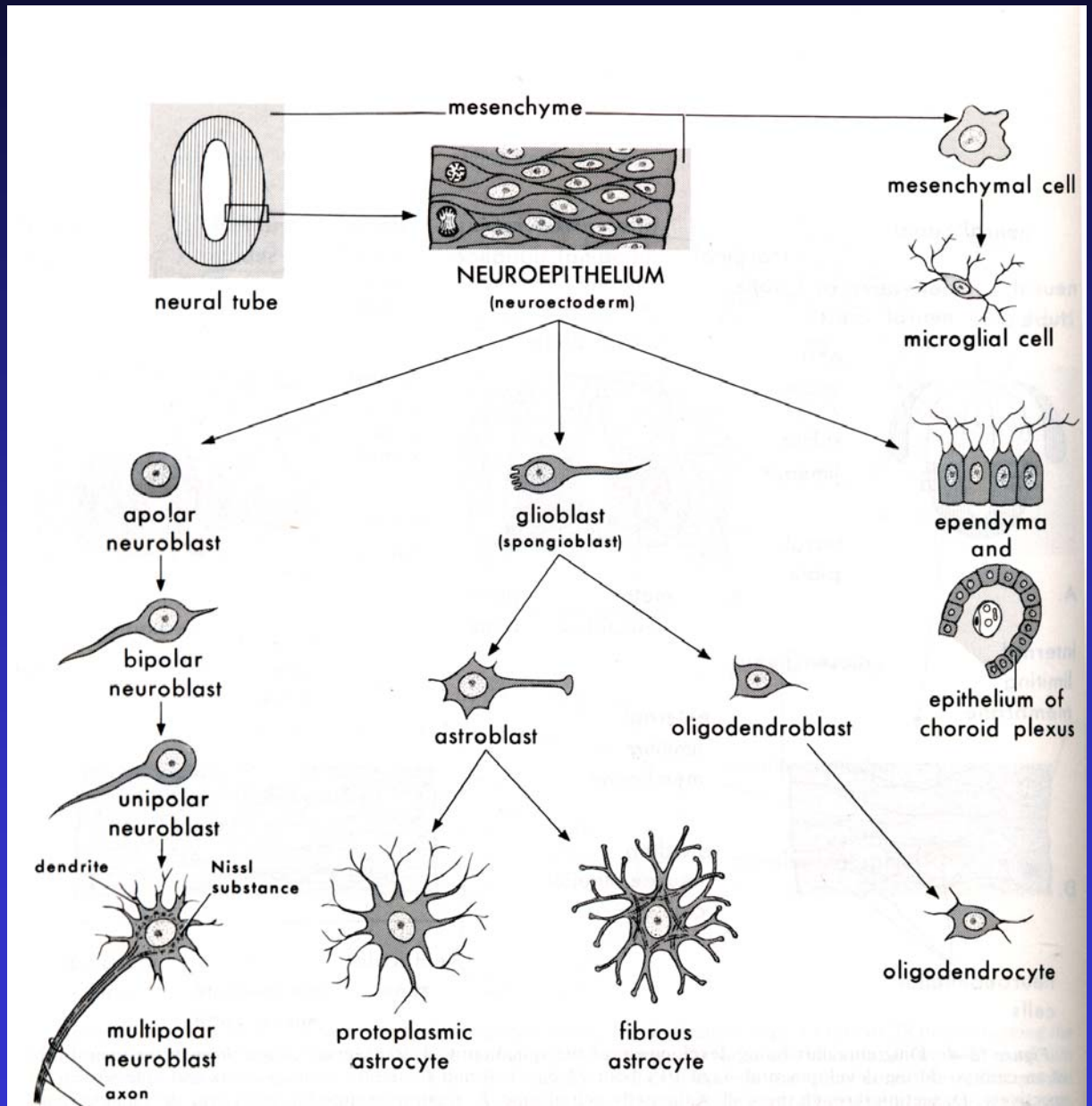


Cephalic flexure, Cervical flexure, Pontine flexure


Midbrain
Midbrain flexure
Cervical flexure
Forebrain
Hindbrain
Optic vesicle
A
Pontine flexure
Branchial nerves
Midbrain
B
Cerebellum
Pontine flexure
Junction of brain and spinal cord
Infundibulum
Cerebral vesicle
Spinal cord
Optic nerve
C
Developing cerebral hemisphere
Corpus striatum
Olfactory bulb
Diencephalon
Cerebellum
4th ventricle
Diencephalon
Spinal cord
D
Cerebral hemisphere
Diencephalon
Cerebral agreedu
Lateral ventricle
Cerebellum
Third ventricle
4th ventricle
Cranial nerves
Central canal of spinal cord
E


Cerebrum
Thalamus
CorpusCallosum
Hypothalamus
Pineal Body
Midbrain
Cerebellum
Pons
Medulla
oblongata

Histogenesis of CNS cells



Cell Types

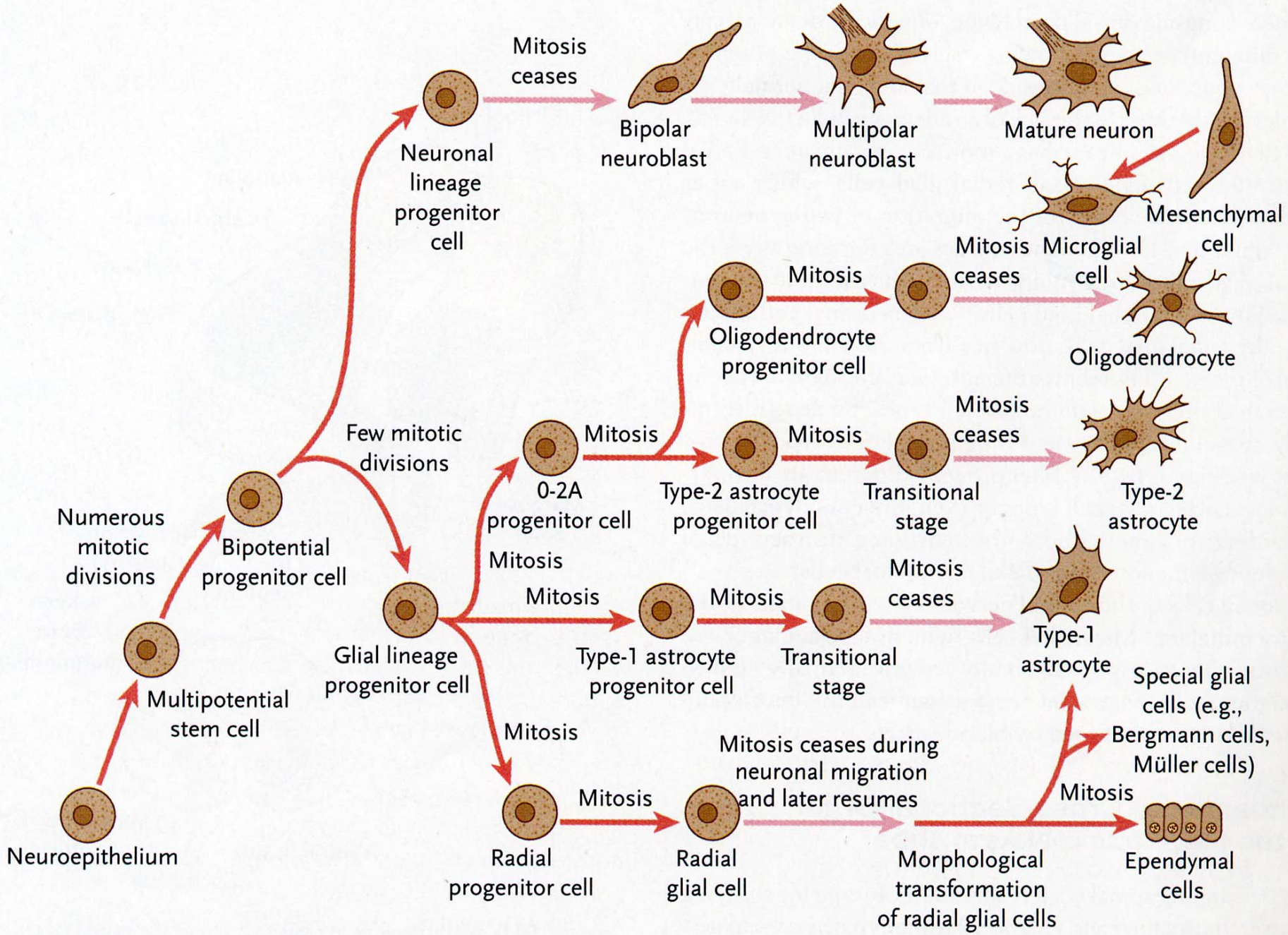
Neuroepithelium – Multipotential Stem Cell

Bipotential Progenitor Cell

Neuronal vs. Glial Cell Lineage

Neuronal Lineage (neurofilament expression):
Bipolar neuroblast, Multipolar neuroblast, Neuron

Glial Lineage (glia fibrillary acidic protein, GFAP):
Radial glia, Type-1 Astrocyte, Type-2 Astrocyte, Oligodendrocyte


Mitosis ceases
Bipolar neuroblast
Multipolar neuroblast
Mature neuron
Neuronal lineage progenitor cell
Mesenchymal cell
Microglial cell
Mitosis ceases
Mitosis
Oligodendrocyte progenitor cell
Oligodendrocyte
Few mitotic divisions
Mitosis
Mitosis
Mitosis ceases
0-2A progenitor cell
Type-2 astrocyte progenitor cell
Transitional stage
Type-2 astrocyte
Numerous mitotic divisions
Bipotential progenitor cell
Mitosis
Mitosis
Mitosis
Mitosis ceases
Glial lineage progenitor cell
Type-1 astrocyte progenitor cell
Transitional stage
Type-1 astrocyte
Special glial cells (e.g., Bergmann cells, Müller cells)
Multipotential stem cell
Mitosis
Mitosis ceases during neuronal migration and later resumes
Mitosis
Mitosis
Neuroepithelium
Radial progenitor cell
Radial glial cell
Morphological transformation of radial glial cells
Ependymal cells

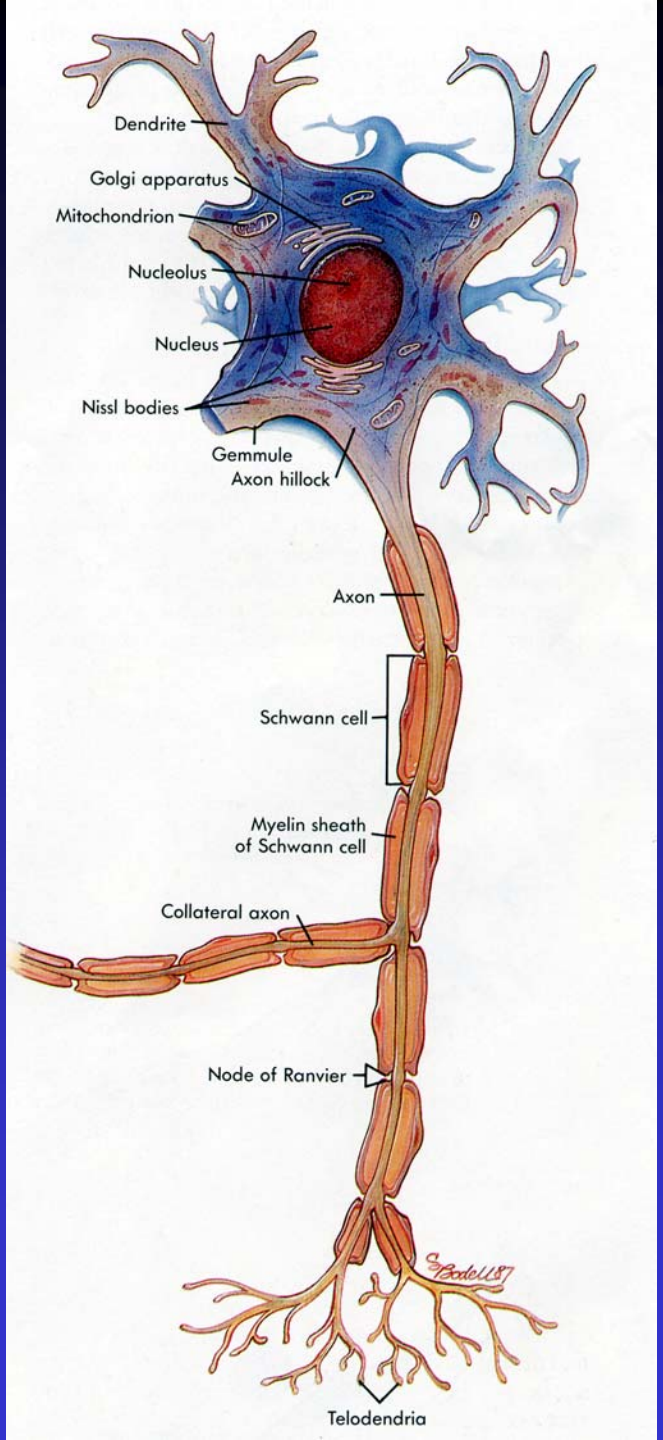
Dendrite

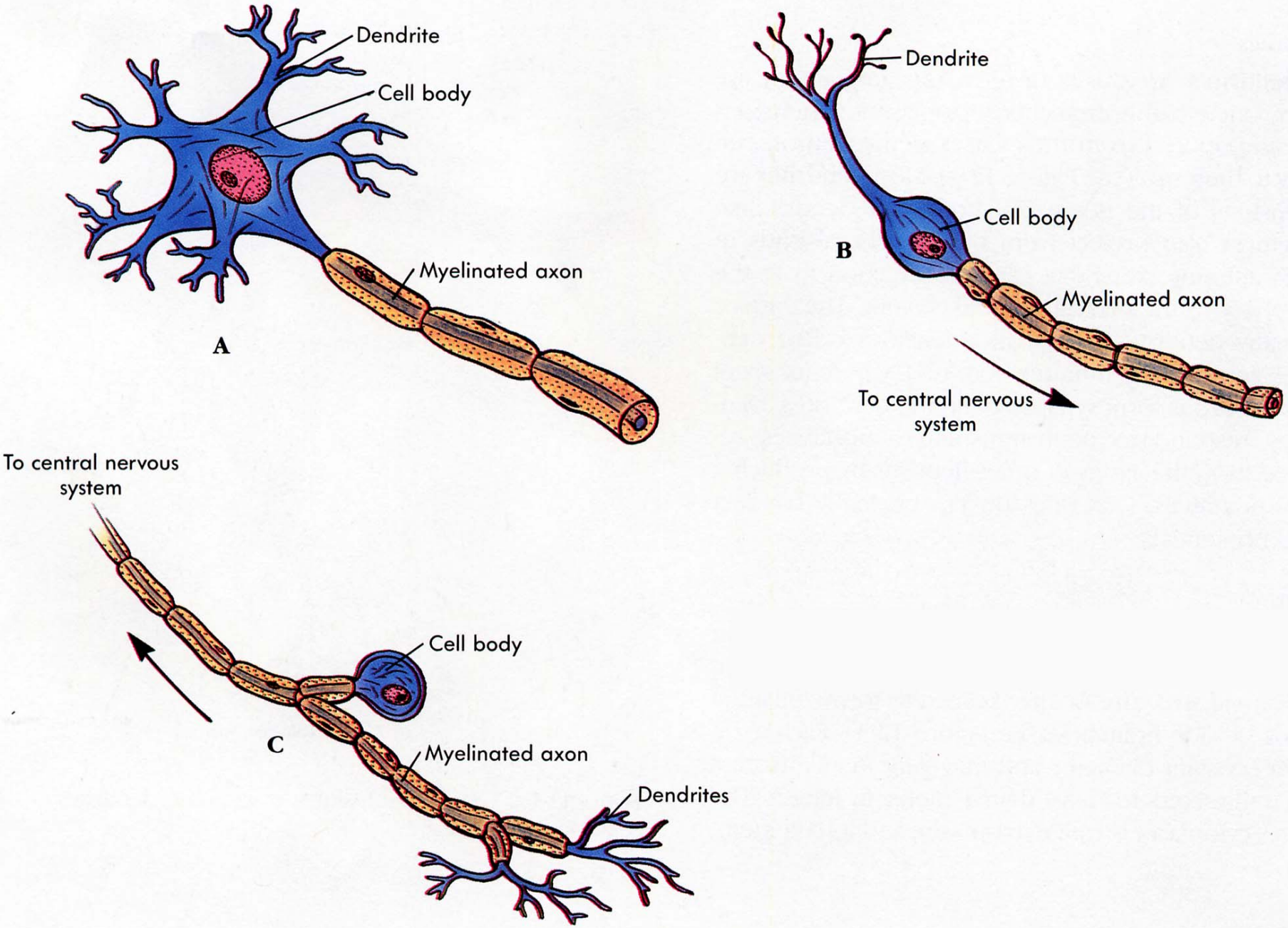
Cell Body

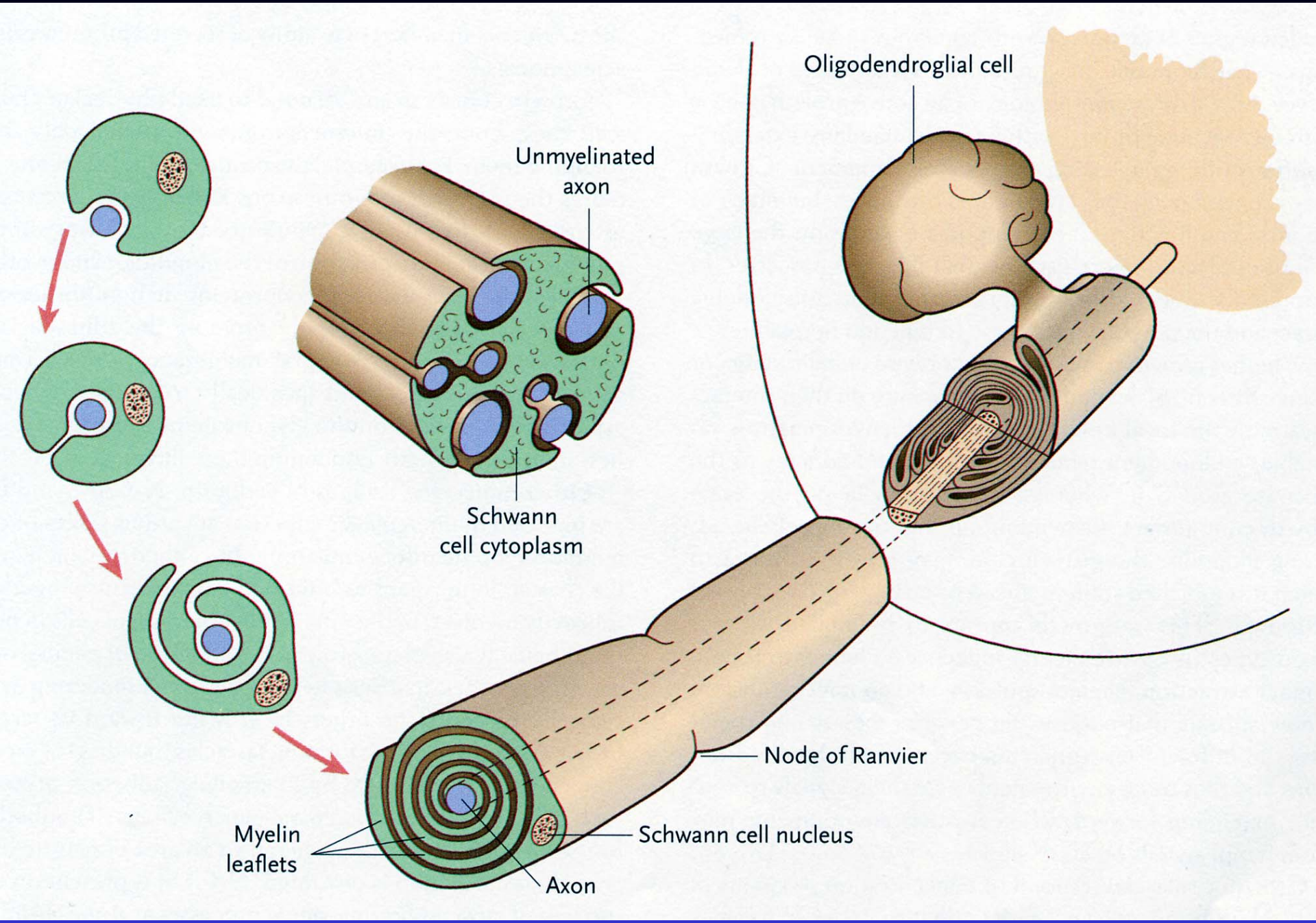
Axon

Schwann Cell

Myelin Sheath

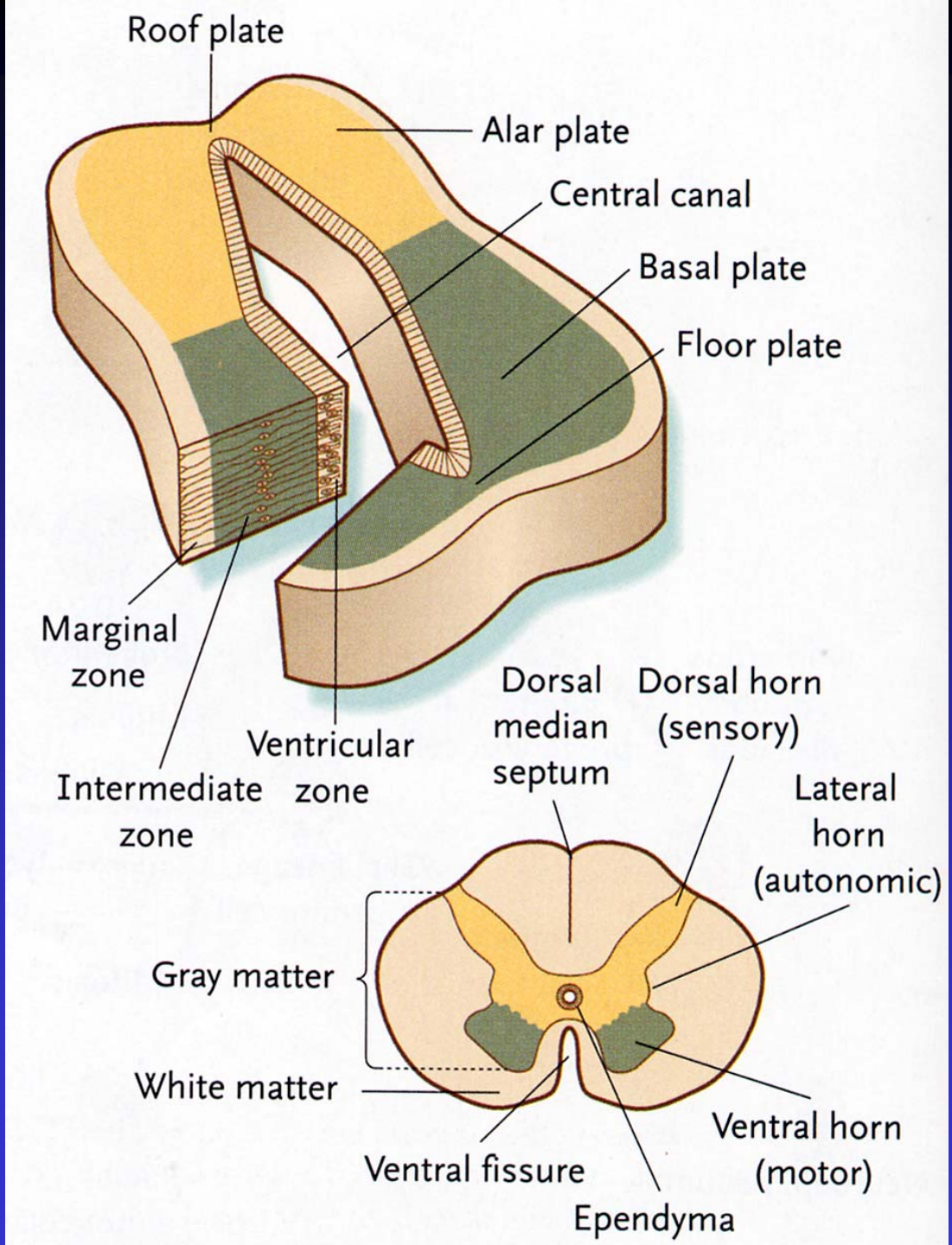



Dendrite
Cell body
Myelinated axon
A
Dendrite
Cell body
B
Myelinated axon
To central nervous system
To central nervous system
Cell body
C
Myelinated axon
Dendrites


Oligodendroglial cell
Unmyelinated axon
Schwann cell cytoplasm
Node of Ranvier
Myelin leaflets
Schwann cell nucleus
Axon

Spinal Cord

- Central Canal – Lumen
- Ventricular Zone – Cells lining the Central Canal becomes Gray matter
- Intermediate Zone
- Marginal Zone – neuronal cell processes; no cell bodies, becomes White matter



6 Parts of the Spinal Cord

2 Alar Plates (Left and Right)

Sulcus Limitans separates Alar and Basal plates

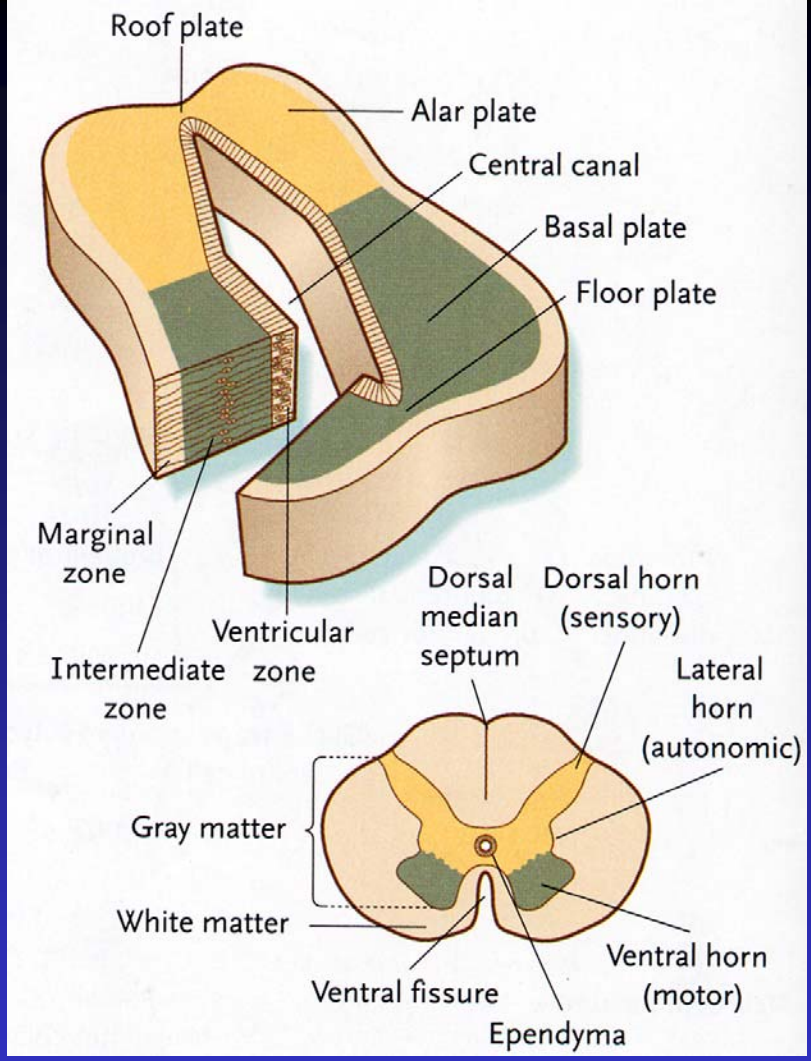
2 Basal Plates (Left and Right)

Roof Plate connecting Alar plates

Floor Plate connecting Basal plates

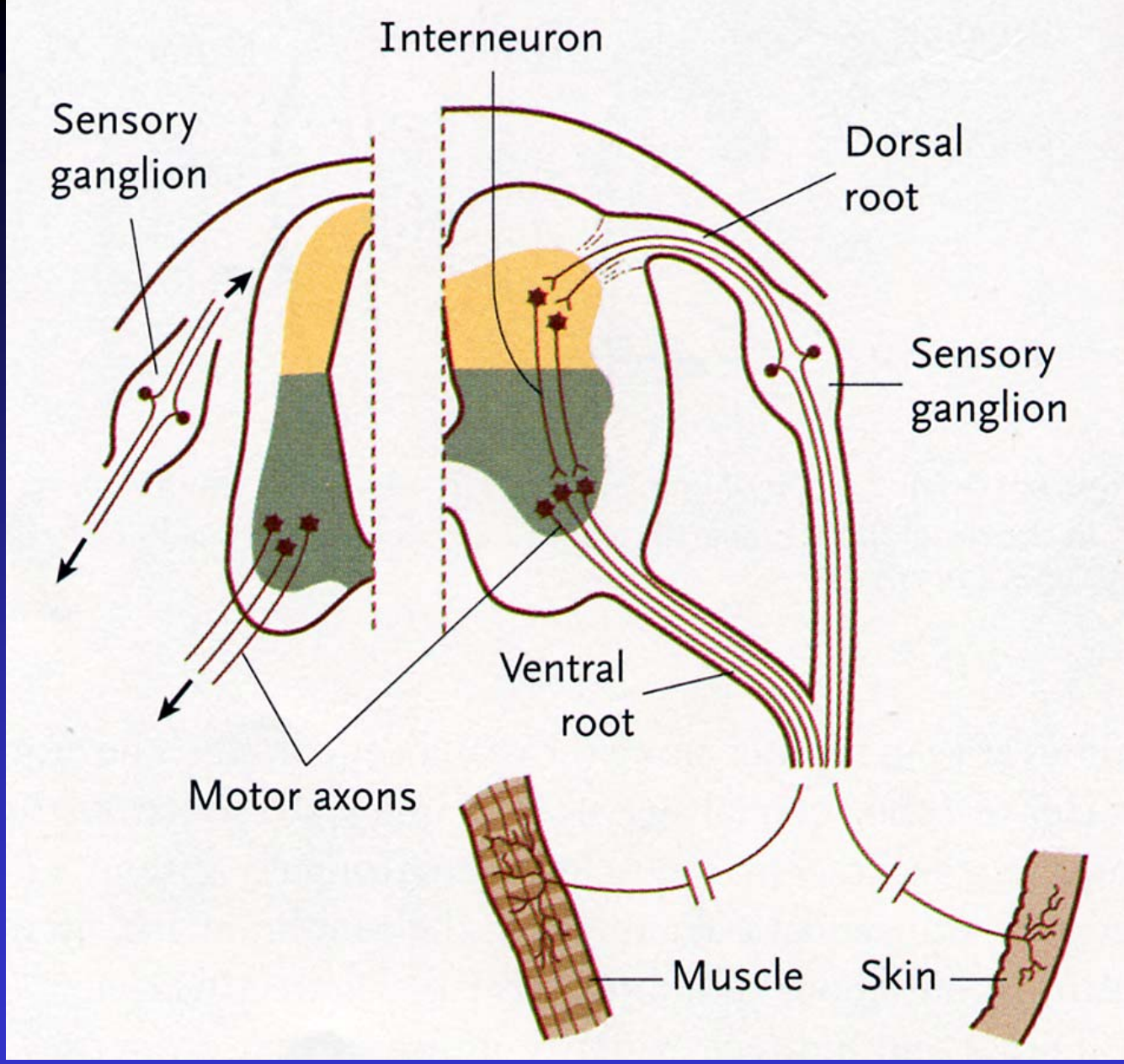
Basal plates → Motor – Ventral Horn

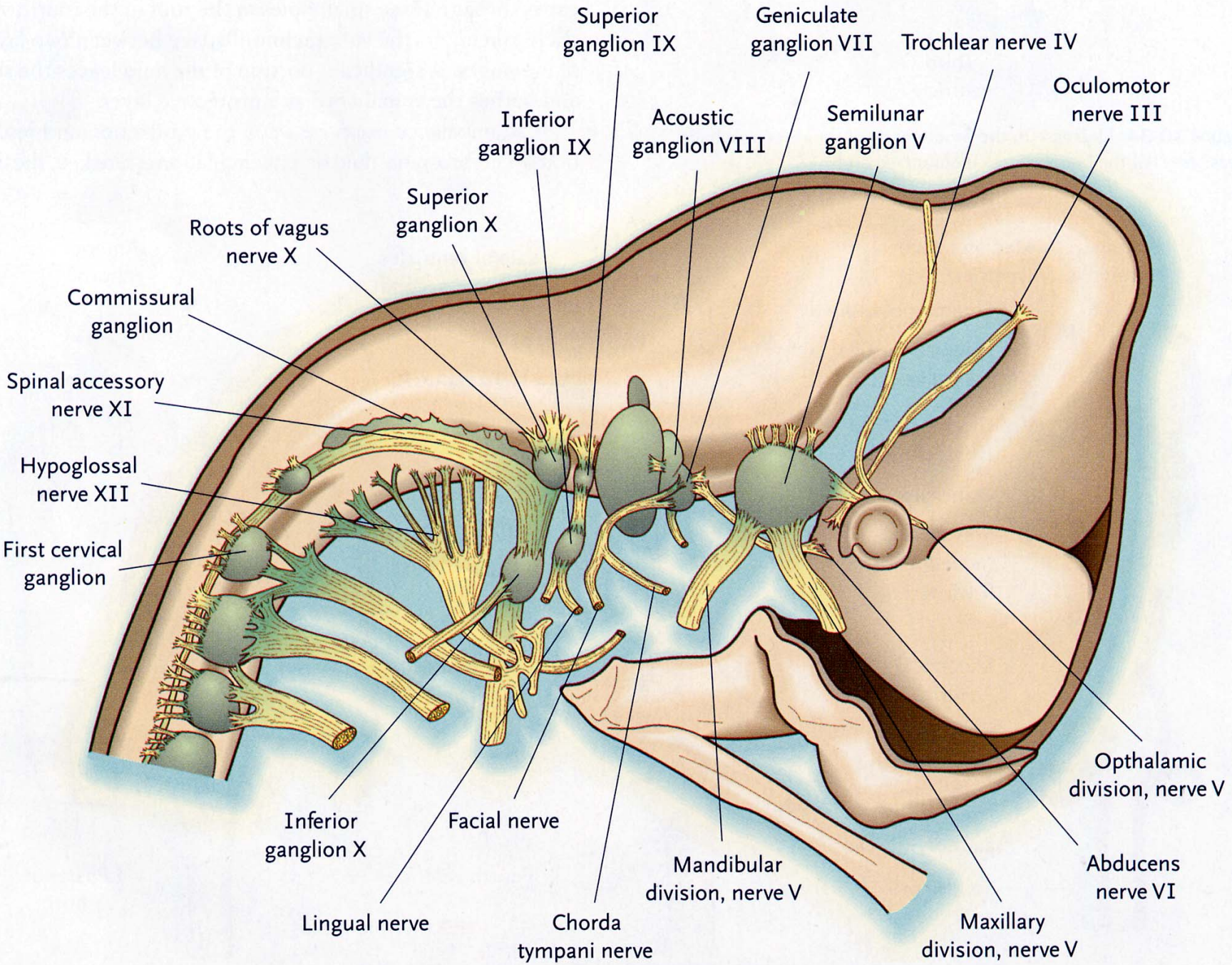
Alar plates → Sensory – Dorsal Horn



Nerves

- Motor
- Sensory
- Autonomic
  - Sympathetic
  - Parasympathetic




Superior ganglion IX
Geniculate ganglion VII
Trochlear nerve IV
Oculomotor nerve III
Inferior ganglion IX
Acoustic ganglion VIII
Semilunar ganglion V
Superior ganglion X
Roots of vagus nerve X
Commissural ganglion
Spinal accessory nerve XI
Hypoglossal nerve XII
First cervical ganglion
Opthalamic division, nerve V
Abducens nerve VI
Maxillary division, nerve V
Mandibular division, nerve V
Facial nerve
Inferior ganglion X
Lingual nerve
Chorda tympani nerve

Cranial Nerves

I – Olfactory; Telencephalon; No Ganglion; Sensory

II – Optic; Diencephalon; No Ganglion; Sensory

III – Oculomoter; Mesencephalon; Cilary Ganglion; Motor and Parasympathetic

IV – Troclear; Metencephalon; No Ganglion; Motor

V – Trigeminal (semilunar); Metencephalon, trigeminal placode; Trigeminal Ganglion; Sensory and Motor

VI – Abducens; Metencephalon; No Ganglion; Motor

VII – Facial; Metencephalon; 4 Ganglia – Superior, Inferior (Geniculate), Sphenopalatine, Submandibular; Motor, Sensory, Parasympathetic

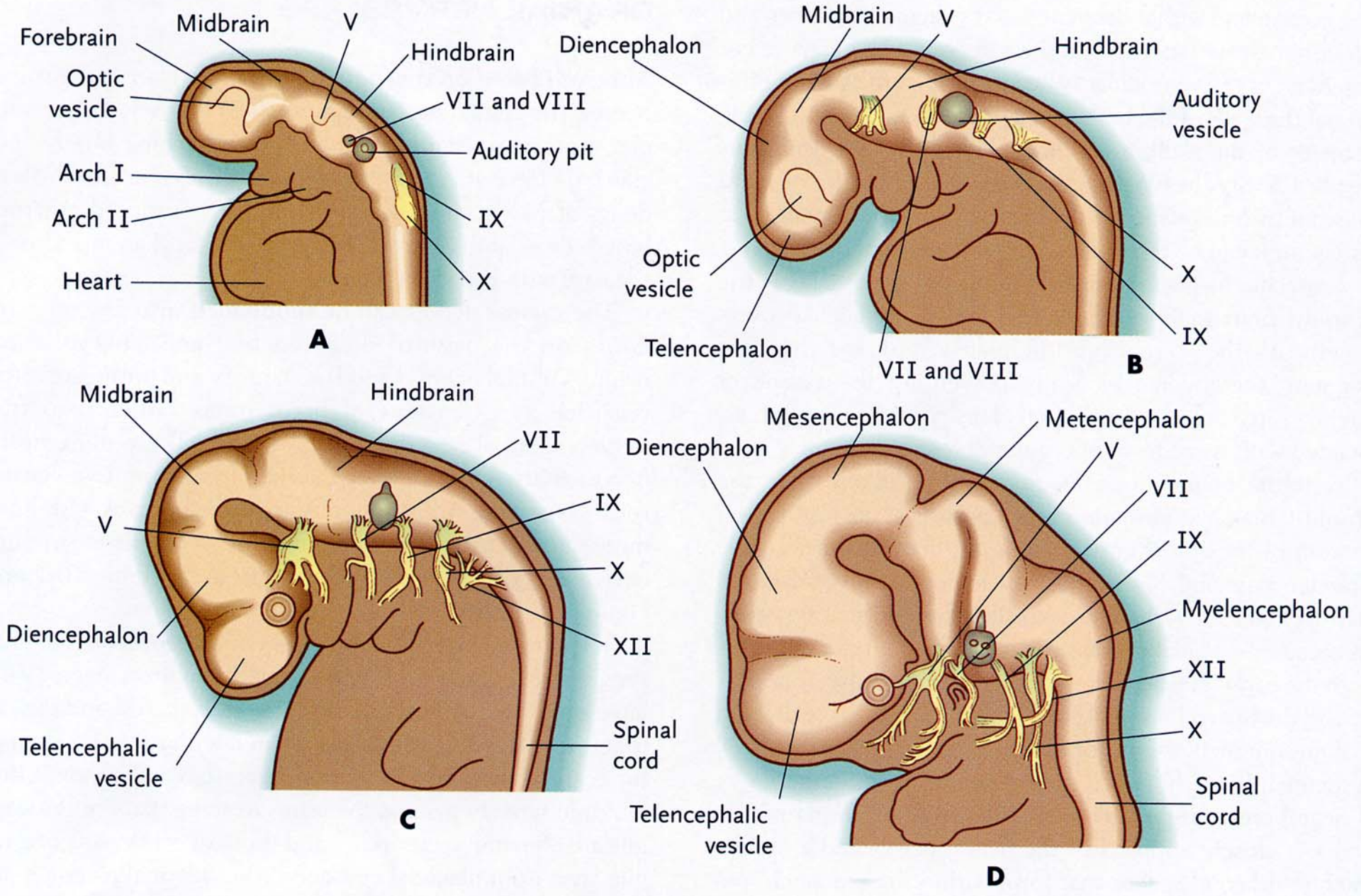
VIII – Vestibulocochlear; Metencephalon, 2 Ganglia – Acoustic, Vestibular; Sensory

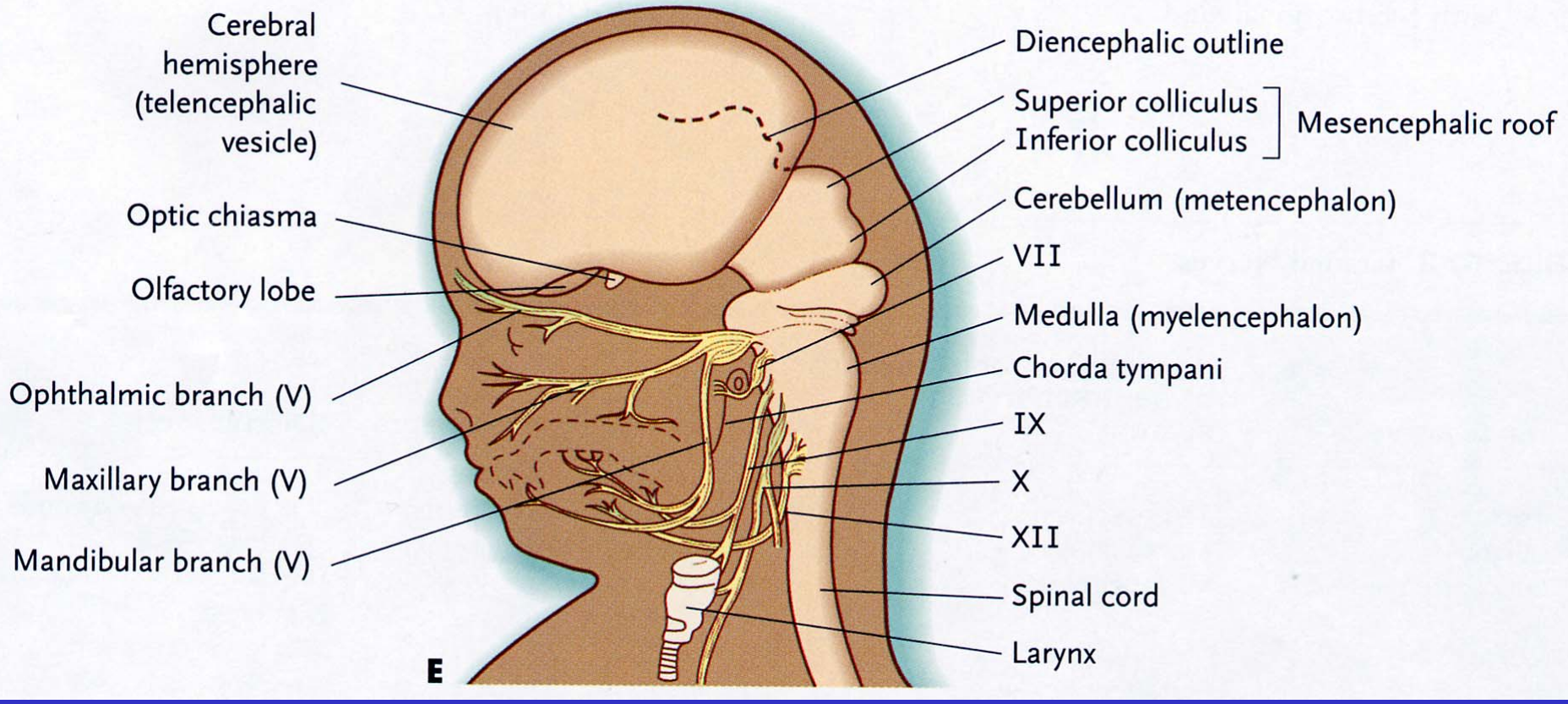
IX – Glossopharnygeal; Myelencephalon; 3 Ganglia – Superior, Inferior (Petrosal), Otic; Motor, Sensory, Parasympathetic

X – Vagus; Myelencephalon; 3 Ganglia – Superior, Inferior (Nodose), Vagal parasympathetic; Motor, Sensory, Parasympathetic

XI – Accessory; Myelencephalon; No Ganglia; Motor

XII – Hypoglossal; Myelencephalon; No Ganglia; Motor


Forebrain
Midbrain
V
Hindbrain
Optic vesicle
VII and VIII
Auditory pit
Arch I
Arch II
IX
Heart
X
A
Diencephalon
Midbrain
V
Hindbrain
Auditory vesicle
Optic vesicle
X
IX
Telencephalon
VII and VIII
B
Midbrain
Hindbrain
VII
IX
V
X
Diencephalon
XII
Telencephalic vesicle
Spinal cord
C
Mesencephalon
Metencephalon
Diencephalon
V
VII
IX
Myelencephalon
XII
X
Telencephalic vesicle
Spinal cord
D


Cerebral hemisphere (telencephalic vesicle)
Optic chiasma
Olfactory lobe
Ophthalmic branch (V)
Maxillary branch (V)
Mandibular branch (V)
Diencephalic outline
Superior colliculus
Inferior colliculus
Mesencephalic roof
Cerebellum (metencephalon)
VII
Medulla (myelencephalon)
Chorda tympani
IX
X
XII
Spinal cord
Larynx
E

Anomalies

Defective Neural Tube Closure
- Spinal Cord – Rachischisis
- Brain – Craniochisis (lethal)

Spina Bifida – Defective closure of anterior or posterior neuropore – lacking neural arch, bulging membranous sac called a Cele, containing cerebral spinal fluid +/- neural tissues

Spina bifida occulta – Defect in Neural Arch – mildest form

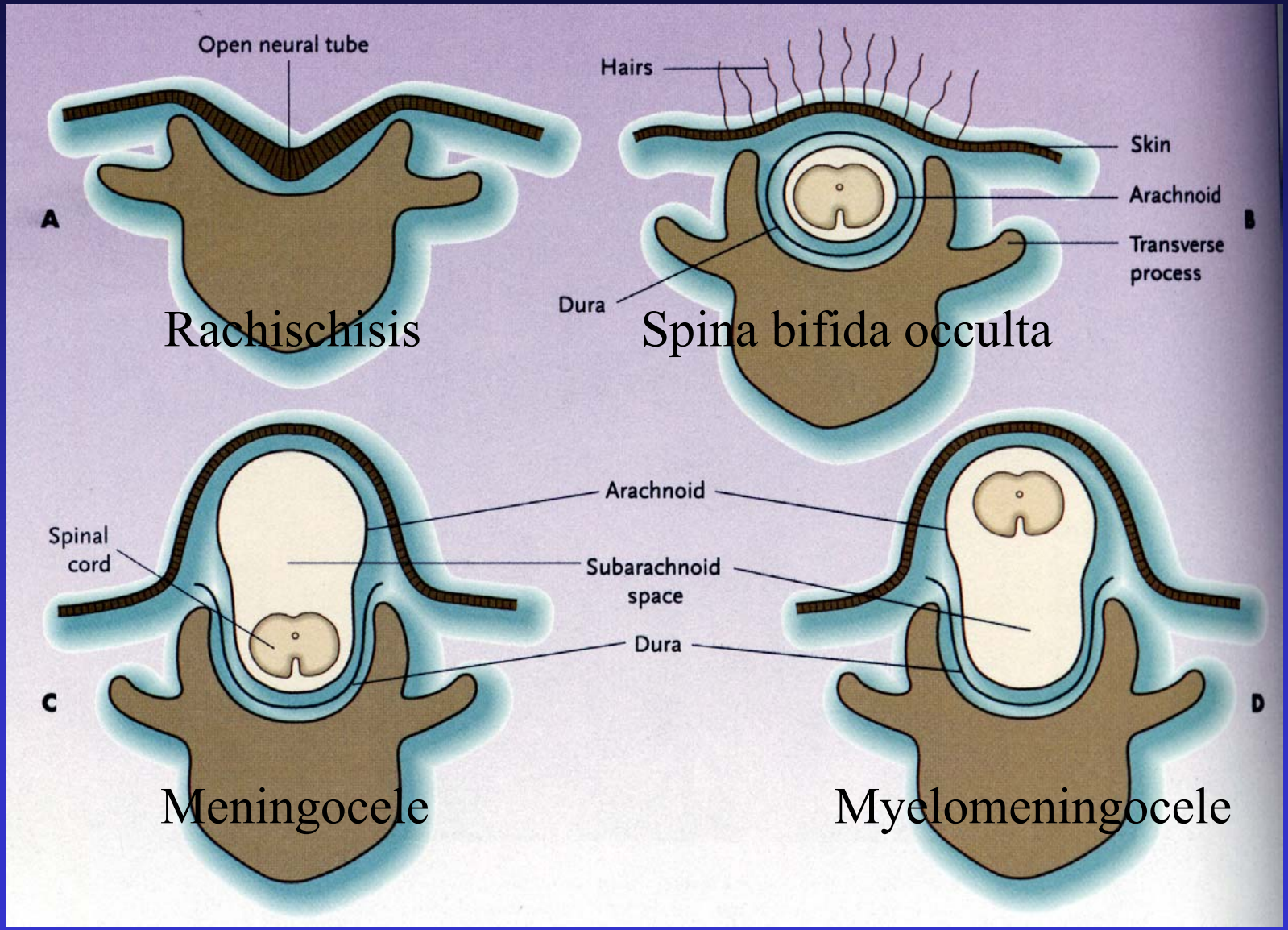
Meningocele – protruding dura and arachnoid tissues

Meningomyelocele – protruding spinal tissues

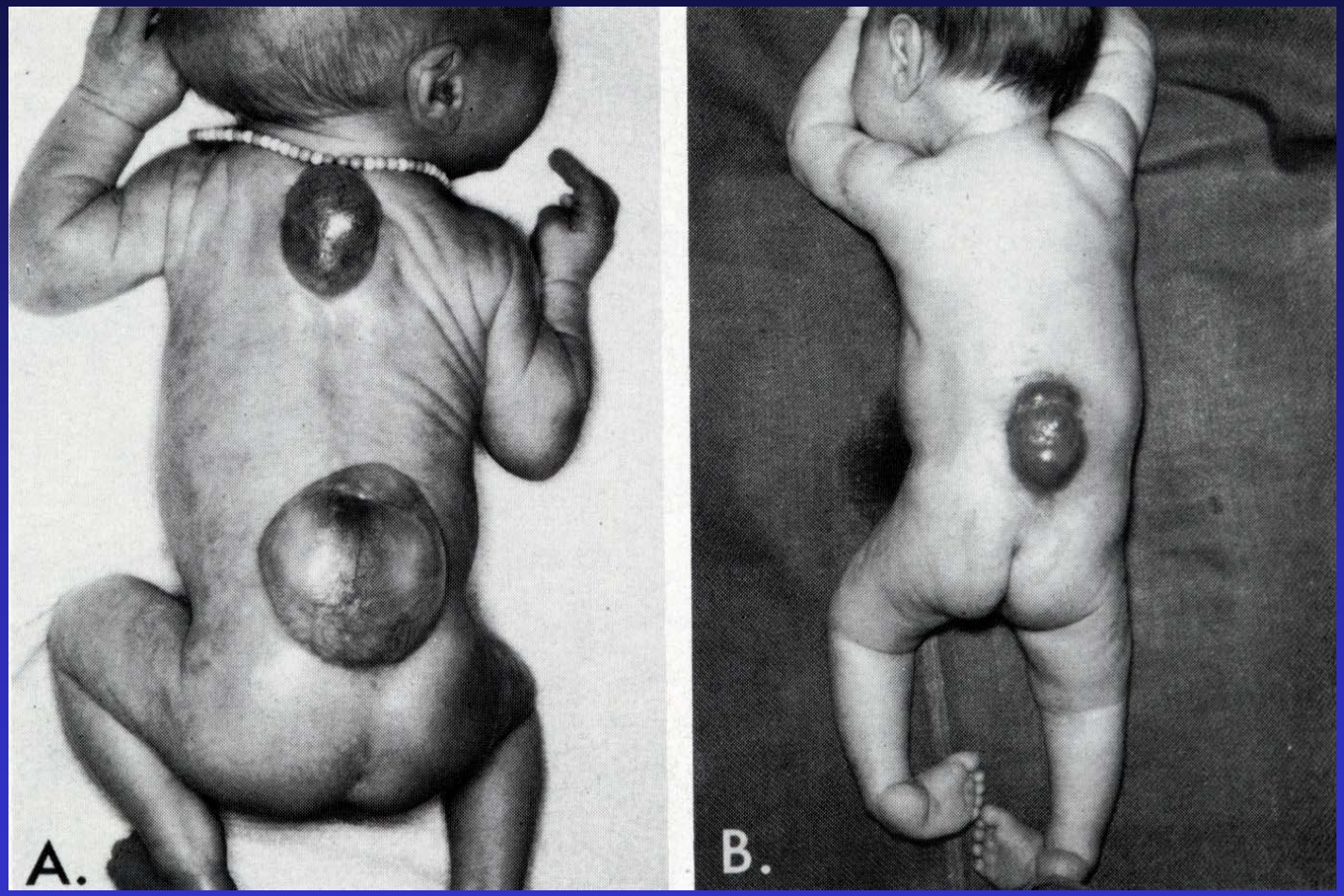
Meningoencephalocele – protruding brain tissues

Meningohydroencephalocele – protruding brain and ventricular tissues

Anomalies – Spinal Cord



Spinal Abnormalities



Spina bifida

Brain Abnormalities

microcephaly

holoprosencephaly

hydrocephaly

Early Heart Development

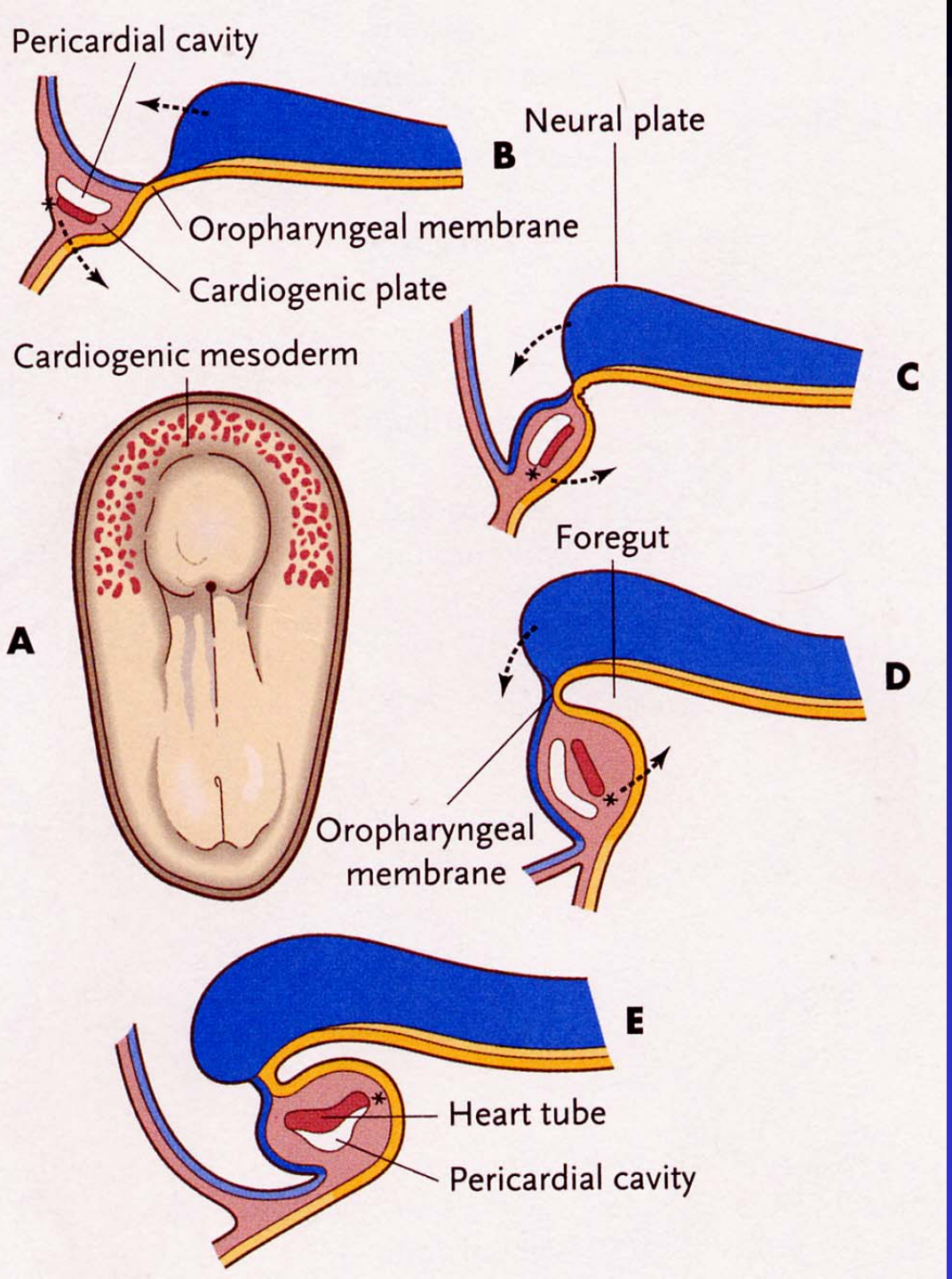
Precardiac mesoderm – horseshoe shaped extending back on both sides of the foregut

Endoderm induces early heart tissue

Mesoderm splits → somatic and splanchnic, cardiogenic plate is splanchnic and anterior to the oropharyngeal membrane

Space between somatic and splanchnic mesoderm will form pericardial cavity

180o rotation of the anterior embryo places the heart posterior to the oropharyngeal membrane


Pericardial cavity
B
Neural plate
Oropharyngeal membrane
Cardiogenic plate
Cardiogenic mesoderm
C
A
Foregut
D
Oropharyngeal membrane
E
Heart tube
Pericardial cavity

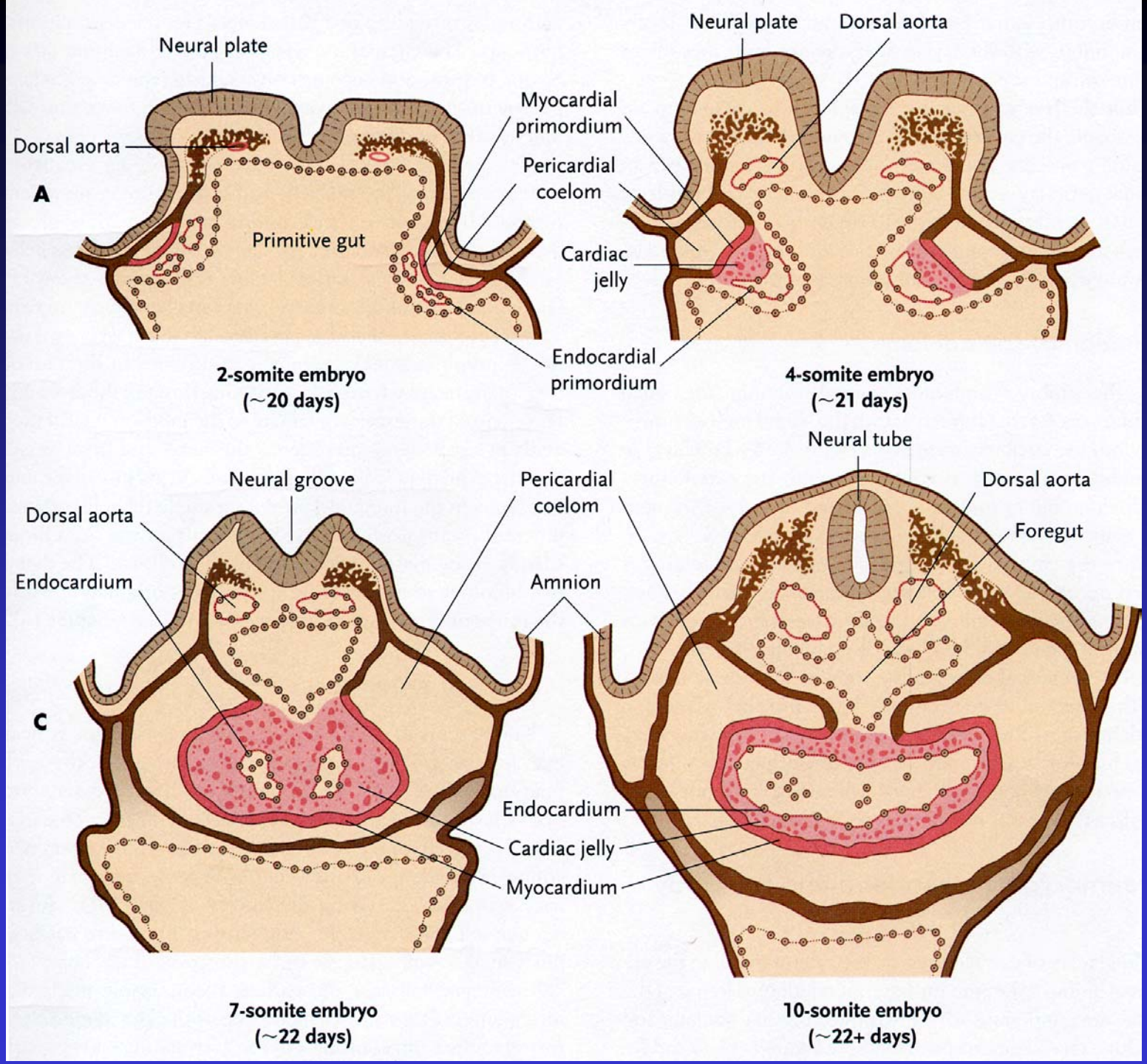
Heart Formation

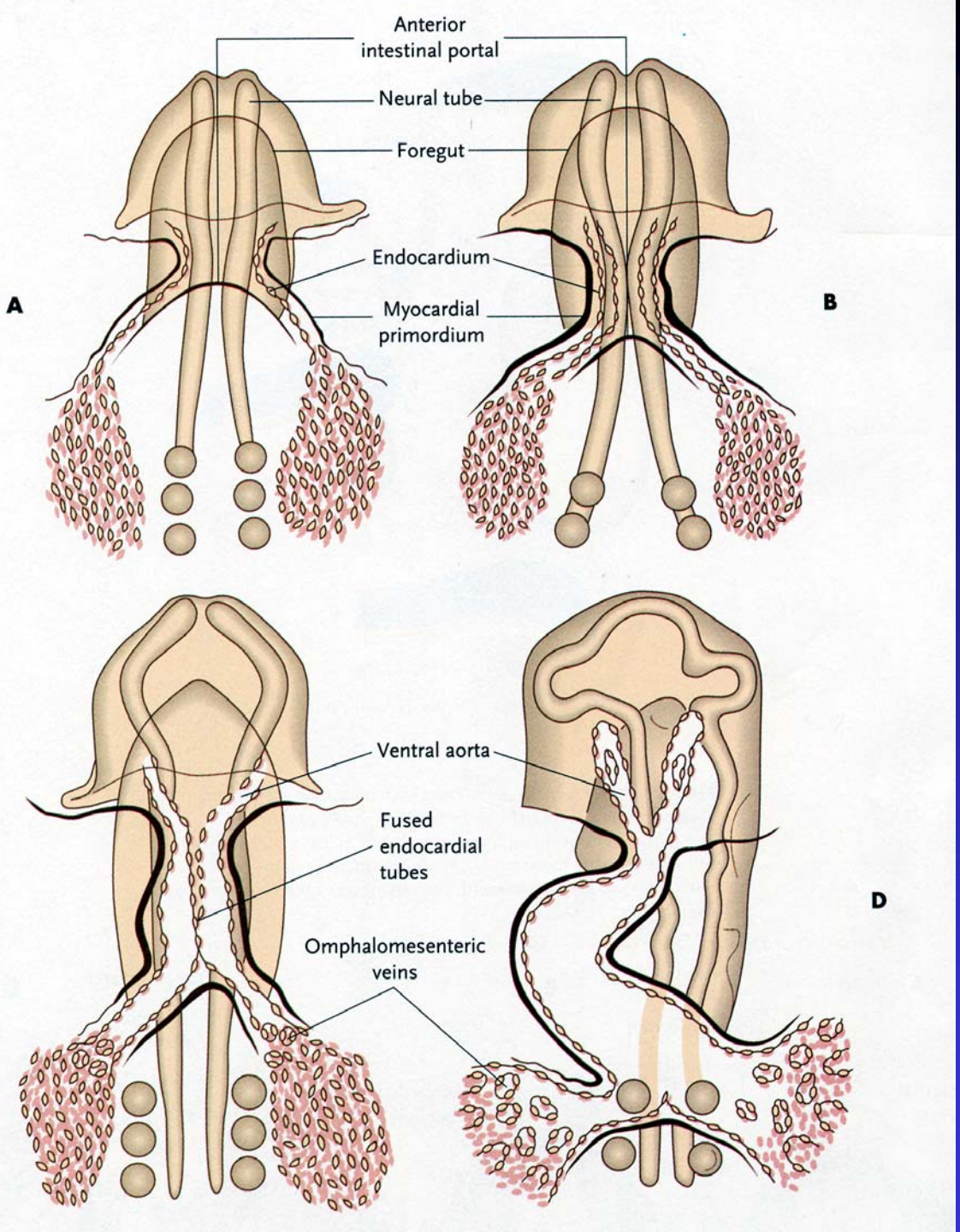
Vesicles in the pre-cardiac splanchnic mesoderm fuse to form paired endocardial primordia on both sides of the foregut

Endocardial primordia fuse along the midline to form the primitive tubular heart

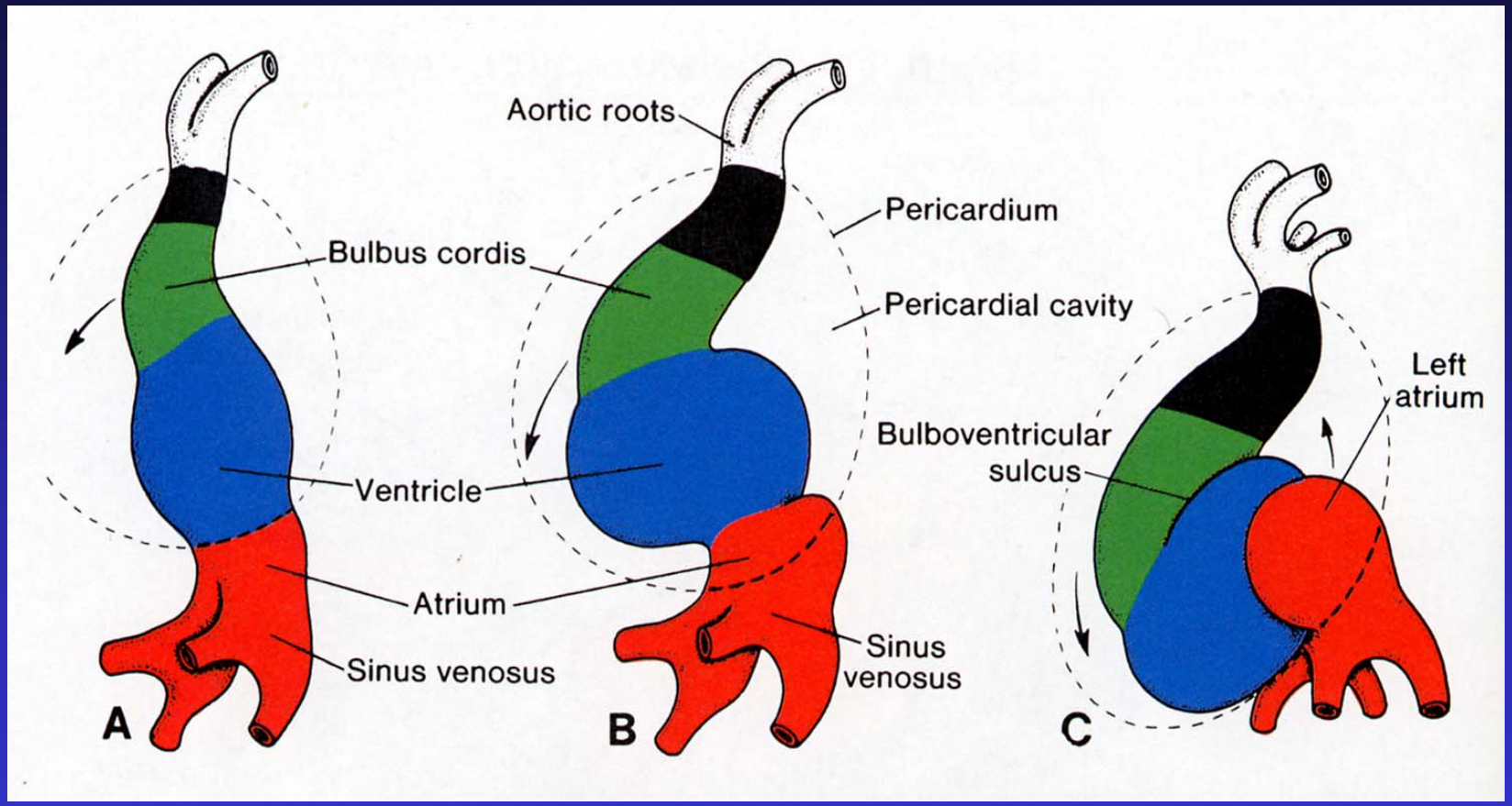
Inner endocardial lining becomes the endocardium, surrounded by matrix called cardiac jelly

Myocardium surrounds the cardiac jelly

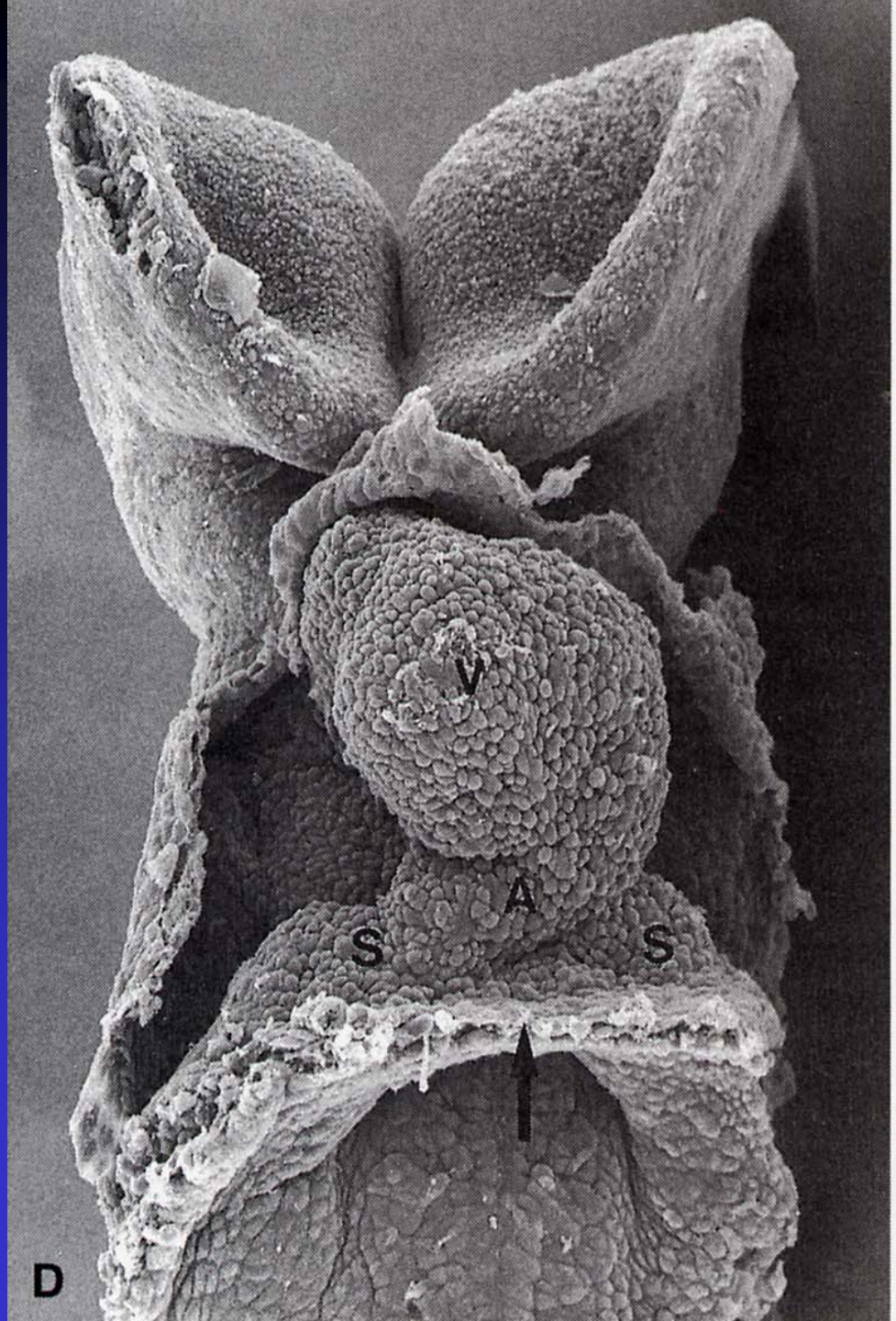

Neural plate
Dorsal aorta
A
Primitive gut
Myocardial primordium
Pericardial coelom
Cardiac jelly
Endocardial primordium
2-somite embryo (~20 days)
Neural plate
Dorsal aorta
4-somite embryo (~21 days)
Neural groove
Dorsal aorta
Endocardium
C
Pericardial coelom
Amnion
Endocardium
Cardiac jelly
Myocardium
7-somite embryo (~22 days)
Neural tube
Dorsal aorta
Foregut
10-somite embryo (~22+ days)


Anterior intestinal portal
Neural tube
Foregut
Endocardium
Myocardial primordium
A
B
Ventral aorta
Fused endocardial tubes
Omphalomesenteric veins
C
D

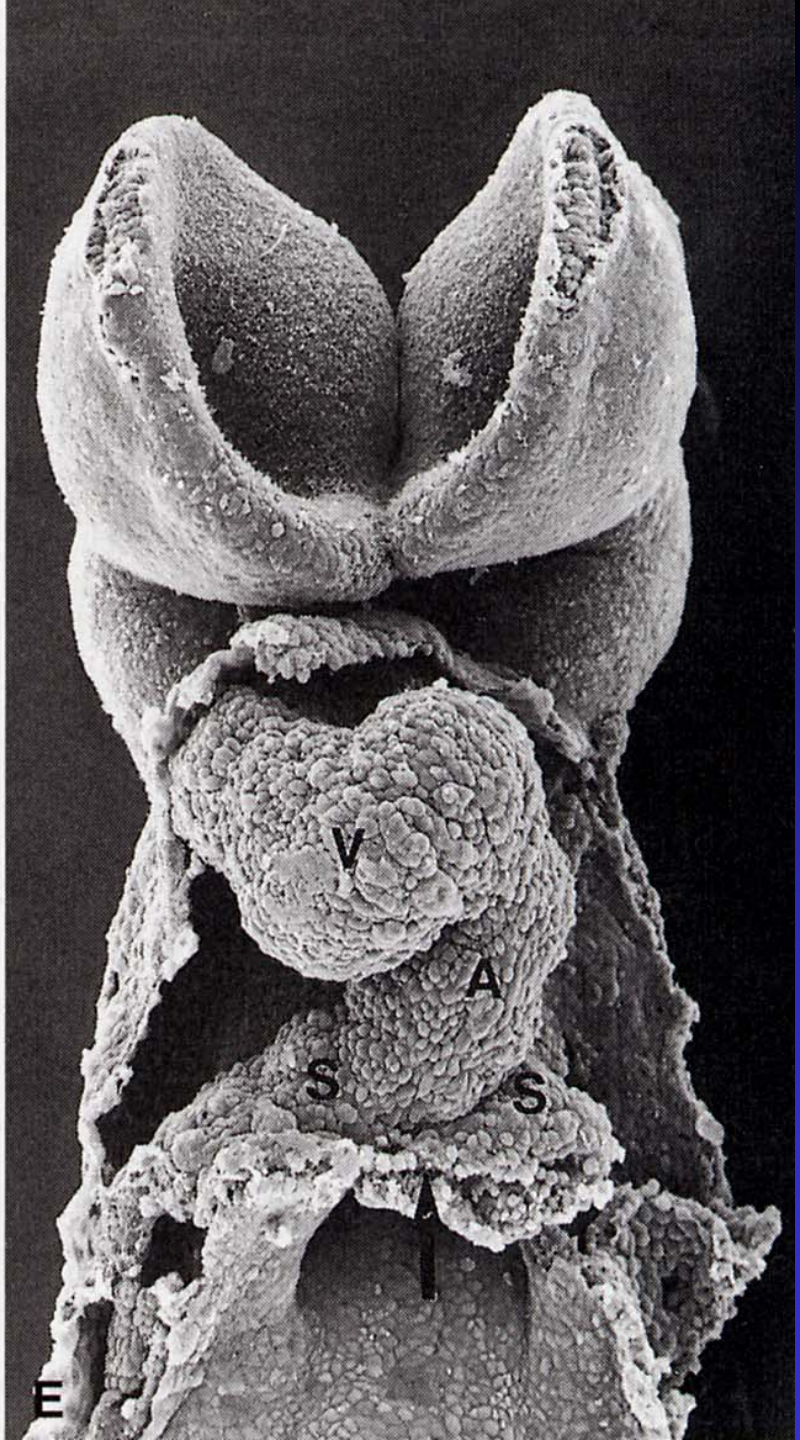
Heart Formation



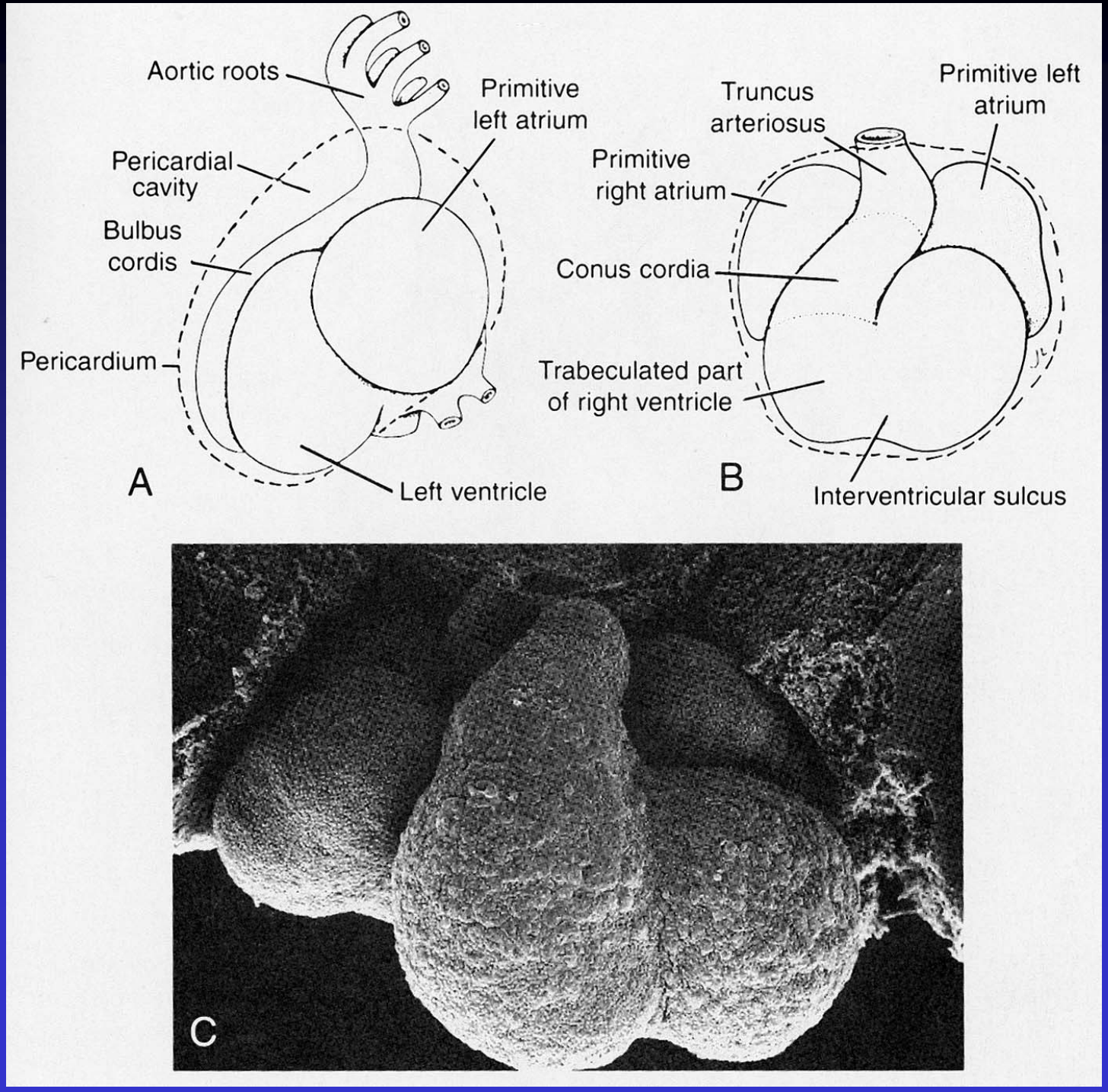
Tubular heart forms an S-shaped loop



D



E


Aortic roots
Primitive left atrium
Pericardial cavity
Bulbus cordis
Pericardium
Left ventricle
A
Truncus arteriosus
Primitive left atrium
Primitive right atrium
Conus cordia
Trabeculated part of right ventricle
Interventricular sulcus
B
C

Blood and Vessels

Blood forms from blood islands in the Yolk Sac

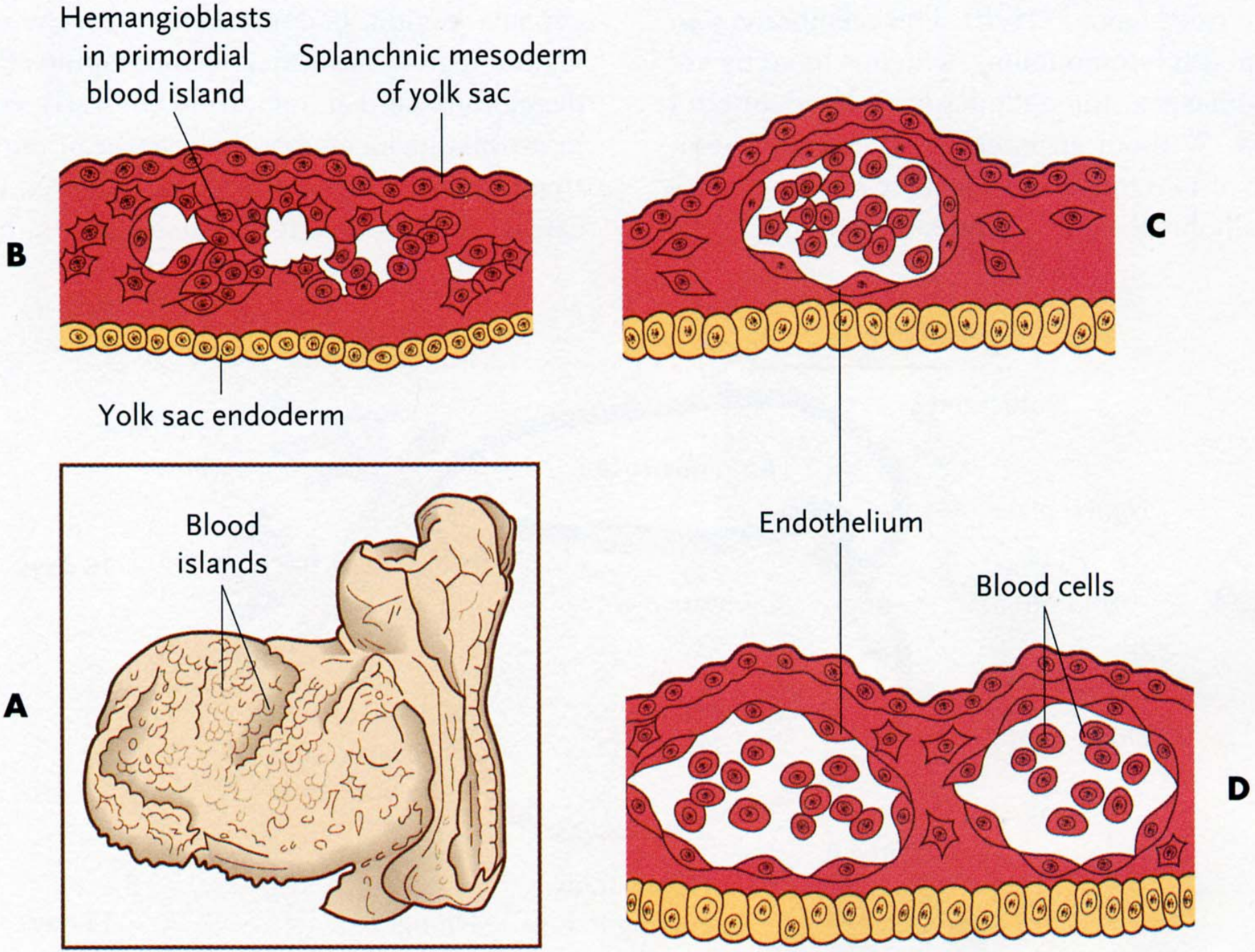
Extraembryonic splanchnic mesoderm

Induced by extraembryonic endoderm

Stem cell = hemangioblasts in the blood islands

Blood-forming cells = hemocytoblasts

Vessel forming cells = endothelial cells


Hemangioblasts in primordial blood island
Splanchnic mesoderm of yolk sac
B
Yolk sac endoderm
C
Endothelium
Blood islands
A
Blood cells
D