

sonic hedgehog gene

- ▶ produced at base of limbs in zone of polarizing activity, involved in patterning along anterior posterior axis

wnt-7 gene

- ▶ Produced at apical ectodermal ridge (thickened ectoderm at distal end of each developing limb). Necessary for proper organization along dorsal-ventral axis.

FGF gene

- ▶ Produced at apical ectodermal ridge. Stimulates mitosis of underlying mesoderm. providing for lengthening of limbs.

Homeobox gene

- ▶ Involved in segmental organization



Day 0

- ▶ Fertilization by sperm forming zygote, initiating embryogenesis

Within week 1

- ▶ Implantation (as a blastocyst).  
hGG secretion begins

Within week 2

- ▶ Bilaminar disk (epiblast, hypoblast

Within week 3

- ▶ Gastrulation.  
Primitive streak, notochord,  
and neural plate begin to form.



Weeks 3 – 8

- ▶ Organogenesis. Extremely susceptible to teratogens.  
Neural tube formed by neuroectoderm and closed by week 4.

## Week 4

- ▶ Heart begins to beat.  
Upper and lower limb buds begin to form.

## Week 8

- ▶ Fetal movement; fetus looks like a baby.

## Week 10

- ▶ Genitalia have male/female characteristics.



Alar plate (dorsal)

- ▶ Sensory, same orientation as spinal cord

Basal plate (ventral)

► Motor

Rule of 2's for 2nd week

- ▶ 2 germ layers (bilaminar disk): epiblast, hypoblast. 2 cavities: amniotic cavity, yolk sac. 2 components to placenta: cytotrophoblast, syncytiotrophoblast.

Rule of 3's for 3rd week

- ▶ 3 germ layers (gastrula): ectoderm, mesoderm, endoderm.



Rule of 4's for 4th week

- ▶ 4 heart chambers. 4 limb buds grow.

Surface ectoderm

- ▶ Adenohypophysis ( from Rathke's pouch); lens of eye; epithelial linings of skin, ear, eye, and nose; epidermis. retina, and olfactory epithelium, salivary, sweat, and mammary glands.

## Neuroectoderm

- ▶ Neurohypophysis, CNS neurons, oligodendrocytes, astrocytes, ependymal cells, pineal gland.  
retina, spinal cord , think CNS and brain.

Neural crest

- ▶ ANS, dorsal root ganglia, melanocytes, chromaffin cells of adrenal medulla, enterochromaffin cells, pia and arachnoid, celiac ganglion, Schwann cells, odontoblasts, parafollicular (C) cells of thyroid, laryngeal cartilage, bones of the skull.  
cranial nerves, celiac ganglion  
Neural crest-think PNS and non-neural structures nearby.  
Odonto = teeth, Think Crest toothpaste.



cranipharyngioma

- ▶ benign Rathke's pouch tumor with cholesterol crystals, calcifications.

Endoderm

- ▶ Gut tube epithelium and derivatives (e.g., lungs, liver, pancreas, thymus, parathyroid, thyroid follicular cells).

Mesoderm

- ▶ Muscle, bone, connective tissue, serous linings of body cavities (e.g., peritoneum), spleen (derived from foregut mesentery), cardiovascular structures, lymphatics, blood, urogenital structures. Kidneys, adrenal cortex. Notochord induces ectoderm to form neuroectoderm (neural plate). Its postnatal derivative is the nucleus pulposus of the intervertebral disk.

## Teratogens

- ▶ Most susceptible in 3rd – 8th weeks (organogenesis) of pregnancy.  
Before week 3: all-or-none effects. After week 8: growth and function affected.



AGE inhibitors

- ▶ Renal damage

Alcohol

- ▶ Leading cause of birth defects and mental retardation; fetal alcohol syndrome

Alkylating agents

- ▶ Absence of digits, multiple anomalies

## Aminoglycosides

- ▶ CNVIII toxicity



CoCaine

- ▶ Abnormal fetal development and fetal addiction; placental abruption

Diethylstilbestrol (DES)

- ▶ Vaginal clear cell adenocarcinoma

Iodide

- ▶ Congenital goiter or hypothyroidism

Lithium

- ▶ Ebstein's anomaly (atrialized right ventricle)



Maternal diabetes

- ▶ Caudal regression syndrome  
(anal atresia to sirenomelia)

Smoking (nicotine. GO)

- ▶ Preterm labor, placental problems, IUGR, ADHD

## Tetracyclines

- ▶ Discolored teeth

## Thalidomide

- ▶ Limb defects ("flipper" limbs)



Valproate

- ▶ inhibition of intestinal folate absorption

Vitamin A (excess)

- ▶ Extremely high risk for spontaneous abortions and birth defects (cleft palate, cardiac abnormalities)

Warfarin

- ▶ Bone deformities, fetal hemorrhage, abortion

X-rays, anticonvulsants

- ▶ Multiple anomalies



Fetal alcohol syndrome

- ▶ Leading cause of congenital malformations in the United States. Newborns of mothers who consumed significant amounts of alcohol during pregnancy have an ↑ incidence of congenital abnormalities, including pre- and postnatal developmental retardation, microcephaly, facial abnormalities, limb dislocation, and heart and lung fistulas. Mechanism may include inhibition of cell migration.

Monozygotic

- ▶ 1 zygote splits evenly to develop 2 amniotic sacs with a single common chorion and placenta.  
Conjoined twins have 1 chorion, 1 amniotic sac.

Dizygotic (fraternal) or monozygotic

- ▶ Monozygotes that split early develop 2 placentas (separate/ttised), chorions, and amniotic sacs. Dizygotes develop individual placentas, chorions, and amniotic sacs.

Fetal component

- ▶ Cytotrophoblast composes the inner layer of chorionic villi. Cyto makes Cells. Syncytiotrophoblast is the outer layer and secretes hCG ( structurally similar to LH ; stimulates corpus luteum to secrete progesterone during first trimester).



Maternal component

- ▶ Decidua basalis derived from the endometrium.  
maternal blood in lacunae.

2 umbilical arteries,

- ▶ return deoxygenated blood from fetal internal iliac arteries to placenta,

1 umbilical vein,

- ▶ supplies oxygenated blood from the placenta to the fetus.

Single umbilical artery

- ▶ associated with congenital and chromosomal anomalies.  
Umbilical arteries and veins are derived from allantois.



3rd week—yolk sac forms allantois,

- ▶ Allantois extends into urogenital sinus. Allantois becomes urachus. a duct between bladder and yolk sac.

Failure of urachus to obliterate:

- ▶ 1. Patent urachus —urine discharge from umbilicus 2. Vesicourachal diverticulum — outpouching of bladder

7th week —obliteration of vitelline duct

- ▶ omphalomesenteric duct. Connects yolk sac to midgut lumen.

## Vitelline fistula

- ▶ failure of duct to close — > meconium discharge from umbilicus. Examples: Meckel's diverticulum—partial closure. with patent portion attached to ileum. May have ectopic gastric mucosa — > melena and RUQ pain.



Truncus arteriosus (TA)

- ▶ Ascending aorta and pulmonary trunk

Bulbus cordis

- ▶ Right ventricle and smooth parts  
(outflow tract) of left and right ventricle

Primitive ventricle

- ▶ Portion of the left ventricle

Primitive atria

- ▶ Trabeculated left and right atrium



left horn of sinus venosus (SV)

- ▶ coronary sinus

Right horn of SV

- ▶ Smooth part of right atrium

Right common cardinal vein and right anterior cardinal vein

► SVC

Truncus arteriosus

- ▶ Neural crest migration — > divide trunk into 2 arteries via fusion and twisting of truncal and bulbar ridges — > ascending aorta and pulmonary trunk.  
Pathology—transposition of great vessels + tetralogy of Fallot.



Interventricular septum development

- ▶ 1. Muscular ventricular septum forms. Opening is called the interventricular foramen.
- 2. The aorticopulmonary septum divides the TA into the aortic and pulmonary trunks.
- 3. The aorticopulmonary septum meets and fuses with the muscular ventricular septum to form the membranous interventricular septum, closing the interventricular foramen.

Interatrial septum development

- ▶ 1. Foramen primum narrows as the septum primum grows toward the endocardial cushions.
- 2. Perforations in the septum primum form the foramen secundum as the foramen primum disappears.
- 3. The foramen secundum maintains the right-to-left shunt as the septum secundum begins to grow.
- 4. The septum secundum contains a permanent opening called the foramen ovale.
- 5. The foramen secundum enlarges and the upper part of the septum primum ovale degenerates.
- 6. The remaining portion of the septum primum is now called the valve of the foramen

Fetal erythropoiesis occurs in:

- ▶ 1. Yolk sac (3 – 8 wk) 2. Liver (6 – 30 wk) 3. Spleen (9 – 28 wk)
- 4. Bone marrow (28 wk onward)

Young Liver Synthesizes Blood.

Fetal hemoglobin =  $\alpha^2\gamma^2$ . Adult hemoglobin =  $\alpha^2\beta^2$ .

Blood in umbilical vein

- ▶ 80% saturated with O<sub>2</sub>.



Umbilical arteries

- ▶ low O<sub>2</sub> saturation.

3 important shunts in fetus

- ▶ 1. Blood entering the fetus through the umbilical vein is conducted via the ductus venosus into the IVC to bypass the hepatic circulation.
- 2. Most oxygenated blood reaching the heart via the IVC is diverted through the foramen ovale and pumped out the aorta to the head and body.
- 3. Deoxygenated blood from the SVC is expelled into the pulmonary artery and ductus arteriosus to the lower body of the fetus.

infant take a breath

- ▶ ↓ resistance in pulmonary vasculature causes ↑ left atrial pressure vs. right atrial pressure; foramen ovale closes (now called fossa ovalis); ↑ in O<sub>2</sub> leads to ↓ in prostaglandins, causing closure of ductus arteriosus.

Indomethacin

- ▶ close PDA.



## Prostaglandins

- ▶ keep PDA open.

Umbilical vein –

- ▶ ligamentum teres hepatis

Umbilical arteries

- ▶ medial umbilical ligaments

Ductus arteriosus

- ▶ ligamentum arteriosum



Ductus venosus

- ▶ ligamentum venosum

Foramen ovale

- ▶ fossa ovalis

AllaNtois — urachus —

- ▶ median umbilical ligament

Notochord –

- ▶ nucleus pulposus of intervertebral disk



1st aortic arch derivatives

- ▶ part of Maxillary artery ( branch of external carotid). 1st arch is Maximal.

2nd aortic arch derivatives

- ▶ Stapedial artery and hyoid artery.

3rd –

- ▶ common Carotid artery and proximal part of internal carotid artery. C is 3rd letter of alphabet.

4th –

- ▶ on left, aortic arch; on right, proximal part of right subclavian artery. 4th arch (4 limbs) = systemic.



6th —

- ▶ proximal part of pulmonary arteries and (on left only) ductus arteriosus. 6th arch = pulmonary and the pulmonary-to-systemic shunt (ductus arteriosus).

presencephalon

- ▶ Telencephalon, diecephalon.

cerebral hemispheres

- ▶ lateral ventricles

Thalamis etc

- ▶ 3rd ventricle



Maternal component

► medibrain

rhombencephalon

- ▶ metencephalon and myelencephalon

metencephalon

- ▶ pons and cerebellum

myelencephalon

- ▶ medulla



Neuropores fail to fuse (4th week)

- ▶ persistent connection between amniotic cavity and spinal canal. Associated with low folic acid intake during pregnancy. Elevated  
a-fetoprotein (AFP) in amniotic fluid and maternal serum.  
increase AFP + acetylcholinesterase in CSF.

Spina bifida occulta—

- ▶ failure of bony spinal canal to close, but no structural herniation. Usually seen at lower vertebral levels. Dura is intact

## Meningocele

- ▶ meninges herniate through spinal canal defect

## Myelomeningocele

- ▶ meninges and spinal cord herniate through spinal canal defect



## Anencephaly

- ▶ Malformation of anterior end of neural tube; no brain and calvarium, elevated AFP, polyhydramnios (no swallowing center in brain).

## Holoprosencephaly

- ▶ decrease separation of hemispheres across midline: results in cyclopia; associated with Patau's syndrome, severe fetal alcohol syndrome, and cleft lip/palate.

Arnold-chiari type II—

- ▶ cerebellar tonsillar herniation through foramen magnum with aqueductal stenosis and hydrocephaly.often presents with syringomyelia, thoracolumbar myelomeningocel.

Dandy-Walker

- ▶ large posterior fossa; absent cerebellar vermis with cystic enlargement of 4th ventricle. Can lead to hydrocephalus and spina bifida



## Syringomyelia

- ▶ enlargement of the central canal of spinal cord. Crossing fibers of spinothalamic tract are typically damaged first. "Cape-like," bilateral loss of pain and temperature sensation in upper extremities with preservation of touch sensation. Syringomyelia (Greek) = tube, as in syringe. Often presents in patients with Arnold-Chiari II malformation. Most common at C8-T1.

## Branchial apparatus

- ▶ Composed of branchial clefts, arches, and pouches.  
Also called pharyngeal apparatus.

Branchial clefts

- ▶ derived from ectoderm, also called branchial grooves.  
Also called branchial grooves.

Branchial arches

- ▶ derived from mesoderm ( muscle and arteries) and neural crests( bones and cartilage).



Branchial pouches

- ▶ derived from endoderm

CAP covers outside from inside

- ▶ Clefts = ectoderm, Arches = mesoderm, Pouches = endoderm

Branchial arch 1 derivatives

- ▶ Meckel's cartilage: Mandible, Malleus, incus, sphenomandibular ligament. Muscles: Muscles of Mastication (temporalis, Masseter, lateral and Medial pterygoids), Mylohyoid, anterior belly of digastric, tensor tympani, tensor veli palatini, anterior 2/3 of tongue. Nerve: CN V2 and CN V3.

Branchial arch 2 derivatives

- ▶ Reichert's cartilage: Stapes, Styloid process, lesser horn of hyoid, Stylohyoid ligament. Muscles: muscles of facial expression, Stapedius, Stylohyoid, posterior belly of digastric. Nerve: CN VII.



Branchial arch 3 derivatives

- ▶ Cartilage: greater horn of hyoid. Muscle: stylopharyngeus.  
Nerve: CN IX.

Branchial arches 4 – 6 derivatives

- ▶ Cartilages: thyroid, cricoid, arytenoids, corniculate, cuneiform.  
Muscles (4th arch): most pharyngeal constrictors, cricothyroid, levator veli palatini.  
Muscles (6th arch): all intrinsic muscles of larynx except cricothyroid.  
Nerve: 4th arch — CN X (superior laryngeal branch); 6th arch — CN X (recurrent laryngeal branch).

Arch 1 derivatives supplied

- ▶ CN V2 and V3.

Arch 2 derivatives

- ▶ CN VII.



Arch 3

- ▶ CN IX.

Arch 4 and 6 derivatives

- ▶ by CN X.

## Branchial arch innervation

- ▶ These Cns are the only ones with both .sensory and motor components (except V2. which is sensory only). Think of arches in terms of actions-chewing 1) facial expression (2l. Stylopharyngeus (3), swallowing (4), speaking (6i

1st cleft develops into

- ▶ external auditory meatus.



2nd through 4th clefts form

- ▶ temporary cervical sinuses, which are obliterated by proliferation of 2nd arch mesenchyme.

Persistent cervical sinus

- ▶ branchial cleft cvst within lateral neck.

1st pouch develops into

- ▶ middle ear cavity, eustachian tube, mastoid air cells.  
1st pouch contributes to endoderm-lined structures of ear.

2nd pouch develops into

- ▶ epithelial lining of palatine tonsil.



3rd pouch (dorsal wings) develops into

- ▶ inferior parathyroids. 3rd pouch contributes to 3 structures (thymus, left and right inferior parathyroids).

3rd pouch (ventral wings) develops into

► thymus.

4th pouch (dorsal wings) develops into

- ▶ superior parathyroids

Aberrant development of 3rd and 4th pouches

- ▶ DiGeorge syndrome → leads to T-cell deficiency (thymic aplasia) and hypocalcemia (failure of parathyroid development).



MEN 2A:

- ▶ mutation of germline RET(neural crest cells). —Adrenal medulla (pheochromocytoma). —Parathyroid (tumor): 3rd/4th pharyngeal pouch. —Parafollicular cells (medullary thyroid cancer): 4th/5th pharyngeal pouch

1st arch

- ▶ Malleus/incus  
Tensor tympani (V3)

2nd arch

- ▶ Stapes  
Stapedius (VII)

1st cleft

- ▶ [external auditory meatus



1st branchial membrane

- ▶ Tympanic membrane

1st pouch

- ▶ Eustachian tube, middle ear cavity. mastoid air cells

## Tongue development

- ▶ 1st branchial arch forms anterior: A (thus sensation via CN V „ taste via CN VII).
- 3rd and 4th arches form posterior A (thus sensation and taste mainly via CN IX, extreme posterior via CN X).
- Motor innervation is via CN XII. Muscles of the tongue are derived from occipital myotomes.
- Taste - CN VII, IX, X (solitary nucleus). Pain - CN V3, IX, X.
- Motor - CN XII.

## Thyroid development

- ▶ Thyroid diverticulum arises from floor of primitive pharynx, descends into neck. Connected to tongue by thyroglossal duct, which normally disappears but may persist as pyramidal lobe of thyroid. Foramen cecum is normal remnant of thyroglossal duct. Most common ectopic thyroid tissue site is the tongue. Thyroglossal duct cyst in midline neck and will move with swallowing (vs. persistent cervical sinus leading to branchial cyst in lateral neck).



Cleft lip

- ▶ failure of fusion of the maxillary and medial nasal processes (formation of 1° palate).

Cleft palate

- ▶ failure of fusion of the lateral palatine processes, the nasal septum, and/or the median palatine process (formation of 2° palate).

## Diaphragm embryology

- ▶ Diaphragm is derived from: 1. Septum transversum==central tendon 2. Pleuroperitoneal folds 3. Body wall 4. Dorsal mesentery of esophagus = crura  
Several Parts Build Diaphragm.

“C3, 4, 5 keeps the diaphragm alive.”

- ▶ Diaphragm descends during development but maintains innervation from above C3 – C5.

Abdominal contents may herniate into the thorax because of incomplete development (diaphragmatic hernia) → hypoplasia of thoracic organs due to space compression, scaphoid abdomen, cyanosis.



Foregut

- ▶ pharynx to duodenum

Midgut –

- ▶ duodenum to transverse colon

Hindgut

- ▶ – distal transverse colon to rectum

Developmental defects of anterior abdominal wall due to failure of

- ▶ -Rostral fold closure: sternal defects —Lateral fold closure: omphalocele, Gastroschisis —Caudal fold closure: bladder exstrophy



## Duodenal atresia

- ▶ failure to recanalize (trisomy 21),

jejunal, ileal, colonic atresia

- ▶ due to vascular  
accident (apple peel atresia),

6th week—

- ▶ midgut herniates through umbilical ring - rapid growth

10th week

- ▶ return to abdominal cavity- + rotate around SMA

Pathology—intestinal obstruction, twisting around SMA (volvulus).



## Gastroschisis

- ▶ – failure of lateral body folds to fuse → extrusion of abdominal contents through abdominal folds.

Omphalocele —

- ▶ persistence of herniation of abdominal contents into umbilical cord.  
covered by peritoneum

## Tracheoesophageal fistula

- ▶ Abnormal connection between esophagus and trachea. Most common subtype is blind upper esophagus with lower esophagus connected to trachea, Results in cyanosis, choking and vomiting with feeding, air bubble on CXR, and polyhydramnios.

Congenital pyloric stenosis

- ▶ Hypertrophy of the pylorus causes obstruction. Palpable "olive" mass in epigastric region and nonbilious projectile vomiting at  $\approx$  2 weeks of age. Treatment is surgical incision. Occurs in 1/600 live births, often in 1st-born males.



Pancreas is derived from

- ▶ the foregut. Ventral pancreatic bud becomes pancreatic head, uncinuate process (lower half of head), and main pancreatic duct. Dorsal pancreatic bud becomes everything else (body, tail, isthmus, and accessory pancreatic duct).

## Annular pancreas

- ▶ ventral pancreatic bud abnormally encircles 2nd part of duodenum; forms a ring of pancreatic tissue that may cause duodenal narrowing.

Pancreas divisum

- ▶ ventral and dorsal parts fail to fuse at 8 weeks.

Spleen arises from

- ▶ arises from dorsal mesentery (hence is mesodermal) but is supplied by artery of foregut (celiac artery).



## Pronephros

- ▶ week 4; then degenerates

## Mesonephros

- ▶ functionous as interim kidney for 1st trimester; later contributes to male genital system

## Metanephros

- ▶ permanent; beginnings first appear during 5th week of gestation;  
nephrogenesis continues through 32-36 weeks of gestation

Ureteric bud

- ▶ derived from caudal end of mesonephros; gives rise to ureter, pelvises, and, through branching, calyces and collecting ducts; fully canalized by 10th week



Metanephric mesenchyme

- ▶ ureteric bud interacts with this tissue; interaction induces differentiation and formation of glomerulus and renal tubules to distal convoluted tubule

Uteropelvic junction with kidney-

- ▶ last to canalize -» most common site of obstruction (hydronephrosis) in fetus.

Potter's syndrome

- ▶ Bilateral renal agenesis —\* oligohydramnios — > limb deformities, facial deformities, pulmonary hypoplasia. Caused by malformation of ureteric bud.  
Babies who can't "Pee" in utero develop Potter's.

Horseshoe kidney

- ▶ Inferior poles of both kidneys fuse. As they ascend from pelvis during fetal development, horseshoe kidneys get trapped under inferior mesenteric artery and remain low in the abdomen. Kidney functions normally. Note: horseshoe kidney (partial fusion) vs, cake kidney (complete fusion).



female

- ▶ Default development, Mesonephric duct degenerates and paranmesonephric duct develops.

Male

- ▶ SRY gene on Y chromosome codes for testis-determining factor. Mullerian inhibiting substance secreted by testes (Sertoli cells) suppresses development of paramesonephric ducts. Increase androgens (Leydig cells) — > development of mesonephric ducts.

Mesonephric (wolffian) duct

- ▶ Develops into male internal structures (except prostate) — Seminal vesicles, Epididymis, Ejaculatory duct, and Ductus deferens. SEED.

Paramesonephric (müllerian) duct

- ▶ Develops into fallopian tube, uterus, and up 1/3 of vagina.



Bicornuate uterus

- ▶ Results from incomplete fusion of the paramesonephric ducts. Associated with urinary tract abnormalities and infertility.

Genital tubercle

- ▶ Glans penis  
Glans clitoris

Urogenital sinus

- ▶ Corpus spongiosum
- Vestibular bulbs

Urogenital sinus

- ▶ Bulbourethral glands (of Cowper)  
Greater vestibular glands(of Bartholin)



Urogenital sinus

- ▶ Prostate gland
  - Urethral and paraurethral glands (of Skene)

Urogenital folds

- ▶ Ventral shaft of penis (penile urethra)
- Labia minora

Labioscrotal swelling

- ▶ Scrotum
- ▶ Labia majora

# Hypospadias

- ▶ abnormal opening of penile urethra on inferior (ventral) side of penis due to failure of urethral folds to close.  
Hypospadias is more common than epispadias. Fix hypospadias to prevent UTIs.  
Hypo is below.