**Gastrulation - Cell Lineages**

- Blastocyst inner cell mass (embryoblast)
- Blastocoel
- Abembryonic pole

**Day 6**

- Blastocyst adheres to endometrium at embryo pole
- Trophoblast proliferation production of hCG (maintains corpus luteum)

- Inner cell mass → Epiblast
- Hypoblast
- Extraembryonic → Endoderm/Mesoderm

- Amnion forms from epiblast
- Cavitation – Formation of an internal space within a tissue

**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

From BM Carlson, 1999
**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**

**Bottle Cells**

First cells to go through the Streak form the Endodermal

These cells integrate and displace hypoblast cells

**Endoderm**

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**
Mesoderm

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

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 Protein 4; represses dorsal ectoderm

Noggin and Chordin – BMP4 inhibitors; de-represses ectoderm

**Æ**

**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

Paraaxial Mesoderm - Somites

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
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
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

Readings:
Chapter 5
Chapter 10
- P. 208-214
- P. 218-219 (Peripheral Nerve)
- p. 239-240 (Cranial Nerve)
Notochord induces overlying ectoderm → neural plate –
Thickening of cell layer

Anterior Inducer:
Noggin/Chordin

Posterior Inducer:
FGF-8,

Middle of third week:
Neural Plate

Notchord induces overlying ectoderm → neural plate –
Thickening of cell layer

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

Neural Crest

Early CNS Development

Neural Tube Formation

Anterior Neuropore

Central Fusion
Completion – Closure of Neuropores

Posterior

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

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

Specification and Position-Specific Gene Expression
Cephalic flexure, Cervical flexure, Pontine flexure

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
Dendrite
Cell Body
Axon
Schwann Cell
Myelin Sheath

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

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

Nerves
Motor
Sensory
Autonomic
Sympathetic
Parasympathetic
Cranial Nerves

I – Olfactory; Telencephalon; No Ganglion; Sensory
II – Optic; Diencephalon; No Ganglion; Sensory
III – Oculomotor; Mesencephalon; Ciliary 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 – Glossopharyngeal; 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
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

Spinal Abnormalities

Spina bifida

Brain Abnormalities

microcephaly
holoprosencephaly
hydrocephaly

Early Heart Development

Precordial mesoderm – horseshoe shaped extending back
  on both sides of the foregut
Endoderm induces early heart tissue
Mesoderm splits \( \rightarrow \) somatic and splanchnic, cardiogenic
  plate is splanchnic and anterior to the oropharyngeal
  membrane
Space between somatic and splanchnic mesoderm will form
  pericardial cavity
180° rotation of the anterior embryo places the heart
  posterior to the oropharyngeal membrane
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.

Tubular heart forms an S-shaped loop.
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