

Marcello Cherchi's notes on

EMBRYOLOGY

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(Please let me know of any errors! mherc1@uic.edu)

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FERTILIZATION and development of the BLASTOCYST (Lec. 1, 2)

DAY 1:

Fertilization occurs at the ampulla (SA 48).

DAY 2:

Two-cell stage at 30 hours after fertilization (SA 34).

Four-cell stage at 40 hours after fertilization (SA 34).

DAY 3:

Morula (SA 34).

DAY 4:

Early blastocyst.

DAY 5:

Late blastocyst (SA 35).

Inner cell mass (or embryoblast) = group of cells at the pole towards the uterine lining.

Trophoblast (or outer cell mass) = outer sphere of cells. (Will differentiate into cytotrophoblast and syncytiotrophoblast.)

Blastocyst cavity (or blastocoele) = hollow space within trophoblast.

DAY 6:

Blastocyst has implanted itself on the endometrial surface of the uterus (SA 36) and trophoblast cells begin to penetrate the uterine epithelium (SA 35).

DAY 8: (SA 41-2)

Blastocyst is partially embedded in the endometrial stroma (SA 41).

Amniotic cavity forms in the epiblast.

Inner cell mass has differentiated into two layers which constitute the **bilaminar disc**:

- 1) **Epiblast layer**
- 2) **Hypoblast layer**

Trophoblast has differentiated into:

- 1) **Syncytiotrophoblast** = outer, multinucleated zone at the juncture between the blastocyst and the endometrial stroma.
- 2) **Cytotrophoblast** = inner layer of mononucleated cells.

Blastocyst cavity

DAY 9: (SA 43)

The blastocyst is almost entirely embedded in the uterine lining, and a **closing plug** (or fibrin coagulum) fills in the remaining gap.

Trophoblastic **lacunae** appear. Enlarged blood vessels appear in the endometrial lining.

The blastocyst cavity is now called the **primitive yolk sac** (or exocoelomic cavity). Its inner side is lined by the **exocoelomic (Heuser's) membrane**.

DAY 12: (SA 44)

The primitive yolk sac is now known as the **exocoelomic cavity**.

Endoderm cells line the inside of the primitive yolk sac in the hemisphere towards the uterus.

Extraembryonic endoderm develops between the trophoblast externally and the amnion and exocoelomic membrane internally.

Large cavities develop in the extraembryonic endoderm and when they become confluent, they form a space called the **extraembryonic coelom**.

The trophoblastic lacunae enlarge. The enlarging blood vessels become **maternal sinusoids**, which establish the **uteroplacental circulation**.

DAY 13: (SA 45-7)

The hypoblast produces additional cells that migrate along the inside of the exocoelomic membrane. These cells proliferate and gradually form a new cavity within the exocoelomic cavity. This new cavity is called the **secondary yolk sac** or **definitive yolk sac**, which is much smaller than the original exocoelomic cavity or primitive yolk sac (see SA 46).

The extraembryonic coelom expands and forms a large cavity known as the **chorionic cavity**.

The only place where the extraembryonic mesoderm traverses the chorionic cavity is in the **connecting stalk**, which will eventually become the **umbilical cord**.

GASTRULATION: formation of the GERM LAYERS (Lec. 3)

By the beginning of the 3rd week (day 14) we no longer speak of a blastocyst; rather, we speak of the formation of the germ layers.

Gastrulation begins with the **primitive streak**, which begins as an opacity at the caudal end (i.e. what will eventually become the feet) of the epiblast surface (SA 55). It elongates.

The appearance of the primitive streak determines the orientation of the embryo. The cells of the embryo are no longer totipotent.

The **primitive node** is the cephalic end (i.e. what will eventually become the head) of the primitive streak.

The epiblast now gives rise to the three germ layers: (SA 56)

- (1) **Ectoderm** (closest to uterine pole). This will develop into epidermis, nervous system and other organs.
- (2) **Mesoderm**. This will develop into muscle, connective tissues, vessels. (It will develop the following sections from central to peripheral:
 - (a) paraxial mesoderm
 - (b) intermediate mesoderm
 - (c) lateral mesoderm
- (3) **Endoderm** (farthest from uterine pole). This will develop into epithelial lining of respiratory passage and digestive tract.

In greater detail: All the tissues in the body arise from the three embryonic germ layers as follows (RRK 78-80, 82; DU 8-10):

(1) ECTODERM:

Surface ectoderm: epidermis, hair, nails, cutaneous and mammary glands, anterior pituitary gland, enamel of teeth, inner ear, lens

Neuroectoderm:

Neural crest: cranial and sensory ganglia and nerves, medulla of adrenal gland, pigment cells, brachial arch cartilages, head mesenchyme

Neural tube: central nervous system, retina, pineal body, posterior pituitary

(2) MESODERM:

Head: skull, muscles and connective tissue of head, dentine

Paraxial: muscles of trunk and skeleton (except skull), dermis of skin, connective tissue

Intermediate: urogenital system (including gonads, ducts and accessory glands)

Lateral: connective tissues of muscle and viscera and limbs, serous membranes of pleura, pericardium and peritoneum, blood and lymph cells, cardiovascular and lymphatic systems, spleen, adrenal cortex

(3) ENDODERM: epithelial parts of all of the following: trachea, bronchi, lungs, gastrointestinal tract, liver and pancreas, urinary bladder, urachus, pharynx, thyroid, tympanic cavity, pharyngotympanic tube, tonsils, parathyroids

From the cephalic end (the primitive streak) towards the caudal end there develop the following structures: (SA 56, 69)

- **Prochordal plate** (will become the neural plate)
- **Neural plate**, along the center of which is the...
- **Notochord process:** This will be the “scaffolding” of the body, as it will develop into the vertebral column pillar and nucleus pulposus. It also induces the ectoderm to the neural plate (?).
- **Primitive node**, in which there is the...
- **Primitive pit**
- **Cloacal membrane** “The contact area involving endoderm and ectoderm forms the cloacal membrane” (SA 268). “During the 4th and 7th weeks of development, the urorectal septum divides the cloaca into the anorectal canal and primitive urogenital sinus. The cloacal membrane itself is then divided into the urogenital membrane, anteriorly, and the anal membrane, posteriorly” (SA 283).
- **Allantois:** This is an outpouching from the yolk sac. It extends to the connecting stalk. It is involved with early blood formation and contributes to the development of the urinary bladder.
- **Connecting stalk**

The process of formation of the neural plate, neural fold and neural tube (SA 70, 77) is called **neurulation**.

Intraembryonic mesodermal proliferation will develop as follows:

- By day 20 the **paraxial mesoderm (thickened plate) [PM]** divides into paired cuboidal structures called **somites** (SA 69), which will eventually form the vertebral column. The number of somites increases day by day (SA 76), proceeding from cephalad to caudad.
- The **intermediate mesoderm (connecting PM and LPM)** will form the urogenital system.
- The **lateral mesoderm (thin plate) [LPM]** will form the limbs. It divides into two layers, the *splanchnic mesoderm* (which will form all connective tissue and muscle)

and the *somatic mesoderm* (which will form the connective tissues of the deep layer of the lateral and ventral body walls and limbs).

By the beginning of the 4th week (day 28), cells forming the ventral and medial walls of the somite lose their compact organization, become polymorphous, and shift their position to surround the notochord. These cells, collectively known as the **sclerotome**, form a loosely woven tissue known as **mesenchyme**.

The remaining dorsal somite wall, now referred to as the **dermomyotome**, gives rise to a new layer of cells. These new cells constitute the **myotome**, and each myotome will provide musculature for its own segment.

Each somite will give rise to its own (SA 76):

- **sclerotome** (the cartilage and bone component, viz. the vertebral column and ribs)
- **myotome** (providing the segmental muscle component)
- **dermatome** (the segmental skin component)

There is a folding in the horizontal plane into two lateral folds, right and left.

PLACENTATION (Lec. 4)

The **placental membrane** consists of:

- Syncytiotrophoblast
- Cytotrophoblast
- Connective tissue in the chorionic villi
- Endothelium of capillaries

The placenta has a variety of **functions** (RRK 702-6):

- Respiration
- Nutrition
- Excretion
- Storage
- Hormonal production: hCG (human chorionic gonadotrophin), E₂, progesterone
- Human chorionic somatomammotropin (hCS)
- hPL

A number of harmful substances can cross the placenta, e.g. drugs, rubella.

Various other substances *cannot* cross the placenta: bacteria, heparin, transferin, IgS, IgM.

Types of twins:

- **Dizygotic** twins (DZ) are from two zygotes. They are *fraternal* twins.
- **Monozygotic** twins (MZ) are from a single zygote. They are *identical* twins.

The incidence of twinning varies in different parts of the world. In the U.S.A. the incidence of natural twinning is 1 in 95 births.

PARTURITION (Lec. 4)

The expected date of delivery (EDD) is calculated by adding 9 months and 7 days to the last noted menstrual period (LNMP).

The actual **onset of labor** (can occur anywhere from 38 to 40 weeks) is when the uterus **contracts at regular intervals**. Irregular contractions (around 36 weeks) do not constitute the onset of labor.

Labor can last from 2 to 48 hours. If labor lasts too long there can be maternal distress, which in turn causes fetal distress and can result in death.

Episiotomy = small incision to expand perineal opening. It is better to do this surgically than to let it tear by itself.

A **twisted cord** (i.e. the fetus twisting itself up in the umbilical cord) can result in death of the fetus.

CONGENITAL MALFORMATIONS (Lec. 4)

Congenital malformations ("birth defects") are any developmental defects present at birth. They can be structural, functional, metabolic, behavioral or hereditary in nature. **Teratology** is the study of the causes of these disorders (SA 122).

Types of birth defects: (SA 122-4)

Anomaly: Any type of structural abnormality.

Malformation: Intrinsically abnormal development leading to any morphological defect.

Disruption: A defect induced extrinsically, e.g. by a teratogen.

Deformation: Abnormal form, shape or position.

Dysplasia: Abnormal organization.

Causes of congenital anomalies:

1. Genetic factors (6-7%): e.g. chromosomal abnormalities.
2. Environmental factors (7-10%): e.g. drugs, water contaminants and other teratogens (SA 124).

3. Multifactorial inheritance (20-25%): combination of genetic and environmental factors.
4. Idiopathic (50-60%): unknown etiology.

Genetic factors can be either numerical or structural:

1. **Numerical** genetic factors

- Trisomy: due to nondisjunction. *Down syndrome (trisomy 21*, i.e. the person has an extra copy of chromosome 21) is an example (SA 134).
- Monosomy: due to a missing chromosome (SA 134). Examples include *Turner syndrome* 35, X or 45, X O (SA 137).

2. **Structural** genetic factors usually result from chromosome breakage.

- Deletion. Example: *cri du chat syndrome* results from partial deletion of the short arm of chromosome 5 (SA 138).

If the mother suffers infections during pregnancy, this can harm the fetus. **Rubella virus** can cause cataracts, deafness, cardiac defects (SA 124). **Herpes simplex virus** can cause hepatomegaly (enlargement of the liver), hydrancephaly (partial or complete absence of cerebral hemispheres), anemia (SA 126).

There are different **critical periods** in embryonic and fetal development. Different organ systems are susceptible to different degrees at different times.

Development of MUSCULOSKELETAL SYSTEM (Lec. 5)

The limb buds begin to appear in the 4th week. The **upper limb bud** is more prominent and develops one day before the **lower limb bud**. The upper limb will also ossify earlier than the lower limb.

The limb buds develop as small projections, at the apex of which is an **apical ectodermal ridge (AER)** (SA 154). As the limb grows, it is more differentiated proximally than distally. As it grows, vasculature grows with it. If you remove a bud and place it elsewhere on the embryo, it will grow in the new location, fully vascularized.

The AER is always at the most distal part of the developing limb.

The patterning of the digits is dependent on a group of cells located at the base of the limbs on their posterior border known as the **zone of polarizing activity (ZPA)**. These cells establish a morphogen gradient that appears to involve retinoic acid (vitamin A) and a series of **homeobox genes** to produce the normal sequence of digits (SA 155).

In 7th week the upper limb rotates (90° laterally) and the lower limb rotates (90° medially).

There are various neural tube closure defects:

- **Spina bifida occulta:** The posterior bony wall of the spinal canal fails to close (SA 162).
- **Meningocele:** Hernial protrusion of the meninges through a defect in the vertebral column (SA 152).
- **Meningomyelocele:** Hernial protrusion of a part of the meninges and substance of the spinal cord through a defect in the vertebral column (SA 386).
- **Myelocele:** Hernial protrusion of the substance of the spinal cord through a defect in the bony spinal canal.
- **Syringomyelocele:** Spina bifida in which the cavity of the protruding sac is connected with the central canal of the spinal cord.

There are various limb defects:

- **Amelia:** Complete absence of limb (SA 158).
- **Meromelia:** Partial absence of limb (SA 158).
- **Brachydactyly:** Abnormal shortness of fingers and toes.
- **Polydactyly:** Presence of supernumerary digits (fingers or toes) (SA 159).
- **Syndactyly:** Two or more fingers or toes are more or less completely grown together or adherent (SA 159). Webbed fingers or toes.
- **Club foot (talipes equinovarus):** A deformity of the foot in which the heel is turned inward from the midline of the leg and the foot is plantarflexed (SA 160).
- **Achondroplasia:** Imperfect ossification within the cartilage of long bones. Can result in dwarfism (SA 162).
- **Congenital dislocation of hip** consists of underdevelopment of the acetabulum and head of the femur (SA 160).

Development of CARDIOVASCULAR SYSTEM (Lec. 6)

The cardiovascular system is the first system to function in the embryo. The **primitive heart** develops in the **cardiogenic area** (SA 183) in the 3rd week. It arises from the **splanchnic mesoderm**, from splanchnic mesenchymal cells. Two angioblastic cords canalize to form two endothelial heart tubes which fuse in the midline into a single heart tube when the embryo folds cephalocaudally (forming the **anterior fold**) and laterally (SA 183 bottom).

Initially the central portion of the cardiogenic area is located anterior to the prechordal plate and the neural plate. With closure of the neural tube and formation of the brain vesicles, however, the central nervous system grows so rapidly in a cephalic direction that it extends over the central cardiogenic area and the future pericardial cavity. As a result of the growth of the brain and cephalic folding of the embryo, the prechordal plate is pulled forward, while the heart and pericardial cavity become located in the cervical region and finally in the thorax (SA 183).

As the head folds, the heart elongates and develops five constrictions and dilations (SA 189):

- (1) **Sinus venosus:** caudal, receives all venous blood from the right and left sinus horns (SA 188)
- (2) **Primitive atrium**
- (3) **Primitive ventricle** (SA 188)
- (4) **Bulbus cordis**
- (5) **Truncus arteriosus:** forms the aortic sac.

By the **4th week** the heart is already beating!

During the 4th and 5th weeks the primitive heart is divided into the typical 4-chambered human organ as follows:

Partitioning of the heart

1. **Partitioning of the atrioventricular canal:** Dorsal and ventral endocardial cushions form, dividing the AV canal into right and left AV canals (SA 197)
2. **Partitioning of the primitive atrium:** (SA 195)
 - a. The **septum primum** is a sickle-shaped crest which grows from the roof of the common atrium into the lumen (SA 195).
 - b. Foramen primum (ostium primum)
 - c. The **septum secundum** grows from the ventral cranial wall, but never forms a complete partition in the atrial cavity (SA 196).
 - d. The **foramen ovale** is the opening left by the septum secundum (SA 196).

Changes in sinus venosus (SA 192)

The **right horn** increases in growth and becomes incorporated into the right atrium.

The **left horn** decreases in growth and becomes the coronary sinus.

Partitioning of the ventricle

- **Muscular ridge** eventually becomes the **interventricular septum** (SA 203).
- **Interventricular foramen** eventually becomes the **membranous septum** (SA 205).

Development of the valves and cardiac conducting system

Endocardial cushions form, which eventually give rise to the **AV valves** (mitral and tricuspid) and **semilunar valves** (aortic, pulmonary) (SA 197).

Formation of aortic arches and derivatives

During the 4th and 5th weeks, **aortic arches** arise from the **aortic sac**. The aortic sac contributes a branch to each new arch as it forms, thus giving rise to a total of six pairs of arteries (although the 5th arch never forms, or forms incompletely and then regresses).

This arterial pattern becomes modified and some vessels regress completely (SA 212; see illustrations on pp. 214-5).

Arch Fate

- I Mostly disappears; a portion of it remains and becomes the **maxillary artery**.
- II Mostly disappears; portions of it remain as the stem of **stapedial arteries**.
- III Forms **common carotid arteries**.
- IV The left part forms the **aortic arch**.
The right part forms the **subclavian artery**.
- V Degenerates or never develops.
- VI The right side becomes the proximal segment of the **right pulmonary artery**.
The left part persists during intrauterine life as the **ductus arteriosus**.

Partitioning of the bulbus cordis and truncus arteriosus

The **bulbus cordis** forms within the bulbar ridge; eventually this will form the aorta and pulmonary trunk. If I understand correctly, it seems that there is a single tube which septates (via the aorticopulmonary septum). The proximal end of this septated tube is called the **conus cordis**, and it forms the outflow tracts of both ventricles. The distal end of this septated tube is called the **truncus arteriosus**, and it divides into the aorta and the pulmonary trunk (SA 186-7; see illustrations on p. 14 of the handout to lecture 6).

Shunts in fetal circulation (NE 217)

- (1) **Ductus venosus** regulates fetal blood flow by shunting most of the blood (which would otherwise go to the liver) directly into the inferior vena cava (SA 224, 226).
- (2) **Foramen ovale** between the left and right atria (SA 196).
- (3) **Ductus arteriosus** between the pulmonary artery and the aorta (SA 215-6, 225).

At birth, the closure of the ductus arteriosus is mediated by bradykinin (SA 226).

Development of RESPIRATORY SYSTEM (Lec. 7)

The respiratory system develops from the **laryngotracheal groove**. The **respiratory diverticulum** (laryngotracheal diverticulum or lung bud) appears as an outgrowth of the foregut. Initially the esophagus and trachea are a single tube, but during the 3rd or 4th weeks of fetal life, the **tracheoesophageal fold** forms in this tube and eventually becomes the **tracheoesophageal septum**, thereby forming a separate trachea and lung buds (ventrally) and esophagus (dorsally) (SA 232 ff.).

The development of the esophagus and trachea is subject to various congenital abnormalities (SA 234). **Tracheoesophageal fistulas** can generally be repaired through surgery. Other deformities generally result in death: tracheal stenosis, atresia, respiratory distress syndrome, congenital lung cysts, agenesis of lungs.

The lungs of premature infants often have not developed sufficiently to secrete adequate surfactant. As a result, surface membrane tension in the alveoli is high, and there is great risk that the alveoli will collapse during expiration. This results in **respiratory distress syndrome** (SA 239).

The branchings of the lungs develop sequentially: (SA 237)

4th wk.	Bronchial buds Secondary or stem bronchi Tertiary or segmental bronchi
5-16 wks.	Pseudoglandular period
16-26 wks.	Canalicular period
26 wks. to birth	Terminal sac period. From this point on, respiratory exchange can occur. If the baby is born prior to this point, it will not be able to respire.
late fetal life to childhood	Alveolar period

Development of DIGESTIVE SYSTEM (Lec. 8)

Primitive gut forms during 4th week.

The **dorsal** part of the embryonic stomach grows faster and will become the **greater curvature** of the adult stomach. After the 90° rotation, this (previously) dorsal part will end up on the left.

The **anterior part** of the embryonic stomach grows more slowly and will become the **lesser curvature** of the adult stomach. After the 90° rotation, this (previously) anterior part will end up on the right.

For an excellent illustration of the rotation of the gut see GR 204-5.

This initial 90° rotation (around a vertical axis) is followed by another rotation (around an anterior-posterior axis) such that the lesser curvature ends up somewhat superior.

I. Foregut

A. Derivatives: primitive pharynx and respiratory system, esophagus, stomach, 1st part of duodenum, liver, gallbladder, bile duct, pancreas.

B. Celiac artery

II. Midgut

A. Derivatives: small intestines (most of duodenum), jejunum, ileum, cecum, appendix, ascending colon, proximal 2/3 of transverse colon

B. Superior mesenteric artery

III. Hindgut

- A. Derivatives: distal 1/3 of transverse colon, descending colon, sigmoid colon, rectum, superior portion of anal canal, epithelium of urinary bladder, most of urethra
 - B. Inferior mesenteric artery
-

Development of the URINARY SYSTEM

The urogenital system can be divided into the functionally separate urinary system and genital system. Embryologically and anatomically, however, these two components are closely related (SA 272).

The urinary system develops from the **intermediate mesoderm** (SA 272) (or, as Dr. Ashiru calls it, "IPM, intermediate plate mesoderm").

There are three sets of **kidneys** in development (SA 272-4):

- (1) **Pronephros** ("forekidneys") appear early but disappear by the 4th week. They are not functional. Their degeneration leaves a pathway which gets utilized by the next phase.
- (2) **Mesonephros** ("midkidneys") appear in the 4th week as the pronephros are receding. The mesonephros may function for a short time during the early fetal period (SA 272).
- (3) **Metanephros** ("hindkidneys") appear in the 5th week, and are destined to become the permanent kidney. It develops from the *metanephric mesoderm*. The collecting ducts of the permanent kidney develop from the *ureteric bud* (=an outgrowth of the mesonephric duct). The metanephros becomes functional at the end of the 1st trimester (SA 283).

The ureteric bud will also give rise to 1 to 3 million collecting tubules (SA 276).

The permanent kidney is initially located in the pelvic region, but then **ascends** to a more cranial position in the abdomen. (Dr. Ashiru says that the final position is attained by the 9th week of development, and notes that the ascent is "stopped" by the adrenal glands.) During this ascent, the kidneys are vascularized by arteries that originate from the aorta at continuously higher levels (SA 279). The lower vessels usually degenerate, but **accessory renal arteries** are common and represent the persistence of embryonic vessels that formed during the ascent of the kidneys (SA 282).

The **urogenital sinus** comprises three parts (SA 283-4):

- (1) **Vesical** (the cranial part of the UG sinus), pertaining to the bladder.
- (2) **Pelvic** (the middle part of the UG sinus), which in the male will give rise to the prostatic and membranous parts of the urethra.

(3) **Phallic** (the caudal part of the UG sinus), pertaining to the genitalia.

Congenital abnormalities

- **Renal agenesis** (unilateral or bilateral) due to the absence of the metanephric diverticulum or ureteric bud (SA 279).
- **Non rotation** or **abnormal rotation** of kidneys. (Remember that the kidneys are not in a coronal plane; their hila are disposed anteromedially.)
- **Ectopic kidneys** may be found in positions other than the normal ones.
- **Horseshoe kidney:** when the two kidneys are connected at their posterior poles due to a fusion of the two metanephric diverticula (SA 281).
- **Congenital polycystic disease of the kidney** is a condition in which numerous cysts form, causing renal insufficiency and death unless a transplant is made (SA 278).
- **Urachal anomalies** may include a fistula, cyst or sinus (SA 285).
- **Exstrophy of the bladder** is a ventral wall defect in which the bladder mucosa is exposed (SA 285-6).
- **Duplication of the ureter** (partial or complete) may result from early splitting of the ureteric bud (SA 279-80).
- **Pelvic kidney** results when, during its ascent, a kidney fails to pass through the arterial fork (formed by the umbilical arteries) and remains close to the common iliac artery (SA 280-1).

Development of the GENITAL SYSTEM

The **cloaca** partitions into rectal and urogenital areas. Failure to separate results in congenital abnormalities. “The contact area involving endoderm and ectoderm forms the cloacal membrane” (SA 268). “During the 4th and 7th weeks of development, the urorectal septum divides the cloaca into the anorectal canal and primitive urogenital sinus. The cloacal membrane itself is then divided into the urogenital membrane, anteriorly, and the anal membrane, posteriorly” (SA 283).

The genital organs develop from the mesodermal epithelium medial to the mesonephros, from the gonadal ridge, and from the primary sex cords.

Sex is determined at fertilization (SA 286). The oocyte always contributes an X sex chromosome. The spermatocyte can contribute either an X or a Y chromosome. Embryos with an XX sex chromosome develop into females, while embryos with an XY sex chromosome develop into males (SA 291).

At the 5th week of intrauterine development the gonads are still “indifferent” or “undifferentiated” (SA 287). The gonads develop from the intermediate mesoderm.

The gene for **testis determining factor (TDF)** is encoded on the **sex determining region of the Y chromosome (SRY)** (SA 286).

If TDF is present (it usually begins being secreted during the 8th week), the gonads develop into testes. TDF also stimulates the synthesis of **Müllerian inhibitory substance (MIS)** by Sertoli cells, which in turn blocks the development of ovarian tubes (SA 292).

There is no factor which specifically stimulates ovarian development. Rather, in the *absence* of TDF, the gonads develop into ovaries. (See SA p. 289 table 15.1 and p. 292 table 15.2 for a summary of the hormonal influences on gonadal development.)

The gonads initially appear as a pair of longitudinal ridges, called the **genital** or **gonadal ridges** (SA 286).

	TDF present (male)	TDF absent (female)
Medulla of gonad	Testes are primarily from the medulla (SA 288).	The degenerating rete ovarii are from the medulla.
Cortex of gonad	The tunica albuginea is the vestige of the cortex (SA 289).	The primordial follicle (which will give rise to the ovary) is primarily from the cortex.

Male external genitalia:

- The **urethral folds** close, thereby forming the penile (spongy) portion of the urethra (SA 298). Failure to close leads to *posterior urethral valve lesion*.
- The **genital tubercle** and **urethral folds** give rise to the phallus (viz. the glans penis).
- The **genital swelling** gives rise to the scrotum (SA 298).

Female external genitalia:

- The **urethral folds** give rise to the labia minora (SA 302).
- The **genital swellings** give rise to the labia majora (SA 298, 302).
- The **genital tubercle** forms the clitoris.
- The **urogenital groove** forms the vestibule of the vagina (i.e. the cleft between the labia minora) (SA 302).
- The **hymen** is derived from the mesenchyme.

The **inguinal canal** is the path through which the testes descend. Their descent is guided by the **gubernaculum** (SA 305 ff.).

Male	Embryonic structure	Female
Testis	<i>Indifferent gonad</i>	Ovary
Seminiferous tubules	<i>Cortex of gonad</i>	Ovarian follicles
Rete testis	<i>Medulla of gonad</i>	Rete ovarii
Gubernaculum testis	<i>Gubernaculum</i>	<ul style="list-style-type: none"> • Ovarian ligament • Round ligament of the uterus
<ul style="list-style-type: none"> • Ductuli efferentes • Paradidymis 	<i>Mesonephric tubules</i>	<ul style="list-style-type: none"> • Epoophoron • Paroophoron
<ul style="list-style-type: none"> • Appendix of epididymis • Duct of epididymis • Ductus deferens • Ureter, pelvis, calyces and collecting tubules of kidney • Ejaculatory duct and seminal vesicle 	<i>Mesonephric duct</i>	<ul style="list-style-type: none"> • Appendix vesiculosa • Duct of epoophoron • Duct of Gartner • Ureter, pelvis, calyces and collecting tubules of kidney
Appendix of testis	<i>Paramesonephric duct</i>	<ul style="list-style-type: none"> • Hydatid (of morgagni) • Uterine tube • Uterus
Urinary bladder	<i>Urogenital sinus</i>	<ul style="list-style-type: none"> • Urinary bladder • Urethra • Vagina • Urethral and paraurethral glands • Greater vestibular glands
Seminal colliculus	<i>Sinus tubercle</i>	Hymen
<ul style="list-style-type: none"> • Penis • Glans penis • Corpora cavernosa penis • Corpus spongiosum penis 	<i>Phallus</i>	<ul style="list-style-type: none"> • Clitoris • Glans clitoridis • Corpora cavernosa clitoridis • Bulb of the vestibule
Ventral aspect of penis	<i>Urogenital folds</i>	Labia minora
Scrotum	<i>Labioscrotal swellings</i>	Labia majora

Congenital abnormalities

- In the male, incomplete closure of the urethral groove results in **posterior urethral valve lesion** (according to Dr. Ashiru).
- **Hypospadias**: Dr. Ashiru described this as a condition in which the “genitalia are incompletely developed.” SA (p. 299) says that it is a condition in which the fusion of the urethral folds is incomplete and abnormal openings of the urethra occur along the inferior aspect of the penis (which makes it sound like what Dr. Ashiru calls a posterior valve lesion).
- **Epispadias** is a condition in which the urethral meatus is found on the dorsum of the penis (SA 300).
- **True hermaphroditism** is a condition in which both testicular and ovarian tissue is present (SA 304).
- In **pseudohermaphroditism** the genotypic sex is masked by a phenotypic appearance that closely resembles the other sex. When the pseudohermaphrodite has a testis the patient is called a male pseudohermaphrodite. When the pseudohermaphrodite has an ovary the patient is called a female pseudohermaphrodite (SA 304).

- Generally the uterus is formed by the joining of bilateral paramesonephric ducts. Failure to join, or incorrect joining results in various types of **duplications of the uterus**. A **uterus didelphys** is a completely doubled uterus and doubled vagina. A **bicornuate uterus** is one in which the uterus has two horns ending in a common vagina (SA 297).
- In the male, the ejaculatory duct may enter the bladder (rather than the prostatic urethra).
- In the female an **imperforate hymen** results in a closed introitus (=opening to the vagina).
- **Testicular feminization syndrome (androgen insensitivity syndrome)** occurs in patients who have 46,XY chromosome complement but have the external appearance of normal females. The tissues of the external genitalia are unresponsive to androgens produced by the testes and develop and differentiate as in the normal female under the influence of estrogen (SA 304-5).
- **Cryptorchidism** is a condition in which the testes do not descend completely from the abdomen into the scrotum. (Normally the descent is complete around the time of birth.) (SA 309).
- **Congenital inguinal hernia** is caused when a loop of intestine descends through the inguinal canal (and possibly into the scrotum) through a patent processus vaginalis (which has failed to close) (SA 308).
- **Hydrocele**: If the processus vaginalis is not completely obliterated, small cysts may form and secrete fluid, resulting in a hydrocele (SA 308).

Development of the HEAD and NECK

The following table from DU 30 (table 9-2) is supplemented with information from SA (319-23).

Pharyngeal pouch	Adult derivatives
1	• Epithelial lining of auditory tube and middle ear cavity
2	• Epithelial lining of palatine tonsil crypts
3	• Inferior parathyroid gland • Thymus
4	• Superior parathyroid gland • Ultimobranchial body

Development of the EAR

The following table from DU 44 (table 14-1) is supplemented with information from SA (ch. 17).

Note that “pharyngeal groove” and “pharyngeal cleft” are synonymous terms.

Embryonic structure	Adult derivatives
Otic vesicle (from surface <i>ectoderm</i> ; SA 347)	Internal ear
• Utricular portion	Utricle, semicircular ducts, vestibular ganglion of CN VIII
• Saccular portion	Saccule, cochlear duct, spiral ganglion of CN VIII
	Middle ear (of <i>endodermal</i> origin; SA 350)
Pharyngeal arch 1	Incus, malleus, tensor tympani m. (SA 351)
Pharyngeal arch 2	Stapes, stapedius m. (SA 351)
Pharyngeal pouch 1	Epithelial lining of auditory tube and middle ear cavity
Pharyngeal membrane 1	Tympanic membrane
	External ear
Pharyngeal groove 1	Epithelial lining of external auditory meatus (SA 354)
Auricular hillocks (from <i>mesenchyme</i> ; SA 355)	Auricle

The eardrum or **tympanic membrane** is made up of three components (SA 354):

- (a) **Ectodermal** epithelial lining at the bottom of the auditory meatus
- (b) **Endodermal** epithelial lining of the tympanic cavity
- (c) An intermediate layer of connective tissue that forms the fibrous stratum

Development of the EYE

The following table from DU 46 (table 15-1) is supplemented with information from SA (ch. 18).

Embryonic structure	Adult derivatives
Neuroectoderm	
• Optic cup	Retina, iris, ciliary body (SA 358-61)
• Optic stalk	Optic nerve (CN II) (SA 363)
Surface ectoderm	
Lens placode	Lens, anterior epithelium of cornea (SA 361-2)
Mesoderm	Sclera, substantia propria of cornea, corneal endothelium vitreous body, extraocular muscles
Hyaloid artery and vein	Central artery and vein of retina (branch of the ophthalmic artery) (SA 363-4)
Neural crest cells	Choroid, sphincter pupillae muscle, dilator pupillae muscle, ciliary muscle

In the adult the **iris** is formed by (SA 360-1):

- (a) The pigment-containing **external layer of the optic cup**
- (b) The unpigmented **internal layer of the optic cup**
- (c) A layer of richly vascularized connective tissue, which contains the pupillary muscles

Note that the optic cup is of neuroectodermal origin (DU 46).

In the adult the **cornea** is formed by (SA 362):

- (a) An epithelial layer derived from **surface ectoderm**
- (b) The substantia propria or stroma, which is continuous with the sclera
- (c) An **epithelial layer**, which borders the anterior chamber

By day 22 of embryonic development a pair of shallow grooves appear on each side of the forebrain. These grooves evaginate and form the **optic vesicles**, which subsequently come into contact with the surface ectoderm and induce changes in the ectoderm which are necessary for the formation of the **lens** (SA 358).

QUESTIONS from Dr. Ashiru's handouts

Questions on fertilization

A pregnant woman who has missed two menstrual periods wants to know her expected date of delivery. In practice, which of the following would you use?

- (a) Menstrual history
- (b) Date of coitus
- (c) Time of ovulation
- (d) Probable time of fertilization
- (e) Vaginal examination

From the information given in lecture, it seems that the correct answer is (a), since the menstrual history would include information about the most recent menstrual cycle (which is needed to determine the expected date of delivery). Specifically, the the EDD (expected date of delivery) equals the LNMP (last noted menstrual period) plus nine calendar months plus seven days.

At which of the following stages of development is division of embryonic material **NOT** likely to result in normal monozygotic twinning?

- (a) Two-cell stage
- (b) Morula
- (c) Blastocyst
- (d) Primitive streak
- (e) Bilaminar embryo

The proper chronological order of the options is as follows (see the inside front cover of SA):

- two-cell stage is at day 2 (or at 30 hrs. after fertilization; SA 34 fig. 2.8)
- morula is at day 3
- blastocyst is at days 4 and 5
- bilaminar embryo is at day 8 (SA 41)
- primitive streak is clearly defined by day 15 or 16 (SA 53).

Monozygotic twins “result from splitting of the zygote at various stages of development. The earliest separation is believed to occur at the two-cell stage[...] In most cases, splitting of the zygote occurs at the early blastocyst stage[...] In rare cases, the separation occurs at the bilaminar germ disc stage just before the appearance of the primitive streak” (SA 114). Thus, for monozygotic twins to form, the zygote must split *before* the appearance of the primitive streak, so (d) is the correct answer.

With respect to dizygotic twins, which of the following is correct?

- (a) Result from the fertilization of two ova by two sperms.
- (b) Result from the division of the embryoblast into two primordia.
- (c) Usually begin to develop during the blastocyst into two primordia.
- (d) Twins usually are identical.
- (e) One chorionic sac is present.

Dizygotic twins “result from simultaneous shedding of two oocytes and fertilization by two different spermatozoa” (SA 114).

In the process of fertilization all of the following occur involving the spermatozoa, **EXCEPT**:

- (a) The acrosomal reaction.
- (b) Capacitation of the sperm.
- (c) Digestion of the cumulus by hyaluronidase.
- (d) Blockage of polyspermy due to zona hardening.
- (e) Degeneration of sperm tails before sperm penetration of the oocyte.

Concerning answer (a): “Before spermatozoa can fertilize the oocyte, they must undergo[...] the acrosome reaction, during which hyaluronidase and trypsin-like substances are released to penetrate oocyte barriers” (SA 39). “The acrosome reaction occurs after binding to the zona pellucida and is induced by zona proteins” (SA 29).

Concerning answer (b): “Before spermatozoa can fertilize the oocyte, they must undergo[...] a capacitation process, during which a glycoprotein coat and seminal plasma proteins are removed from the spermatozoon head” (SA 39). “Capacitation is a period of

conditioning in the female reproductive tract that, in the human, lasts approximately 7 hours" (SA 29).

Concerning answer (c): I cannot find a direct reference to this in SA.

Concerning answer (d): "As a result of the release of cortical oocyte granules, which contain lysosomal enzymes, (a) the oocyte membrane becomes impenetrable to other spermatozoa, and (b) the zona pellucida alters its structure and composition to prevent sperm binding and penetration. In this manner polyspermy is prevented" (SA 30).

Concerning answer (e): "The spermatozoon[...] moves forward until it lies in close proximity to the female pronucleus. Its nucleus becomes swollen and forms the male pronucleus, while **the tail is detached and degenerates**" (SA 30). This occurs after the spermatozoon has penetrated the oocyte, to choice (e) is the correct answer.

Routine ultrasound examination of a pregnant woman revealed the presence of 10 live embryos. (This is a true clinical case.) Which of the following is the probable cause?

- (a) The inner cell mass has divided into 10 independent embryos.
- (b) Progesterone secretion was increased.
- (c) The woman was treated with an anti-fertility drug.
- (d) Ten oocytes were fertilized by ten sperms.
- (e) Release of gonadotropins was reduced.

Concerning answer (a): In lecture, Dr. Ashiru said that this was an unlikely cause of the multiple pregnancy.

Concerning answer (b): Progesterone "causes the uterine mucosa to enter the progesterational or secretory stage in preparation for implantation of the embryo" (SA 28), but is not directly conducive to multiple embryos.

Concerning answer (c): Treatment with an anti-fertility drug should reduce fertility, not lead to multiple embryos.

Concerning answer (d): In lecture, Dr. Ashiru said that this was the most probable cause.

Concerning answer (e): Gonadotropins stimulates ovulation (SA 23, 26), so reducing the release of gonadotropins should reduce fertility (rather than increase it).

Questions on gastrulation and germ layers

The notochordal plate infolds to form the:

- (a) Neural tube
- (b) Neurenteric canal
- (c) Notochordal process
- (d) Notochordal canal
- (e) Notochord

Judging from the following quotations, it appears that (a) is the correct answer: "Prenotochordal cells invaginating in the primitive pit move forward in a cephalic direction until they reach the prechordal plate. These prenotochordal cells become intercalated in the hypoblast such that, for a short time the midline of the embryo consists of two cell layers that form the **notochordal plate**. As the hypoblast is replaced by endoderm cells moving in at the streak, cells of the notochordal plate and detach from the endoderm. They then form a solid cord of cells, the definitive notocord, that underlies the neural tube and serves as the basis for the axial skeleton" (SA 53-4; see also p. 64). "The elongated, slipper-shaped neural plate gradually expands toward the primitive streak. By the end of the 3rd week, the lateral edges of the neural plate become more elevated to form neural folds, while the depressed midregion forms a groove, the neural groove. Gradually, the neural folds approach each other in the midline, where they fuse. This fusion begins in the region of the future neck (4th somite) and proceeds in cephalic and caudal directions. As a result, the **neural tube** is formed" (SA 67-70).

The primitive streak:

- (a) Extends from the primitive node to the oropharyngeal membrane.
- (b) Is caudal to the notochord.
- (c) Becomes the vertebral column.
- (d) Is a thickening of endoderm.
- (e) Induces the formation of the neural tube.

The correct answer appears to be (b) from the following references:

The **notochord** is cephalad to the **primitive pit** (SA p. 56 fig. 4.3A).

"The cephalic end of the primitive node consists of a slightly elevated area surrounding the small primitive pit" (SA 53). In other words, the **primitive pit** and the **primitive node** are at the same cranial-caudal location.

The **primitive node** is cephalad to the **primitive streak** (SA p. 55 fig. 4.2A; p. 59 fig. 4.5A; p. 64).

Therefore the notochord is cephalad to the primitive streak. Another way of stating this is that **the primitive streak is caudal to the notochord**, which is why (b) is the answer to this question.

During the second week of development all of the following structures are formed **EXCEPT** the:

- (a) Amniotic cavity
- (b) Neural plate
- (c) Yolk sac
- (d) Connecting stalk
- (e) Chorion

Concerning answer (a): The amniotic cavity forms at day 8 (SA 41 and 42 fig. 3.1).

Concerning answer (b): The neural plate forms at day 21 (SA 67), so this is the correct answer.

Concerning answer (c): The yolk sac forms at day 9 (SA 43 fig 3.3).

Concerning answer (d): The connecting stalk forms at day 13 (SA 47 and 46 fig 3.6).

Concerning answer (e): The chorionic cavity (extraembryonic coelom) forms at day 12 (SA 44).

Questions on placentation

Which of the following does **NOT** cross the placental membrane?

- (a) Carbon monoxide
- (b) Thyroxine
- (c) Antibodies
- (d) Uric acid
- (e) Heparin

Concerning answer (a): "Exchange of gases, such as oxygen, carbon dioxide, and **carbon monoxide**, is accomplished by simple diffusion" (SA 109).

Concerning answer (b): "Exchange of gases and metabolic products occurs as the blood passes over the villi. Normally, water, carbon dioxide, metabolic waste products, and hormones are transferred from the fetal blood to the maternal blood, and water, oxygen, metabolites, electrolytes, vitamins, hormones [presumably including **thyroxine?**] and some antibodies pass in the opposite direction" (RRK 703-4).

Concerning answer (c): "Maternal **antibodies** are taken up by pinocytosis by the syncytiotrophoblast and subsequently transported to fetal capillaries" (SA 109).

Concerning answer (d): "Exchange of gases and metabolic products occurs as the blood passes over the villi. Normally, water, carbon dioxide, metabolic waste products [presumably including **uric acid?**], and hormones are transferred from the fetal blood to the maternal blood" (RRK 703-4).

Concerning answer (e): In lecture Dr. Ashiru mentioned that **heparin** cannot cross the placental membrane, so this is the answer (see p. 4 of lecture 4) He qualified this by saying that steroids cannot cross the placental membrane. I am not certain what the justification is for this answer, but Lippincott's *Biochemistry* (p. 149, fig. 14.4) mentions that "Unlike other glycosaminoglycans that are extracellular compounds, heparin is an intracellular component of mast cells" and since no cells of any kind cross the placenta, presumably heparin would be unable to cross it.

See SA 141 table 8.1 for a good summary of teratogens.

Most drugs administered during pregnancy are transported across the placental membrane by:

- (a) Simple diffusion
- (b) Facilitated diffusion
- (c) Active transport
- (d) Pinocytosis
- (e) None of the above

Perhaps it can be assumed from the following quotation that the correct answer to this question is (a): "Sometimes called the placental barrier, the placental membrane is not a true barrier, since many substances pass through it freely" (SA 108). I cannot find any quotation which states in general that drugs cross the placenta by simple diffusion.

Questions on congenital malformations

The infectious agent most likely to cause a triad of congenital anomalies consisting of heart defect, cataracts, and deafness is:

- (a) *Toxoplasma gonadii*
- (b) Varicella (chickenpox)
- (c) Herpes zoster virus
- (d) Rubella virus
- (e) Cytomegalovirus

Concerning answer (a): if the mother is affected by *toxoplasma gonadii* during pregnancy, "The affected child may have cerebral calcification, hydrocephalus, or mental retardation. Chorioretinitis, microphthalmos, and other ocular defects have also been reported" (SA 126).

Concerning answer (b): if the mother is affected by chickenpox during pregnancy, congenital anomalies may "include limb hypoplasia, mental retardation, and muscle atrophy" (SA 126).

Concerning answer (c): There appears to be no information about this in SA.

The correct answer is (d): "At present, it is well established that rubella virus can cause malformations of the eye (**cataract** and microphthalmia); internal ear (congenital **deafness** due to destruction of the organ of Corti); **heart** (persistence of the ductus arteriosus as well as atrial and ventricular septal defects); and, occasionally, teeth (enamel layer)" (SA 124).

Concerning answer (e): if the mother is affected by cytomegalovirus during pregnancy, defects include "microcephaly, cerebral calcifications, blindness and chorioretinitis, and hepatosplenomegaly" (SA 125).

See SA 141 table 8.1 for a good summary of teratogens.

Late maternal age and nondisjunction of chromosomes during gametogenesis often are related. In which of the following syndromes is late maternal age believed to be a major factor?

- (a) Cri-du-chat syndrome
- (b) Turner syndrome
- (c) Klinefelter syndrome
- (d) Edward syndrome
- (e) Down syndrome

Concerning answer (a): Cri-du-chat syndrome is a *structural* chromosomal abnormality. “[P]artial deletion of the short arm of chromosome 5 is the cri-du-chat syndrome” (SA 138). No connection with maternal age is stated.

Concerning answer (b): Turner syndrome is a *numerical* chromosomal abnormality found in females. It is “characterized by the absence of ovaries” (SA 137). No connection with maternal age is stated.

Concerning answer (c): Klinefelter syndrome is a *numerical* chromosomal abnormality found in males. Characteristics include “sterility, testicular atrophy, hyalinization of the seminiferous tubules, and in most cases gynecomastia” (SA 136). No connection with maternal age is stated.

Concerning answer (d): I cannot find anything in SA concerning Edward syndrome.

Concerning answer (e): Down syndrome is a *numerical* chromosomal abnormality. “Down syndrome is usually caused by the presence of an extra copy of chromosome 21[...] Women **over 35 years** have a greater risk of having an affected child” (SA 134-5).

A 30-year-old woman gave birth to an infant with mental retardation and other anomalies, which included growth deficiency, microcephaly, short palpebral fissures, maxillary hypoplasia, and a thin upper lip. During her pregnancy, she drank both alcoholic beverages and coffee regularly and smoked a pack of cigarettes daily. Which of the following is probably responsible for the child's condition?

- (a) Mother's age
- (b) Alcohol ingestion
- (c) Cigarette smoking
- (d) Coffee
- (e) Genetic factors

Concerning answer (a): The mother's being age 30 is not considered a risk factor.

Concerning answer (b): “A well-documented association exists between maternal **alcohol ingestion** and congenital abnormalities. Defects include craniofacial abnormalities (**short palpebral fissures** and **hypoplasia of the maxilla**), limb deformities (altered joint mobility and position), and cardiovascular defects (ventricular septal abnormalities).

These malformations, together with **mental retardation** and **growth deficiency**, make up the 'fetal alcohol syndrome'" (SA 130).

Concerning answer (c): "Cigarette smoking has not been linked to major birth defects. Smoking does contribute to intrauterine growth retardation and premature delivery, however. There is also evidence that it causes behavioral disturbances" (SA 130).

Concerning answer (d): I can find no information in SA concerning teratogenic effects of caffeine.

Concerning answer (e): Although genetic factors may be involved, the mother's consumption of alcohol seems more likely to be the cause of the congenital defects.

Questions on the musculoskeletal system

Each of the following statements about the apical ectodermal ridge is correct **EXCEPT**:

- (a) It first appears in the upper limb bud.
- (b) It exerts an inductive influence on the limb mesenchyme.
- (c) It appears at the proximal end of the limb bud.
- (d) It promotes growth and development of the limb.
- (e) Injury to it results in severe limb defects.

Answer (a) is true: "Development of the upper and lower limbs is similar, except that morphogenesis of the lower limb is approximately 1-2 days behind that of the upper limb" (SA 155).

Answers (b) and (d) are true: the apical ectodermal ridge "exerts an inductive influence on the underlying mesenchyme" (SA 154).

Answer (c) is false (and is therefore the answer to the question as posed): "Mesenchyme signals ectoderm at the limb tip [i.e. at the *distal* end] to thicken and form the apical ectodermal ridge (AER)" (SA 154).

Questions on the cardiovascular system

The most common type of defect of the cardiac septa is:

- (a) Secundum-type ASD
- (b) Muscular-type ventricular septal defect (VSD)
- (c) Primum-type ASD
- (d) Membranous-type VSD
- (e) Sinus venosus-type ASD

"Ventricular septal defects (VSD) involving the membranous portion of the septum[...] are the most common congenital cardiac malformation" (SA 207).

Closure of the foramen primum results from fusion of the:

- (a) Septum primum and the septum secundum
- (b) Septum secundum and the septum spurium
- (c) Septum primum and the endocardial cushions
- (d) Septum secundum and the endocardial cushions
- (e) Septum primum and the right sinoatrial valve

I cannot find any structure named “foramen primum” in SA, but if by this term Dr. Ashiru means “oval foramen” then the following quotation is relevant: “Closure of the oval foramen is caused [when] the septum primum is pressed against the septum secundum” (SA 227; see also p. 196). See illustrations in SA 201-2, 206.

A female infant with congestive heart failure and a continuous systolic and diastolic murmur was diagnosed as having a patent ductus arteriosus. Which of the following statements is correct?

- (a) The ductus arteriosus is a remnant of the left fourth aortic arch.
- (b) The ductus arteriosus is closed during fetal development.
- (c) The ductus arteriosus shunts blood from the umbilical vein to the inferior vena cava.
- (d) The ductus arteriosus closes just before birth.
- (e) In the fetus, most of the blood from the pulmonary trunk flows into the aorta.

Note that “A patent ductus arteriosus is one of the most frequently occurring abnormalities of the great vessels (8/10,000 births), especially in premature infants” (SA 216).

Answer (a) is incorrect. The ductus arteriosus is a remnant of the 6th aortic arch (SA 215).

Answers (b) and (d) are incorrect. “Closure of the ductus arteriosus by contraction of its muscular wall occurs almost immediately after birth and is mediated by bradykinin, a substance released from the lungs during initial inflation” (SA 226).

Answer (c) is incorrect. The ductus arteriosus shunts blood from the pulmonary trunk into the descending aorta (SA 225-6).

Answer (e) is correct.

The fetal right atrium is mainly derived from the:

- (a) Primitive pulmonary vein
- (b) Right pulmonary vein

- (c) Primitive atrium
- (d) Sinus venarum
- (e) Sinus venosus

I am not sure what the answer to this is. Given the following quotations, perhaps the correct answer is simply (c).

Concerning answer (a): "Initially a single embryonic **pulmonary vein** develops as an outgrowth of the posterior left atrial wall" (SA 196).

Concerning answer (b): "Although initially one vein enters the left atrium, ultimately **four pulmonary veins** enter as the branches are incorporated into the expanding atrial wall" (SA 197).

Concerning answer (c): "While the cardiac loop is being formed, local expansions become visible throughout the length of the tube. The atrial portion, initially a paired structure located outside the pericardial cavity, forms a **common atrium** and becomes incorporated into the pericardial cavity" (SA 186). "The right horn, which now forms the only communication between the original sinus venosus and the atrium, is incorporated into the right atrium to form the smooth-walled part of the right atrium" (SA 190). Also see SA 195 concerning septum formation in the common atrium.

Concerning answer (d): "On the right side [of the fully developed heart], the original embryonic right atrium becomes the trabeculated right atrial appendage containing the pectinate muscles, while the smooth-walled **sinus venarum** originates from the right horn of the sinus venosus."

Concerning answer (e): "In the middle of the 4th week, the **sinus venosus** receives venous blood from the right and left sinus horns" (SA 188).

Congenital heart disease is the most common cardiac condition in childhood and most frequently results from:

- (a) Maternal medications
- (b) Genetic and environmental factors
- (c) Rubella virus
- (d) Fetal distress
- (e) Mutant genes

"It is estimated that 8% of cardiac malformations are due to genetic factors, 2% are due to environmental agents, and the vast majority are due to a complex interplay between genetic and environmental influences (multifactorial causes)" (SA 211).

Questions on the respiratory system

Each of the following anomalies of the lower respiratory tract is uncommon **EXCEPT**:

- (a) Tracheal stenosis
- (b) Tracheal diverticulum
- (c) Trachial atresia
- (d) Congenital emphysema
- (e) Tracheoesophageal fistula

“The most frequent abnormality (90% of cases) occurs with the upper esophagus ending in a blind pouch and the lower segment forming a fistula with the trachea” (SA 234).
“These defects occur in approximately 1 in 3000 births” (SA 232).

A fetus born prematurely during which of the following periods of lung development may survive?

- (a) Organogenetic
- (b) Terminal sac
- (c) Pseudoglandular
- (d) Canalicular
- (e) Embryonic

The terminal sac period is from 26 weeks to birth (SA 237 table 13.1). “During the 7th month, sufficient capillaries are present to guarantee adequate gas exchange, and the premature infant is able to survive” (SA 237).

Hyaline membrane disease was suspected in a premature infant who showed signs of labored breathing and tachypnea at birth. This condition is caused by which of the following?

- (a) Deficiency of pulmonary surfactant
- (b) Excess pulmonary surfactant
- (c) Abnormal differentiation of type I alveolar cells
- (d) Intrauterine asphyxia
- (e) Atelectasis

Answer (a) seems to be correct, according to the following: “Surfactant appears to be particularly important for survival of the premature infant. When insufficient amounts of surfactant are present, the air-water (blood) surface membrane tension becomes high, and the risk is great that alveoli will collapse during expiration. As a result, respiratory distress syndrome (RDS) develops. This is a common cause of death in the premature infant. In these cases, the partially collapsed alveoli contain a fluid with a high protein content, many hyaline membranes, and lamellar bodies, probably derived from the surfactant layer. The disease is, therefore, also known as hyaline membrane disease” (SA 239). Surfactant generally begins being produced at week 24 (CO 129).

The lungs at birth are about half inflated with liquid derived largely from the:

- (a) Lung tissues
- (b) Nasal mucus
- (c) Amniotic fluid
- (d) Tracheal glands
- (e) Maternal blood

From the following quotation, it is not clear to me whether the correct answer to this question is (a) or (c): "Before birth, the lungs are filled with fluid that contains a high chloride concentration, little protein, some mucus from the bronchial glands, and surfactant from the alveolar epithelial cells (type II). The amount of surfactant in the fluid increases, particularly during the last 2 weeks before birth. Fetal breathing movements begin before birth and cause aspiration of amniotic fluid" (SA 238).

Questions on the digestive system

Each of the following statements about the developing duodenum is true **EXCEPT**:

- (a) It is a derivative of the foregut and midgut.
- (b) The yolk stalk is attached to the apex of the duodenal loop.
- (c) It is supplied by branches of the foregut and midgut arteries.
- (d) It becomes C-shaped as the stomach rotates.
- (e) Its lumen is temporarily obliterated by epithelial cells.

Answer (a) is true: the duodenum "is formed by the terminal part of the foregut and the cephalic part of the midgut" (SA 253).

If I understand the following quotation correctly, apparently answer (b) is false (and is therefore the answer to the question as posed): "In the 5-week-old embryo, the midgut is suspended from the dorsal abdominal wall by a short mesentery and communicates with the yolk sac by way of the vitelline duct or yolk sac[...] Development of the midgut is characterized by rapid elongation of the gut and its mesentery, resulting in formation of the primary intestinal loop. At its apex, the loop remains in open connection with the yolk sac by way of the narrow vitelline duct" (SA 258).

Answer (c) is true: "Since the foregut is supplied by the celiac artery and the midgut is supplied by the superior mesenteric artery, the duodenum is supplied by branches of both arteries" (SA 253).

Answer (d) is true: "As the stomach rotates, the duodenum takes on the form of a C-shaped loop and rotates to the right" (SA 253).

Answer (e) is true: "During the 2nd month, the lumen of the duodenum is obliterated by proliferation of cells in its walls. However, the lumen is recanalized shortly thereafter" (SA 253).

Pyloric stenosis is characterized by vomiting, usually starting in the 2nd or 3rd week after birth. The narrowing of the pyloric lumen results primarily from:

- (a) Hypertrophy of the longitudinal muscular layer.
- (b) A diaphragm-like narrowing of the pyloric lumen.
- (c) Hypertrophy of the circular muscular layer.
- (d) Persistence of the solid stage of pyloric development.
- (e) A so-called fetal vascular accident in the pylorus.

Answer (c) is correct: "Pyloric stenosis occurs when the circular and, to a lesser degree, the longitudinal musculature of the stomach in the region of the pylorus is hypertrophied. This is one of the most common abnormalities of the stomach in infants and is believed to develop during fetal life. There is an extreme narrowing of the pyloric lumen, and the passage of food is obstructed, resulting in severe vomiting" (SA 251).

The junction of the endodermal epithelium of the hindgut and the ectodermal epithelium of the proctodeum or anal pit is believed to be indicated by the:

- (a) Pectinate line
- (b) Levator ani muscle
- (c) White line
- (d) External sphincter
- (e) Superior ends of the anal columns

The correct answer is (a): "The upper part of the anal canal is[...] endodermal in origin[...] The lower third of the anal canal, however, is of ectodermal origin[...] The junction between the endodermal and ectodermal parts is formed by the pectinate line, which is located just below the anal columns" (SA 268-9).

Anorectal agenesis is more common in males than in females and is usually associated with a rectourethral fistula. The embryologic basis of the fistula is:

- (a) Failure of the proctodeum to develop.
- (b) Agenesis of the urorectal septum.
- (c) Failure of fixation of the hindgut.
- (d) Abnormal partitioning of the cloaca.
- (e) Premature rupture of the anal membrane.

Dr. Ashiru says that the correct answer is (d). This finds support in the following quotation: "During the 4th and 7th weeks of development, the urorectal septum divides the cloaca into the anorectal canal and primitive urogenital sinus. The cloacal membrane

itself is then divided into the urogenital membrane, anteriorly, and the anal membrane, posteriorly” (SA 283). According to Dr. Ashiru, anorectal agenesis is a result of a failure of the cloaca to partition properly.

It is tempting to consider answer (a) based on the following quotations: “the anal membrane is surrounded by mesenchymal swellings, and in the 8th week it is located at the bottom of an ectodermal depression known as the anal pit or proctodeum” (SA 268). “Rectoanal atresias [=anorectal agenesis?] occur in 1 in 5000 live births when there is incomplete formation of the hindgut, resulting in imperforate anus with or without a fistula connecting the rectum with the perineum or parts of the urogenital system” (SA 269). However, Dr. Ashiru seems to prefer answer (d).

Questions on the urinary system

The metanephric diverticulum (ureteric bud) is derived from the:

- (a) Mesonephric duct
- (b) Splanchnic mesoderm
- (c) Metanephric mesoderm
- (d) Urogenital sinus
- (e) Somatic mesoderm

“The metanephros or permanent kidney develops from two sources. It forms its own excretory tubules or nephrons like the other systems, but its collecting system originates from the **ureteric bud**, an outgrowth of the **mesonephric duct**” (SA 309; see also p. 274).

Questions on the genital system

The feminization of the external genitalia is determined by the:

- (a) Sinovaginal bulbs
- (b) H-Y antigen
- (c) Ovaries
- (d) Absence of androgens
- (e) Epoothoron

The correct answer is (d). Testosterone is the major androgen produced by the testes (SA 292). In the female, “In the absence of androgens, the indifferent external genitalia are stimulated by estrogens and differentiate into labia majora, labia minora, clitoris, and part of the vagina” (SA 293).

Questions on the ear

Structures derived from the first pharyngeal arch and pouch include the:

- (a) tympanic antrum
- (b) tympanic cavity
- (c) tubotympanic recess
- (d) auditory tube
- (e) all of the above.

The first pharyngeal pouch gives rise to the external auditory meatus (=“tympanic antrum?”), the tympanic (or middle ear) cavity, the tubotympanic recess, the auditory (eustachian) tube, and the tympanic membrane (SA 319), so the correct answer is (e).

The otic vesicle, or otocyst, gives rise to the:

- (a) Sacculle
- (b) Cochlear duct
- (c) Utricle
- (d) Endolymphatic duct
- (e) All of the above

The correct answer is (e) (see SA 347).

Questions on the eye

Which of the following is **not** derived from neuroectoderm?

- (a) Epithelium of the iris
- (b) Optic nerve
- (c) Corneal epithelium
- (d) Sphincter pupillae muscle
- (e) Retina

Concerning answer (a), “the iris is formed by the pigment-containing external layer and the unpigmented internal layer of the optic cup as well as by a layer of richly vascularized connective tissue, which contains the pupillary muscles” (SA 360-1), and the optic cup is derived from neuroectoderm (DU 46).

Concerning answer (b), see the discussion of answer (e) below, which makes it clear that the optic nerve is derived from neuroectoderm.

Concerning answer (c): “the cornea is formed by (1) an epithelial layer derived from the surface ectoderm, (2) the substantia propria or stroma, which is continuous with the sclera, and (3) an epithelial layer, which borders the anterior chamber” (SA 362). Apparently none of these layers derive from neuroectoderm, so (c) is the correct answer.

Concerning answer (d): “the region between the optic cup and the overlying surface epithelium is filled with loose mesenchyme. In this tissue, the sphincter and dilator pupillae muscles are formed. These muscles develop from the underlying ectoderm of the optic cup” (SA 360), and the optic cup is neuroectoderm (DU 46). However, I am a bit confused by the fact that DU 46 lists the sphincter and dilator pupillae muscles as derived from neural crest cells, which are of ectodermal origin (SA 381); does this mean that the muscles are derived from “neuroectoderm”?

Concerning answer (e): “Development of the inner layer of the optic cup is[...] complicated. The posterior four-fifths[...] contains cells[...] that differentiate into light-receptive elements, rods and cones. Adjacent to this photoreceptive layer is the mantle layer, which, as in the brain, gives rise to neurons and supporting cells[...] On the surface is a fibrous layer that contains axons of the nerve cells of the deeper layers. Nerve fibers in this zone converge toward the optic stalk, which develops into the optic nerve” (SA 358-9). Thus, since the retina is derived ultimately from the optic cup and the optic cup is derived from neuroectoderm (DU 46), it is clear that the retina is derived from neuroectoderm.

The epithelium of the iris develops from the:

- (a) Inner layer of the rim of the optic cup
- (b) Outer layer of the rim of the optic cup
- (c) Both layers of the rim of the optic cup
- (d) Mesenchyme near the rim of the optic cup
- (e) Mesenchyme between the developing lens and cornea

Concerning answer (c): “the region between the optic cup and the overlying surface epithelium is filled with loose mesenchyme. In this tissue, the sphincter and dilator pupillae muscles are formed. These muscles develop from the underlying ectoderm of the optic cup. **In the adult, the iris is formed by the pigment-containing external layer and the unpigmented internal layer of the optic cup** as well as by a layer of richly vascularized connective tissue, which contains the pupillary muscles” (SA 360-1), so (c) is the correct answer.

Questions on head and neck

Which of the following cranial nerves supplies muscles derived from the first pair of pharyngeal arches?

- (a) Vagus
- (b) Glossopharyngeal
- (c) Facial
- (d) Trigeminal
- (e) Hypoglossal

The correct answer is (d). See SA 315 table 16.1.

A 25 year old woman consulted her physician about a swelling in the median plane of her neck, just inferior to the hyoid bone. This mass is likely to be a:

- (a) Cervical cyst
- (b) Thyroglossal cyst
- (c) Inferior parathyroid cyst
- (d) Tonsillar cyst
- (e) Ultimobranchial cyst

Concerning answer (a): "lateral cervical cysts[...] are remnants of the cervical sinus and are most often located just below the angle of the jaw. They may, however, be found anywhere along the anterior border of the sternocleidomastoid muscle" (SA 324).

Concerning answer (b): "A thyroglossal cyst may be located at any point along the migratory pathway of the thyroid gland but is always located near or in the midline of the neck. As indicated by its name, it is a cystic remnant of the thyroglossal duct" (SA 330), so (b) is the correct answer.

Concerning answer (c): I can't find any information in SA concerning inferior parathyroid cysts.

Concerning answer (d): I can't find any information in SA concerning tonsillar cysts, but Dr. Lieska says that such a cyst would be superiorly located.

Concerning answer (e): I can't find any information in SA concerning ultimobranchial cysts, though SA 322 discusses the development of the ultimobranchial body.

Which of the following structures is derived from the fourth pair of pharyngeal pouches?

- (a) Thymic corpuscles
- (b) Superior parathyroid glands
- (c) Inferior parathyroid glands
- (d) Thyroid gland
- (e) Tympanic membrane

The correct answer is (b). (See SA 322.)